SYNTHESIS OF HETEROCYCLIC STEROIDS CONTAINING VICINAL METHOXYL (AND HYDROXYL) GROUPS IN THE A RING AND RELATED MODEL SYSTEMS— POSSIBLE POTENTIATORS OF DRUG ACTIVITY IN CANCER CHEMOTHERAPY

By

MOHAMED MOHAMED HASHEM II

Bachelor of Science
Alexandria University
Alexandria, Egypt
1963

Master of Science
Alexandria University
Alexandria, Egypt
1967

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
May, 1975

SYNTHESIS OF HETEROCYCLIC STEROIDS CONTAINING VICINAL METHOXYL (AND HYDROXYL) GROUPS IN THE A RING AND RELATED MODEL SYSTEMS— POSSIBLE POTENTIATORS OF DRUG ACTIVITY IN CANCER CHEMOTHERAPY

Thesis Approved:

K A Berlin
Thesis Adviser

O C Dermer

Nell Pundit

Norman N Durham

Norman N Durham
Dean of the Graduate College

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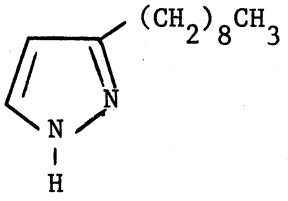
CHAPTER I

HISTORICAL

Pyrazoles

It is surprising to note that only two naturally occurring pyrazole-containing compounds 1[244] and 2[143,302,363] are known, while synthetic examples are innumerable. Knorr[236] (in 1885) introduced the name



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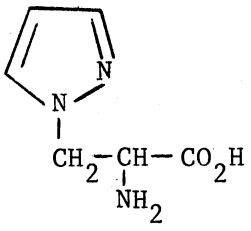


2

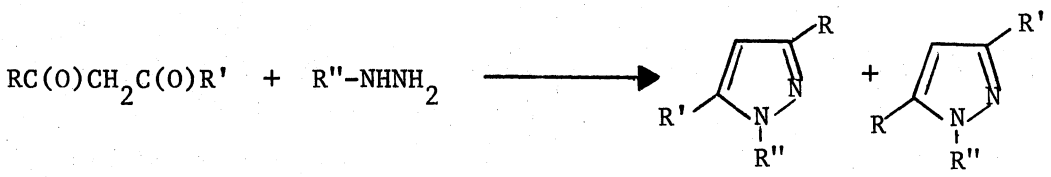
pyrazole for this class of compounds to denote that the nucleus was derived from pyrrole by replacement of a carbon with nitrogen. N-Substituted alkyl- and arylpyrazoles continue to be a very important family in organic chemistry since Chemical Abstracts devotes an entire subsection to pyrazoles and derivatives. A survey of the literature revealed thirteen books, monographs, and review articles on pyrazoles[42, 197,211,219,243,254] and pyrazole derivatives[130,227,310,385] (concentrated in the years 1953-1967) besides the countless number of papers in the years 1885-1953.

Seventeen different methods have found application in the labora-

tory as synthetic approaches to pyrazoles (excluding fused pyrazoles).

A. Synthesis of Pyrazoles

(1) From β-dicarbonyl compounds and their functional derivatives (ethers, enol ethers, acetals, enamines, etc.) with hydrazine and its derivatives:



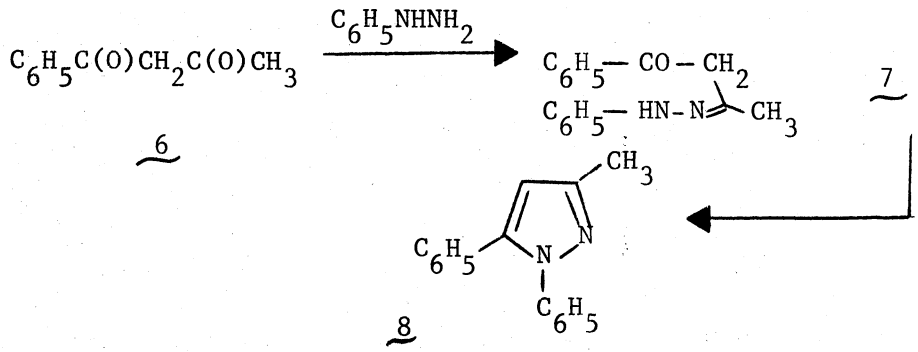
3 4 5a 5b

When the β-dicarbonyl compound is unsymmetrical (3, R ≠ R'), two isomeric pyrazole derivatives (5a and 5b) are usually formed if a substituted hydrazine (4, R" ≠ H) is used. Only a single compound is obtained from hydrazine itself (4, R" = H)[20,21,234,237,297,316] or by using symmetrical β-dicarbonyl compounds (3, R = R').

Many structural and experimental factors are involved in selective formation of one of the two isomeric compounds but at present the controlling influence of such factors is not fully understood. In many experiments the structure of the products has not been established,[45,251,315] or was assigned without definitive experimental evidence, or on the strength of simple analogies.[10,19,23] Only in a few examples have structures been established on the basis of rather rigorous experimental evidence.[137,139,140,322]

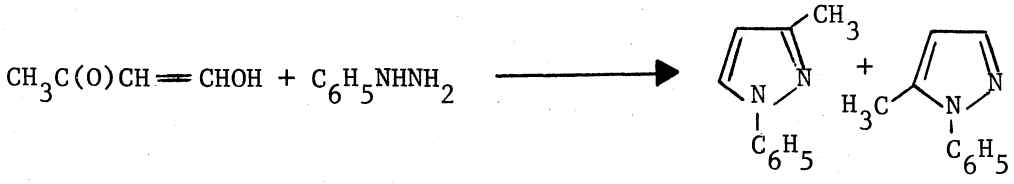
Benzoylacetone (6) reacts with phenylhydrazine to give a monophenylhydrazone 7. As with other β-diketones, no bis-phenylhydrazone

is obtained. On heating or by treatment with acids or with hydrogen chloride in pyridine, the phenylhydrazone is converted to a single product,[30] 3-methyl-1,5-diphenylpyrazole (8).



6 7 8

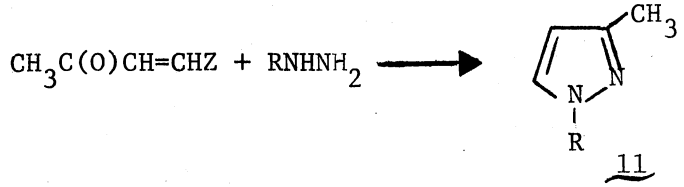
The reaction of hydrazines with β-keto aldehydes (α-hydroxymethylene ketones) appears to be more complex than the reaction with β-diketones. For example, hydroxymethyleneacetone (9) and phenylhydrazine yield, in acetic acid solution, the two possible isomeric pyrazoles (10a) and (10b).[95,96] Several attempts have been made to devise methods for



9 10a 10b

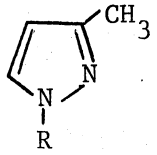
the selective synthesis of one of the two possible isomeric pyrazoles through the use of specific functional derivatives of a β-dicarbonyl compound such as acetals of β-keto aldehydes, enol ethers, enol esters, enamines and β-chlorovinyl ketones.

The following examples represent only a small fraction of the many that can be found in the literature:



11

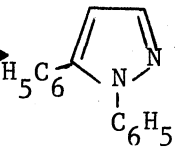
Z		R	Reference
Alkyl-O	(12)	p-$O_2NC_6H_4$	78
Alkyl-O	(13)	CH_3	78
$C_6H_5C(O)O$	(14)	C_6H_5	78
C_6H_5-C(O)O	(15)	p-$O_2NC_6H_4$	78
Cl	(16)	C_6H_5	297

$CH_3C(O)CH_2CH(OR')_2$ + $RNHNH_2$ ⟶  (Ref. 138)

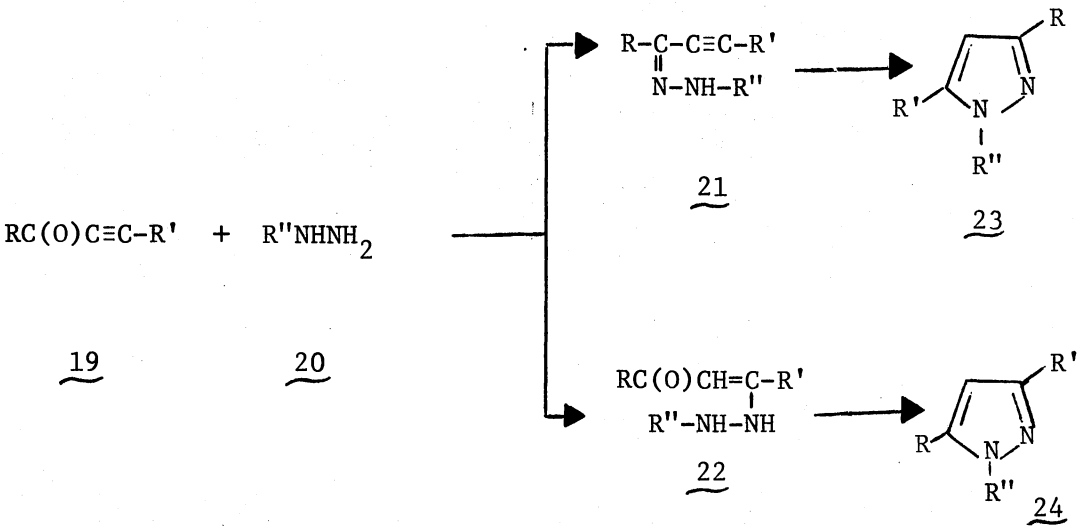
17

R' = CH_3, C_2H_5; R = CH_3, p-$O_2NC_6H_4$

18

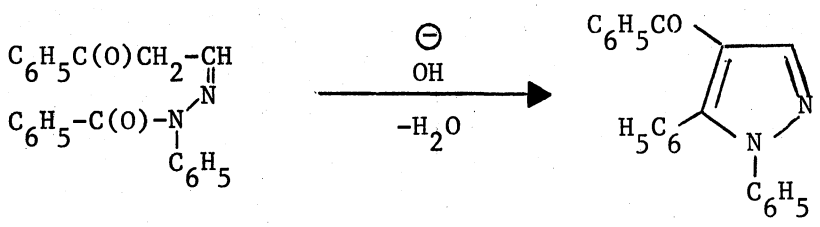
$CH_3C(O)CH{=}CHNHC_6H_5$ + C_6H_5-$NHNH_2$ ⟶  (Ref. 47)

(2) From acetylenic carbonyl compounds with hydrazine and its derivatives: Hydrazine gives pyrazoles directly and the open-chain compounds 21, 22 have never been isolated,[36,63] when R=H. When a substituted hydrazine is employed, the two isomeric pyrazoles 21 and 22 may be formed. However, methylhydrazine (20, R" = CH_3) and phenylpropiolalde-



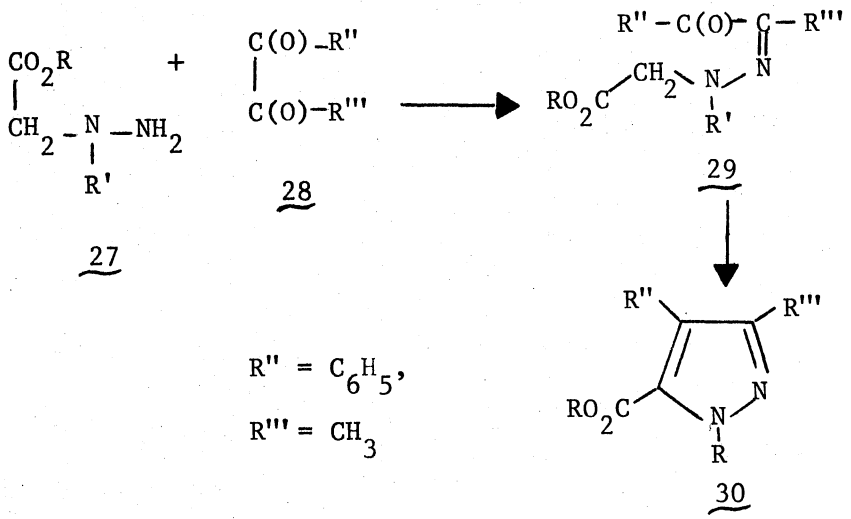
hyde (19, R = H, R' = C_6H_5) give a single pyrazole, 1-methyl-5-phenylpyrazole (23, R=H, R' = C_6H_5, R" = CH_3).[28] Apparently, formation of the methylhydrazone (21, R = H, R' = C_6H_5, R" = CH_3) is favored over the addition of the hydrazine to the triple bond. Another unexpected result is the reaction of phenylhydrazine or semicarbazide with phenylpropiolaldehyde (19, R = H, R' = C_6H_5) which gives only the hydrazone derivative, 21, and not the corresponding pyrazole.[30] This has been attributed to the formation of a "trans" form of the hydrazone, 21, which cannot cyclize.

(3) By ring closure at the 4,5-positions: A few examples are known of this type of synthesis. One case includes the cyclization of some 1-aroyl-1-phenylhydrazones of β-keto aldehydes 25 (benzoylacetaldehyde and p-toluylacetaldehyde) in the presence of alcoholic NaOH.[25]



25 26

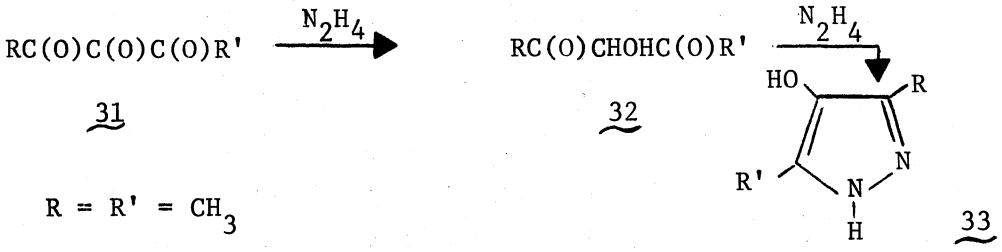
More recently,[9] hydrazinoacetic esters 27 were allowed to react with α-dicarbonyl compounds 28 and resulted in ring closure at the 4,5-positions.



27 28 29 30

$R'' = C_6H_5$, $R''' = CH_3$

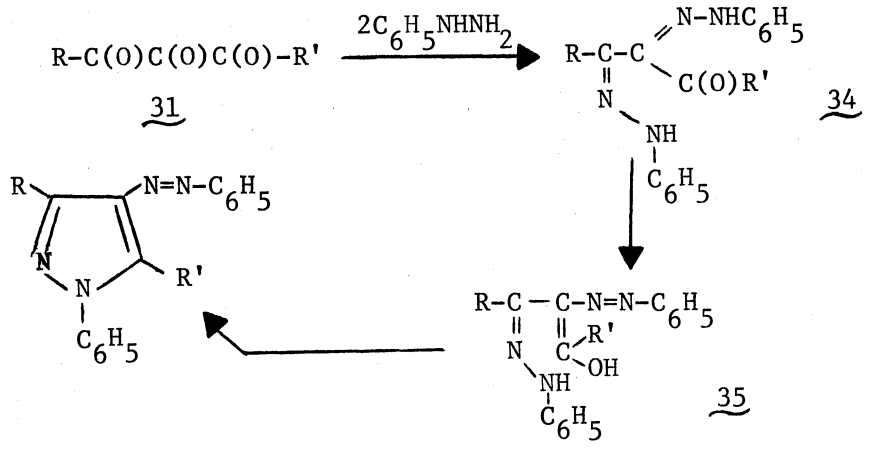
(4) From 1,2,3-tricarbonyl compounds and their functional derivatives with hydrazine and its derivative: Compounds containing three adjoining carbonyl groups 31 react with hydrazine to yield 4-hydroxypyrazoles (33).[335] Further clarification is required to explain the



31 32 33

$R = R' = CH_3$

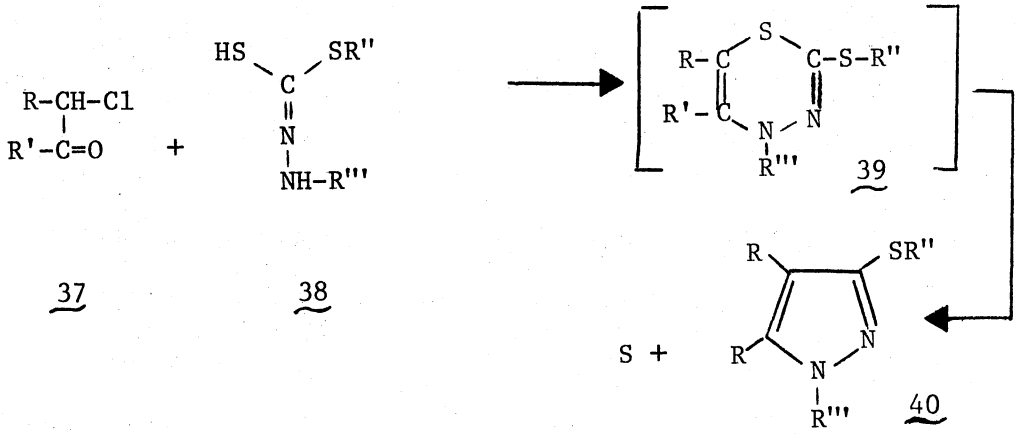
course of this type of reactions, since a reduction process is involved, and the role of hydrazine is not understood. Arylhy-



31 34 35 36

drazines behave differently to form 4-(arylazo)pyrazoles,[298] probably through formation of osazones 35 as intermediates .

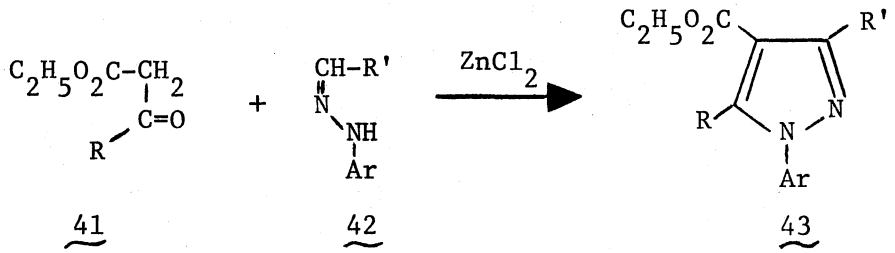
(5) From α-halo carbonyl compounds with mono- and di-thiocarbohydrazide: The reaction of S-alkyldithiocarbohydrazides 38 with α-halocarbonyl compounds 37 results in 3-alkylmercaptopyrazoles 40.[336] The



37 38 39 40

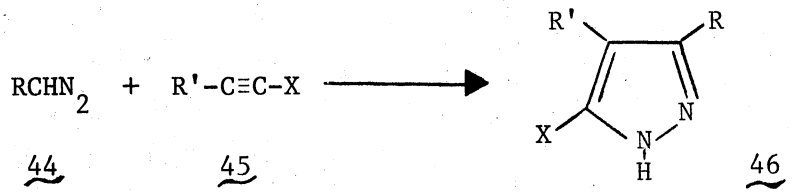
mechanism of this reaction is still unknown. Formation of 1,3,4-thiadiazine 39 which later was desulfurized was proposed with no further evidence.

(6) From aldehyde arylhydrazones with β-keto esters: Arylhydrazones of aliphatic and aromatic aldehydes 42 condense with β-keto esters 41 in presence of anhydrous zinc chloride at 120-140° to yield esters of pyrazole-4-carboxylic acids 43.[287] The intermediate steps in this reaction are not known.



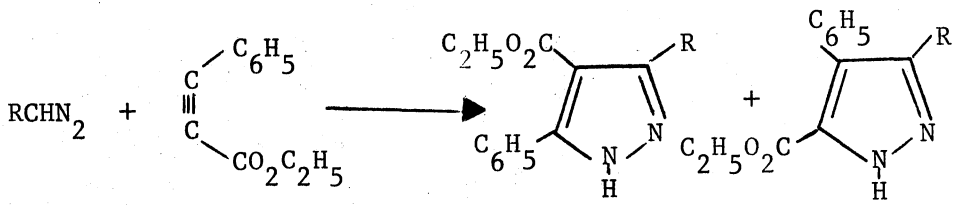
41 42 43

(7) From aliphatic diazo compounds: (a) With acetylene derivatives: Acetylene derivatives react readily with aliphatic diazo compounds to yield pyrazoles. With some asymmetrical acetylene derivatives the addition of the diazoalkene system to the triple bond usually takes place giving rise to a single product.[111,231] With other substituents



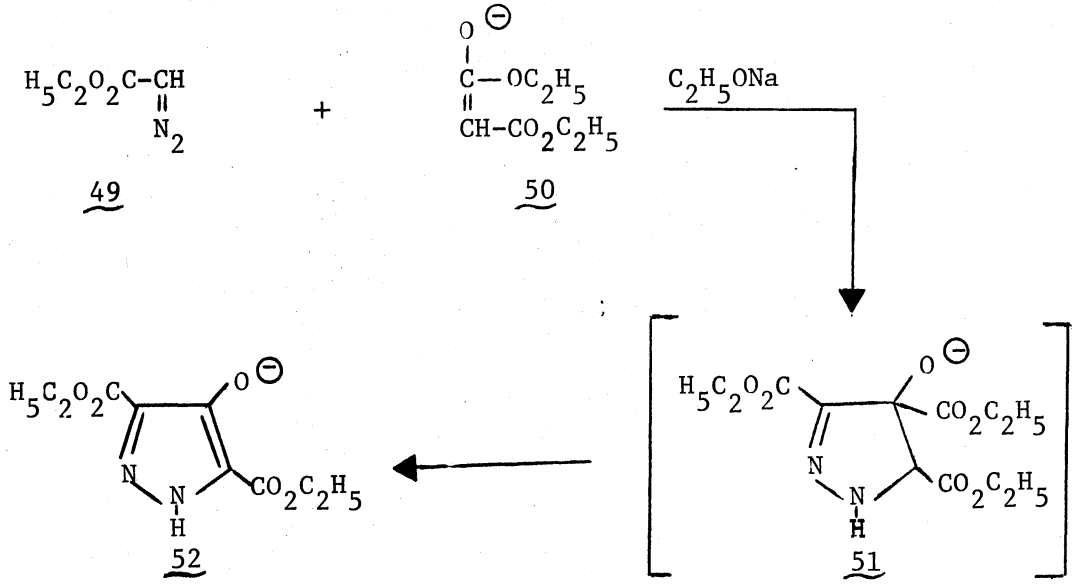
44 45 46

two isomeric products are obtained. Thus, phenylacetylene and ethyl phenylpropiolate (47) give isomers 48a and 48b.[231]



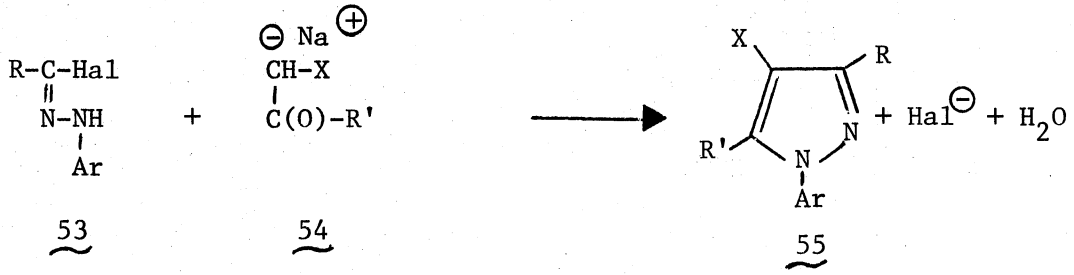
47 48a 48b

(b) With malonic esters: Some substituted malonic esters and diethyl malonate (50) yield 4-hydroxypyrazole derivatives by reaction with ethyl diazoacetate (49) in the presence of $NaOC_2H_5$.[49]



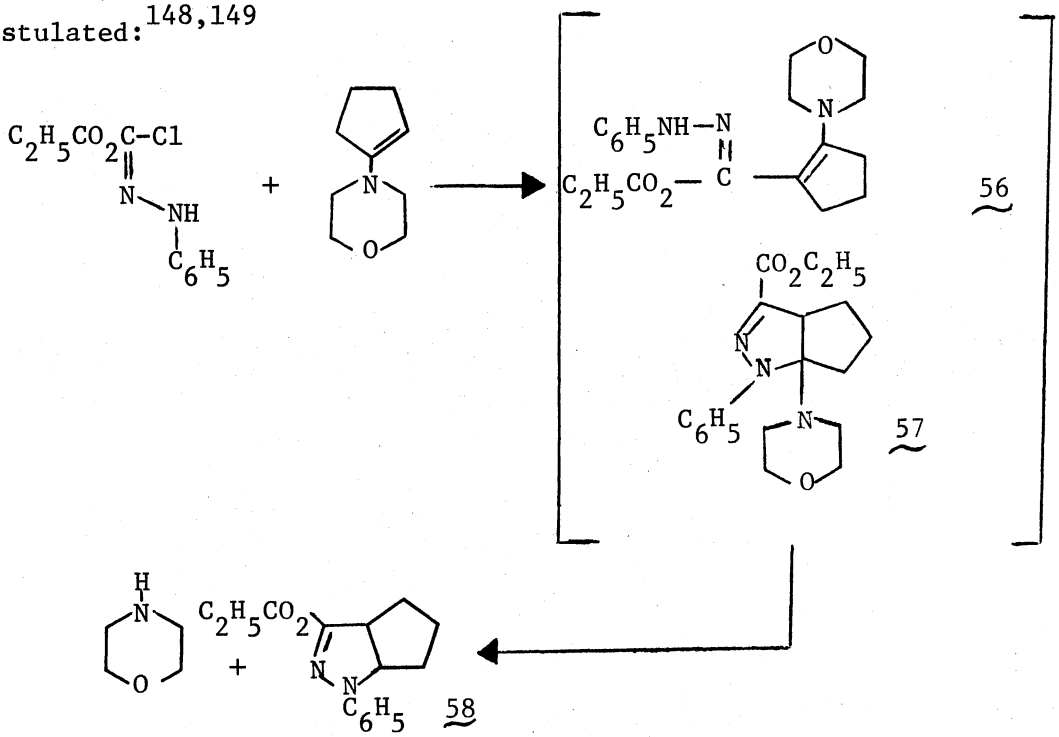
49 50 51 52

(8) From hydrazonoyl halides: (a) With alkaline salts of compounds containing activated methylene group: One of the more general syntheses of the pyrazole ring utilizes the reaction of hydrazonoyl halides 53 (R = -Ar, $-CO_2C_2H_5$, $CH_3C(O)$, Ar-N=N-, $ArSO_2$-, etc.) with the anion of activated methylene compounds as 54. The products are substituted pyrazoles (55, R' = H, aryl or alkyl group, X = an activating group, e.g., CO_2R, $C(O)NH_2$, CN, SO_2R, C(O)R, etc.)[52]



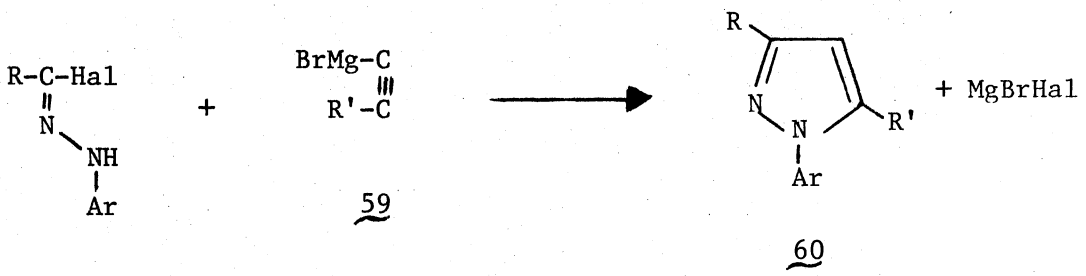
53 54 55

(b) With enamines: The importance of this relatively new procedure is that it offers, generally in high yields, compounds (e.g., 4-alkylpyrazoles) that are not easily obtained by other methods.[148,149] Open form (like 56) or cyclic form (like 57) intermediates have been postulated:[148,149]



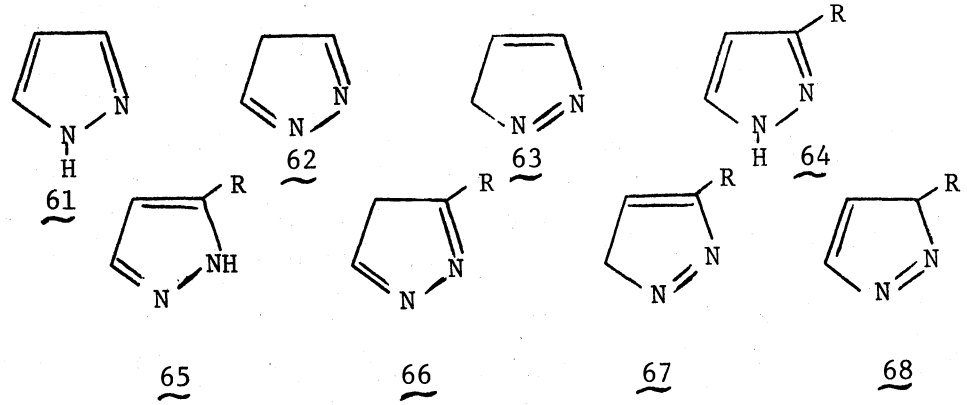
56 57 58

(c) With organomagnesium derivatives of acetylenic compounds:[161] This is a novel method and only rarely found in the literature.

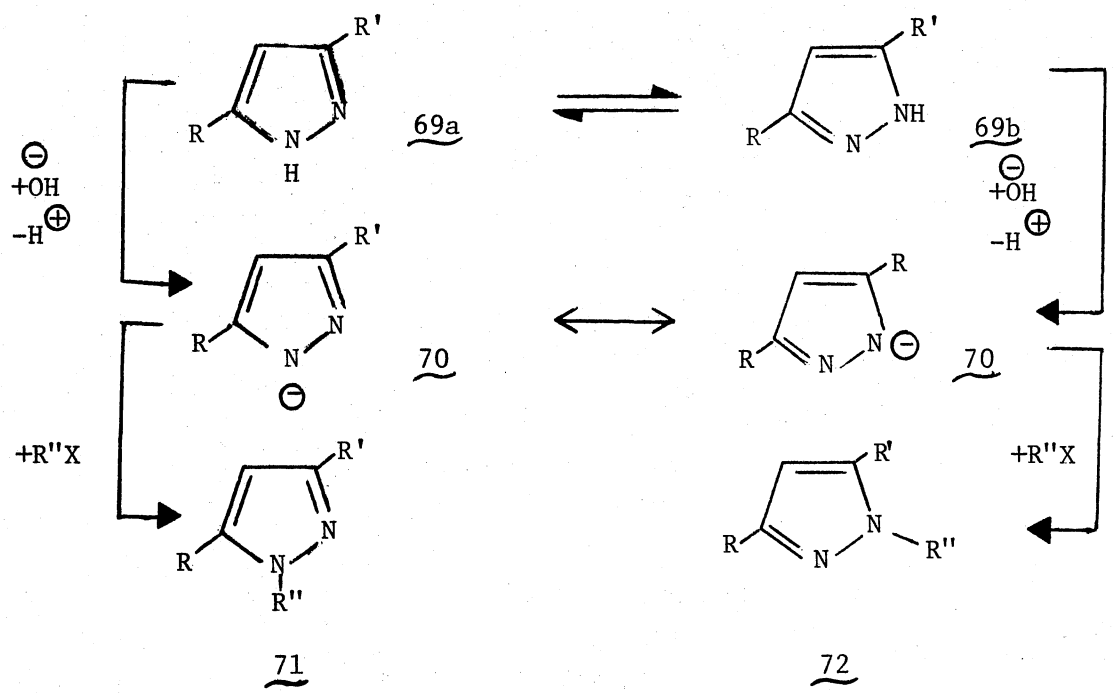


B. The General Character of Pyrazoles

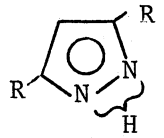
(1) Tautomerism and isomerism: Three tautomeric forms can be written for unsubstituted pyrazoles (61, 62, and 63) and five forms (64, 65, 66, 67, 68) for compounds in which the two carbon atoms adjacent to nitrogens carry different substituents.



Evidence for only the common forms 64 and 65 has been obtained. However, forms 62 and 66 and forms 63, 67, and 68 can apparently exist only with derivatives[42,243] in which all four hydrogen atoms of the nucleus are substituted.[12,200,201] Such compounds often show a tendency to rearrange to yield "true" pyrazoles.[42,243] Alkylation or arylation of an unsymmetrically substituted pyrazole 69 yields normally two isomeric products 71 and 72.[73] This establishes that the hydrogen atom can be bound to either nitrogen atom in the parent molecule. Actually when alkylation is



carried out in presence of strong base, intermediate formation of a resonance-stabilized anion 70 has been postulated. It is impossible to represent by a classical structure a pyrazole molecule in which a hydrogen atom is connected equally to two nitrogen atoms, but complete symmetry of the monomeric molecule is possible.[243] The system may be described as one which includes an aromatic sextet of π-electrons with



the double and single C-C and C-N bonds of equal length, and possessing a hydrogen atom in some way connected to both nitrogen atoms simultaneously.[252]

(2) Spectroscopic properties: Nuclear magnetic resonance studies of pyrazole structures have established the relative amounts of the tautomers present under different conditions.[143,167,282,388] It has been found[57,141] that the hydrogen atoms in positions 3 and 5 of N-sub-

stituted pyrazoles for some reason have the same chemical shifts, though they are chemically non-identical. It has been also shown that 1,3-dialkylpyrazoles are stronger bases than any other position isomers.[385]

The effects of several shift reagents on the PMR spectra of some pyrazole derivatives have been recorded.[97] The effects of substitution (on the pyrazole ring), lanthanide-shift reagents, solvent changes, and tautomerism were investigated by the ^{13}C chemical shifts of some pyrazoles.[132] It was concluded that ^{13}C chemical shifts are of limited value for ascertaining the positions of tautomeric equilibrium for rapidly interconverting azole tautomers.[132] The synthesis and NMR spectra of some heterosteroids with a pyrazole D ring was reported by J. Lematre and J. Soulier (1967).[252]

NMR analysis indicated the phenyl group at position 15 of 78 exerts a long-range shielding effect on the proton of position 7, which appears as a doublet centered at 7.05 ppm ($J_{6,7}$ = 8.5 Hz). Similarly, NMR analysis showed 80 had the methyl group situated on N-16.[252]

A rather comprehensive analysis of the ultraviolet spectra of more than 50 pyrazoles was recorded[86] in various solvents and conditions of pH. Alkylpyrazoles show maxima in the region 210-225 nm (log $\varepsilon_{max.}$ = 3.5-4.0). A small bathochromic effect of alkyl substituents as a rule does not exceed 2-3 nm. The maxima for all arylpyrazoles lie between 250-280 nm (log $\varepsilon_{max.}$ = 3.4-4.2). The introduction of such chromophoric groups as $-NO_2$, -C(O)R, -CHO, $-CO_2C_2H_5$ into alkylpyrazoles gives rise to a bathochromic shift of the order of 25-40 nm.[86,162] Ultraviolet spectra of various pyrazoles are available from other sources too.[78]

Infrared analysis of pyrazoles in the crystalline form and in concentrated solution reveal an absorption band corresponding to the N-H

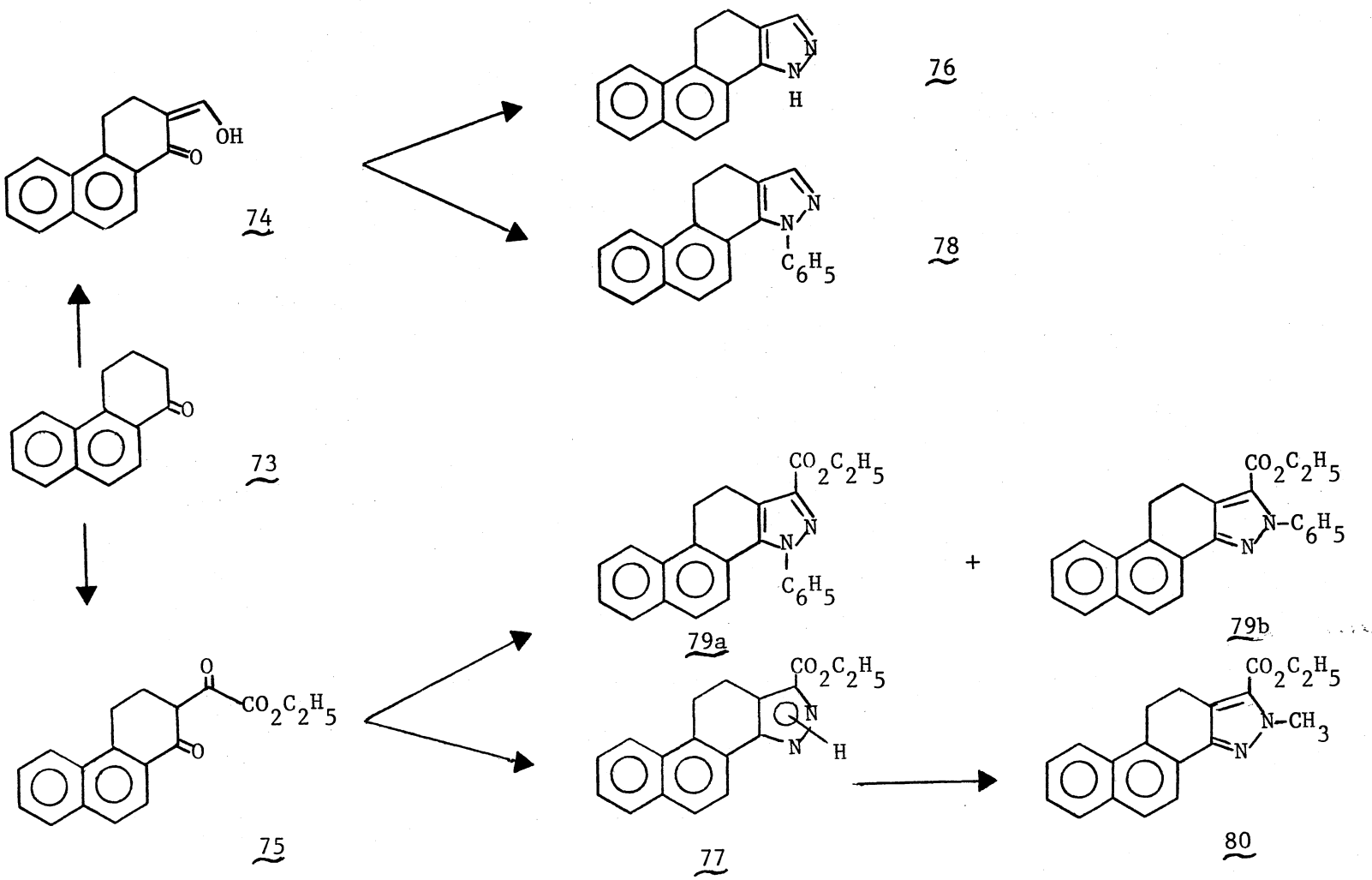
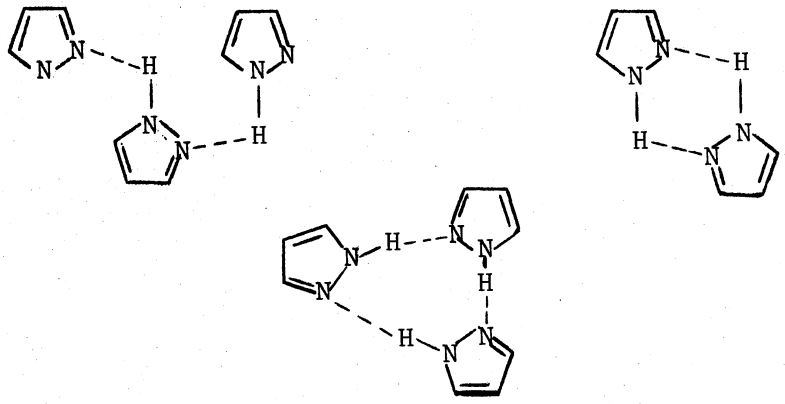
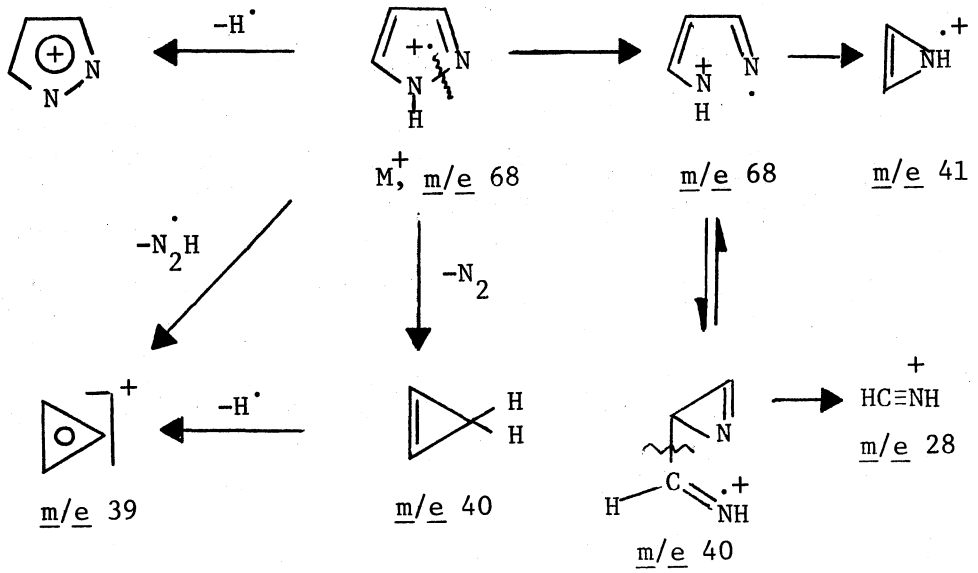


Figure 1. Synthesis of Some Phenanthropyrazoles[252]

group at 2.7-3.0μ (3500-3100 cm^{-1}), the breadth of the band suggesting hydrogen bonding.[275] It was concluded that the association of pyrazoles may be either linear or in cyclic dimers or trimers.[14]

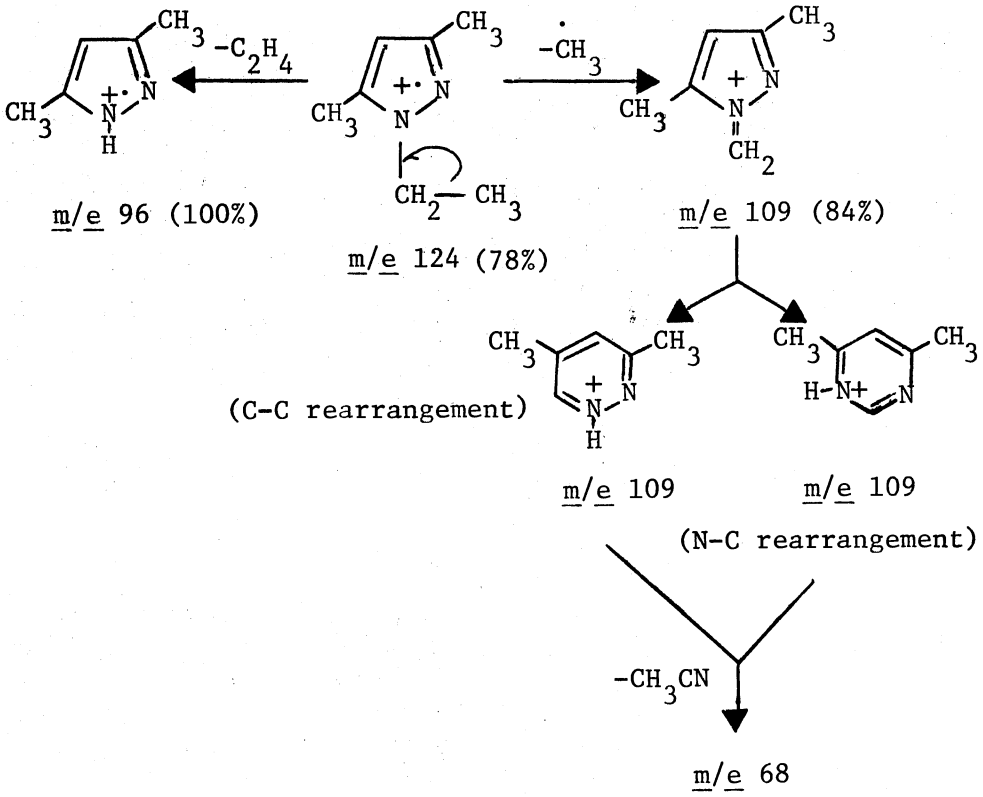


Infrared spectra of other pyrazole derivatives are included in a number of papers.[65,162,164,275] Orgel[306] (1951) noted that the maximum electron density occurs at C(4), in agreement with the results of electrophilic substitution experiments. The mass spectrum of pyrazole revealed[67] an intense molecular ion. The m/e 41 peak most probably resulted from loss of HCN from the molecular ion whereas m/e 39 can be due to $C_3H_3^+$.

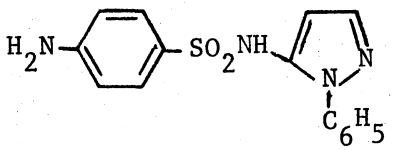


Three isobaric possibilities were shown[67] to exist for m/e 40. The ion at m/e 28 is most likely due to $CH_2N^{+\cdot}$ rather than $N_2^{+\cdot}$.

The mass spectrum of 1-ethyl-3,5-dimethylpyrazole[67] has an intense M^+-CH_3 ion, showing the importance of α-cleavage in N-alkylpyrazoles. Ring expansion of the ion may be produced via rearrangements of C-C or N-C bonds. As expected, the M^+-CH_3 species shows marked loss of CH_3CN.



(3) Biochemical and medicinal applications of pyrazoles: The use of pyrazole derivatives in medicine is undoubtedly the principal one. Certain alkylpyrazoles have shown quite significant bacteriostatic, bacteriocidal, and fungicidal actions.[127,163,176,268,324] In this respect sulfonamides based on pyrazole ("sulfapyrazoles") are of particular interest, e.g., Orisul (81), which has a prolonged bacteriostatic action in vivo.[7,165,320]

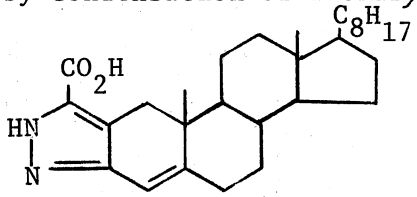


81

Alkyl- and arylpyrazoles have a sharply pronounced sedative action on the central nervous system.[311,375] Steroidal compounds whose structures include pyrazole rings are of interest as possible psychopharmacological agents.[100,102] Pyrimidinopyrazoles are being studied in the fight against cancer.[151] In a series of pyrazoles synthesized[395] for the most part by the reaction between β-diketones and hydrazines or semicarbazides, 2-benzoyl-3,5-dimethylpyrazole appeared to be more active than 3,5-dimethylpyrazole in preliminary screening.

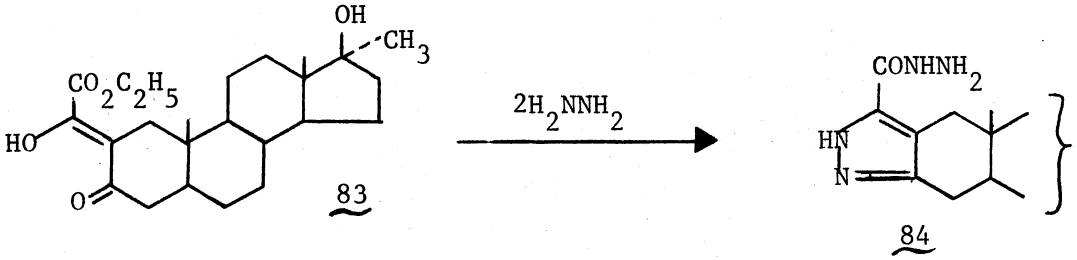
C. Pyrazolosteroids

The first pyrazolosteroid was 5'-carboxycholest-4-eno[3,2-c]pyrazole (82)[334] obtained by condensation of 2-oxalylcholestenone with



82

hydrazine. Additional transformations were performed on 2-oxalyl-17α-methyldihydrotestosterone, which was obtained from ethyl oxalate, sodium

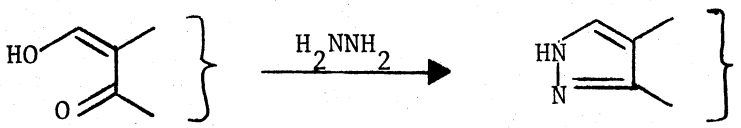


83 84

methoxide, and the corresponding 3-ketosteroid.[332]

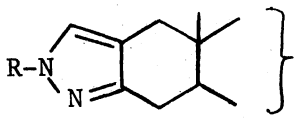
It has been mentioned previously that steroido[3,2-c]pyrazoles form a new class of steroid hormones with interesting physiological activity.[100] The main method of synthesis of the compounds of this class

is the condensation of (2-hydroxymethylene)-3-ketosteroids with an excess of hydrazine. The requisite hydroxymethylene ketones are obtained by

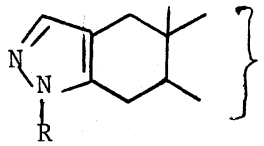


formylation of the corresponding ketones with ethyl formate in the presence of NaH or $NaOC_2H_5$ (in C_6H_6 or dioxane) with either saturated or unsaturated ketones.[326]

It would be expected that the condensation of (2-hydroxymethylene)-3-ketosteroids with substituted hydrazines should give, depending on the reaction conditions, mixtures of 1'- and 2'-substituted pyrazoles 85a and 85b.



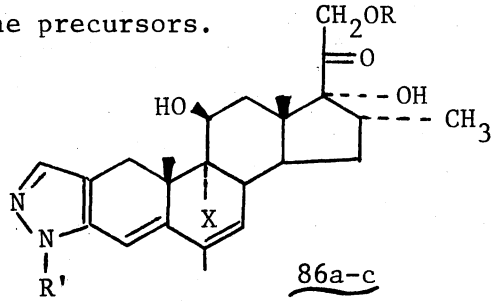
85a



85b

However, it was shown[102] that for an alkylhydrazine (in which the substituted nitrogen has more nucleophilic character) only the isomer 85a was obtained. For phenylhydrazine, the β-nitrogen atom was more nucleophilic and isomer 85b was obtained.

Extensive studies of the steroidopyrazoles have been reported[181,182] in which certain 8α-pregn-4-eno[3,2c]pyrazole derivatives 86 (based on cortisol and its 16 α-methyl and dihydro derivatives) were prepared through hydroxymethylene precursors.

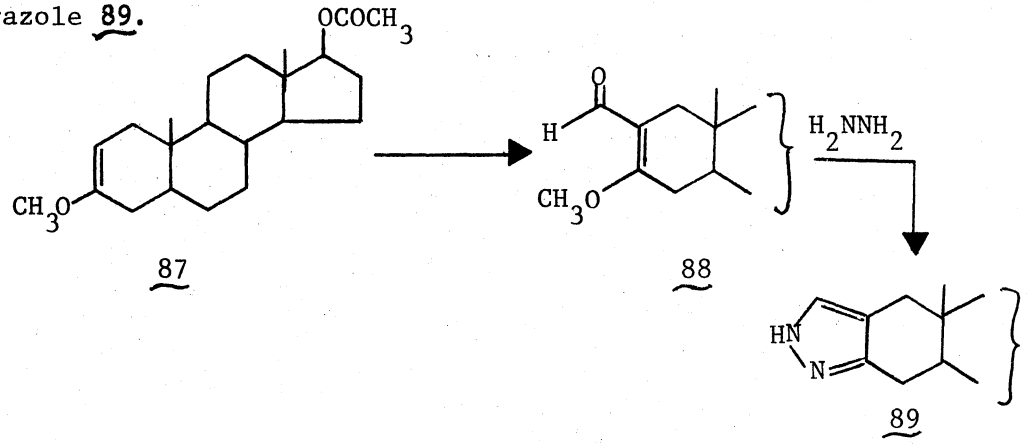


86a-c

where in (a), R = H; R' = H; in (b), R = CH_3CO; R' = C_6H_5; X = H,F

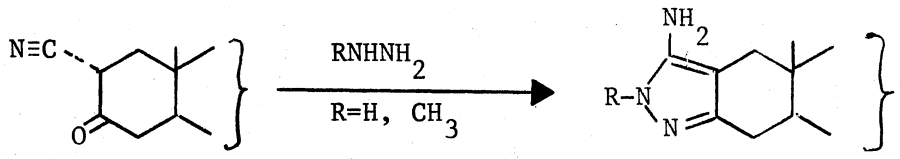
in (c), R = H; R' = p-F-C_6H_4; X = H,F.

Treating the acetate 87 in two steps formed the corresponding 5α-pyrazole 89.

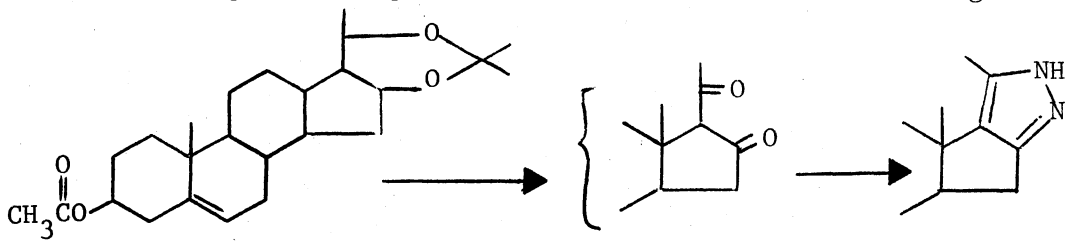


87 88 89

A series of 5'-amino-substituted steroidopyrazoles were obtained by condensation of 2α-cyano-3-ketosteroids with hydrazine.



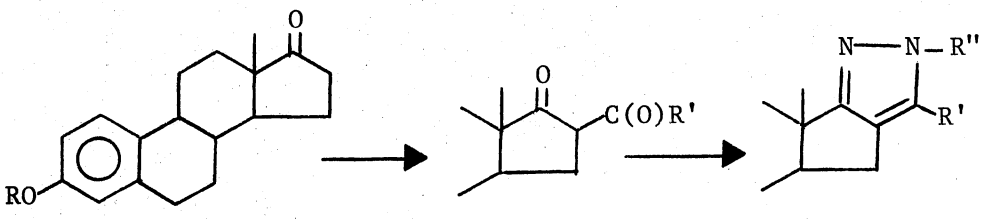
The 16β, 20α-isopropylidenedioxysteroids of type 90 are also of interest for the synthesis of steroidopyrazoles. They are readily converted into 16,20-diones, which with hydrazine in ethanol form pyrazole derivatives 91 in which the heterocyclic ring is condensed with a steroid component in positions 16 and 17.[121] Other analogs were



90 91

also obtained from 5α-pregnan-3β, 16β,20α-triol.[225]

Synthesis of [17,16-c]pyrazoles of the androstane and estrane series is conveniently effected[331] by treatment of 17-ketosteroids with ethyl formate or diethyl oxalate in the presence of sodium hydride or methoxide with subsequent cyclization with hydrazines of the 16-formyl derivatives obtained.



where R = H, CH_3,  ; R' = H, $CO_2C_2H_5$; R'' = H, CH_3

On heating in a bomb with methyl iodide, 1'-methylsteroido[3,2-c]-pyrazoles are converted into 1',2'-dimethylpyrazolium salts, which are stable, high-melting compounds, but of relatively low solubility in water.[102]

All the androstrano[3,2-c]pyrazoles have a characteristic absorption maxima in the UV spectrum at 223 nm (ε ≃ 5000); this band is displaced in 0.01 N alcoholic HCl solution to 229 nm (ε ≃ 6200). When a conjugated double bond is present, the steroidopyrazoles have absorption maxima in the 261 nm region (ε ≃ 10,000). The bathochromic shift of the maxima in the acid solution is explained by the protonation of the pyrazole ring, since such a phenomenon is not observed in alcoholic alkali solution.[102]

The fusion of a coplanar pyrazole ring to the steroid nucleus leads to substitution of the C(3) oxygen atom by nitrogen, which changes the nucleophilic environment in this region. In this instance there is a change in the distance between the active centers of the steroid mole-

cule at C(3) and C(17), since the length of the C=N bond is ca. 1.4 Å, and the length of the C=O bond in the original ketone is 1.2 Å. This shows some influence of the strength of the bond of the steroid molecule with the chelate receptors and can lead to selectivity in the reaction between the steroid and the receptor.[102]

A significant fall in the estrogenic activity of certain [3,2c]-pyrazolosteroids has been observed.[102,308] Such physiological activities were absent for compounds with the pyrazole ring attached to positions 16 and 17.[331]

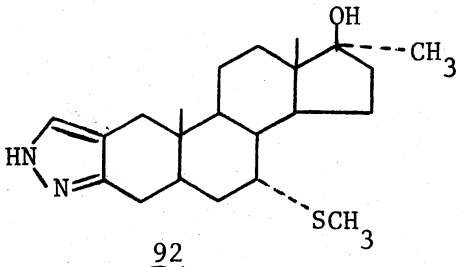
The [3,2-c]-2'-phenylpyrazole of 9α-fluoro-6,16α-dimethyl-Δ^6-hydrocortisone (86c) has been claimed to be the most potent anti-inflammatory steroid yet known, being some 2000 times as potent as hydrocortisone in the rat systemic granuloma assay.[357] Other compounds of the series include the [3,2-c]pyrazole of 16α-methylcortisone, which has four times the activity of the parent steroid,[357] and the [3,2-c]pyrazole of 9α-fluoro-16α-methylhydrocortisone 86a, which has 10 to 20 times the activity of hydrocortisone.[181]

Certain steroidal [3,2-c]pyrazoles[102,100] are already known to posess very favorable anabolic-to-androgenic ratios. One representative of these compounds, 17α-hydroxy-17α-methylandrostano[3,2-c]pyrazole (86c), has shown to be active by the oral route on a preliminary clinical trial.[102]

Dimethyl carbamates and dialkyl phosphates of 5-hydroxypyrazoles have been used as cholinesterase inhibitors.[136,170,383] There is some evidence that 3,5-dimethylpyrazole has a stimulant action on plants.[100, 102] Besides the traditional interest in pyrazole derivatives, which has been the basis of numerous dyes and drugs, a number of pyrazole anesthe-

tics have appeared.[300,373]

The hypocholesterolemic and antiatherosclerotic effects of 17α-methyltestosterone (93) and a new protein-anabolic steroid, 7α-ethylthio-17β-hydroxy-17α-methyl-5α-androstano[3,2-c]pyrazole (92), have been com-



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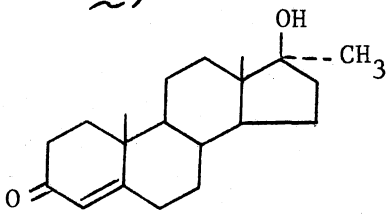
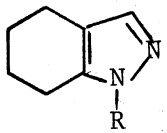


93

pared in male rabbits fed a diet supplemented with cholesterol and coconut oil.[291] Methyltestosterone (93) does not lower serum sterol levels significantly when administered subcutaneously at 0.3, 1.0, or 3 mg/kg (body wt.) at 48-hr. intervals. Under the same conditions, 92 is an effective hypocholesterolemic agent; a 20% lowering was reported at doses of 3 mg/kg.[77] It also brought about an increase in the oxidation of cholesterol-4-^{14}C to bile acids of male rats with bile fistula, and the fecal excretion of ^{14}C-bile acids from ingested tagged cholesterol was increased. In rabbits the frequency and severity of artificially induced atheroma was noticeably decreased by pyrazole 92.[291]

D. Tetrahydroindazoles

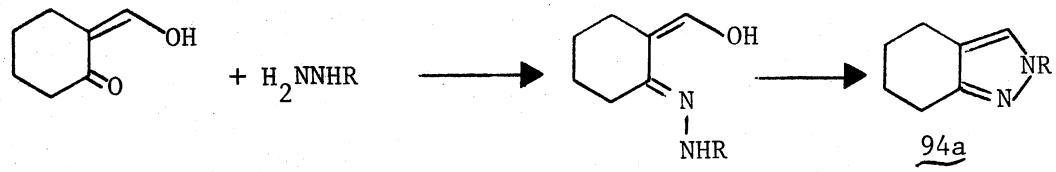
(1) Synthesis and biological application: Cyclotetramethylene-



94

pyrazoles (94) [or cyclohexenopyrazoles: or 4,5,6,7-tetrahydroindazoles, R = H] are usually prepared by the reaction of (2-hydroxymethylene)cyclohexanone with hydrazine hydrate.[5] Presumably the intermediate is a hydrazone, which should lead to a 2-substituted derivative 94a when a

substituted hydrazine is employed. However, the 1-derivatives appear

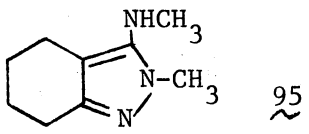


94a

in many cases to be the more stable, and the product may consist entirely of the 1-substituted compound.[22] The enol acetate or benzoate may provide a more convenient starting material than the hydroxymethylene compound.[42]

Ring closure of 2-chlorocyclohexanone phenylhydrazone is a reported preparation of tetrahydroindazole.[248] 2-Cyclohexanecarbaldehyde behaved similarly with hydrazine hydrate.[338] Diazomethane and cyclohexene gave tetrahydroindazole in poor yield.[286] Tetrahydroindazoles have also been obtained by the hydrogenation of certain indazoles using Pt in acetic acid.[147] The imino group of tetrahydroindazole undergoes dialkylation readily.[29] Fractional crystallization of the picrates or perchlorates of 1- and 2-substituted alkylated products was commonly used to separate the isomers.[8] Bredereck and co-workers[67] were able to obtain 4,5,6,7-tetrahydroindazole [(94), R = H] (24%) by condensing 2-(dimethylaminomethylene)cyclohexanone with hydrazine.

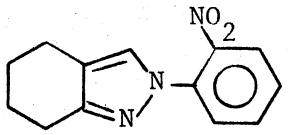
Scuri and co-workers[347] have recently shown that substituted tetrahydroindazoles like 95 exhibited analgesic action superior to that



95

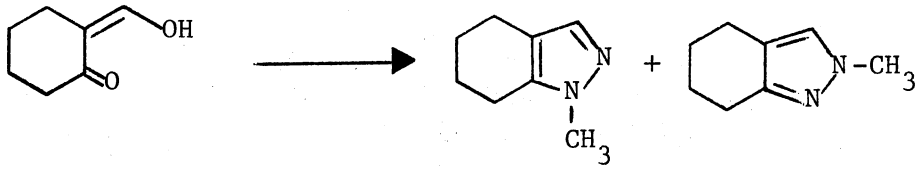
of phenylbutazone, acetylsalicylic acid, aminopyrine, and benzidamine. The anti-inflammatory activity of 95 was found to be equal to that of

phenylbutazone. The authors labeled the compound "tetridamine" and surveyed it pharmacologically in mice, rats, guinea pigs, and cats. Tetridamine showed antitussive, local anesthestic, choleretic, and spasmolytic activities. Unlike many other antiinflammatory drugs, this compound was not ulcerogenic and was able to prevent the formation of experimental ulcers. N-Substituted tetrahydroindazoles like 96 [303] were demonstrated to have some herbicide activities. It was also used as a plant growth regulator.

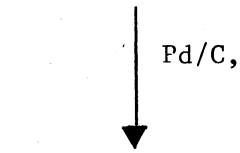


96

(2) Spectral properties of tetrahydroindazoles: (a) NMR and UV studies of N-substituted isomers: Albright and Goldman[8] and later Butler[8] used NMR to differentiate between isomeric tetrahydroindazoles 98 and 99. Reaction of 2-(hydroxymethylene)cyclohexanone (97) with



97 98 99



100

methylhydrazine in methanol at 0° gave a mixture of 98 [29] (14%) and 99 [22] (86%) as shown by NMR analysis, while reaction of methylhydrazine sul-

fate gave a mixture of 1:2 98 (33%) and 99 (67%). Reaction of the mixture with picric acid, followed by repeated recrystallizations of the mixture, gave pure picrate of 99. The picrate was converted to 99, which when dehydrogenated with 10% Pd-C in boiling decalin[6,242] produced 2-methylindazole (100).[24] The characteristic UV spectrum of 100, which differs significantly from that of 1-methylindazole (98)[45,330], allowed the unequivocal assignment of structure 99.

The mixture of 98 and 99 showed signals in the PMR spectrum at δ 3.70, δ 3.80, δ 7.03 and δ 7.25, while in pure 99 the signal of the methyl group was observed at δ 3.80 and the pyrazole proton at δ 7.03. Therefore, the signals at δ 3.70 and δ 7.25 in the spectrum of the mixture were attributable to 98.

From these spectra it is apparent that when the methyl group is on the pyrazole nitrogen which is bonded to the carbocyclic ring, the absorption appears at higher field* and in the pyrazole proton signal at lower field (structure 98) than in the isomer (structure 99). The difference, therefore, between the chemical shift of the methyl proton signal and the signal for the proton on the pyrazole nucleus is characteristic for each isomer and may be used to assign structures to isomeric pyrazoles. Additional examples are summarized in Table I.

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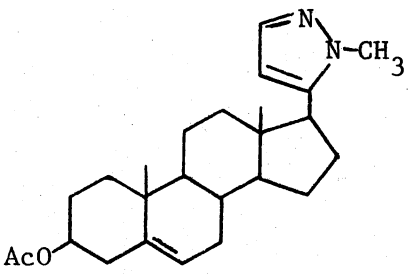
*Similar variations in the chemical shifts of C(18) and C(19) methyl groups in steroids have been discussed by N. S. Bhacca and D. H. Williams ("Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, Calif., 1964, p. 16), who pointed out that "as a given angular methyl group is able to 'see' less of the remaining skeleton, it will appear at lower field".

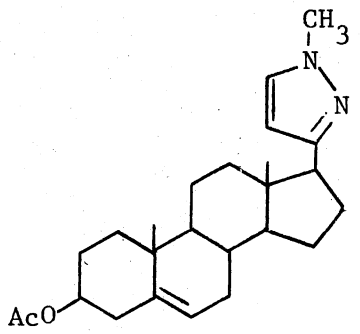
TABLE I

NMR SPECTRA OF ISOMERIC N-METHYL-3(5)H-PYRAZOLES[8]

Compound	Chemical Shift (δ) Pyrazole Proton	$N-CH_3$	$\delta_H-\delta_{N-CH_3}$
1-Methyl-4,5,6,7-tetrahydroindazole (98)	7.25	3.70	3.55
2-Methyl-4,5,6,7-tetrahydroindazole (99)	7.03	3.80	3.25
17-(1-Methyl-5-pyrazolyl)-5-androsten-3β-ol acetate (101)	7.42	3.83	3.59
17-(1-methyl-3-pyrazolyl)-5-androstan-3β-ol acetate (102)	7.27	3.87	3.40
17β-Hydroxy-17α-methylandrostano[3,2-c]2'-methylpyrazole (103)	7.79	4.25	3.54



101



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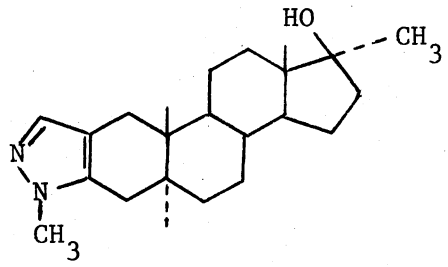
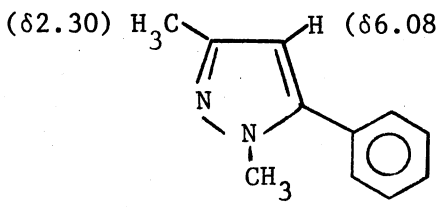


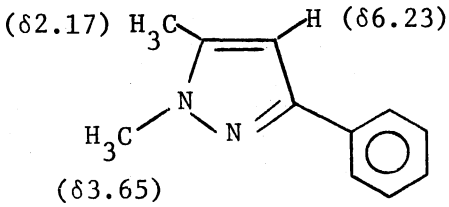
103

Albright and Goldman[8] examined the PMR spectra of pyrazoles 104-107, whose structures were known from their UV spectra.[394]



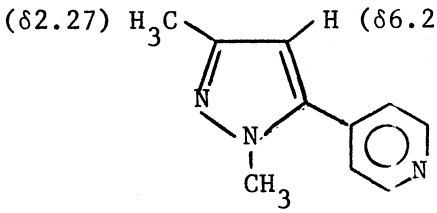
(δ2.30) (δ6.08) (δ3.80)

104



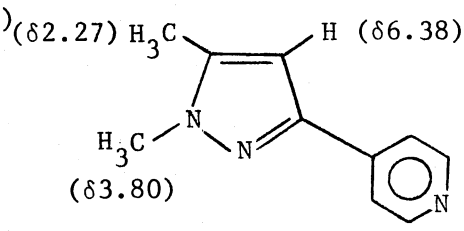
(δ2.17) (δ6.23) (δ3.65)

105



(δ2.27) (δ6.20) (δ3.85)

106

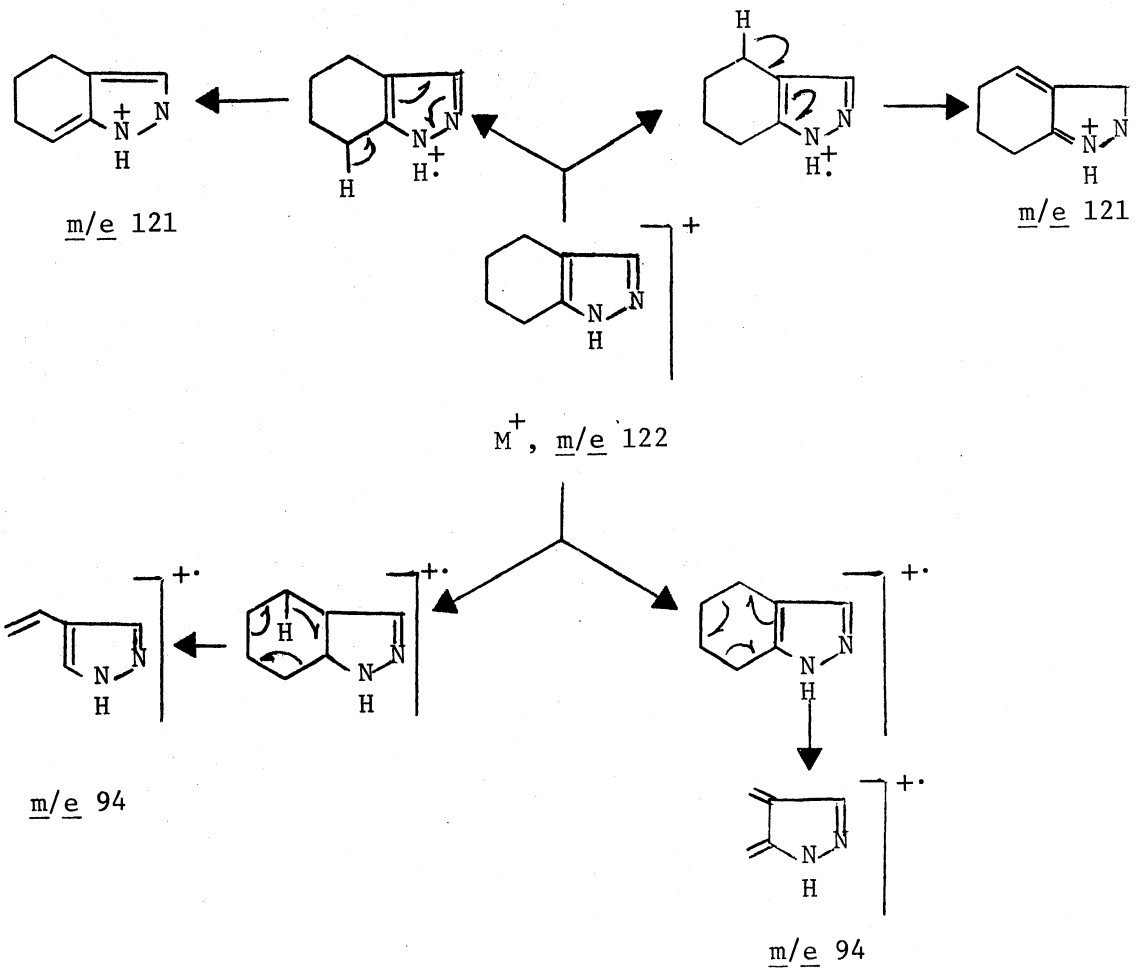


(δ2.27) (δ6.38) (δ3.80)

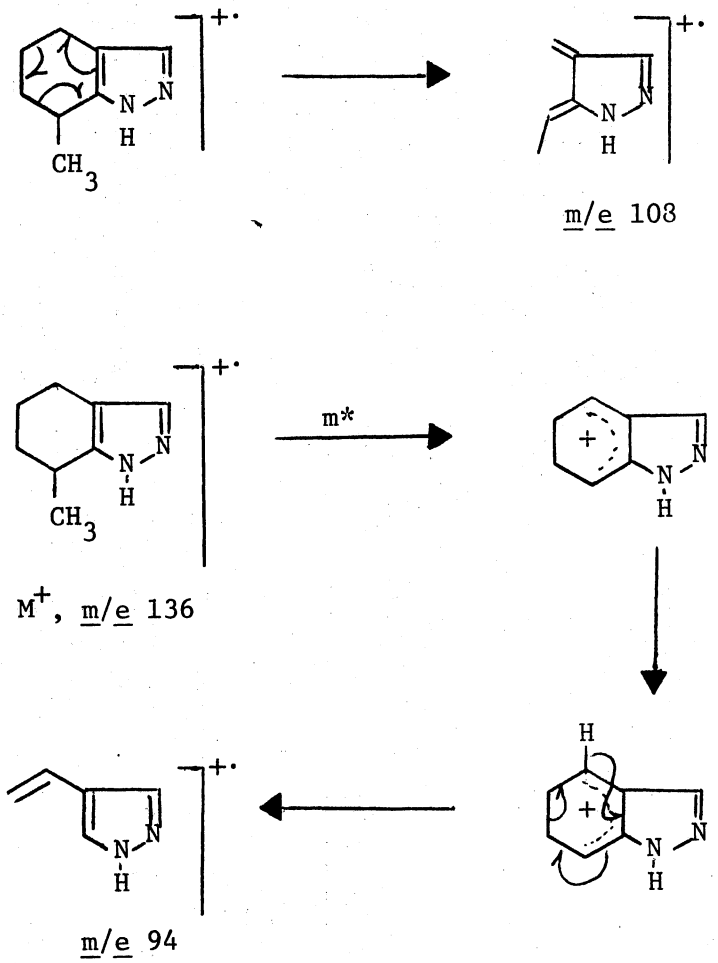
107

The N-methyl proton signals of pyrazoles 104 and 106 are found at lower field than in the corresponding isomers 105 and 107. This shift to lower field may be attributed to deshielding by the aromatic groups which are in close proximity to the methyl groups in structures 104 and 106. The UV spectra of 104 and 106 provided evidence for such interaction, for inhibition of resonance of the aromatic group with the pyrazole nucleus had been noted.[394] Jacquier and co-workers[37] (1967) confirmed these results by preparing some substituted N-nitrophenyltetrahydroindazoles and comparing their NMR and UV data simultaneously.

(b) Mass spectral data: The mass spectrum of 4,5,6,7-tetrahydroindazole (94) was studied by Audier and co-workers[18] in 1971.



The mechanistic fragmentation pathways were reported by those authors. For the 7-methyl analog, the following scheme was suggested.[125]

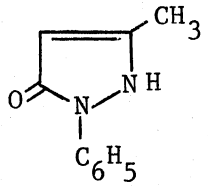


Considerable effort on a variety of pyrazoles is needed in this field before fragmentation patterns can be rapidly used as a diagnostic tool to identify unknown pyrazoles.

Pyrazolones[386]

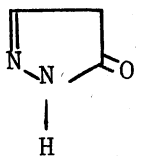
One of the first synthetic organic drugs to be marketed and used before the correct structure had been assigned was 3-methyl-1-phenyl-2-pyrazolin-5-one (108). It was prepared by the reaction of ethyl aceto-

acetate with phenylhydrazine by Knorr in 1883.[235]

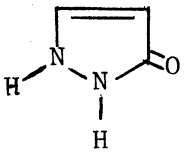


108

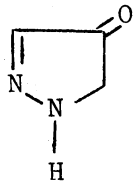
Pyrazolinones and pyrazolidinones are oxo derivatives of pyrazolines and pyrazolidines, respectively, and are so named in Chemical Abstracts at present. However, the usual method of naming in the earlier literature is the pyrazolone-pyrazolidone system. Although a large number of tautomeric structures are possible for pyrazolinones, the usual assignment is as shown in 109a, 109b and 109c.



109a

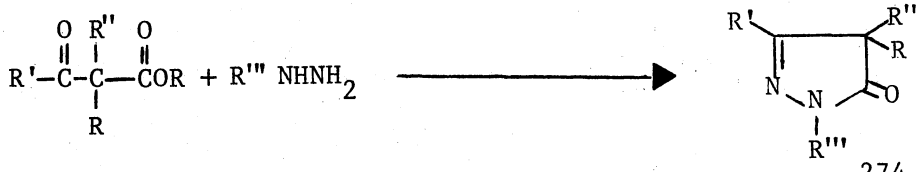


109b



109c

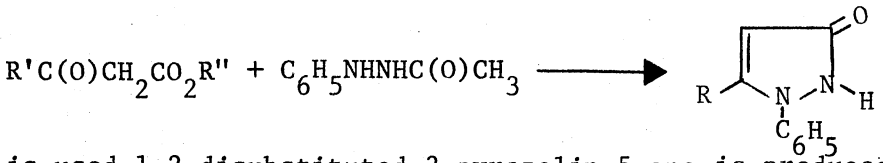
(1) Synthesis of 2-pyrazolin-5-ones: By far the most widely used synthesis for 2-pyrazoline-5-ones is the condensation of a β-keto ester with a hydrazine.[4]



This procedure was modified by using β-thiono esters,[274] α-oximino esters,[329] and β-keto amides.[346]

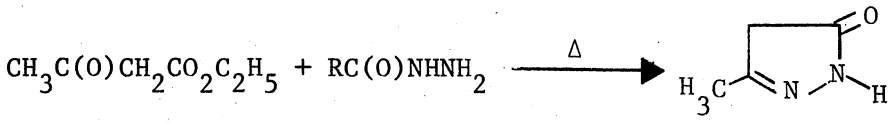
A useful synthesis for 3-pyrazolin-5-ones is the condensation of a β-keto ester with acetylphenylhydrazine. The acetyl group is lost and

the phenyl group appears at N(2).[271] If a symmetrically substituted hy-



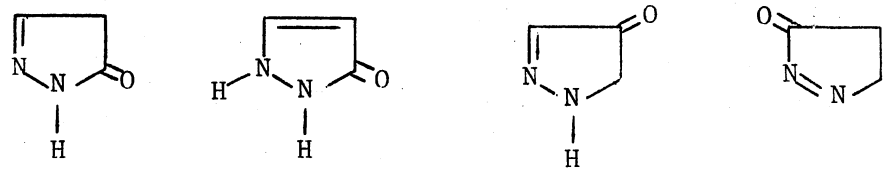
drazine is used 1,2-disubstituted-3-pyrazolin-5-one is produced.[27]

A modified method of synthesis is the use of acid hydrazides.[4,55]



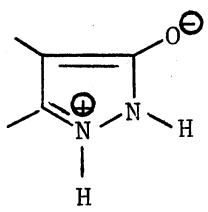
In addition to β-keto esters, the corresponding amides and anilides have been employed in a number of cases[68,346] under very mild conditions.

(2) Spectral properties: Ultraviolet and infrared analysis have established that pyrazolin-5-ones 109a, 109b, and 109d were chief tauto-

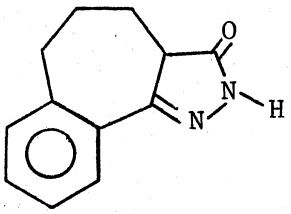


109a 109b 109c 109d

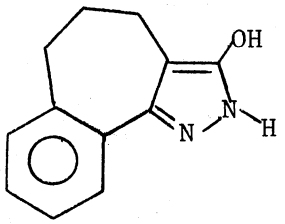
meric contributors.[56] It has also been found[156] that 1-arylpyrazolin-5-ones with no N(2) substitutents are usually of type 109a since no imino or hydroxyl absorption occurs in the infrared spectra of 1,4-diaryl-2-pyrazolin-5-ones. The presence of an absorption peak at 2400-2700 cm^{-1} for some pyrazol-5-ones was attributed to the presence of zwitterionic forms such as shown.[359]



3a,4,5,6-Tetrahydrobenzo-6,7-cyclohepta[1,2-c]pyrazol-3(2H)-one (110) enolizes readily and can be titrated with sodium hydroxide solution (pK_a 9.69).[116] The NMR spectrum (in DMSO) shows a broad two-proton peak at ca. 10.65 ppm (NH and OH) indicating a structure as 110a.

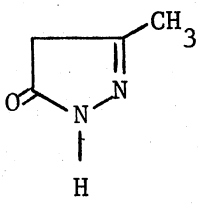


110 (C=O form)

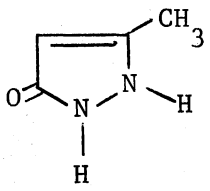


110a (OH form)

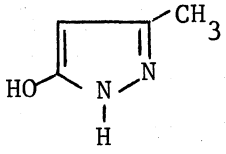
The complex tautomerism of N-substituted pyrazolin-3(5)-ones was studied by A. R. Katritzky[224] using UV spectroscopy and basicity measurements. In aqueous solution (polar medium) the stability of the form was 111b> 111d> 111c> 111a whereas for cyclohexane solution (nonpolar medium) the order was 111d> 111a> 111b, 111c.



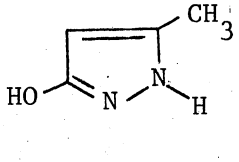
111a



111b



111c



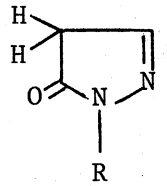
111d

The tautomerism of 1-aryl-2-pyrazolin-5-ones not bearing a 3-substituent has been studied by P. Pauwels[135a] using NMR and IR spectro-

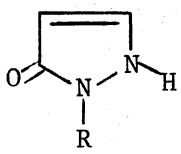
scopy. In CCl_4 and $HCCl_3$ compounds without a substituent at C(4) exist essentially in the CH form (111a). However, with a 4-ethoxycarbonyl substituent the NH form (111b) is favored.

In addition to NMR data which supported form 111a, IR spectroscopy was used to distinguish between the OH form 111c and the NH form 111b. Recent ^{13}CMR analysis suggests that pyrazolin-5-one exists mainly in the OH form.[309]

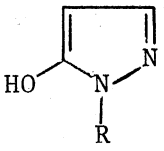
The pyrazol--3- and 5-ones can exist in a number of forms, namely 112a, 112b and 112c. PMR spectra of a number of these compounds have



112a (Δ^2-5-one form)



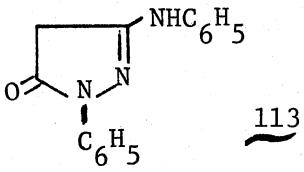
112b (Δ^3-5-one form)



112c (3-OH form)

been used, in conjunction with other spectroscopic techniques, to determine the structure of the predominant tautomers in solution[213] and to identify definitively the Δ^2-5-one structures. Thus, in CCl_4 or $DCCl_3$ solutions, compounds without a 4-substituent have been shown to exist essentially in the Δ^2-5-one form.[299] However, in the presence of a 4-ethoxycarbonyl substituent, the Δ^2-5-one form predominates.

Labeling (^{15}N) studies and NMR analysis were reported[255] on 3-anilino(^{15}N)-1-phenyl-2-pyrazolin-5-one (113). The only species



113

present in $DCCl_3$, pyridine, or DMSO was the α-oxo amino isomer as shown by absorption by the 4-methylene group and the presence of ^{15}N-H coupling in the ^{15}N-anilino derivative.

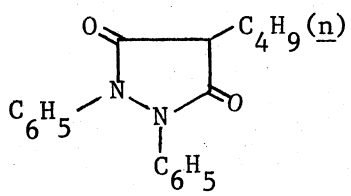
(3) Medicinal applications: Since the synthesis of antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) by Knorr in 1883, pyrazolinones have been widely used in medicine as analgesics[238] and antipyretics.[238] The discovery of this drug led to a widespread search for other effective pyrazolinones and led to the discovery of aminopyrine (4-dimethylamino analog of antipyrine) and phenylbutazone (4-butyl-1, 2-diphenyl-3,5-pyrazolidinedione) and their application in medicine. At the present, antipyrine enjoys little use today in the U.S.A. (owing to replacement by the more effective salicylates) although it is used mainly in Europe, South America, and the Mid-East.

Antipyrine is absorbed rapidly from the gastrointestinal tract.[157] Metabolism is rather rapid as water solubility is high and distribution in the tissues is in proportion to their water content.[157] About 30-40% of ingested antipyrine is converted to 4-hydroxyantipyrine and excreted in the urine conjugated with glucuronic acid[157].

The mechanism of action of aminopyrine is not known. The action of aminopyrine in rheumatic fever is equal to that of the salicylates,[157] and it is effective in reduction of inflammation due to edema and necrosis.[387] The chief toxic manifestation of aminopyrine is agranulocytosis. In some individuals there seems to be a hypersensitivity to this drug. Other toxic effects are central nervous system involve-

ments, rash, and hemoglobin alterations.

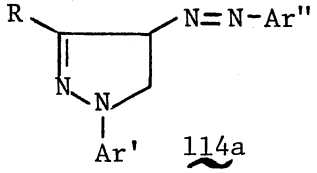
Phenylbutazone (114) (synthesized by H. Stenzl in 1946) is clinically the most useful of the pyrazolinone and pyrazolidinone series. Hemming and Kuzell[178] (1953) have published an extensive review on the



114

biological properties and medical uses of phenylbutazone. The principal action of phenylbutazone is inhibition of inflammatory action, although it is also a mild analgesic and antipyretic. It has a very striking clinical effect in many arthritic cases, giving rapid and complete relief from pain. Its field of usefulness is very similar to that of the corticosteroids, and as a consequence, it has been suggested that it may be a stimulant of the pituitary-adrenal system.[240] Pyrazolinones, either alone or as mixtures with other materials, have been claimed to be effective as germicides,[15] for treatment of influenza,[85] as antimicrobial agents,[155] as fungicides,[198] as antiactinics,[319] and as antidiuretics.[187]

Pyrazolinones and pyrazolidinones are also used in photography as color couplers, sensitizers, developers, and antihalation agents.[402] However, the most important commercial use for pyrazolinones is as dyes.[401] They have been extensively employed for this purpose since 114a was synthesized by Zieyler and Locher in 1887;[401] this dye is still widely used as an approved food color.

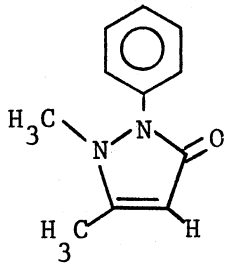


114a

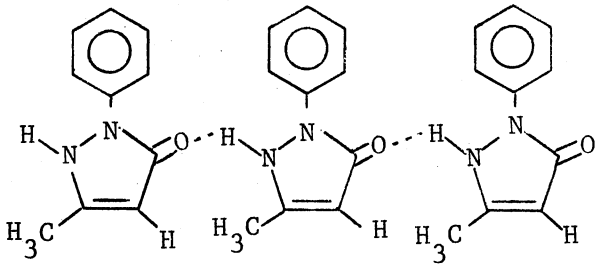
Ar' = Ar" = 4-$NaO_3SC_6H_4$

R = CO_2Na

The presence or absence of biological action in some compounds is ascribed, in some cases, to their capacity for forming or not forming hydrogen bonds.[34] This capacity has substantial influence on their physiochemical properties and therefore on their pharmacodynamic activity. Thus, whereas 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (antipyrine) (115), which is soluble in water and moderately soluble in ether, has analgetic properties, its demethylated analog, the 1-phenyl-3-methyl-5-pyrazolone, being insoluble in water and only slightly soluble in ether, has no analgetic activity. This discrepancy may derive from the fact that the former compound does not form intermolecular hydrogen bonds, whereas the latter compound 108 does,[115] although this is speculative.

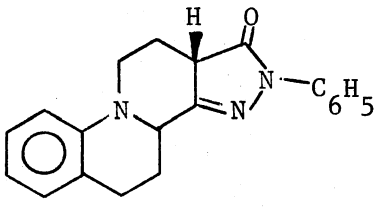


115

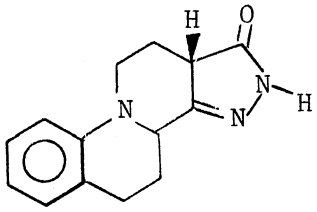


108

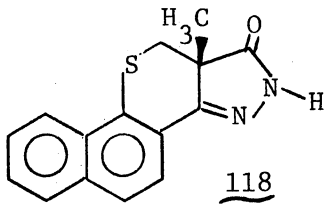
(4) Pyrazolonosteroids: Although the following steroidopyrazolones have been recently synthesized, their biological activities have not been investigated or apparently reported.



116
[Ref. 214]

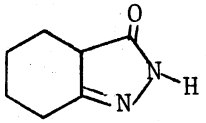


117
[Ref. 340]



118 [Ref. 144]

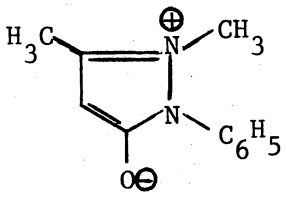
(5) Tetrahydroindazolones: Properties of tetrahydroindazolones:



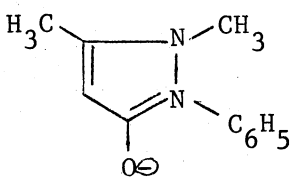
119

(a) Pharmacological: Tetrahydroindazolones have been found to have analgesic and antipyretic properties.[263] They are usually prepared by reaction of an alkyl 2-oxocyclohexanecarboxylate with hydrazine and alkylation of the product.[42]

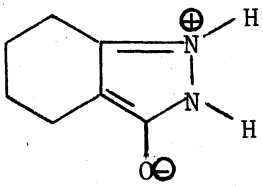
(b) Spectral: Some indazolones yield molecular complexes with substituted barbituric acids.[333] Spectral studies of indazolones indicate that they are resonance hybrids to which ionic structures are strong contributors.[359]



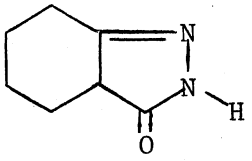
120a



120b



121

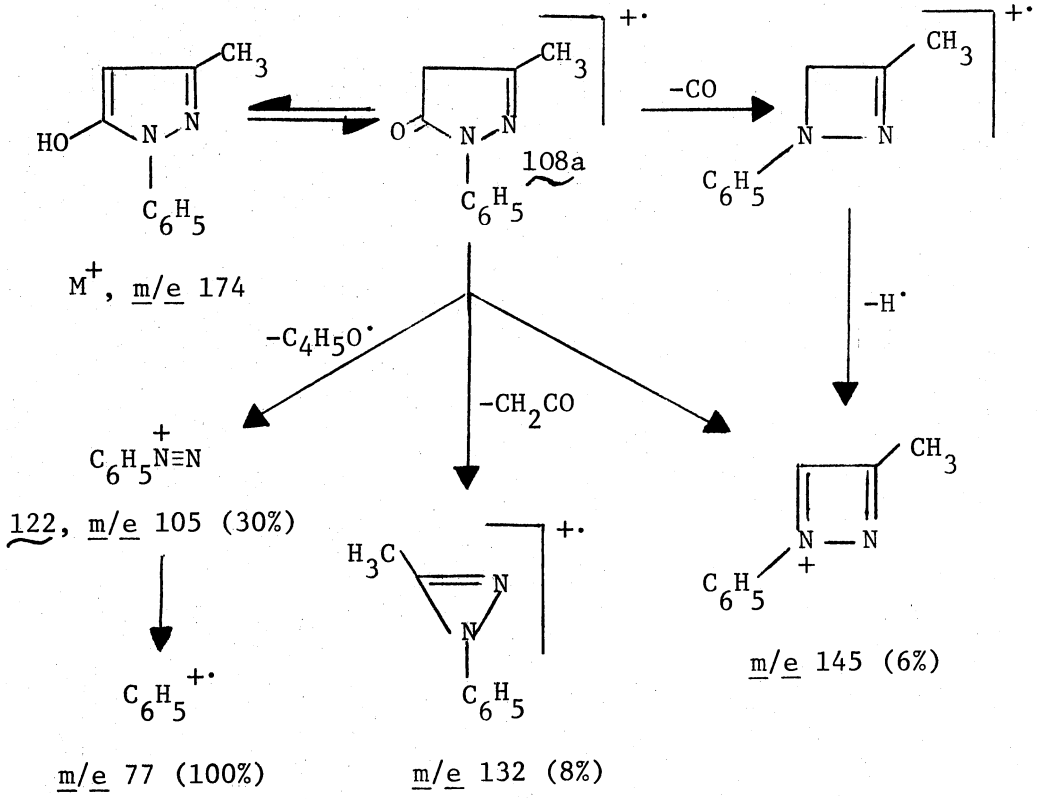


119

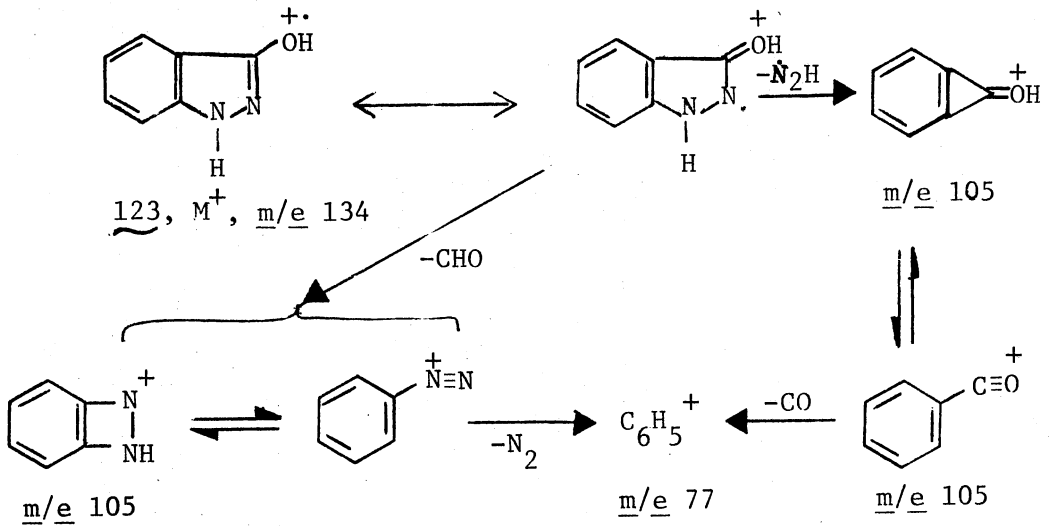
It was suggested that the structure of 4,5,6,7-tetrahydro-3-indazolone (119) more closely approximates 121. To support this conclusion the IR spectrum of 119 contain a doublet at 1600-1620 cm^{-1}. The authors claimed that although it is known that $C{=}NH^{+}$ group absorption appears at 1660 to 1680 cm^{-1}, the resulting shift to the longer wavelength is only explicable by the existence of the zwitterion 121. The carbonyl group, whose double bond character was reduced by the dipolar structure, absorbed at 1600-1620 cm^{-1} [thus accounting for the broadness of the

absorption band in this area] 1613(s), 1588(vs), 1545(ms) cm^{-1}. A band at 2700-2200(s) with a peak at 2640 cm^{-1} was assigned to C-N^+ and 3064 cm^{-1} to N-H.

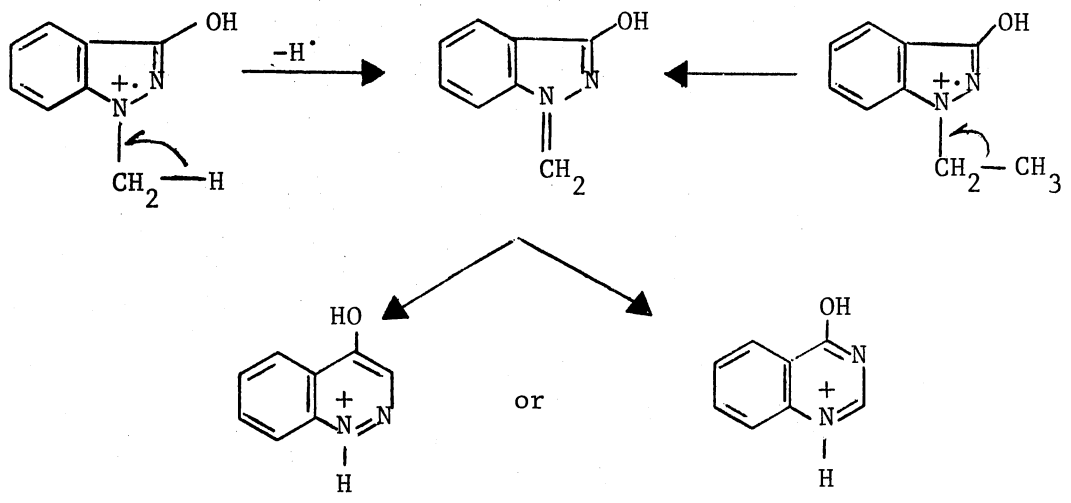
The mass spectrum of 1-phenyl-3-methyl-5-pyrazolone[301] (108a) indicates that the main fragmentation is ring fission with formation of the benzenediazonium cation 122. Loss of CO and CHO from M^+ are unimportant processes. A tentative rationale for the spectrum was shown.[301]



It has been shown[119] that the parent indazolone 123 exists in the enol form in the ground state. The fragmentation is thus easily explained with this formulation for the radical cation. Loss of 29 mass units in the initial fragmentation is probably due to elisions of $\dot{N}_2H$ (90%) and $\dot{C}HO$ (10%). The rationale for these decompositions is shown.



1-Methylindazolone shows a fragmentation pattern basically similar to that of the parent compound. N-Methylindazolones undergo ring expansion, and β-fission (loss of CH_3) leads to the base peak.

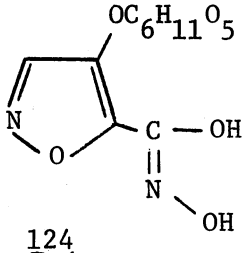


Isoxazoles[39,245,317]

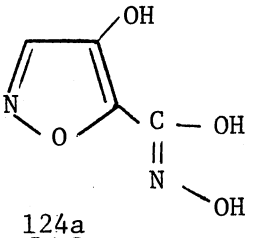
The chemistry of isoxazole is associated with the name of Ludwig Claisen, who recognized in 1888 the cyclic structure of the product

(3-methyl-5-phenylisoxazole) that Ceresol[89] had obtained in 1884 from the action of hydroxylamine on benzoylacetone. Claisen suggested for it the name monoazole, which was modified by Hantzsch[171] to isoxazole, which is used by Chemical Abstracts.

Until recently no natural product containing the isoxazole ring was known, with the possible exception of the glycoside hiptazin (124) isolated in 1920 by Görter[158] and described on the basis of rather doubtful chemical evidence as a derivative of (4-hydroxyisoxazol-5-yl)formohydroxamic acid (124a).

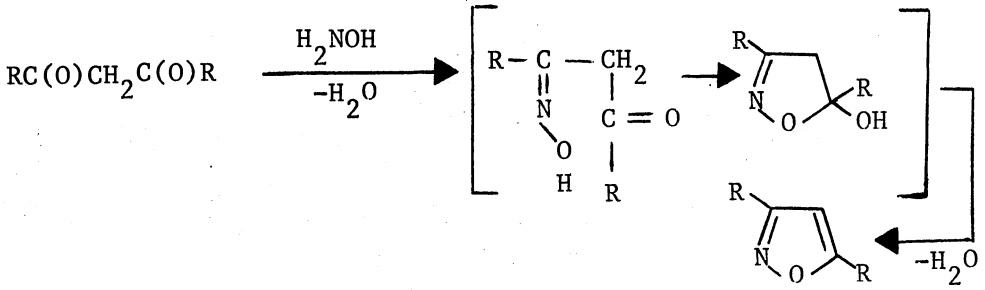


124



124a

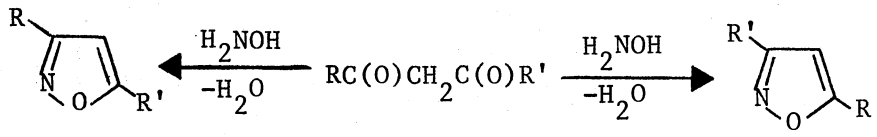
(1) Synthesis: (a) Synthesis from 1,3-dicarbonyl compounds and hydroxylamine: The reaction of 1,3-dicarbonyl compounds with hydroxylamine is the most widely used for the synthesis of isoxazoles. Formation of stable, stereoisomeric monoxime intermediates has been frequently observed with 1,3-diketones in which one of the hydrogen atoms of the $-C(O)-CH_2-C(O)-$ group has been replaced by a substituent.[75] In a few



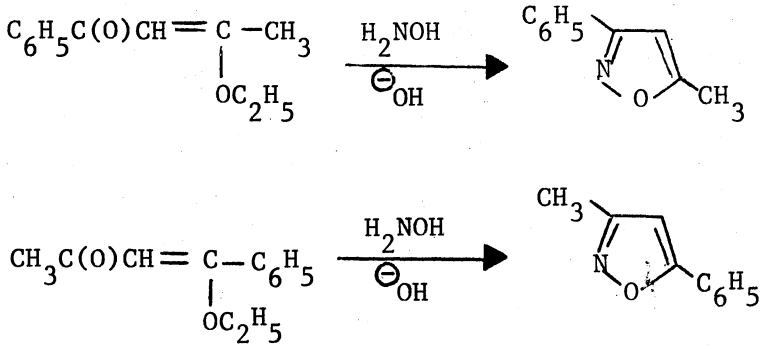
instances the formation of dioximes in the reaction of hydroxylamine with 1,3-diketones has also been reported.[75,105] The dioximes yield isoxazoles on heating, or by the action of oxidizing agents,[26] or when

treated with acid or alkali.

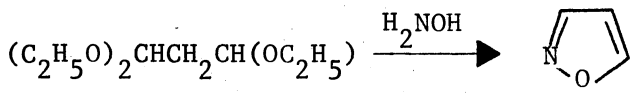
In the case of unsymmetrical diketones containing two different groups, R and R', the two isomeric isoxazoles corresponding to two enolic forms of the dicarbonyl compounds could result.[94]



Although several isoxazole syntheses reportedly give only one isomer, critical analysis of the reaction mixture and the product's structure is lacking.[350] A single isomer of unequivocal structure can be prepared by the action of hydroxylamine under appropriate experimental conditions with ethers of the enolic forms of unsymmetrical diketones.[284]

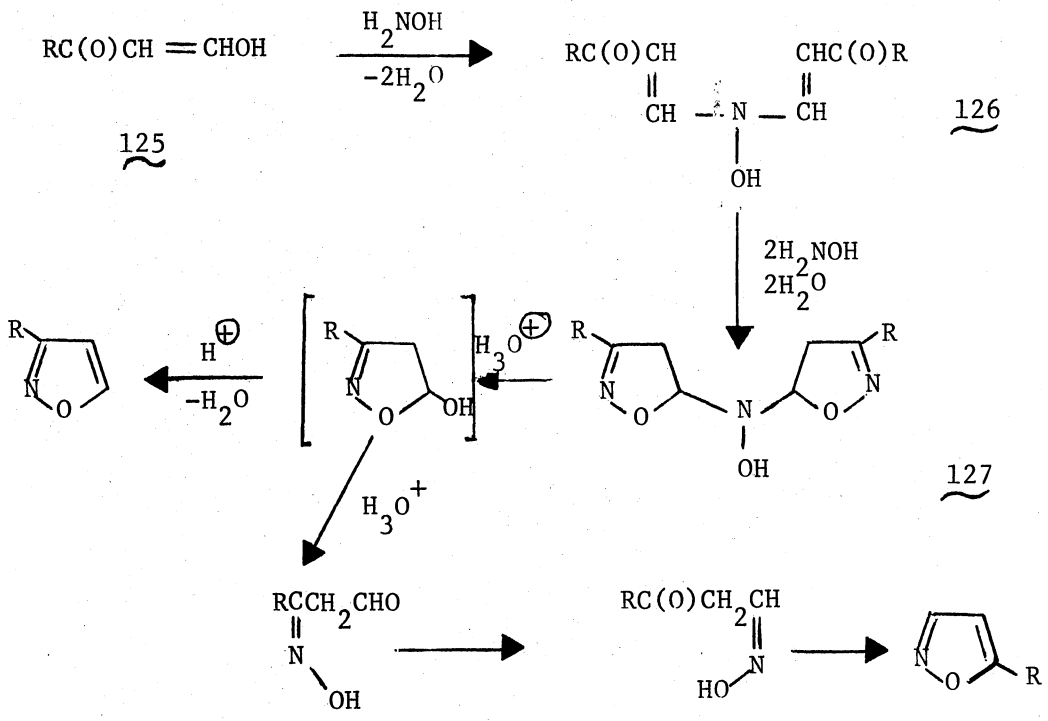


1,1,3,3-Tetraethoxypropane can be condensed with hydroxylamine to give unsubstituted isoxazole itself.[318] Von Anwers (1934) investi-



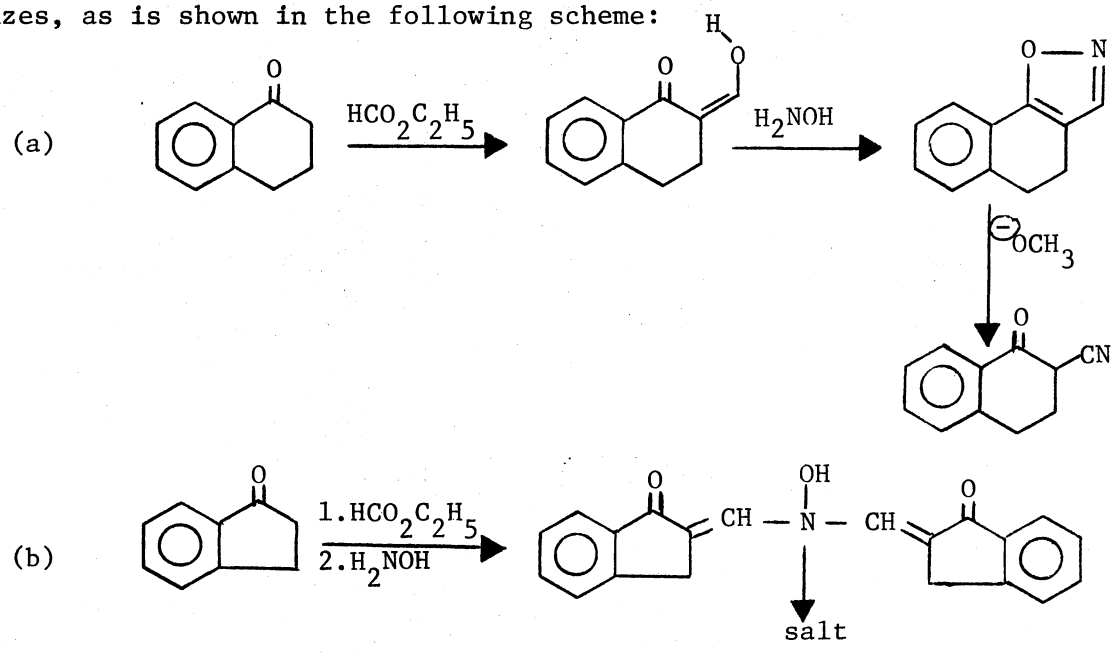
gated the behavior of α,β-unsaturated ketones toward hydroxylamine.[31] Keto aldehydes are postulated to react in [a] hydroxymethylene form 125 to give intermediate 126 which condenses with two extra moles of

hydroxylamine yielding the sesquioxime 127. Acid treatment of the sesquioxime gives either the 3- or the 5-substituted isoxazole depending



on the concentration of the acid used.

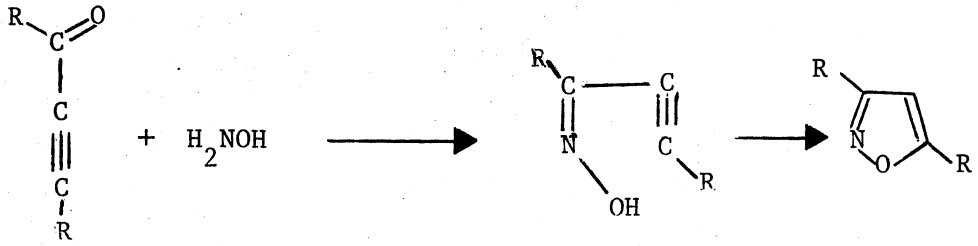
Johnson and Shelberg[215] utilized the difference in behavior of α-hydroxymethylene derivatives of cyclanones to distinguish between ring sizes, as is shown in the following scheme:



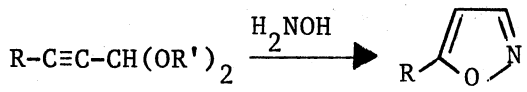
This different behavior is probably best ascribed to strain effects. Isoxazole ring closure occurs easily in cyclohexanone derivatives. Very little chemical evidence for the structures was given in the examples shown.

Only a few 4-monosubstituted isoxazoles have been prepared by the reaction of hydroxylamine with β-dialdehydes. 4-Phenylisoxazole, for example, has been prepared from phenylmalonaldehyde and isoxazole-4-carboxylic acid from carbomethoxymalonaldehyde.[307]

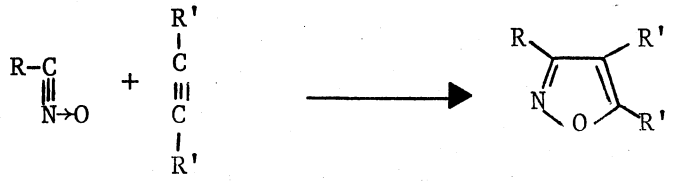
(b) Synthesis from α-acetylenic ketones or aldehydes with hydroxylamines: This method was once widely used;[285] it has been recently ap-



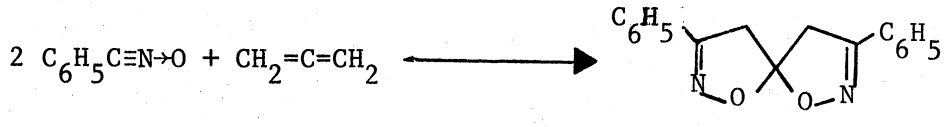
plied to determine the configuration of oximes.[217] The process was later modified by the use of acetals of α,β-acetylenic aldehydes for preparation of 5-substituted isoxazoles.[31,216]



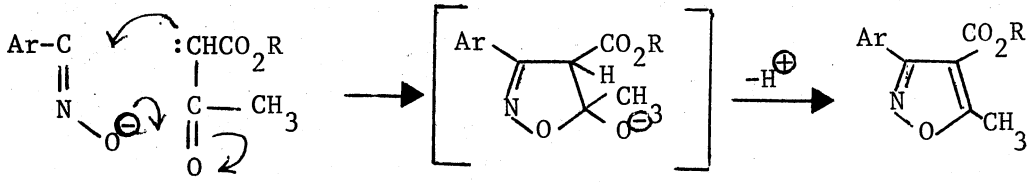
(c) Synthesis from nitrile oxides: Nitrile oxides condense with



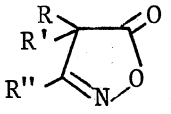
acetylenes to yield isoxazoles in good yields. The substituent R may be aromatic,[159] heterocyclic,[160] or alicyclic.[35] If allene is used with benzonitrile oxide a spirobisisoxazoline is obtained.[356]



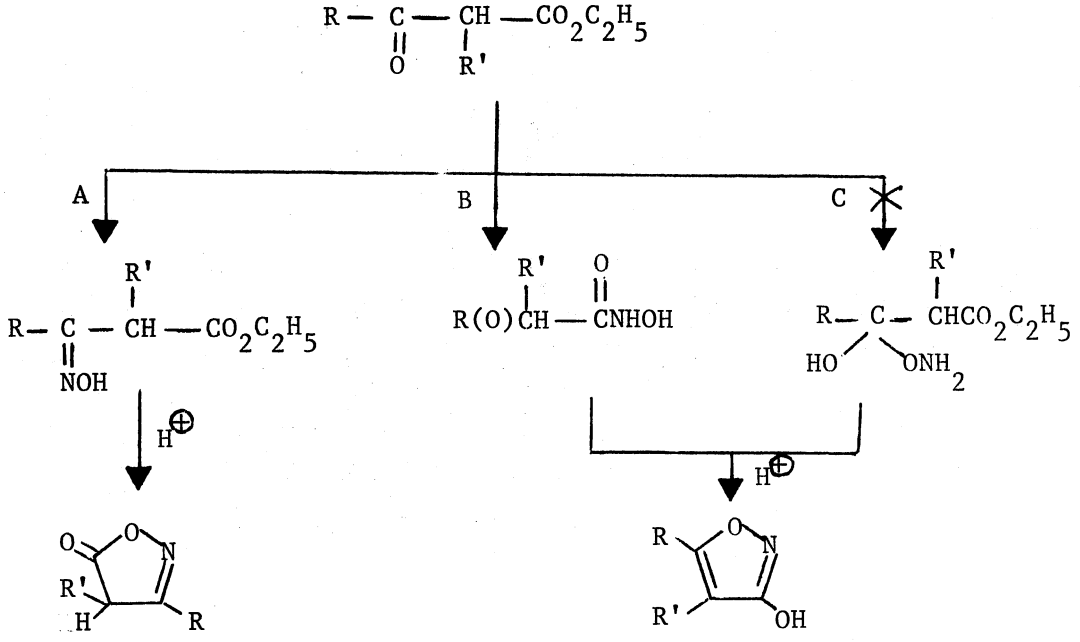
A general mechanism for changing nitrile oxides to isoxazoles was suggested:[39,245,317]

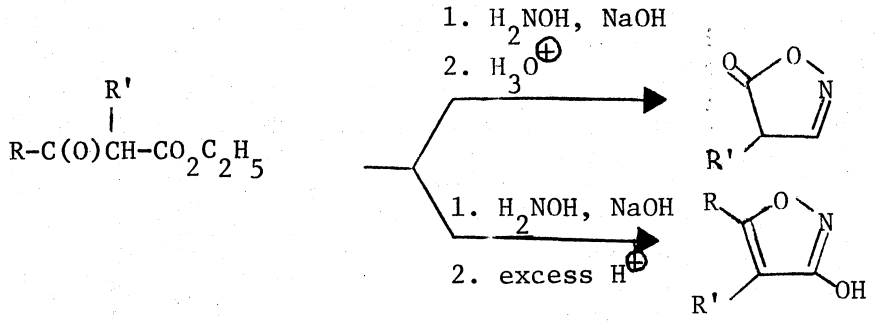


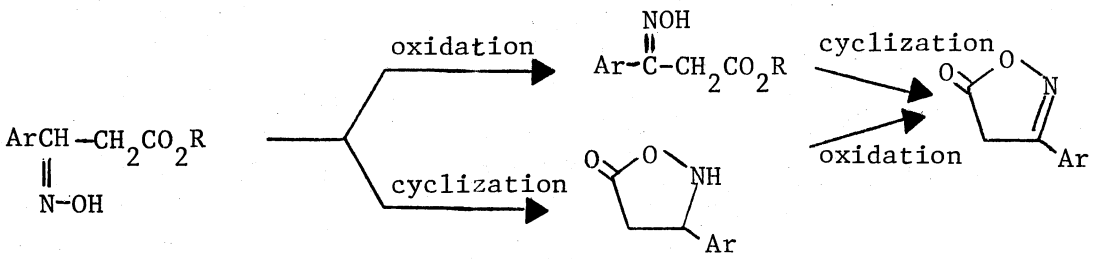
(2) Isoxazolones: Treatment of $R'C(O)CHR''O_2C_2H_5$ [R' = CH_3, $(CH_3)_2CH$,

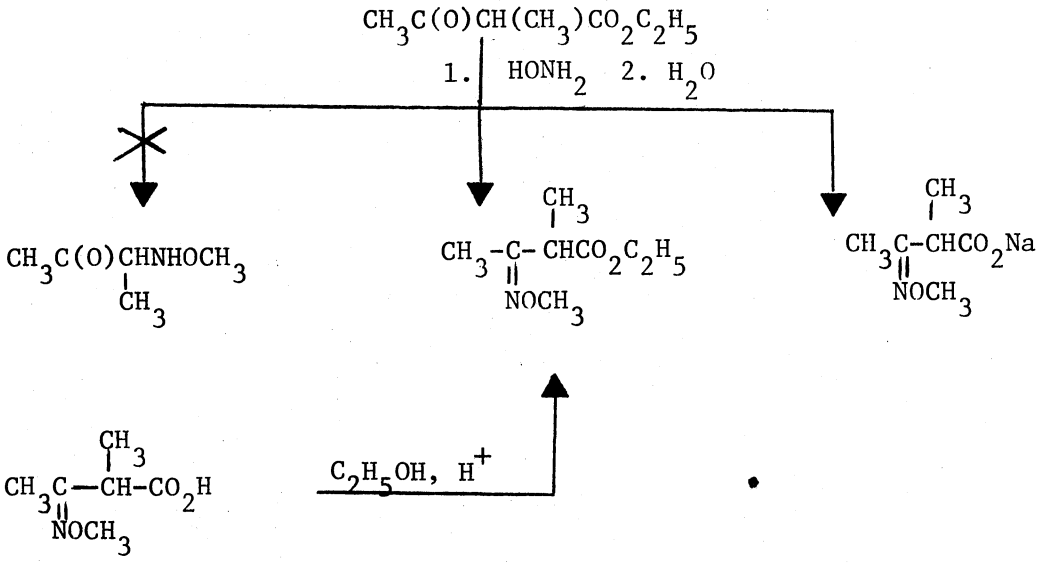


C_2H_5, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; R'' = H, CH_3, C_2H_5, $(CH_3)_2CH$, cyclopentyl, or C_6H_5; (R'R'' = $(CH_2)_4$ or $(CH_2)_5$] with H_2NOH gives mixtures of 3- and 5-isoxazolinones. A mechanism was proposed by Jacquier and co-workers[208] in 1970.

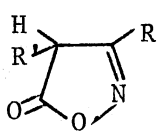




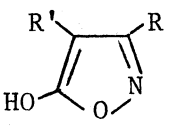




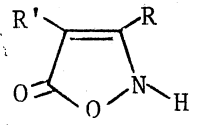
(3) Spectral properties of isoxazoles and isoxazolones: The IR spectra of isoxazole derivatives have been extensively investigated.[61,62,82,223,224] IR and UV data have been used to elucidate the tautomerism of isoxazol-5-ones.[62,353]



C-H form



O-H form

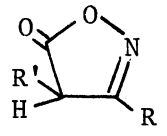


N-H form

The 3-methyl-4-benzoyl derivative exists in the OH form both in the solid state or in solution; however, crystalline 4-substituted 3-phenyl-isoxazolones are to be found in the NH form. In solutions the latter compounds can be in the NH form or in the CH forms or in a mixture of these with the NH isomer predominant.[62] The hydroxy structure has been proved for 3-hydroxy-5-phenylisoxazole.[314]

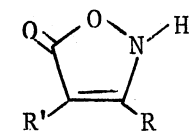
Aminoxazoles exist only in the amino form, independently of the position of the amino group in the ring.[62] 3(5)-Amino isoxazolones possess an amino and a carbonyl group.[44]

Jacquier and co-workers[208] were able to estimate the amount of amino tautomer (N-H) in solutions of 3-monoalkyl and 3,4-dialkylisoxazol-in-5-ones, from their NMR, IR and UV spectra. The authors also investi-gated the tautomerism of 2-methyl-3,4-dialkyl-3-isoxazolin-5-ones 128 and 5-methoxy-3,4-dialkylisoxazoles (129).



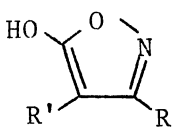
C-H form

128a



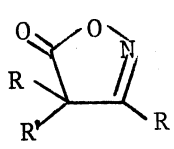
N-H form

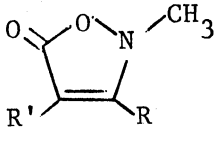
128b

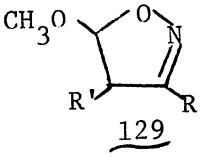


O-H form

128c



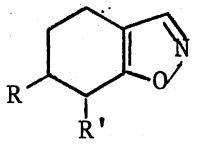




129

128a

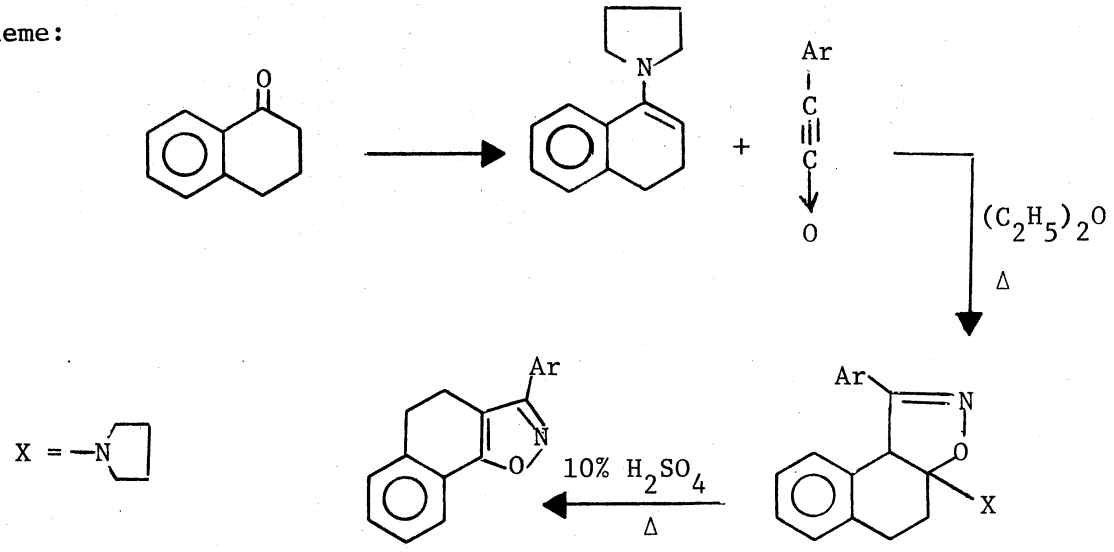
(4) Naphtho[2,1-d]isoxazole: The 4,5,6,7-tetrahydronaphtho[2,1-d]-

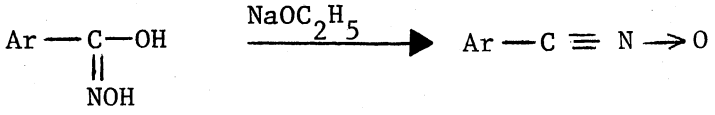


R = R' = H

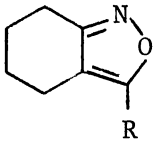
R = R' = benzo

isoxazoles have not been found frequently in the literature contrary to their simple analogs. Bianchi-Frati (1966)[54] obtained 3-arylnaphtho-[2,1-d]isoxazoles in fairly good yields according to the following scheme:

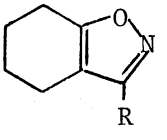




More recently (1970) Jacquier and co-workers[209] studied the formation of cyclotetramethyleneisoxazoles 130a and 130b in detail. The

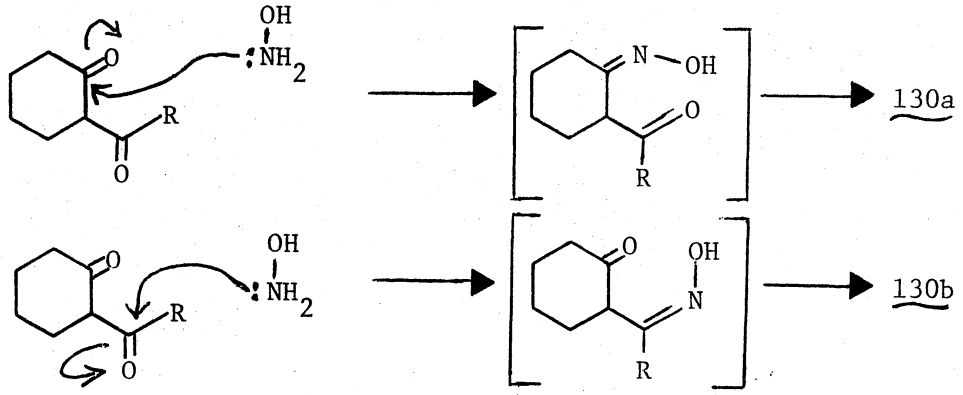


130a

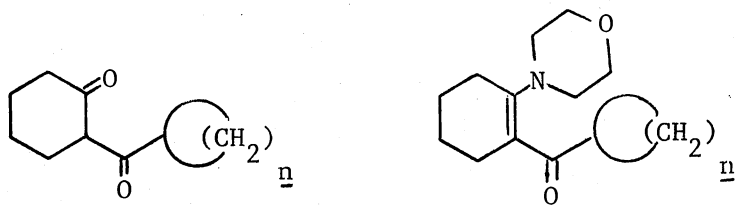


130b

authors proposed the following mechanisms for the formation of 130a and 130b:



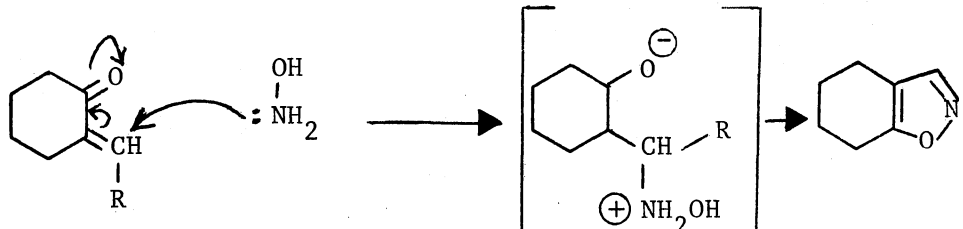
The comparison of the NMR, IR and MS data and gas chromatograms of 130a (R = CH_3) and 130b (R = CH_3) with the products from the H_2NOH treatment of 131 (n = 2,3,4, and 5) and 132 (n = 4 and 5) showed that



131 132

131 (n = 2,4, and 5) gave 130a (R = cyclopropyl, cyclopentyl, and cyclohexyl) and 132 (n = 4 and 5) gave 130a (R = cyclopentyl and cyclohexyl). However, 131 (n = 3) gave both 130a (R = cyclobutyl) and 130b (R = cyclobutyl).

The following reaction was studied in detail[209] by Jacquier and co-workers in 1970.

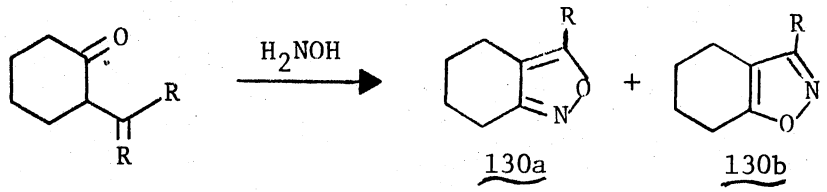


R = $-O-CH(CH_3)_2$

= $-O-CO-CH_3$

= $N(CH_3)_2$

According to reference 209 the following results were obtained:

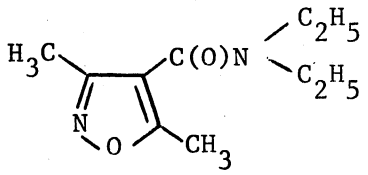


130a 130b

R	% Yield	
	130a	130b
C_6H_5	0%	100%
$-N(CH_3)_2$	10%	90%
H	80%	20%
$-CH(CH_3)_2$	35%	65%
$OCOCH_3$	45%	55%
CH_3	75%	25%

The products were analyzed by NMR, IR, UV, and GC analysis and thus were compared with authentic samples. The yields were quite variable and substituent-dependent.

(5) Isoxazole derivatives of pharmacological significance: Although the close chemical similarity between pyrazoles and isoxazoles made it likely that isoxazole derivatives would find application in the pharmaceutical field, systematic investigations of their pharmacological behavior have been carried out only relatively recently. New interest in this field was aroused in 1955 by the discovery that the antibiotic cycloserine (or oxamycin) is a simple derivative of 3-isoxazolidone.

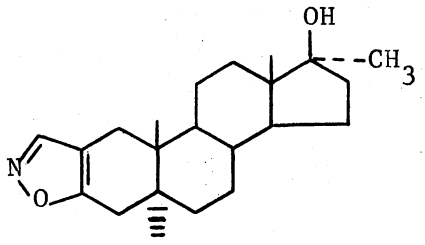


Analeptics containing the isoxazole ring were developed in 1935.[184] Among these substances the most practical appears to be N,N-diethyl-3,5-dimethylisoxazole-4-carboxamide (cycliton) (133), on which an extensive pharmacological and clinical literature is available.[183]

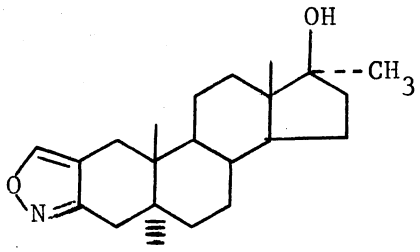
Sulfa drugs containing an isoxazole ring are characterized as having low toxicity and strong activity in vivo against gram-positive and gram-negative bacteria. In comparison with other sulfa drugs they are not skin irritants and do not accumulate in the kidneys. The most important of these substances is 3,4-dimethyl-5-sulfanilamidoisoxazole or Gantrisin.[344]

3,5-Dimethylisoxazole was shown to be a growth inhibitor.[367] Quinoline and isoquinoline derivatives containing an isoxazole ring have been reported to have no antimalarial activity.[367]

Clinton and co-workers[265] reported the synthesis of novel steroidal isoxazole derivatives. The [2,3-d]isoxazole 134 possessed more endocrine activities than did its [3,2-c]analog 135. It has been found[265] that



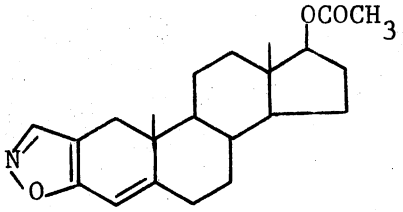
134, [2,3-d]



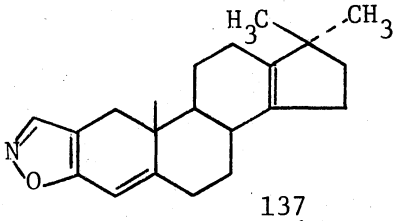
135, [3,2-c]

[2,3-d]isoxazole 134 exhibits 9.7 times more anabolic activity than methyltestosterone, its precursor, while the androgenic activity was only 0.24 times but as twice as active for miotropic activity. Unlike

to the corresponding pyrazoles, these compounds are completely devoid of oestrogenic activity.[101] The [3,2-c]isoxazole 135 was shown to be a strong anabolic agent. Two isoxazolosteroids 136 and 137 were proven to be effective antitumor agents.[88]

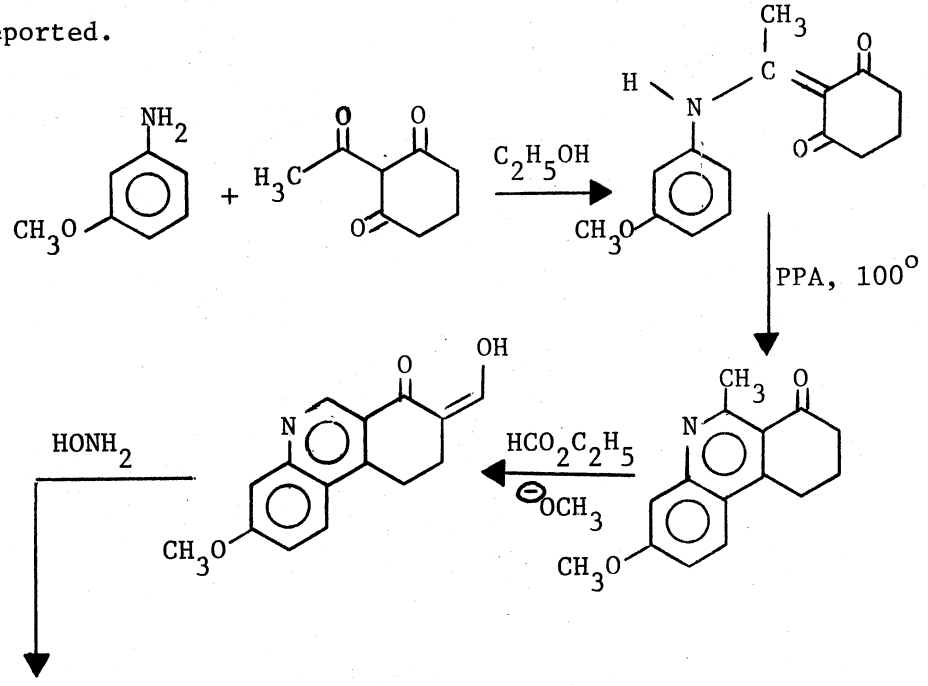


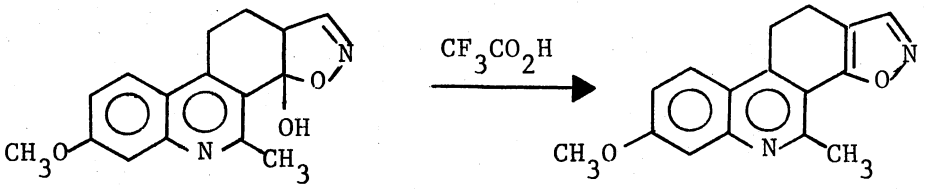
136



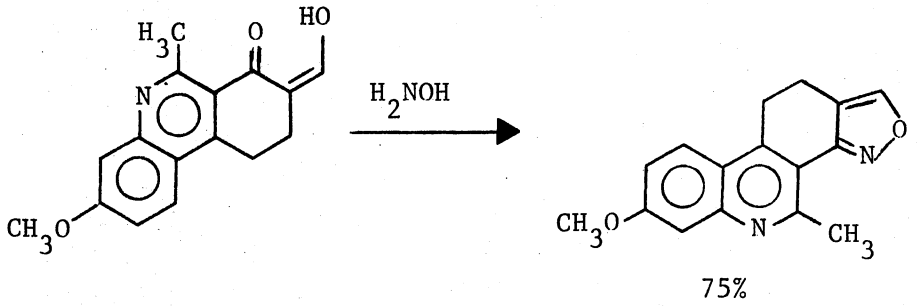
137

Although the following isoxazolosteroids have been synthesized recently[266], their biological activities have not been yet investigated or reported.

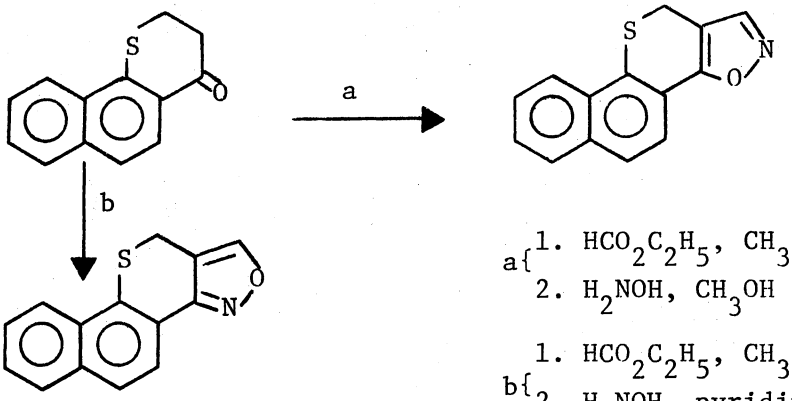




80%



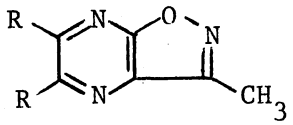
75%



a { 1. $HCO_2C_2H_5$, CH_3ONa
2. H_2NOH, CH_3OH

b { 1. $HCO_2C_2H_5$, CH_3ONa
2. H_2NOH, pyridine

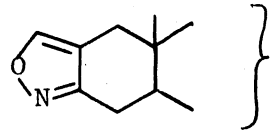
Since pyrazolo[4,3-d]pyrimidines which occur in the formycin antibiotics proved to have antitumor activity,[205] isoxazolo[4,5-b]pyrazine (138) systems have been synthesized[2] to evaluate their potential antitumor activity.



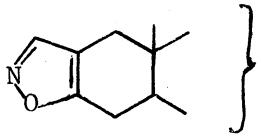
138

R = H and OH

It was shown that the rate of formation of

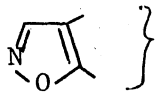


and

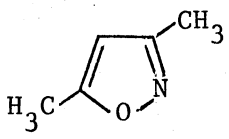


is greatly dependent on the pH of the medium, the solvent, and the tem-

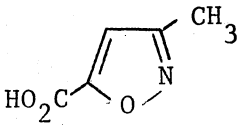
perature.[259] This fact is of great importance for the development of a process for the synthesis of [2,3-d]isoxazolosteroids, which are of greater biological interest as regards their biological activity than their [3,2-c] analogs. In a weakly alkaline medium a mixture of isoxazoles is usually formed.[265] The reaction in glacial acetic yields one isomer preferentially.[265]



Dulin, Gerritsen, and co-workers[124] studied 3,5-dimethylisoxazole (139), which had unusual potency as an inhibitor of free fatty acid re-



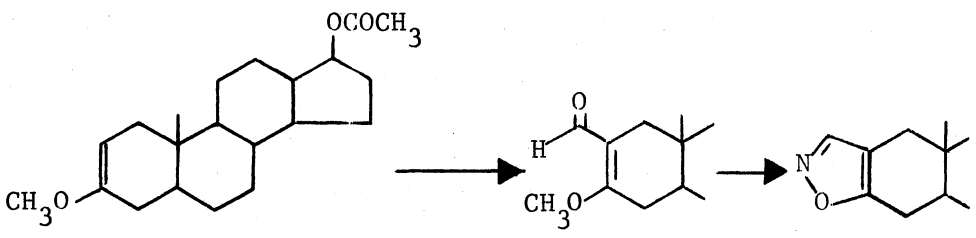
139



140

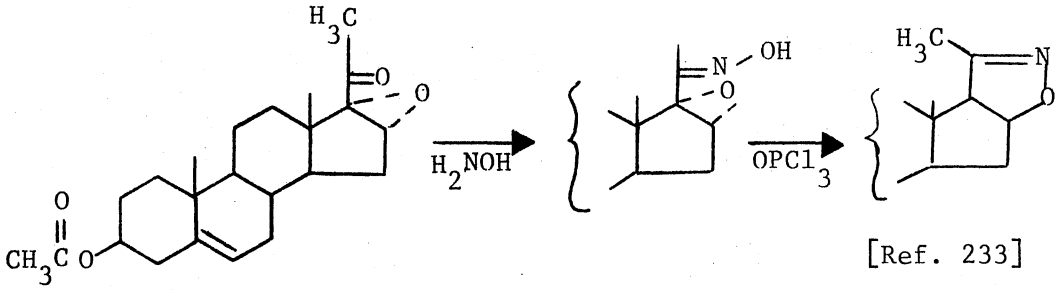
lease and as a hypoglycemic agent in intact rats, and 3-methylisoxazole-5-carboxylic acid (140), which was presumed to be a metabolite of 139.

Cortisone can be converted into 2-(hydroxymethylene)cortisone, which on treatment with hydroxylamine forms 17α,21-dihydroxypregn-4-en-11,20-diono[2,3-d]isoxazole.[399] The acetate of 2-formyl-3-methoxyandrost-2-en-17β-ol (141), obtained by the formylation of the acetate of 3-methyoxy-androst-3-en-17β-ol (142) by the Vilsmeier reagent, was used for the preparation of [2,3-d]isoxazoles.[76]

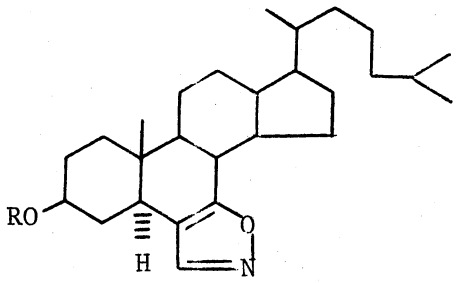


141 142

(6) Other types of steroidoisoxazoles: In general, [2,3-d]isoxa-



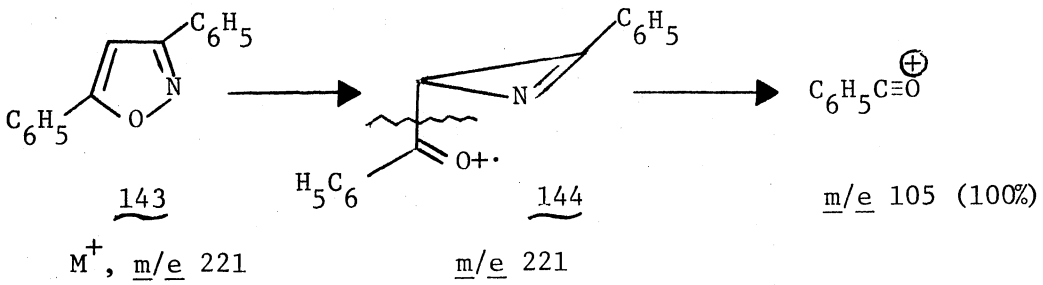
[Ref. 233]



[Ref. 87]

zoles absorb in the UV region at greater wavelength than the [3,2-c]-analogs, that is, at 227 ± 2 and 222 ± 1 nm, respectively.[43]

(7) Mass spectra of isoxazoles: 3,5-Diphenylisoxazole (143) was examined[292] and the spectrum is similar to that of the azirine 144,



143

M^+, m/e 221

144

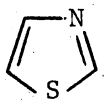
m/e 221

m/e 105 (100%)

which is formed from the isoxazole photochemically[273]. The spectrum of the azirine contains relatively intense ions at m/e 165 and 166 which are absent from the spectrum of the isoxazole 143. This has been ex-

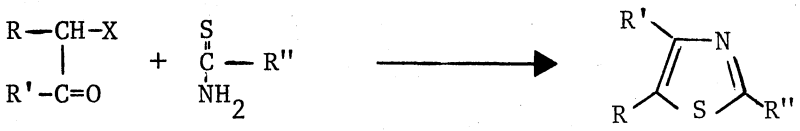
plained by assuming conversion of the azirine to 2,5-diphenyloxazole, which produces strong hydrocarbon ions at m/e 165 and 166 (not shown here).[292,293]

Thiazoles



Thiazoles have always been important in pharmaceutical and biochemical fields. Commercially valuable compounds that contain a thiazole ring are the mercaptothiazoles (which are valuable rubber accelerators), various "sulfa" and antitubercular drugs, the penicillins, and thiamin. Certain thiazole derivatives are used as intermediates in the synthesis of amino acids, peptides, and purines. This application has been discussed by Heilbron.[77] As a consequence of the varied interest in the thiazoles, an extensive body of literature dealing with their syntheses and properties is available.[1,17,41,52,70,107,212,288,303,315,355,365,384,400]

(1) Synthesis: (a) The reaction of α-halo carbonyl compounds and thioamides: Thioformamide produces thiazoles unsubstituted in the



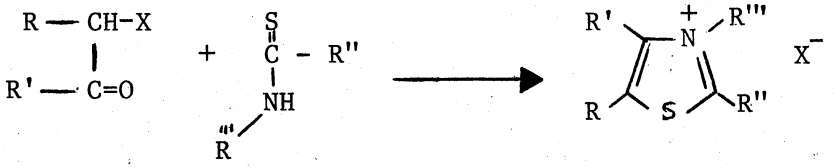
R = Alkyl, aryl, aralkyl, etc.

X = Br, Cl.

R' = H, CH_3, aralkyl, NHAr, etc.

2 position. Thus, chloroacetaldehyde and thioformamide yield thiazole itself.[195]

If an N-substituted thioamide is caused to react with an α-halo carbonyl compound, quaternary thiazolium salts result, sometimes in quantitative yields.[368] Excellent yields (90-95%) of 2-aminothiazole



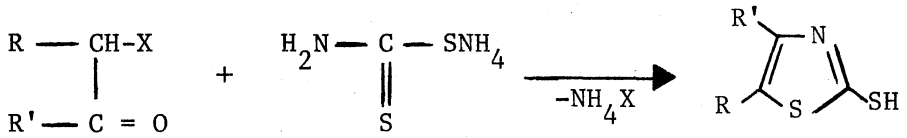
Yield = 100%

$R = R' = R'' = CH_3$

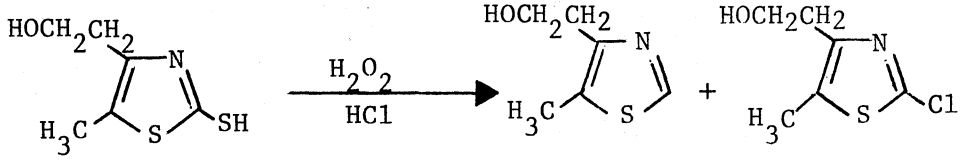
X = Cl

are usually obtained from thiourea.[313,199]

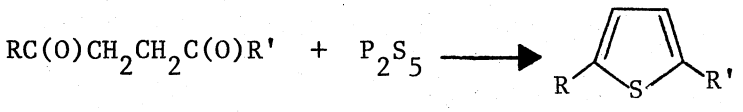
(b) The reaction of ammonium dithiocarbamate and α-halo compounds.[74,154] Use of various halogenated ketones gives 2-mercaptothiazoles:



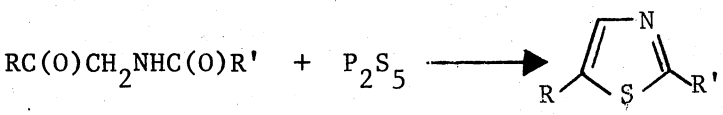
The value of the dithiocarbamate reaction as a synthetic tool is the greater because hydrogen can be substituted for the thiol group via reaction of hydrogen peroxide in the presence of strong acids on the heterocycle.[222]



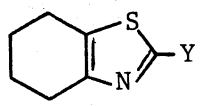
(c) The reaction of α-acylamino carbonyl compounds and phosphorus pentasulfide.[33,222,227] The reaction of 1,4-dicarbonyl compounds with P_2S_5 to produce thiophene derivative is well known.



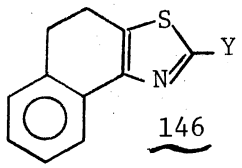
If one of the methylene groups between the carbonyl functions is replaced by an imino function, as in the acylamino carbonyl compounds, thiazoles result.



(2) 4,5,6,7-Tetrahydrobenzothiazoles (145) and 4,5-Dihydronaphtho-[1,2-d]thiazoles (146): (a) Synthesis: The syntheses of 2-amino-4,5,-



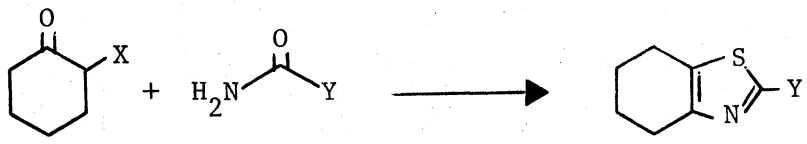
145



146

Y = H, CH_3, NH_2, NHAr,

6,7-tetrahydrobenzothiazole (146), Y = NH_2, have been of great interest in recent years.[53,294] The general method of preparation of these compounds is:

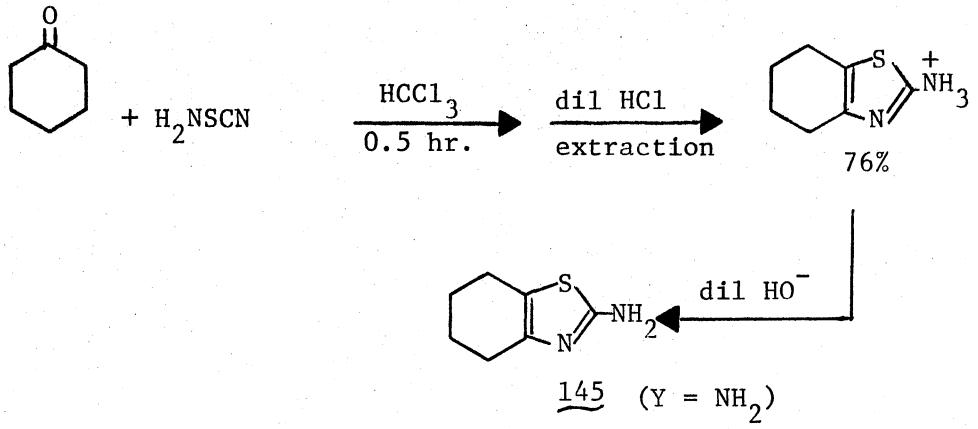


147

X = Br
= Cl

145

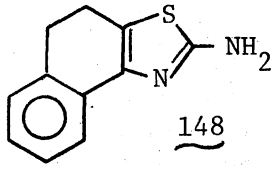
The yields vary from fair to high, depending on the group Y.[295] More recently a German patent (1971)[343] reported a yield of 76% of thiazole 145, Y = NH_2. The base obtained was useful as an insecticide and a source



145 (Y = NH_2)

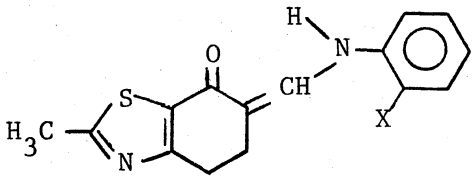
for novel sulfonamides.

2-Amino-4,5-dihydronaphtho[1,2-d]thiazole (148) was prepared in

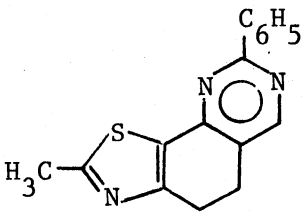


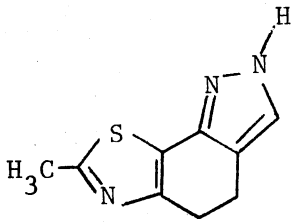
148

1970 and claimed by Japanese workers[270] to be an effective anesthetic for aquatic animals. The mechanism of resistance of aminothiazole in microorganisms was also discussed.[270] The recent interesting work of Fravolini and co-workers[144] deals with new heterocyclic ring systems of which 4,5,6,7-tetrahydrobenzothiazole is a part of this system.



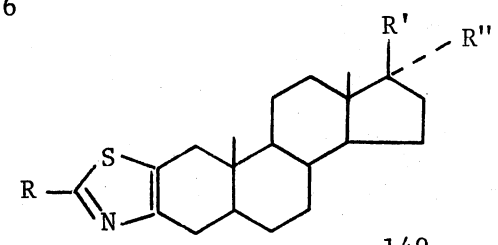
X = NHR, $OCOCH_3$





The thiazole ring system has attracted the interest of chemists and pharmacologists from the discovery of penicillin to the present

date.[43,71] Fusing thiazole rings to ring A of a steroid system has produced compounds showing some activity. The anabolic-to-androgenic ratio of thiazolosteroid 149 was higher than that of the parent carbocyclic steroid.[123,246]



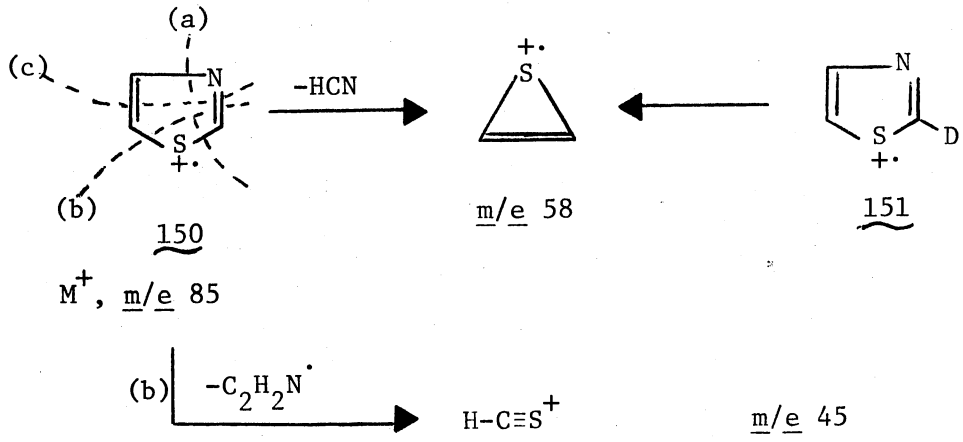
149

R' = C_8H_{17}; R'' = H

R' = OH; R'' = CH_3

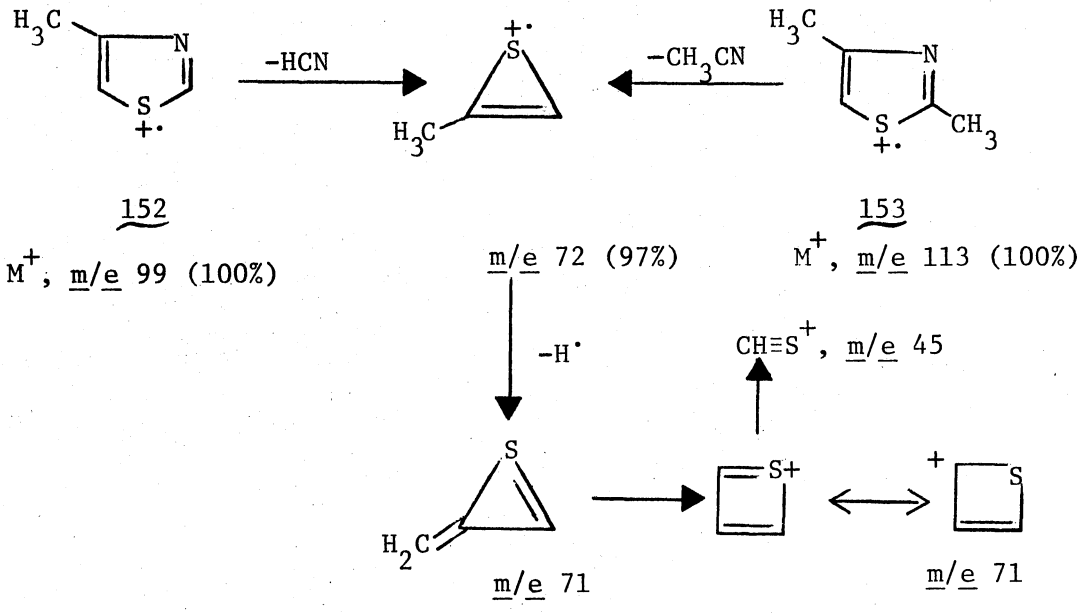
R = H, CH_3, NH_2, C_6H_5NH, CH_2=$CHCH_2NH$

(b) Mass spectra of thiazoles and related compounds: The molecular ion of thiazole (150) is the base peak of the spectrum and the only important fragmentation is loss of HCN to give the thiirene radical cation (m/e 58).[98] In the mass spectrum of thiazole-2-d (151) the M^+–HCN peak is replaced almost entirely by an M^+–DCN peak which confirms the involvement of C(2) in this process.[109]

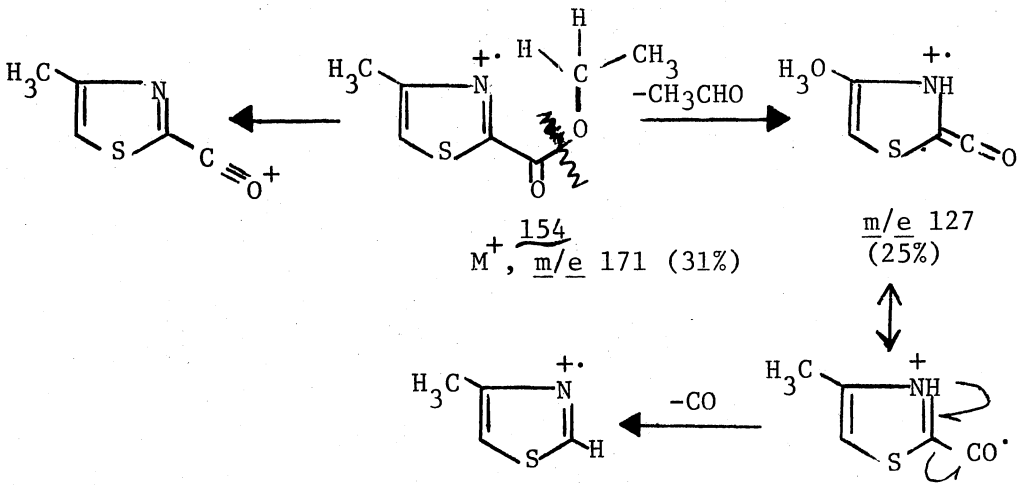


4-Methylthiazole ion (152) does not lose CH_3CN but only HCN, whereas that of 2,4-dimethylthiazole (153) shows an intense M^+–CH_3CN peak.

These basic fragmentations are displayed by a range of simple thiazoles; the full paper should be consulted for further details.[98]

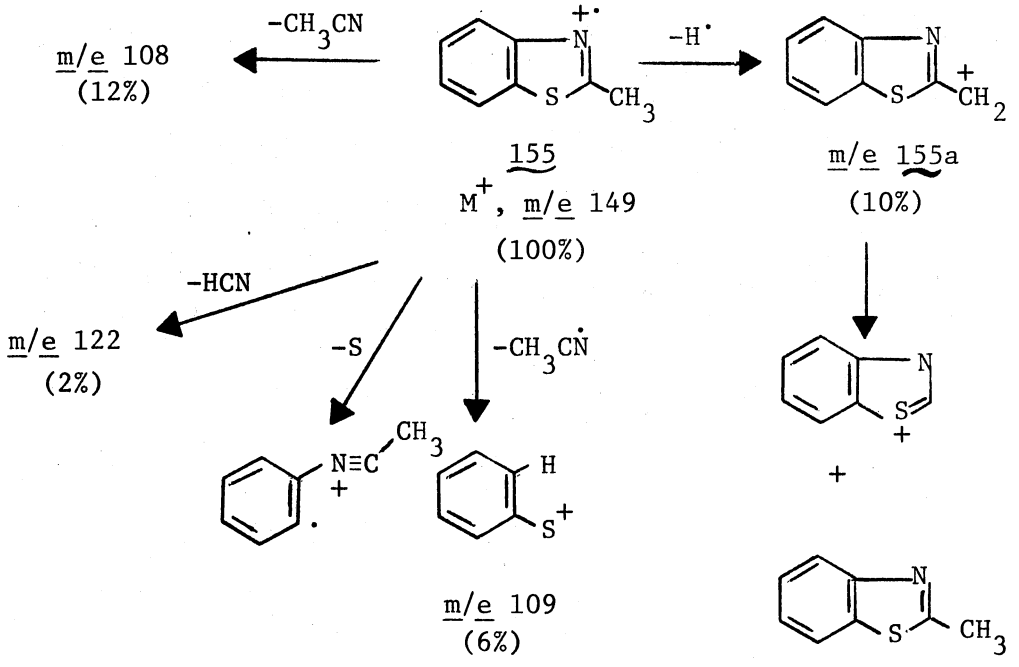


Ethyl 4-methylthiazole-2-carboxylate (154) shows an interesting fragmentation involving lossof the elements of acetaldehyde from the molecular ion.[98] The process can be formulated as involving a six-center intermediate including a hydrogen transfer. This is closely related to the McLafferty rearrangement, and the driving force is presumably the ability of the electron-deficient nitrogen atom in the



molecular ion 154 to act as hydrogen acceptor.

2-Methylbenzothiazole (155) shows the expected loss of CH_3CN (m/e 108) together with a considerable loss of CH_2CN (m/e 109). Loss of HCN also occurs; its formation must necessarily involve much skeletal rearrangement.[272]

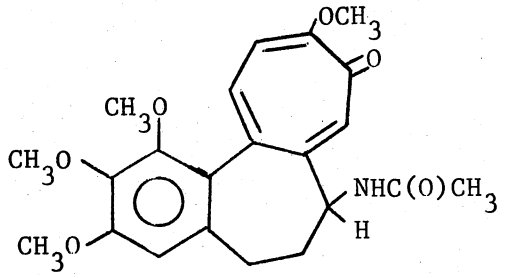


The origin of the hydrogen atom lost in the formation of the M^+-1 species has not been determined by deuterium labeling, and, in fact, the resultant ion was formulated as 155a. The mass spectra of thiazolines[72,232,378] and penicillins have also been studied in detail.

Polymethoxy Cyclic Ketones and Polymethoxy Steroids

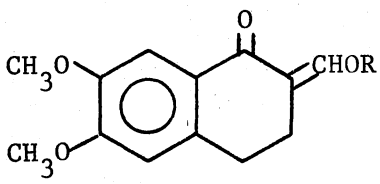
Polymethoxytetralones and polymethoxyphenanthrones have been of interest to many organic and medicinal chemists for years.[38] The possible significance of the methoxyl functionalities in biological activ-

ity is clearly illustrated via their incorporation in such compounds as mescaline, apomorphine and many other narcotics and naturally occurring alkaloids.[221] Campbell (1950)[83] first suggested that the methoxyl groups on the A ring of colchicine (156), among other things, were indirectly responsible for that alkaloid to act as a tumor-growth inhibitor. In order to lower the toxicity of this type of compound and maintain the antitumor activity, Campbell synthesized a series of 2-(alkoxy-



156

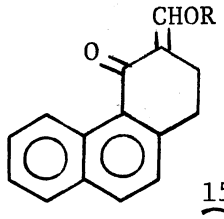
methylene)-1-tetralones 157, but found all examples to be less active



157

$R = C_2H_5, CH(CH_3)_2$

than colchicine. 3-(Hydroxymethylene)-1,2,3,4-tetrahydrophenanthrene-4-one (158) was later prepared by Campbell and co-workers[83] and found to have some antitumor activity when R = H but not when $R = CH_3$. The test



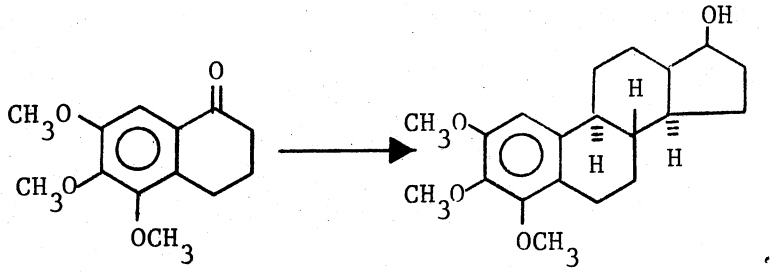
158

$R = H, CH_3$

was run against mouse sarcoma 37 (NIH). Campbell believed without further experimental evidence that the high toxicity of 156 was due to the highly unsaturated nature of ring C.

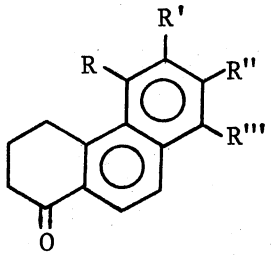
Schlager[339] emphasized the importance of vicinal methoxyl groups

for biological activity. Rao and co-workers[38c] synthesized (+)-2,3,4-trimethoxyestra-1,3-5(10)-trien-17β-ol from 3,4-dihydro-5,6,7-trimethoxynaphthalen-1(2H)-one (159) and found it to possess analgesic activity.



159

S. Imai (1969-71) published[203], in some detail, different routes for the synthesis of some polymethoxyphenanthrones but the methods are of little preparative value.

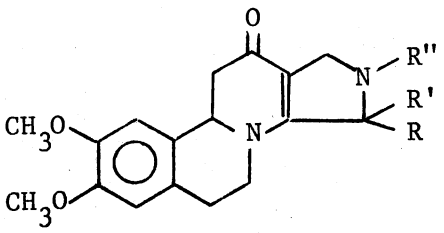


R = R''' = OCH_3, R' = R'' = H

R = R'' = H, R' = R''' = OCH_3

R = R''' = H, R' = R'' = OCH_3

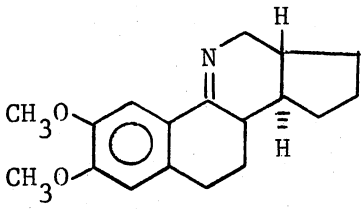
Many publications have appeared in the last few years dealing with the synthesis and/or biological activity of dimethoxy-substituted heterosteroids and alkaloids. Some examples are illustrated here:



[Ref. 206]

R = R' = H, CH_3;

R' = Ac, CH_3



[Ref. 289]

R = R' = H,

R' = Ac, CH_3

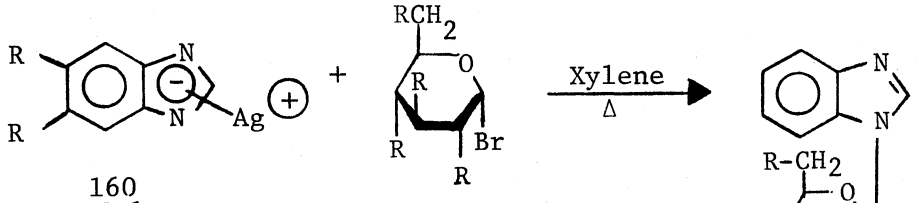
Other examples are found in the literature.[220,309,358,374,398]

Nucleoside Analogs and Related Compounds

It was originally proposed[256] that the term nucleoside be used only for carbohydrate derivatives of purines and pyrimidines isolated from the alkaline hydrolyzate of yeast nucleic acid. This was found too limiting since the major carbohydrate constituents of yeast nucleic acid are either D-ribose or 2-deoxy-D-erythropentose (2-deoxy-D-ribose). It has now been generally accepted[281] that the term purine nucleoside refers to all glycosyl derivatives of purines, both synthetic and natural, and it has been proposed[370] that this terminology should apply to the entire field of heterocyclic glycosides.

(1) Syntheses: Chemical synthesis of various heterocyclic N-glycosides: The chemical preparation of heterocyclic glycosides is a relatively new area in comparison to the related areas of purine and pyrimidine nucleotide chemistry. An early interest in the area of imidazole nucleosides and nucleotides developed rapidly,[370] because purine nucleosides found in nucleic acids depend on imidazole nucleotides as precursors.

(a) Condensation of silver salts of the heterocycle with polyacylglycosyl halides: A general method for the preparation of benzimidazole



160

160, R = CH_3

161, R = NO_2

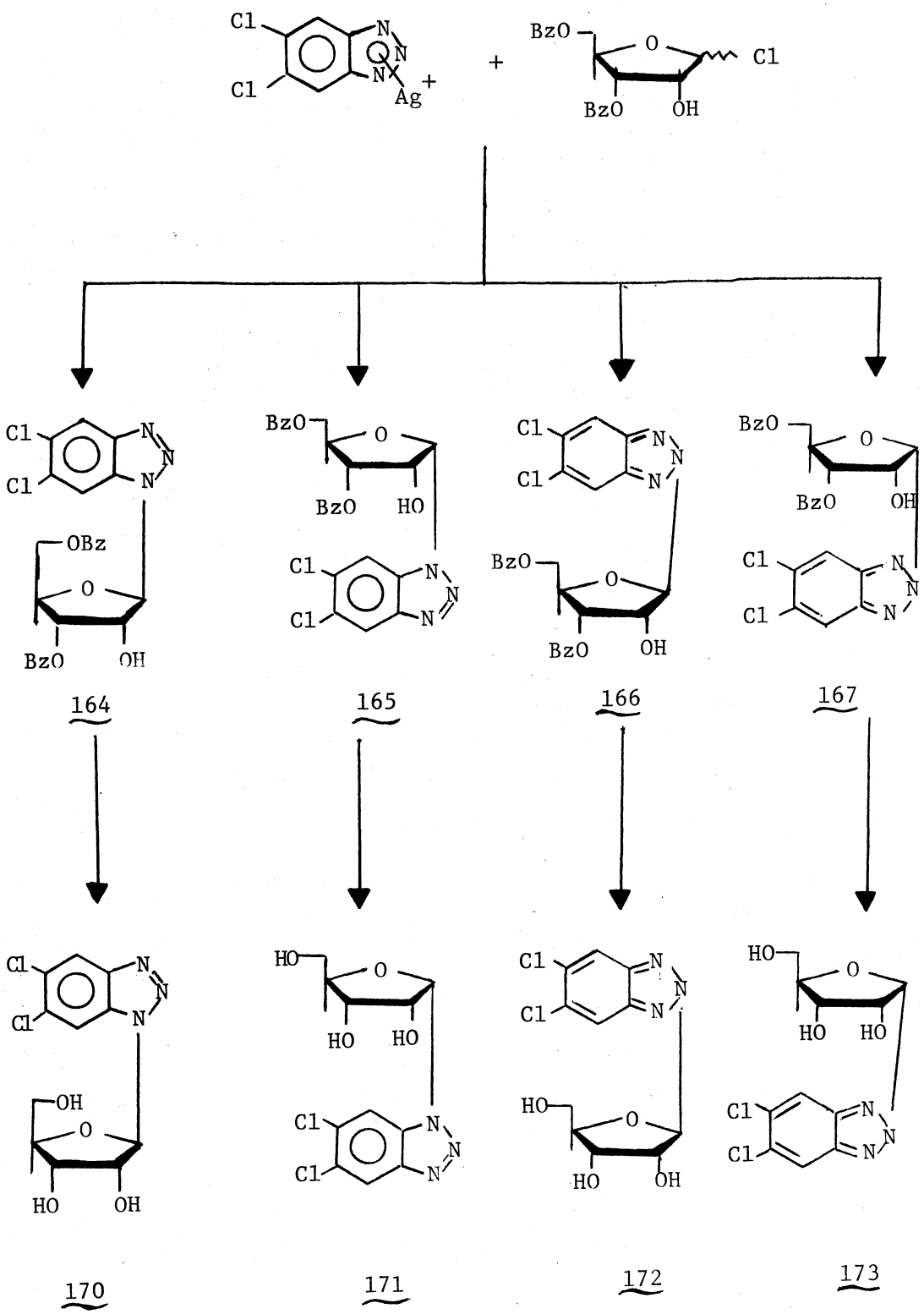
162, R = OAc

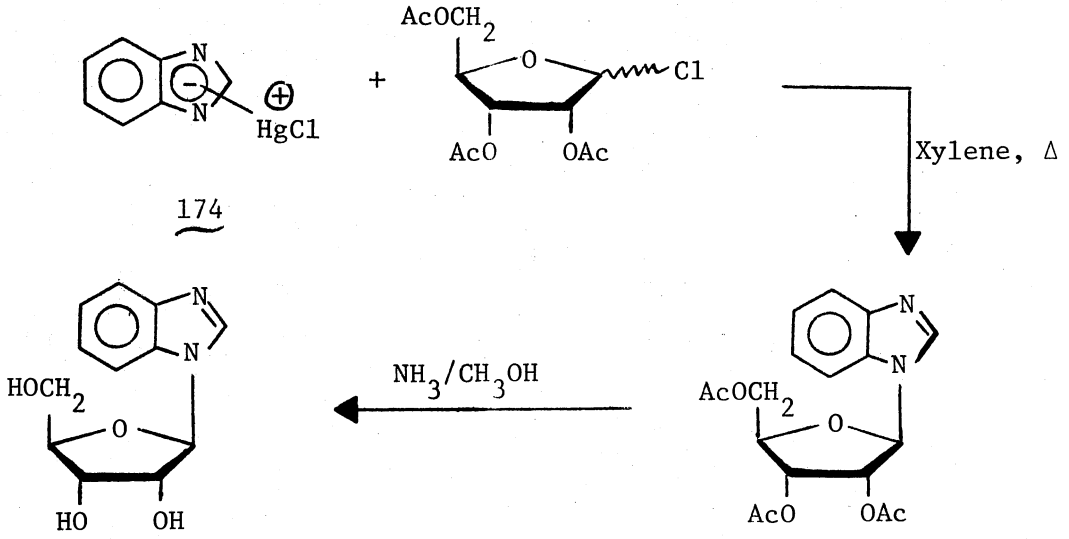
163, R = OH

glycosides has been devised[379] by reaction of silver salts of the appropriate benzimidazole with an acylated glycosyl halide followed by the deacylation of the condensation product. Metathesis of the silver salt of benzimidazole (160) with 2,3,4,5-tetra-O-acetyl-α-D-glucopyranosyl bromide in boiling xylene gave crystalline 1-(tetra-O-acetyl-β-D-glucopyranosyl)benzimidazole (162) in good yield. Deacetylation of 162 with sodium methoxide in absolute ethanol or with dilute hydrochloric acid afforded 1-(β-D-glucopyranosyl)benzimidazole 163. The latter compound was identical with the nucleoside synthesized by Mamalis and co-workers (1950) by a ring-closure method.[261] In a like manner, the condensations of the silver salts of other substituted benzimidazoles[185,261,379] with different bromo sugars, e.g., ribose,[376,380,381] xylose,[380] arabinose,[185] glucose,[99] and galactose,[99] have been reported.[371]

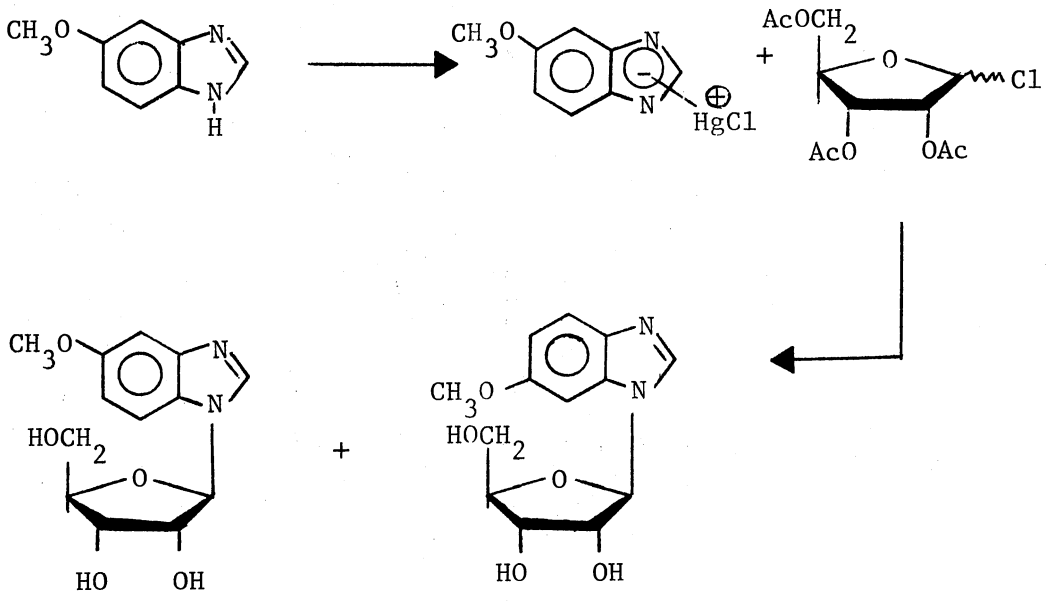
The first chemical synthesis[392] of a benzotriazole nucleoside was accomplished by a condensation of the silver salt of 5,6-dichlorobenzotriazole[385] (169) with 3,5-di-O-benzoyl-D-ribofuranosyl chloride (168) in boiling xylene, which produced four crystalline isomeric and anomeric nucleosides 164, 165, 166 and 167. These were separated by fractional crystallization. Debenzoylation of the nucleosides with methanolic ammonia afforded the corresponding nucleosides 170, 171, 172, and 173. Other benzotriazole N-nucleosides are known.[256,281,370,385,392]

(b) Condensation of halomercury salts of heterocycles with polyacylglycosyl halides: It has been found[117] that the chloromercuri derivatives of benzimidazoles 174 are much superior to silver salts for reaction with poly-O-acylglycosyl halides.[118] The 5'-phosphate and 5'-triphosphate of 1-(β-D-ribofuranosyl)benzimidazole have been prepared[202,393] and reported to possess ATP-like activity. The chloro-


Cl
Cl
N
N
N
Ag+
+
BzO
O
Cl
BzO
OH
OBz
BzO
OH
164
BzO
HO
165
166
167
HO
HO
170
171
172
173



mercurio method was successfully applied to prepare many other nucleoside derivatives.[106,142,278,279] For example, a mixture of 5- and 6-methoxy-1-(α and β-D-ribofuranosyl)benzimidazole was prepared[146] and separated by chromatography:[146]

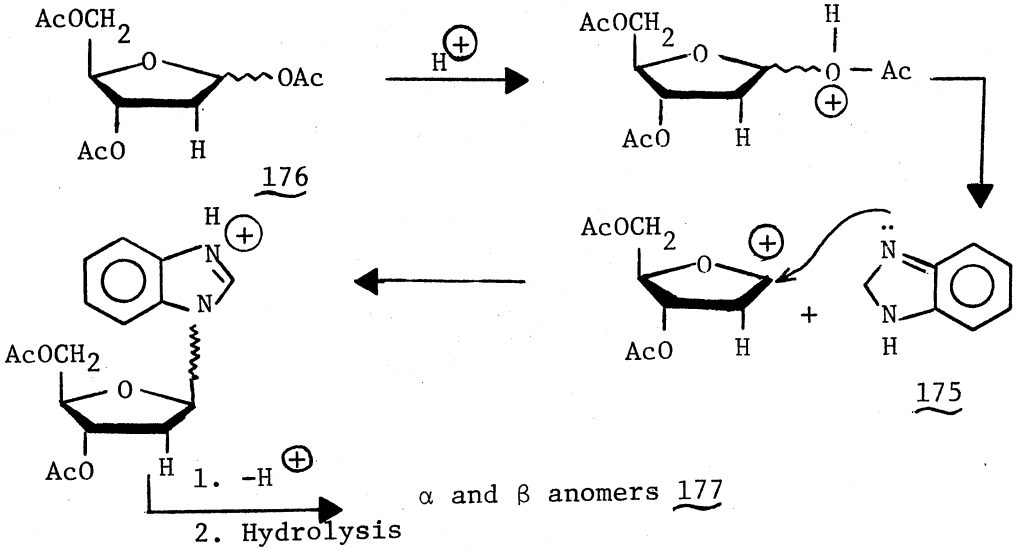


(c) Direct alkylation of the heterocycle with a polyacylglycosyl halide: In this method the metal-free heterocyclic base is caused to react with a poly-O-acylglycosyl halide in boiling dry dioxane. This re-

action is similar to the Hilbert-Johnson method used for the synthesis of pyrimidine nucleosides.[139,226]

A more recent method[11,397] involves the condensation of the heterocyclic compound with acetobromoglucose in dry nitromethane containing mercuric cyanide. In this process a mixture of anomers is usually obtained, more of the β-anomer usually being formed than of the α-anomer.[360] The two anomers are commonly separated by chromatography or fractional crystallization.[11,360]

(d) N-Glycosidation in acid: This technique was first employed in the area of nucleoside synthesis[337] to produce N-glycosylpurines and later applied to various other heterocyclic systems.[370] Thus, benzimidazole 175 was fused at 160° in the presence of chloroacetic acid as a catalyst with the triacetate 176. Subsequent deblocking of the carbohydrate moiety and separation of the α- and β-anomers by fractional crystallization and chromatography (alumina) gave a fair yield of 177α and 177β anomers. There was proposed[382] a reaction mechanism involving alkylation of the benzimidazole nitrogen (tertiary nitrogen) by a 3,5-di-O-acetyl-2-deoxy-D-ribofuranosyl-1-carbonium ion intermediate. This

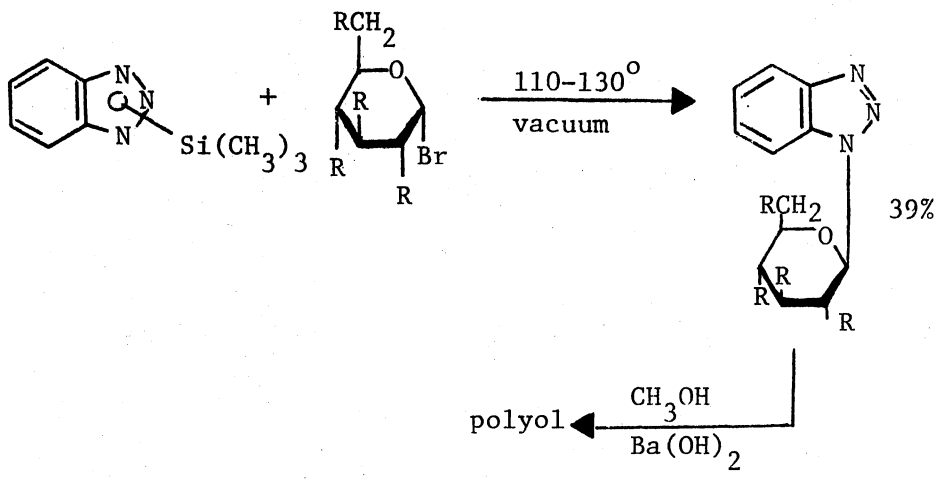


mechanism predicts that a more basic benzimidazole should be glycosylated much more rapidly than an acidic benzimidazole. However, Townsend and co-workers[371] have found that this acid-fusion procedure is inapplicable to many other ribofuranoside systems.

(e) Trimethylsilyl method: This method, developed by Iwai and co-workers[207] (1964), constitutes a modification of the Hilbert-Johnson synthesis of nucleosides.[180] A principal advantage of the approach is that the silylated derivatives may be prepared in excellent yields directly from the heterocyclic base. Silylation is readily accomplished with either chlorotrimethylsilane, hexamethyldisilazane, or trimethylsilyl-N,N-bis(trimethylsilyl)acetamide ["bis-(trimethylsilyl)-acetamide"]; the latter was proved to be an exceptionally powerful silylating agent.[403] The trimethylsilyl derivative procedure frequently affords a mixture of anomeric nucleosides in which substantial proportions of the α-anomer may be present.

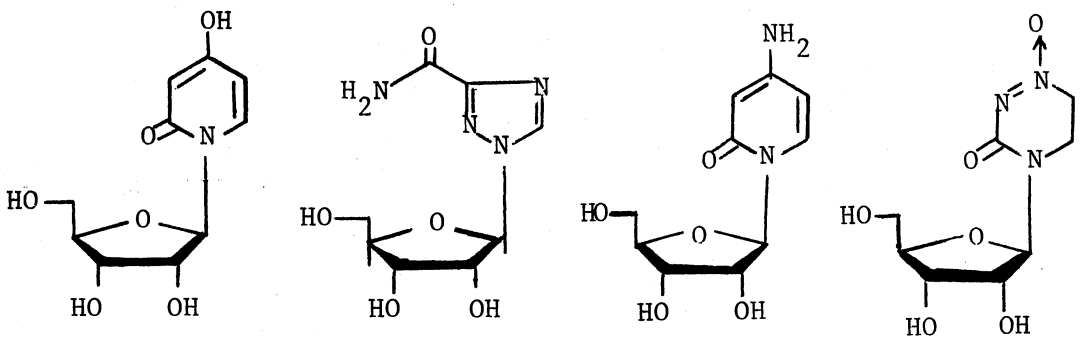
The literature of the trimethylsilyl method has been increasing drastically over the last ten to fifteen years so that only a representative is shown here.[64] Other examples are available in the literature.[160,290,323,348,349,362,391,403,404]

(2) Biological importance of nucleoside analogs:[59,364] The broad-spectrum antiviral activity[348] of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (Virazole) (178)[390] has prompted many investigators to explore the biological activity of other N-glycosyl heterocyclics.[11,389] 3-Deazauridine (179) increased the survival time of mice bearing L-1210 leukemia by 55-65%.[60]



3-Deazacytidine 180 inhibits E. coli at 10^{-7} M.[60] 3-Deazauridine (179) has recently been shown to be more effective against Ara C resistant L-1210 leukemia than the parent sensitive strain.[69]

Virazole (178) was found to be effective against L-1210 leukemia in experimental mice.[228] This was the first instance of a nucleoside to exhibit broad spectrum antiviral activity against both RNA and DNA viruses in animals. A 90% increase in life span was obtained when uridine 180 was administered to mice bearing L-1210 leukemia.[229] Compound 181 was equally effective against 6 MP resistant or Ara C resistant L-1210 and P-388 mouse leukemia.

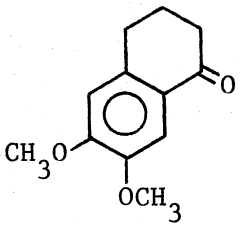


179 178 180 181

CHAPTER II

RESULTS AND DISCUSSION

A major objective of this research has been to synthesize heterosteroids and related model compounds with two methoxyl groups in ring A and special physical properties. As a working hypothesis, it was contended that strategically positioned hetero atoms in the steroid structure (or in the model systems) could greatly increase aqueous solubility, permit electron-pair donation for possible charge transfer complexation to occur with selected anticancer agents, and to provide a "hydropolar head" to facilitate membrane or membrane-wall penetration.[126] We have developed a new synthesis for the key precursor 6,7-dimethoxy-3,4-dihydro-1[2H]-naphthalenone (182)[352] and 6,7-dimethoxy-3,4-dihydro-1-[2H]-phenanthrone (188).



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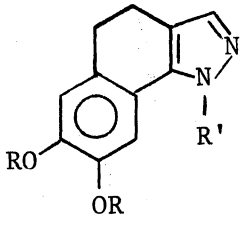
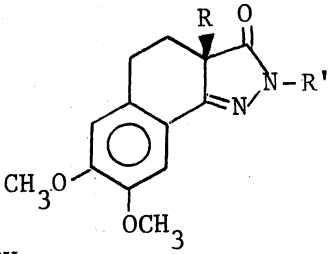
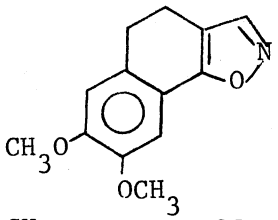


183 R = H, CH_3
R' = H, Ar



184 R = H, CH_3
R' = H, Ar



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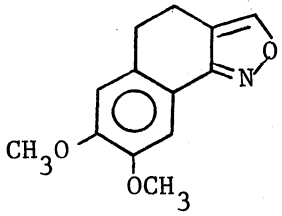

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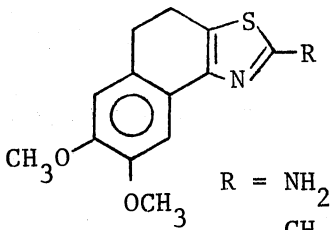
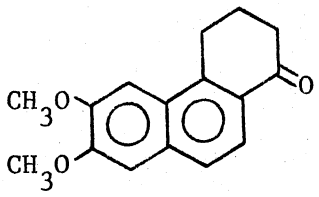


187 R = NH_2, NHC_6H_5, CH_3, $NHCH_2CH=CH_2$



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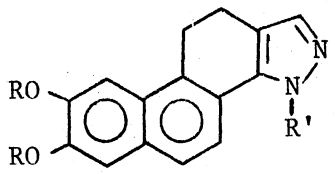
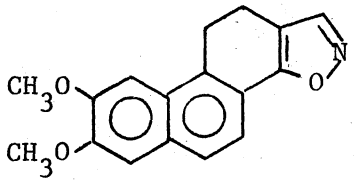


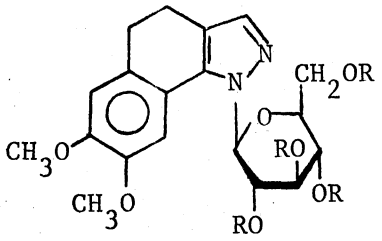
189

R = H, CH_3
R' = H, Ar



190

Consequently, a novel series of substituted pyrazoles (Table II), pyrazolones (Table IV), isoxazoles (Table V), thiazoles (Table VI), and N-glucosides (and derivatives) 191 of some of the pyrazoles have also been prepared. The families are represented by 183, 184, 185, 186, and 187 starting from 182. Likewise, families 189 and 190 were derived from 188.

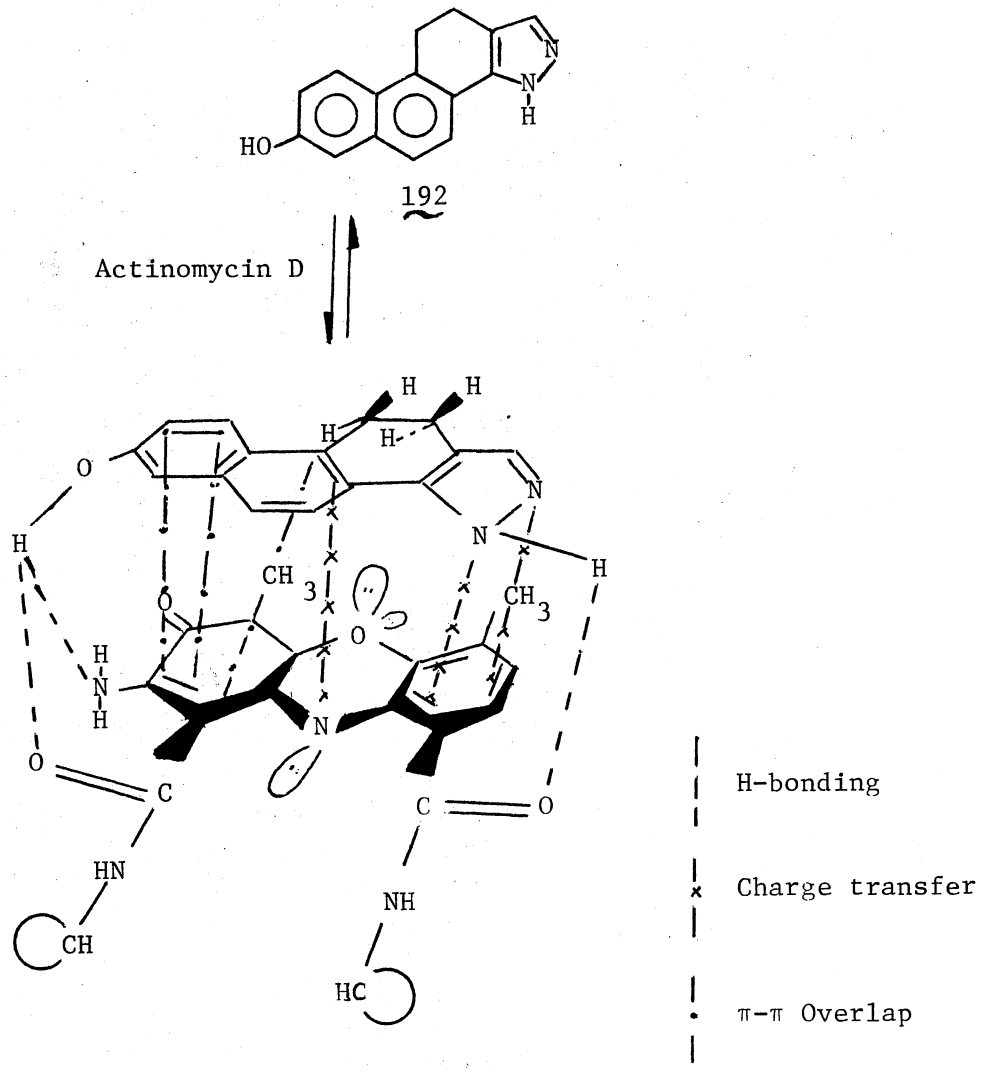


R = C(O) CH_3
R = H

191

Preliminary studies of the action of actinomycin D on the growth of Pseudomonas fluorescens in the presence of 10,11-dihydro-3H-naphth-[1,2-g]indazol-7-ol (192) revealed a potentiation factor of 8 for the latter. However, in mice the factor was only 1.04.[125] Careful PMR studies in D_2O demonstrated that a molecular complex formed between actinomycin D and 10,11-dihydro-3H-naphth[1,2-g]indazol-7-ol (192).[92,126] An upfield shift of 20 Hz for the methylene protons in 192 in the com-

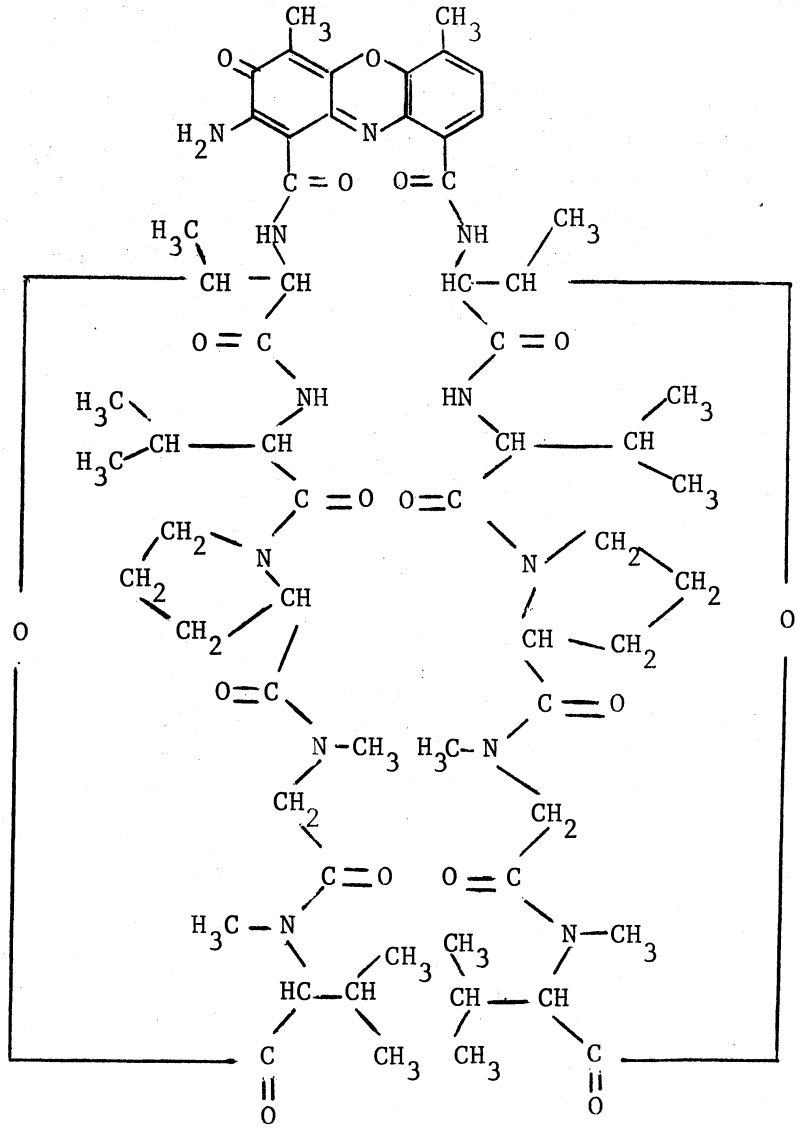
plex suggested a structure for the complex as shown.



UV-fluorescence spectral analysis also supported the formation of the molecular complex. An excitation maximum occurred at 320 nm in 10,11-dihydro-3H-naphth[1,2-g]indazol-7-ol (192) and an emission maximum was observed at 382 nm. When actinomycin D was added to indazole 192 (1:1 molar ratio), it quenched the 382 nm emission peak by 35-40%. DMSO (2M) added prior to complex formation produced only a 5% quenching effect. Thus, the complex must possess much H-bonding which is disrupted by DMSO. DMF also destroyed the complex. Consequently, a structural design for a potentiation agent might include H-bonding atoms as well as

atoms capable of charge transfer if actinomycin D were to be the anti cancer agent examined for complexation. Actinomycin D is a clinically-used antileukemic agent.[260]

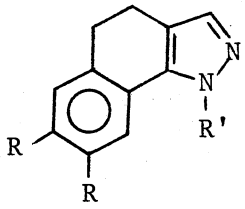
^{13}C Nuclear magnetic resonance of actinomycin D has been studied[260] and the most probable structure was proposed[260] with the carbon atoms



positioned approximately as shown.

TABLE II

7,8-DIMETHOXY-(AND 7,8-DIHYDROXY)-4,5-DIHYDRO-1H-BENZ[g]INDAZOLES AND DERIVATIVES



Compound Name	Cpd.	R	R'	m.p., °C	Yield, %
4,5-Dihydro-7,8-dimethoxy-1H-benz[g] indazole	193	OCH_3	H	179.5-180	72
4,5-Dihydro-1H-benz[g]indazole-7,8-diol	194	OH	H	300-2	50
4,5-Dihydro-7,8-dimethoxy-1-phenyl-1H-benz[g]indazole	195	OCH_3	C_6H_5	125-6	85
4,5-Dihydro-1-phenyl-1H-benz[g]indazole-7,8-diol	196	OH	C_6H_5	276-8	78
4,5-Dihydro-7,8-dimethoxy-1-(p-methoxyphenyl)-1H-benz[g]indazole	197	OCH_3	p-C_6H_4-OCH_3	136-7	52

TABLE II (Continued)

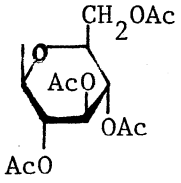
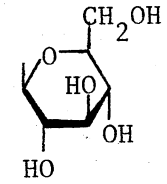
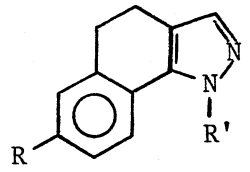
Compound Name	Cpd.	R	R'	m.p., °C	Yield, %
4,5-Dihydro-1-(p-hydroxyphenyl)-1H-benz[g]indazole-7,8-diol	198	OH	p-C_6H_4-OH	295	74
4,5-Dihydro-7,8-dimethoxy-1-(p-tolylsulfonyl)-1H-benz[g]indazole	199	OCH_3	p-SO_2-C_6H_4-CH_3	185-7	30
1-(Chloromercurio)-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole	200	OCH_3	HgCl	>300	100
1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole tetraacetate (ester)	201	OCH_3		170-1	66
1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole	202	OCH_3		167-8	42

TABLE III

1-N-SUBSTITUTED-7-METHOXY-(AND 7-HYDROXY)-4,5-DIHYDRO-1H-BENZ[g]INDAZOLES



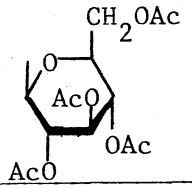
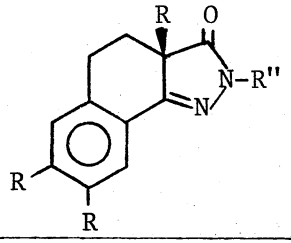
Compound Name	Cpd.	R	R'	m.p., °C	Yield, %
4,5-Dihydro-7-methoxy-1-phenyl-1H-benz[g] indazole	203	OCH_3	C_6H_5	105-6	89
4,5-Dihydro-1-phenyl-1H-benz[g]indazol-7-ol	204	OH	C_6H_5	238-240	72
1-(Chloromercurio)-4,5-dihydro-7-methoxy-1H-benz[g]indazole	205	OCH_3	HgCl	>300	94
1-β-D-Glucopyranosyl-4,5-dihydro-7-methoxy-1H-benz[g]indazole tetra-acetate (ester)	206	OCH_3		155-6	25,42

TABLE IV

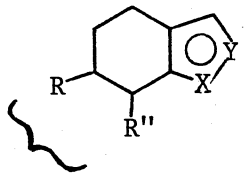
2,3a,4,5-TETRAHYDRO-7,8-DIMETHOXY-3H-BENZ[g]INDAZOL-3-ONES AND THE 2-ARYL ANALOGS



Compound Name	Cpd.	R	R'	R"	m.p., °C	Yield, %
2,3a4,5-Tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one	207	OCH_3	H	H	276	91
2,3a,4,5-Tetrahydro-7,8-dimethoxy-2-phenyl-3H-benz[g]indazol-3-one	208	OCH_3	H	C_6H_5	200-2	92
2-(p-Fluorophenyl)-2,3a,4,5-tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one	209	OCH_3	H	p-C_6H_4F	243-4	65
2,3a,4,5-Tetrahydro-7,8-dimethoxy-3a-methyl-3H-benz[g]indazol-3-one	210	OCH_3	CH_3	H	219-221	82

TABLE V

4,5-DIHYDRO-7,8-DIMETHOXYNAPHTH[2,1-d]-AND [1,2-c]ISOXAZOLES
AND 4,5-DIHYDRO-7,8-DIMETHOXYPHENANTHRO[2,1-d]ISOXAZOLE



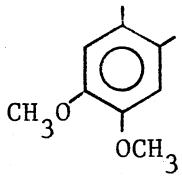
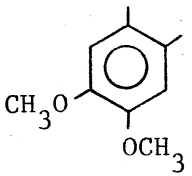
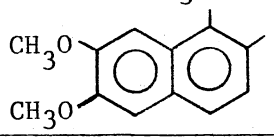
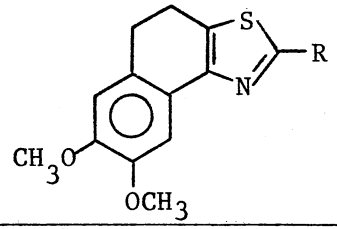
Compound Name	Cpd.	X	Y	R + R"	m.p., °C	Yield %
4,5-Dihydro-7,8-dimethoxynaphth[2,1-d]-isoxazole	185	O	N		189-190	84
4,5-Dihydro-7,8-dimethoxynaphth[1,2-c]-isoxazole	186	N	O		178-179	38
10,11-Dihydro-7,8-dimethoxy-phenanthro-[2,1-d]isoxazole	190	O	N		194-195	85

TABLE VI

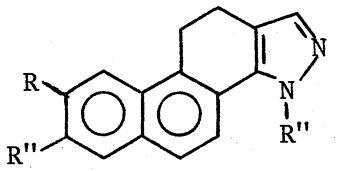
2-SUBSTITUTED-4,5-DIHYDRO-7,8-DIMETHOXYNAPHTHO[1,2-d]THIAZOLES



Compound Name	Cpd.	R	m.p., °C	Yield, %
2-Amino-4,5-dihydro-7,8-dimethoxynaphtho-[1,2-d]thiazole	211	NH_2	235-7	65
2-Anilino-4,5-dihydro-7,8-dimethoxynaphtho-[1,2-d]thiazole	212	$NH-C_6H_5$	180-1	90
2-(Allylamino)-4,5-dihydro-7,8-dimethoxy-naphtho[1,2-d]thiazole	213	$NH-CH_2-CH=CH_2$	88-90	95
4,5-Dihydro-7,8-dimethoxy-2-methylnaphtho-[1,2-d]thiazole	214	CH_3	140-1	88

TABLE VII

10,11-DIHYDRO-7,8-DIMETHOXY-(AND 7,8-DIHYDROXY)PHENANTHRO[1,2-c]PYRAZOLES



Compound Name	Cpd.	R	R'	R''	m.p., °C	Yield, %
10,11-Dihydro-7,8-dimethoxy-3H-phenanthro-[1,2-c]pyrazole	215	OCH_3	OCH_3	H	277.5	98
10,11-Dihydro-3H-phenanthro[1,2-c]pyrazole-7,8-diol	216	OH	OH	H	324-6	74
10,11-Dihydro-7,8-dimethoxy-3-(p-fluorophenyl)phenanthro[1,2-c]pyrazole	217	OCH_3	OCH_3	p-C_6H_4F	195-7	64
10,11-Dihydro-3-(p-fluorophenyl)phenanthro[1,2-c]pyrazole-7,8-diol	218	OH	OH	p-C_6H_4F	256-8	51

TABLE VII (Continued)

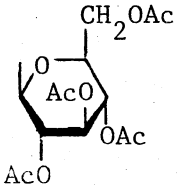
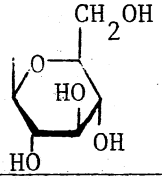
Compound Name	Cpd.	R	R'	R''	m.p., °C	Yield, %
3-(Chloromercurio)-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]-pyrazole	219	H	OCH_3	HgCl	>300	100
3-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole tetraacetate (ester)	220	H	OCH_3		116	52
3-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole	221	H	OCH_3		210-2	14

TABLE VIII

NMR DATA OF STARTING MATERIALS, INTERMEDIATES, AND PRODUCTS

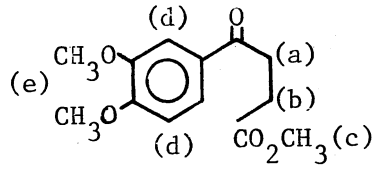
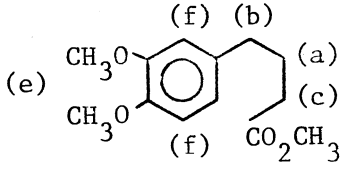
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	222	XLIX	$DCCl_3$	2.75 (t)	2	CH_2 (b)
				3.30 (t)	2	CH_2 (a)
				3.70 (s)	3	CO_2CH_3 (c)
				3.90-3.95 (2s)	6	OCH_3 (e)
				6.90-7.60 (m)	3	ArH (d)
	223	L	$DCCl_3$	1.95 (qt)	2	CH_2 (a)
				2.35 (t)	2	CH_2 (b)
				2.60 (t)	2	CH_2 (c)
				3.65 (s)	3	CH_3 (d)
				3.80-3.85 (2s)	6	OCH_3 (e)
				6.70-6.80 (m)	3	ArH (f)

TABLE VIII (Continued)

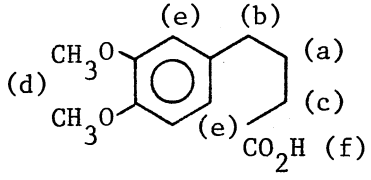
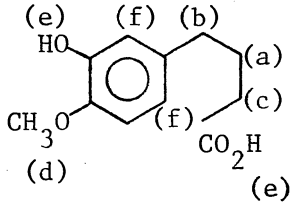
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	224	LI	$DCCl_3$	1.98 (qt)	2	CH_2 (a)
				2.35 (t)	2	CH_2 (b)
				2.65 (t)	2	CH_2 (c)
				3.85-3.88 (2s)	6	OCH_3 (d)
				6.60-6.85 (m)	3	ArH (e)
				8.55 (s)	1	CO_2H (f)
	225	LIV	$DCCl_3$	2.00 (qt)	2	CH_2 (a)
				2.35 (t)	2	CH_2 (b)
				2.60 (t)	2	CH_2 (c)
				3.90 (s)	3	O CH_3 (d)
				5.20-6.20 (b)	2	CO_2H,OH (e)
				6.72 (m)	3	ArH (f)

TABLE VIII (Continued)

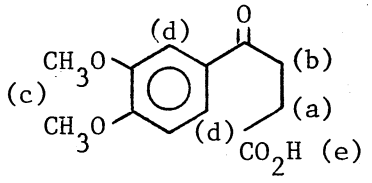
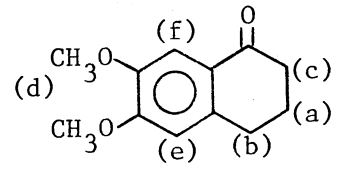
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	226	XLVIII	Pyridine-d_5	2.05 (t)	2	CH_2 (a)
				3.45 (t)	2	CH_2 (b)
				3.70 (s)	3	OCH_3 (c)
				3.72 (s)	3	OCH_3 (c)
				6.85 (s), 6.95 (s), 7.80 (d)	3	ArH (d)
				7.55 (s)	1	CO_2H (e)
	182	LV	$DCCl_3$	2.15 (qt)	2	CH_2 (a)
				2.60 (t)	2	CH_2 (b)
				2.90 (t)	2	CH_2 (c)
				3.90-3.92 (2s)	6	OCH_3 (d)
				6.62 (s)	1	ArH (e)
				7.55 (s)	1	ArH (f)

TABLE VIII (Continued)

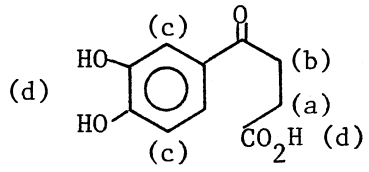
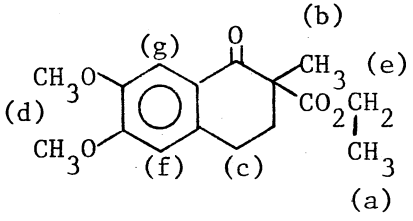
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	227	LIII	DMSO-d_6	2.60 (t)	2	CH_2 (a)
				3.15 (t)	2	CH_2 (b)
				6.80-7.50 (m)	3	ArH (c)
				10.00 (b)	3	CO_2H,OH (d)
	228	LIX	$DCCl_3$	1.18 (t)	3	$-CH_2\underline{CH_3}$ (a)
				1.50 (s)	3	$-CH_3$ (b)
				2.55-2.95 (m)	4	CH_2-CH_2 (c)
				3.95-3.96 (2s)	6	OCH_3 (d)
				4.15 (q)	2	$-\underline{CH_2}CH_3$ (e)
				6.60 (s)	1	ArH (f)
				7.50 (s)	1	ArH (g)

TABLE VIII (Continued)

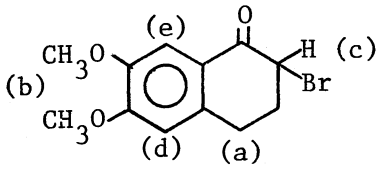
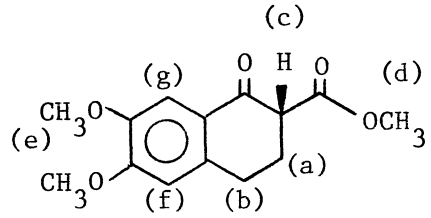
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	229	LVIII	$DCCl_3$	2.5-3.4 (m)	4	CH_2-CH_2 (a)
				3.88-3.91 (2s)	6	OCH_3 (b)
				4.70 (t)	1	C(O)-CH-Br(c)
				6.70 (s)	1	ArH (d)
				7.55 (s)	1	ArH (e)
	230	LX	$DCCl_3$	2.45 (m)	2	CH_2 (a)
				2.98 (t)	2	CH_2 (b)
				3.60 (t)	1	C(O)-CH- (c)
				3.80 (s)	3	CO_2-CH_3 (d)
				3.90-3.92 (2s)	6	OCH_3 (e)
				6.70 (s)	1	ArH (f)
				7.55 (s)	1	ArH (g)

TABLE VIII (Continued)

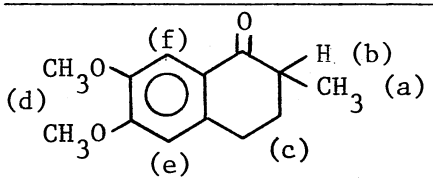
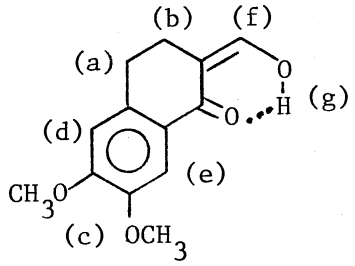
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	231	LVII	$DCCl_3$	1.30 (d)	3	CH_3 (a)
				2.00-2.50 (m)	1	C(O)-CH-CH_3 (b)
				2.90 (m)	4	CH_2CH_2 (c)
				3.91-3.93 (2s)	6	OCH_3 (d)
				6.65 (s)	1	ArH (e)
				7.55 (s)	1	ArH (f)
	232	LVI	$DCCl_3$	2.50 (t)	2	CH_2 (a)
				2.80 (t)	2	CH_2 (b)
				3.90 (s)	6	OCH_3 (c)
				6.70 (s)	1	ArH (d)
				7.35 (s)	1	=CH-O- (f)
				7.48 (s)	1	ArH (e)
				14.50 (s)	1	=C-OH (g)

TABLE VIII (Continued)

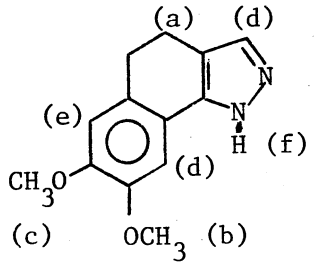
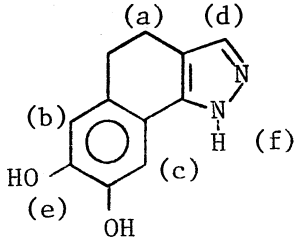
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	193	LXI	$DCCl_3$	2.70-2.90 (m)	4	CH_2CH_2 (a)
				3.75 (s)	3	OCH_3 (b)
				3.90 (s)	3	OCH_3 (c)
				6.75 (s)	1	ArH (e)
				7.35 (s)	2	ArH, N=CH (d)
				9.40-9.75 (bs)	1	N-H (f)
	194	LXII	DMSO-d_6	2.70 (s)	4	CH_2-CH_2 (a)
				6.80 (s)	1	ArH (b)
				7.39 (s)	1	ArH (c)
				7.18 (s)	1	N=CH (d)
				8.80 (bs)	2	Ar-OH (e)
				9.50 (bs)	1	N-H (f)

TABLE VIII (Continued)

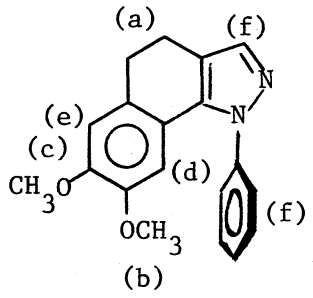
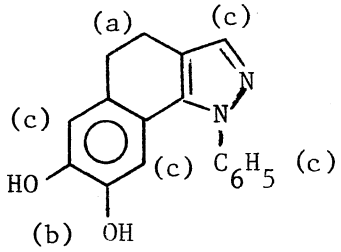
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	195	LXIII	$DCCl_3$	2.60-2.90 (m)	4	CH_2CH_2 (a)
				3.40 (s)	3	OCH_3 (b)
				3.90 (s)	3	OCH_3 (c)
				6.38 (s)	1	ArH (d)
				6.80 (s)	1	ArH (e)
				7.40-7.60 (m)	6	ArH, N=CH (f)
	196	LXIV	Pyridine-$\underline{d}_5$	2.60-2.80 (m)	4	CH_2CH_2 (a)
				4.55-5.90 (bs)	2	ArOH (b)
				6.80-8.75 (m)	8	ArH, N=CH (c)

TABLE VIII (Continued)

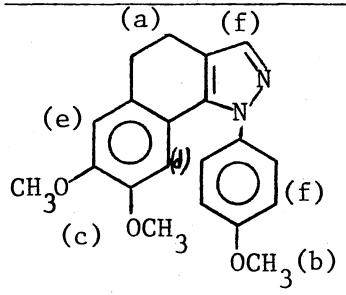
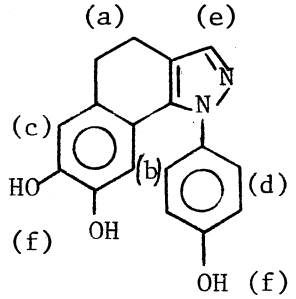
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	197	LXV	$DCCl_3$	2.60-2.80 (m)	4	CH_2CH_2 (a)
				3.42 (s)	3	OCH_3 (b)
				3.85-3.87 (2s)	6	OCH_3 (c)
				6.40 (s)	1	ArH (d)
				6.80 (s)	1	ArH (e)
				6.90-7.50 (m)	5	ArH, N=CH (f)
	198	LXVI	DMSO-d_6	3.50-3.85 (m)	4	CH_2CH_2 (a)
				6.35 (s)	1	ArH (b)
				6.75 (s)	1	ArH (c)
				6.90-7.50 (m)	4	ArH (d)
				8.15 (s)	1	N=CH (e)
				8.75-9.80 (b)	3	ArOH (f)

TABLE VIII (Continued)

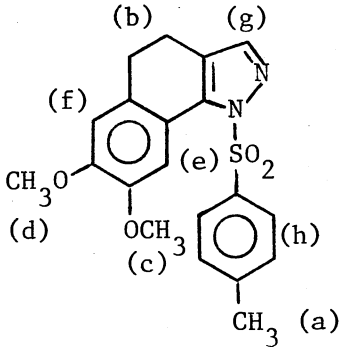
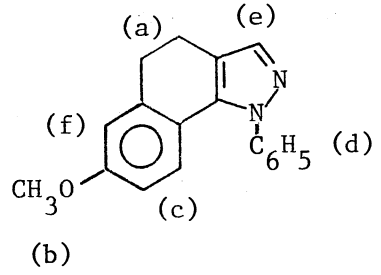
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	199	LXVII	$DCCl_3$	2.35 (s)	3	CH_3 (a)
				2.75 (m)	4	CH_2CH_2 (b)
				3.86 (s)	3	OCH_3 (c)
				3.90 (s)	3	OCH_3 (d)
				6.70 (s)	1	ArH (e)
				7.44 (s)	1	ArH (f)
				7.78 (s)	1	N=CH (g)
				7.20-7.30 (2s) 7.80-7.90 (2s)	4	ArH (h)
	203	LXVIII	$DCCl_3$	2.60-2.95 (m)	4	CH_2-CH_2 (a)
				3.74 (s)	3	OCH_3 (b)
				6.72 (s)	1	ArH (f)
				6.40 (d), 6.55 (d), 6.82 (d)	2	ArH (c)
				7.40 (m)	5	ArH (d)
				7.55 (s)	1	N=CH (e)

TABLE VIII (Continued)

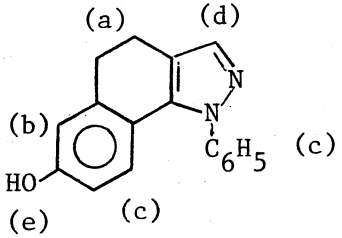
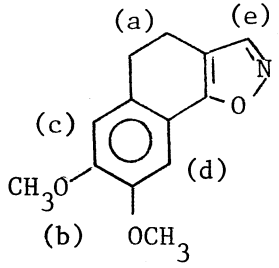
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	204	LXIX	DMSO-d_6	2.60-3.90 (m)	4	CH_2-CH_2 (a)
				6.50 (s)	1	ArH (b)
				6.30-6.60 (m) and 7.50 (m)	7	ArH (c)
				6.55 (s)	1	N=CH (d)
				9.30-9.60 (bs)	1	ArOH (e)
	185	LXX	$DCCl_3$	2.65-3.15 (m)	4	CH_2-CH_2 (a)
				3.88-3.90 (2s)	6	OCH_3 (b)
				6.80 (s)	1	ArH (c)
				7.20 (s)	1	ArH (d)
				8.12 (s)	1	N=CH (e)

TABLE VIII (Continued)

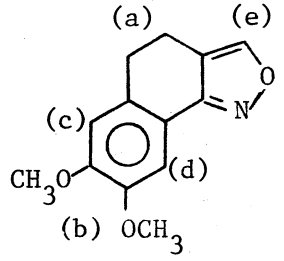
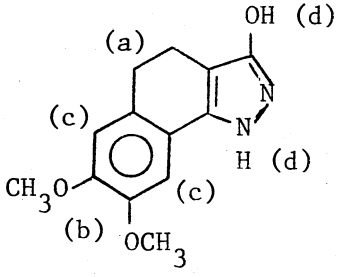
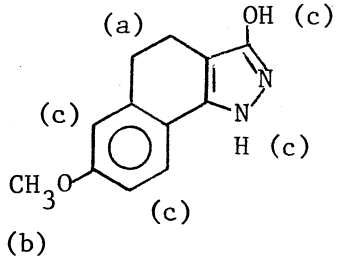
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	186	LXXI	$DCCl_3$	2.60-2.80 (m)	4	CH_2-CH_2 (a)
				3.88-3.90 (2s)	6	OCH_3 (b)
				6.78 (s)	1	ArH (c)
				7.45 (s)	1	ArH (d)
				8.14 (s)	1	ArH (e)
	207	LXXIII	DMSO-d_6	2.50, 2.80 (2t)	4	CH_2-CH_2 (a)
				3.78 (2s)	6	OCH_3 (b)
				6.90, 7.24 (2s)	2	ArH (c)
				10.0-12.6 (vb)	2	=C-OH, NH (d)
	233	LXXII	DMSO-d_6	2.55, 2.85 (2t)	4	CH_2-CH_2 (a)
				3.74 (s)	3	OCH_3 (b)
				6.70-7.50 (m)	5	=C-OH, ArH, NH (c)

TABLE VIII (Continued)

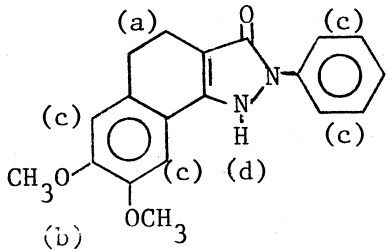
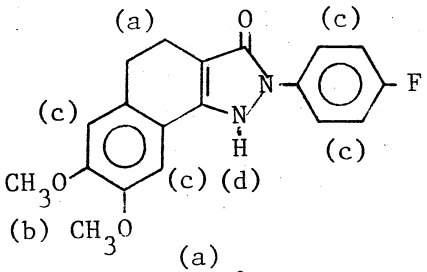
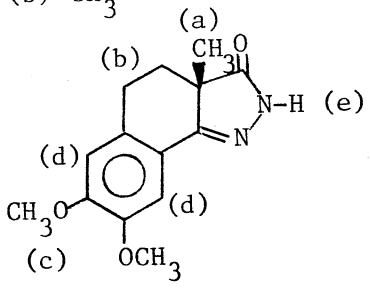
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	208	LXXIV	DMSO-d_6	2.65, 2.85 (2t)	4	CH_2-CH_2 (a)
				3.80-3.81 (2s)	6	OCH_3 (b)
				6.90-7.90 (m)	7	ArH (c)
				11.1-11.15 (bs)	1	N-H (d)
	209	LXXV	DMSO-d_6	2.65, 2.85 (2t)	4	CH_2-CH_2 (a)
				3.80-3.81 (2s)	6	OCH_3 (b)
				6.90-7.90 (m)	6	ArH (c)
				10.2-11.0 (vb)	1	N-H (d)
	210	LXXVI	$DCCl_3$	1.35 (s)	3	CH_3 (a)
				2.0, 3.0 (m)	4	CH_2-CH_2 (b)
				3.80-4.01 (2s)	6	OCH_3 (c)
				6.68, 7.25 (2s)	2	ArH (d)
				9.25 (bs)	1	NH (e)

TABLE VIII (Continued)

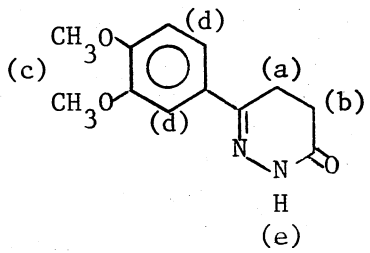
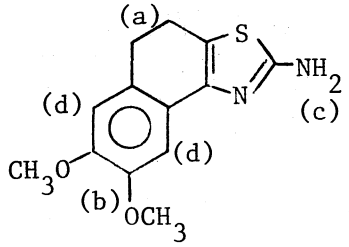
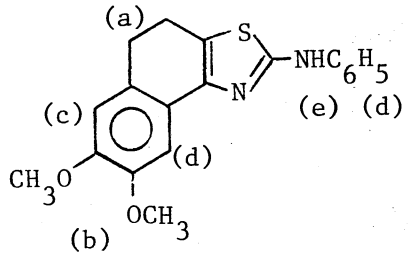
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	234	LII	$DCCl_3$	2.62 (t)	2	CH_2 (a)
				3.00 (t)	2	CH_2 (b)
				3.92 (s)	6	OCH_3 (c)
				6.80-7.45 (m)	3	ArH (d)
				9.38 (s)	1	NH (e)
	211	LXXVII	DMSO-d_6	2.80 (m)	4	CH_2-CH_2 (a)
				3.75 (s)	6	OCH_3 (b)
				6.76-6.78 (2s)	2	NH_2 (c)
				7.18 (s)	2	ArH (d)
	212	LXXVIII	DMSO-d_6	2.95 (m)	4	CH_2-CH_2 (a)
				3.81-3.84 (2s)	6	OCH_3 (b)
				7.75 (s)	1	ArH (c)
				8.00-8.40 (m)	6	ArH (d)
				8.92-9.20 (bs)	1	NH (e)

TABLE VIII (Continued)

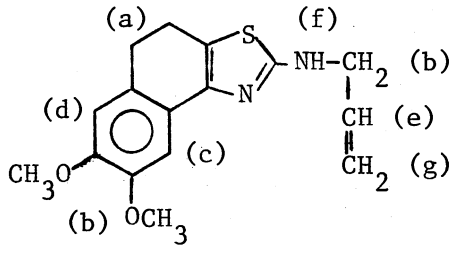
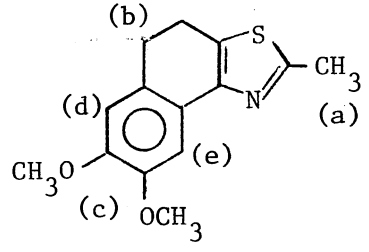
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	213	LXXIX	$DCCl_3$	2.88 (m)	4	CH_2-CH_2 (a)
				3.89-3.91 (m)	8	OCH_3, CH_2 (b)
				6.70 (s)	1	ArH (d)
				7.30 (s)	1	ArH (c)
				5.25 (qt)	1	-CH= (e)
				5.60-6.10 (m)	2	$=CH_2$ (g)
				6.35 (s)	1	NH (f)
	214	LXXX	$DCCl_3$	2.60 (s)	3	CH_3 (a)
				2.90 (s)	4	CH_2-CH_2 (b)
				3.86-3.92 (2s)	6	OCH_3 (c)
				6.74 (s)	1	ArH (d)
				7.48 (s)	1	ArH (e)

TABLE VIII (Continued)

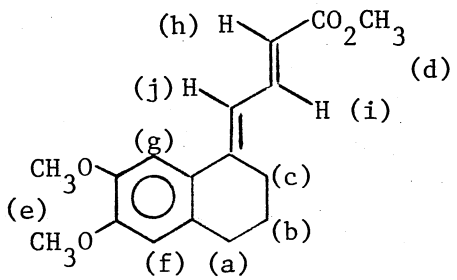
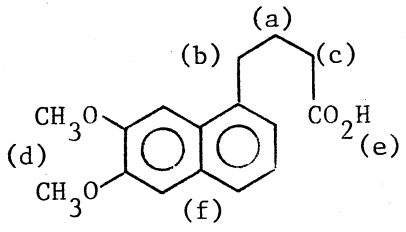
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	235	LXXXI	$DCCl_3$	1.25 (t)	2	CH_2 (a)
				1.90 (qt)	2	CH_2 (b)
				3.35 (t)	2	CH_2 (c)
				3.75 (s)	3	CH_3 (d)
				3.88-3.91 (2s)	6	OCH_3 (e)
				6.65 (d)	1	=CH (h)
				5.88 (d)	1	=CH (j)
				6.55 (s)	1	ArH (f)
				7.15 (s)	1	ArH (g)
				7.94 (2d)	1	=CH (i)
	236	LXXXII	$DCCl_3$	2.15 (qt)	2	CH_2 (a)
				2.55 (t)	2	CH_2 (b)
				3.10 (t)	2	CH_2 (c)
				3.98-4.00 (s)	6	OCH_3 (d)
				5.55 (bs)	1	CO_2H (e)
				7.10-7.65 (m)	5	ArH (f)

TABLE VIII (Continued)

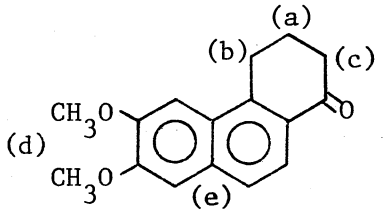
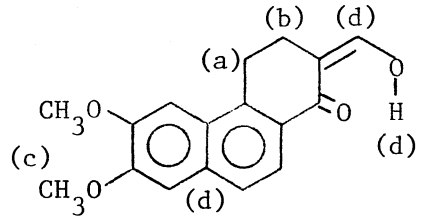
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	188	LXXXIII	$DCCl_3$	2.25 (qt)	2	CH_2 (a)
				2.70 (t)	2	CH_2 (b)
				3.28 (t)	2	CH_2 (c)
				3.99 (2s)	6	OCH_3 (d)
				7.15 (s), 7.25 (s), 7.48, 7.58 (d), 7.98 (d)	4	ArH (e)
	237	LXXXIV	$DCCl_3$	2.70 (t)	2	CH_2 (a)
				3.26 (t)	2	CH_2 (b)
				4.08 (s) 1	6	OCH_3 (c)
				7.10, 7.30, 7.55, (s) 7.65, 7.88, 8.00	6	ArH, C=CH, =C-OH (d)

TABLE VIII (Continued)

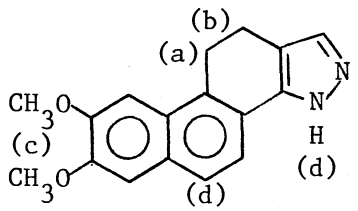
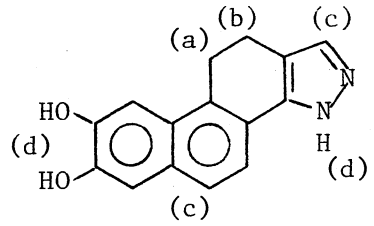
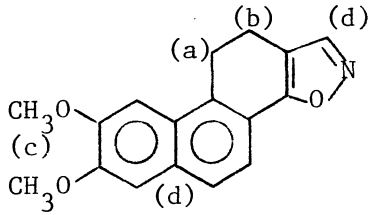
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	215	LXXXV	Pyridine-d_5	2.92 (t)	2	CH_2 (a)
				3.35 (t)	2	CH_2 (b)
				3.88-3.92 (2s)	6	OCH_3 (c)
				5.62, 7.15, 7.30, 7.52, 7.64, 7.70, 7.84, 8.28, 8.35, 8.68 (s)	6	ArH, NH, N=CH, (d) [impurities in pyridine-d_5]
	216	LXXXVI	DMSO-d_6	2.88 (t)	2	CH_2 (a)
				3.16 (t)	2	CH_2 (b)
				7.18-8.26 (m)	5	ArH, N=CH (c)
				9.44-9.62 (2bs)	3	ArOH, NH (d)
	190	LXXXVII	$DCCl_3$	2.90 (t)	2	CH_2 (a)
				3.38 (t)	2	CH_2 (b)
				3.99-4.00 (2s)	6	OCH_3 (c)
				7.15, 7.24, 7.62, 7.66, 8.15 (s)	5	ArH, N=CH (d)

TABLE VIII (Continued)

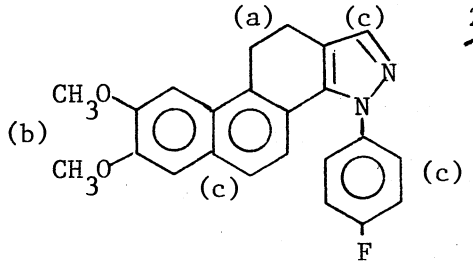
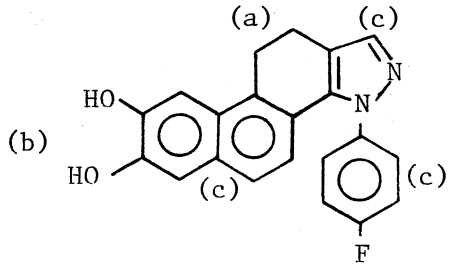
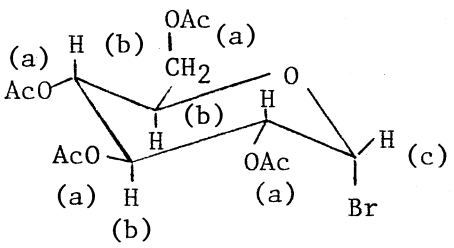
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	217	LXXXVIII	DMSO-d_6	2.84, 3.34 (2t)	4	CH_2-CH_2 (a)
				3.90 - 3.94 (2s)	6	OCH_3 (b)
				6.68 - 7.64 (m)	9	ArH, N=CH (c)
	218	LXXXIX	Pyridine-d_5	2.76, 3.32 (2t)	4	CH_2-CH_2 (a)
				4.60-6.15 (vb)	2	ArOH (b)
				6.98-8.72 (m)	9	ArH, H=CH (c)
	238	XC	$DCCl_3$	2.02-2.10 (3s)	14	$OC(O)CH_3$, CH_2OAc (a)
				4.32 (m), 4.85 (q), 5.15 (t), 5.55 (t)	4	-C(O)-O-CH (b)
				6.60 (d)	1	H-CBr (c)

TABLE VIII (Continued)

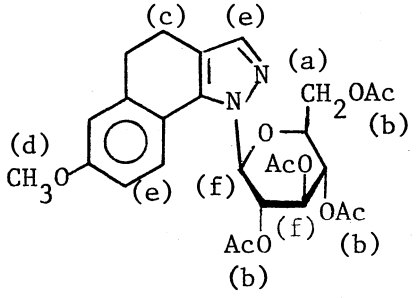
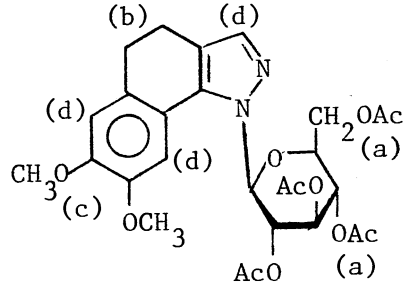
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	206	XCI	$DCCl_3$	1.88 (s)	2	$C(O)-O-CH_2$ (a)
				2.05 (2s)	12	$OC(O)CH_3$ (b)
				2.72 (m)	4	CH_2-CH_2 (c)
				3.82 (s)	3	OCH_3 (d)
				4.25 (m), 5.20-5.65 (m), 6.75 (s), 6.84 (d), 7.35 (s), 7.80 (d)	9	ArH, =N-CH (e) C(O)-O-CH (f)
	201	XCII	Pyridine-d_5	1.8-2.1 (3s)	14	$C(O)-O-CH_2$, $O-C(O)CH_3$ (a)
				2.70 (m)	4	CH_2-CH_2 (b)
				3.78 (s)	6	OCH_3 (c)
				4.04 (s), 4.46 (m), 4.80 (s)	8	ArH, N=CH, C(O)-O-CH (d)
				5.50-8.70 (s,m)		[Impurities in Pyridine-d_5]

TABLE VIII (Continued)

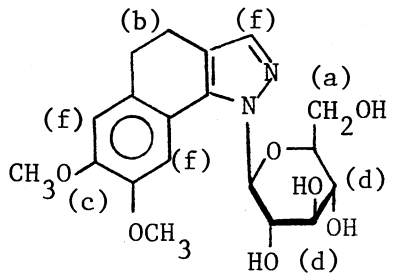
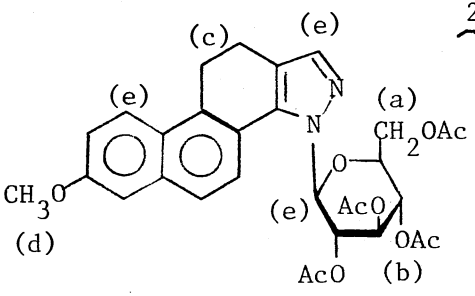
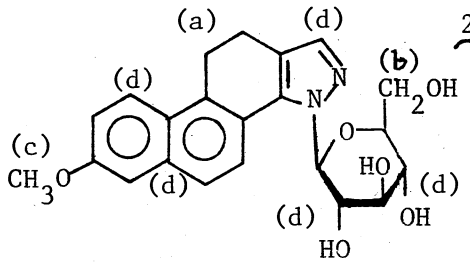
Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	202	XCIII	Pyridine-$\underline{d}_5$	2.02 (d)	2	$-CH_2-O$ (a)
				3.70-3.75 (m)	4	CH_2-CH_2 (b)
				3.70-3.82 (2s)	6	OCH_3 (c)
				4.25-4.40 (m), 4.90 (m), 5.85 (d)	7	$-C\underline{H}-O\underline{H}$ (d)
				7.55-7.70 (2s)	3	ArH, N=CH (f)
	220	XCIV	$DCCl_3$	1.90 (s)	2	$O-CH_2-$ (a)
				2.05-2.15 (3s)	12	$OC(O)CH_3$ (b)
				2.90 (t), 3.30 (t)	4	CH_2-CH_2 (c)
				3.95 (s)	3	OCH_3 (d)
				4.25 (m), 5.30 (m) 5.62 (s), 7.10-7.20 (m), 7.40 (s), 7.15 (d), 8.00 (d)	11	ArH, N=CH, $-C(O)-O-CH-$ (e)

TABLE VIII (Continued)

Structure	Cpd.	Plate	Solvent	δ(p.p.m.)[a]	Integ.	Assignments
	221	XCV	Acetone-d_6	2.90, 3.35 (2t)	4	CH_2-CH_2 (a)
				3.60 (d)	2	O-CH_2 (b)
				3.95 (s)	3	OCH_3 (c)
				5.25 (s), 5.34 (s) 7.10-8.15 (m)	15	ArH, N=CH, C-OH, O-CH (d)

[a]Chemical shifts are measured downfield from TMS. The multiplicity is as follows: singlet, s; doublet, d; triplet, t; multiplet, m; broad, b; broad singlet, bs; quartet, q; quintet, qt; very broad, vb. All sweep widths were 1000 Hz at 100.1 MHz (^{1}H) in all solutions. The lone methoxy group of 6-methoxytetralone has a signal at δ3.81 while the corresponding 2-hydroxymethylene compound has an absorption at δ3.79 (J. G. Morgan, Ph.D. dissertation, O.S.U., 1971). It was noted that all signals for methyl protons on the CH_3O group in all compounds in our work occurred as two singlets (six exceptions were 187, 205, 213, 220, 234, 392, which displayed lone singlets below δ3.90). Thus, it is conceivable that the signal at higher field corresponds to the methyl protons of the 6-methoxy group in our compounds while the signal at lower field corresponds to the methyl protons for the 7-methoxy function. Final confirmation would require additional experiments. The methylene signals of the keto ester 222 and ester 223 and related compounds were assigned on the basis of comparison with the spectrum of 3-benzoylpropanoic acid (found in Sadtler NMR Spectra).

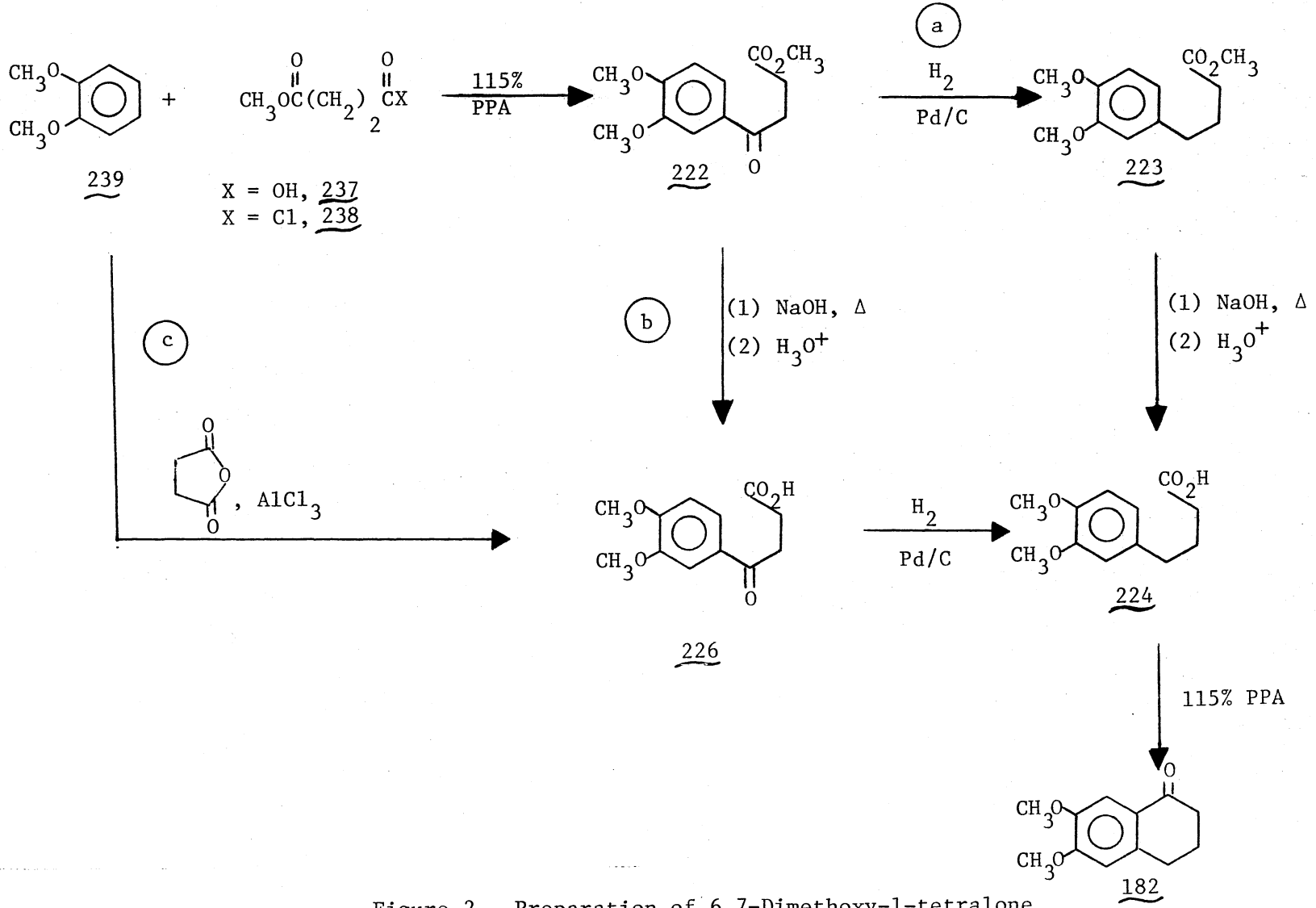


Figure 2. Preparation of 6,7-Dimethoxy-1-tetralone

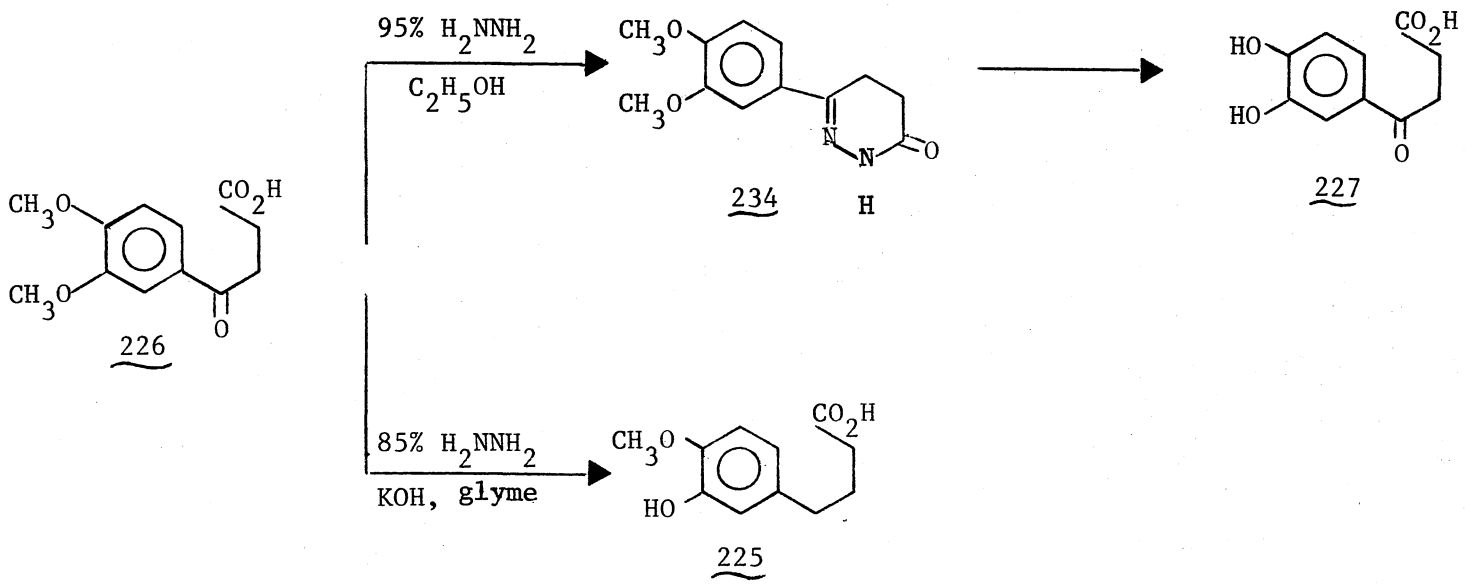


Figure 3. Reaction of Keto Acid 226 With Hydrazine

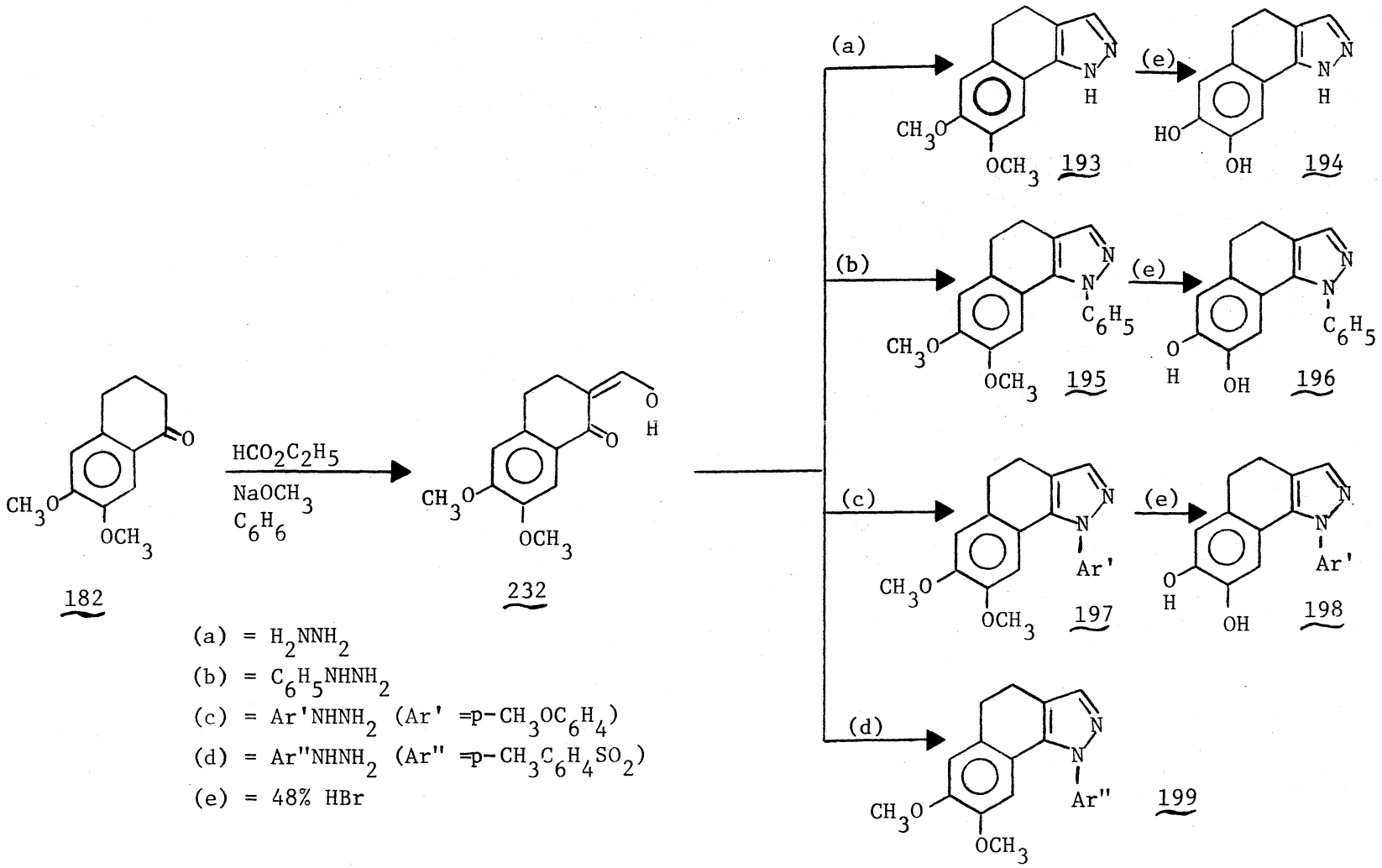


Figure 4. Synthesis of Model Steroidal Pyrazoles

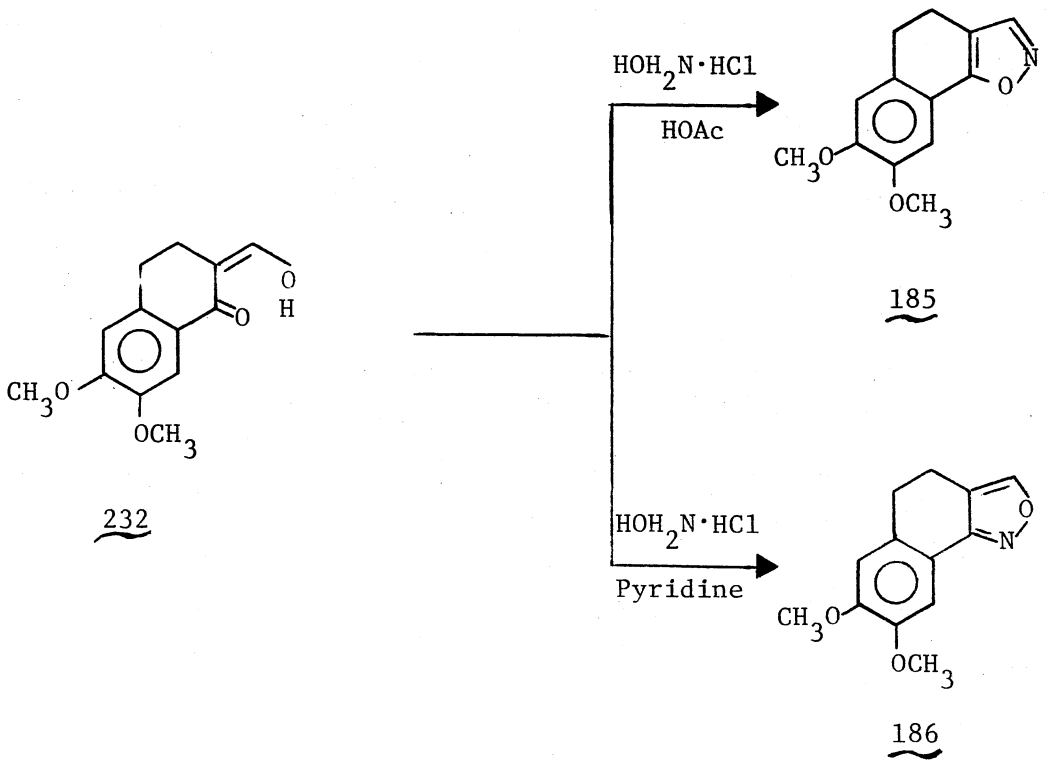


Figure 5. Preparation of Isomeric Isoxazoles

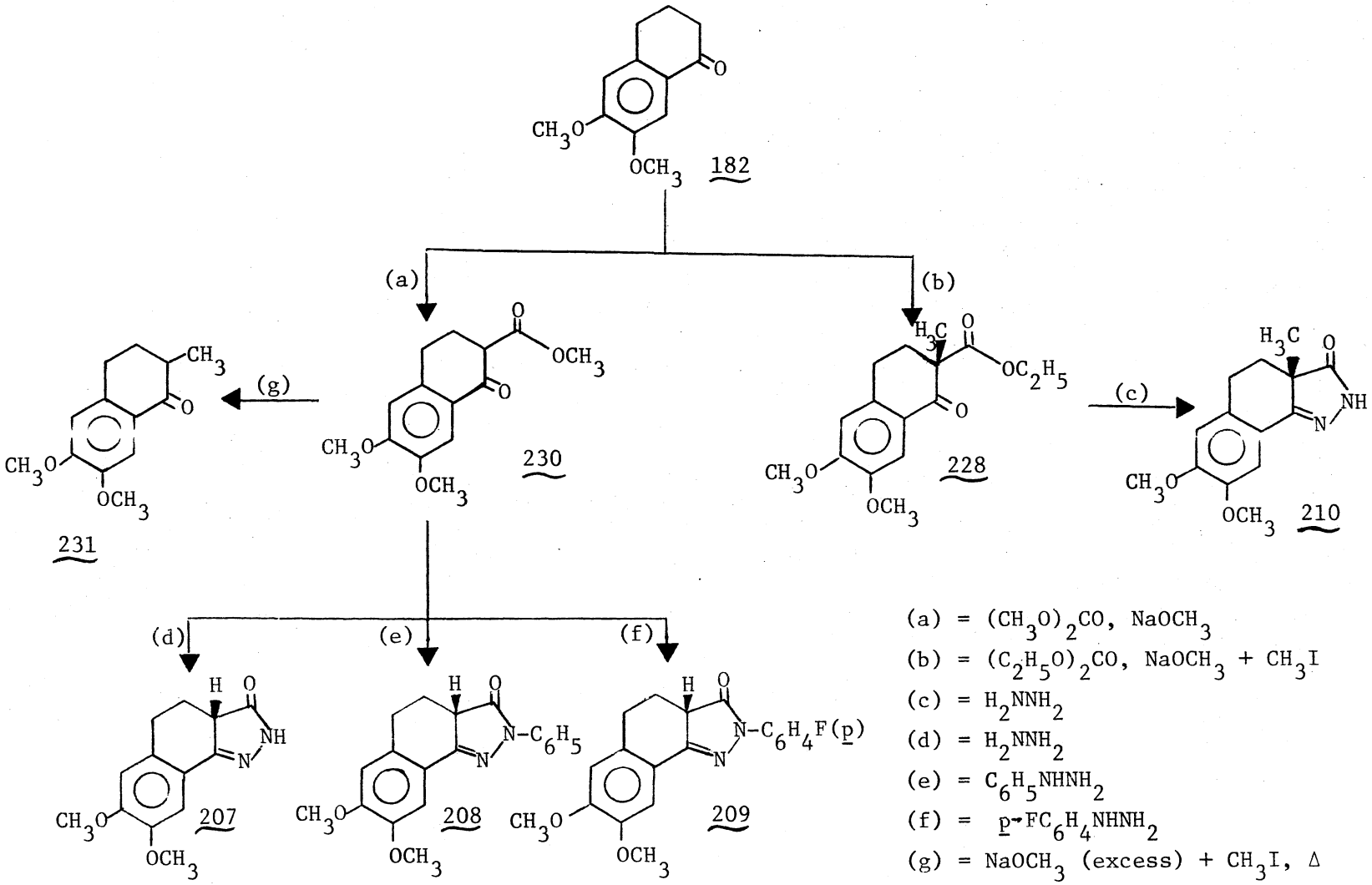


Figure 6. Synthesis of Model Steroidal Pyrazolones

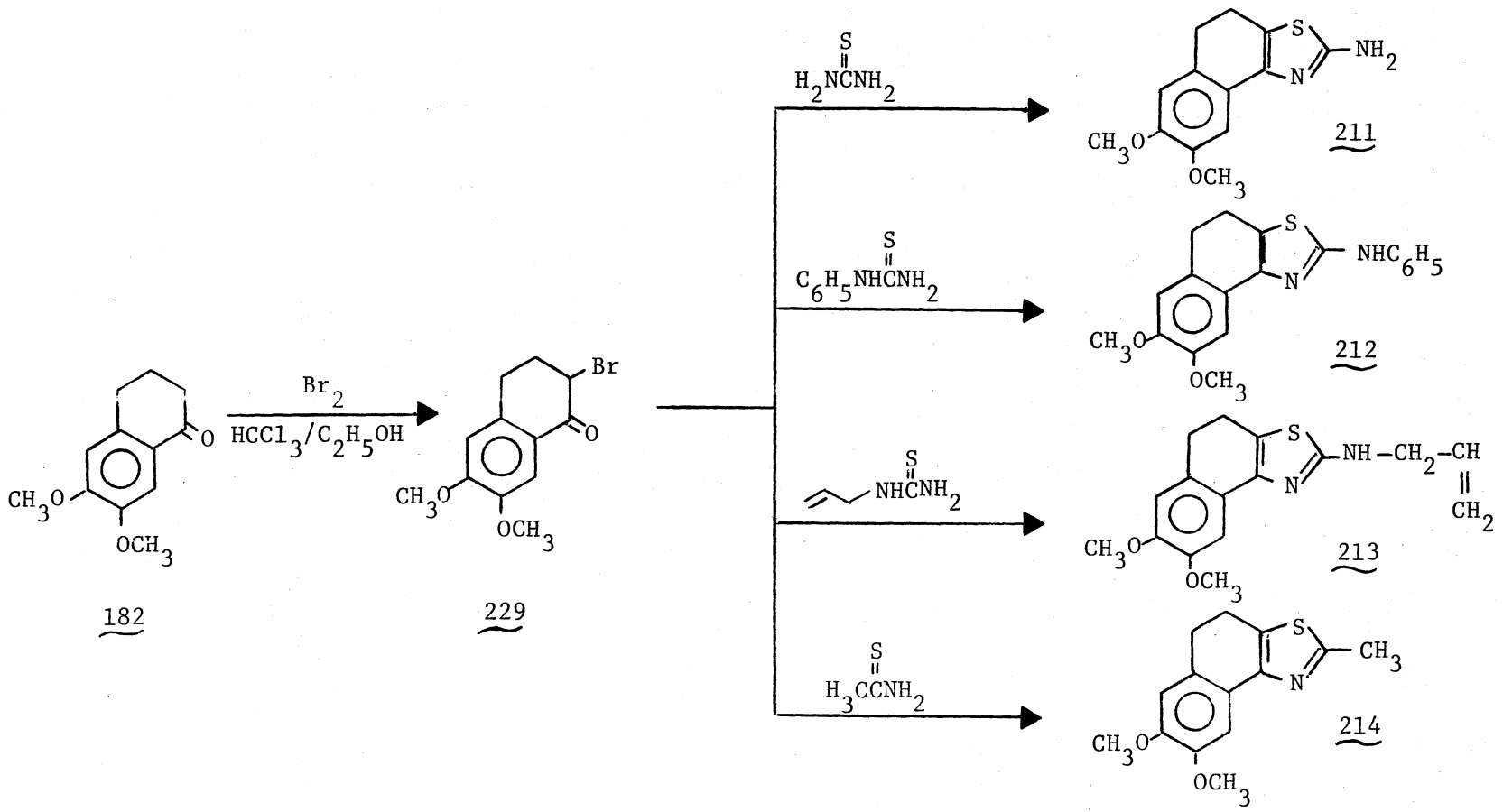


Figure 7. Synthesis of Thiazoles as Models to Steroid Systems

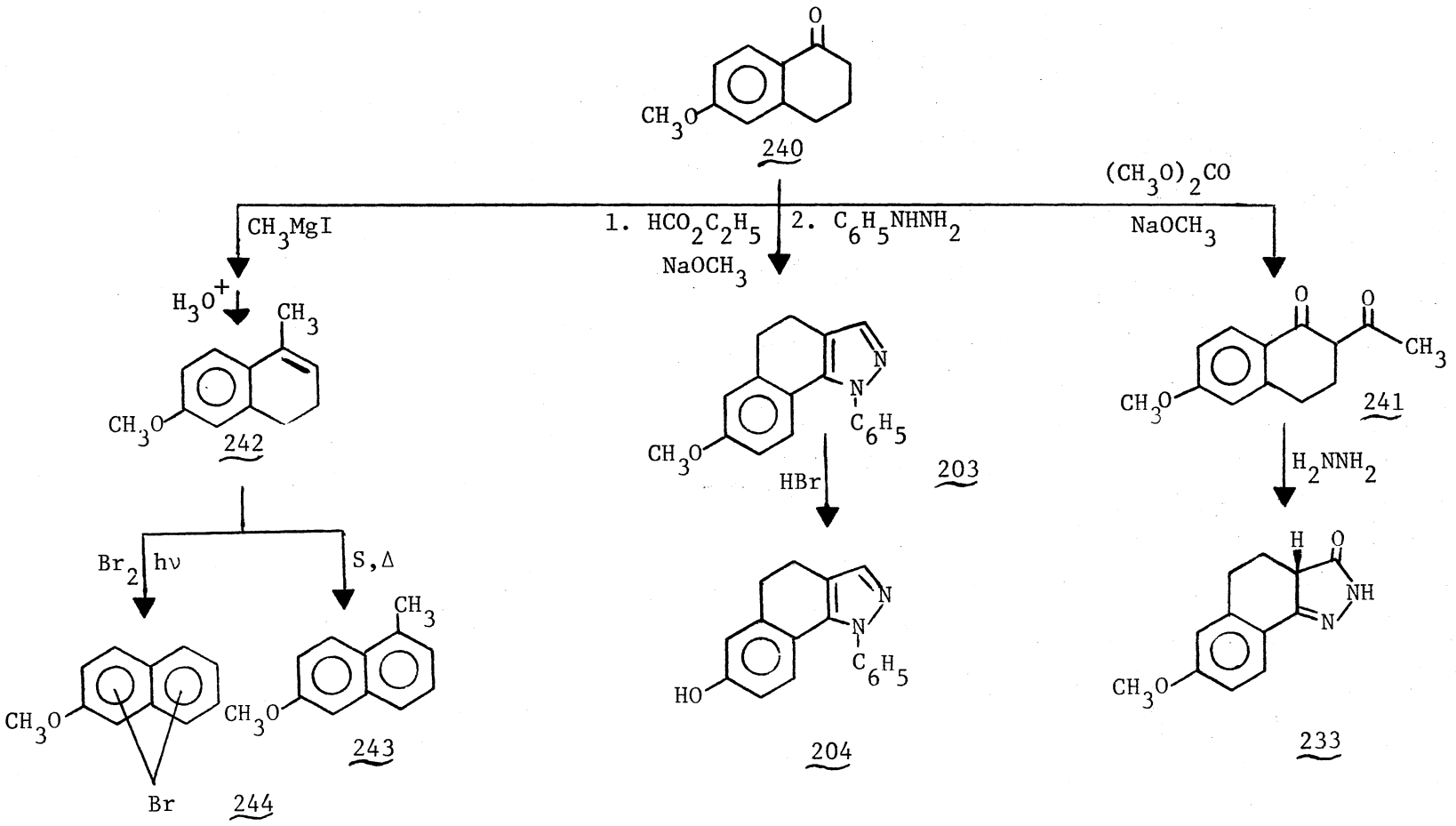


Figure 8. Synthesis of Some Pyrazoles and Pyrazolones From 6-Methoxy-1-tetralone

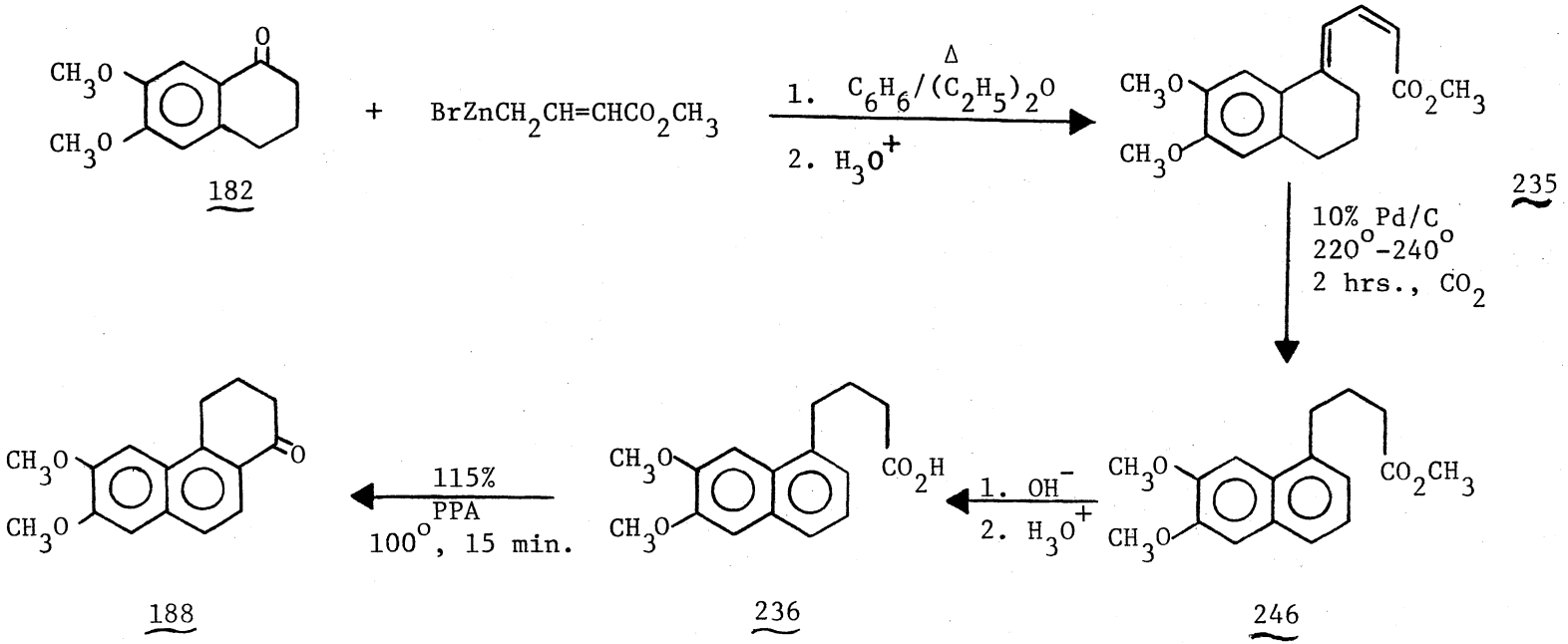


Figure 9. Synthesis of 3,4-Dihydro-6,7-dimethoxy-1(2H)-phenanthrone

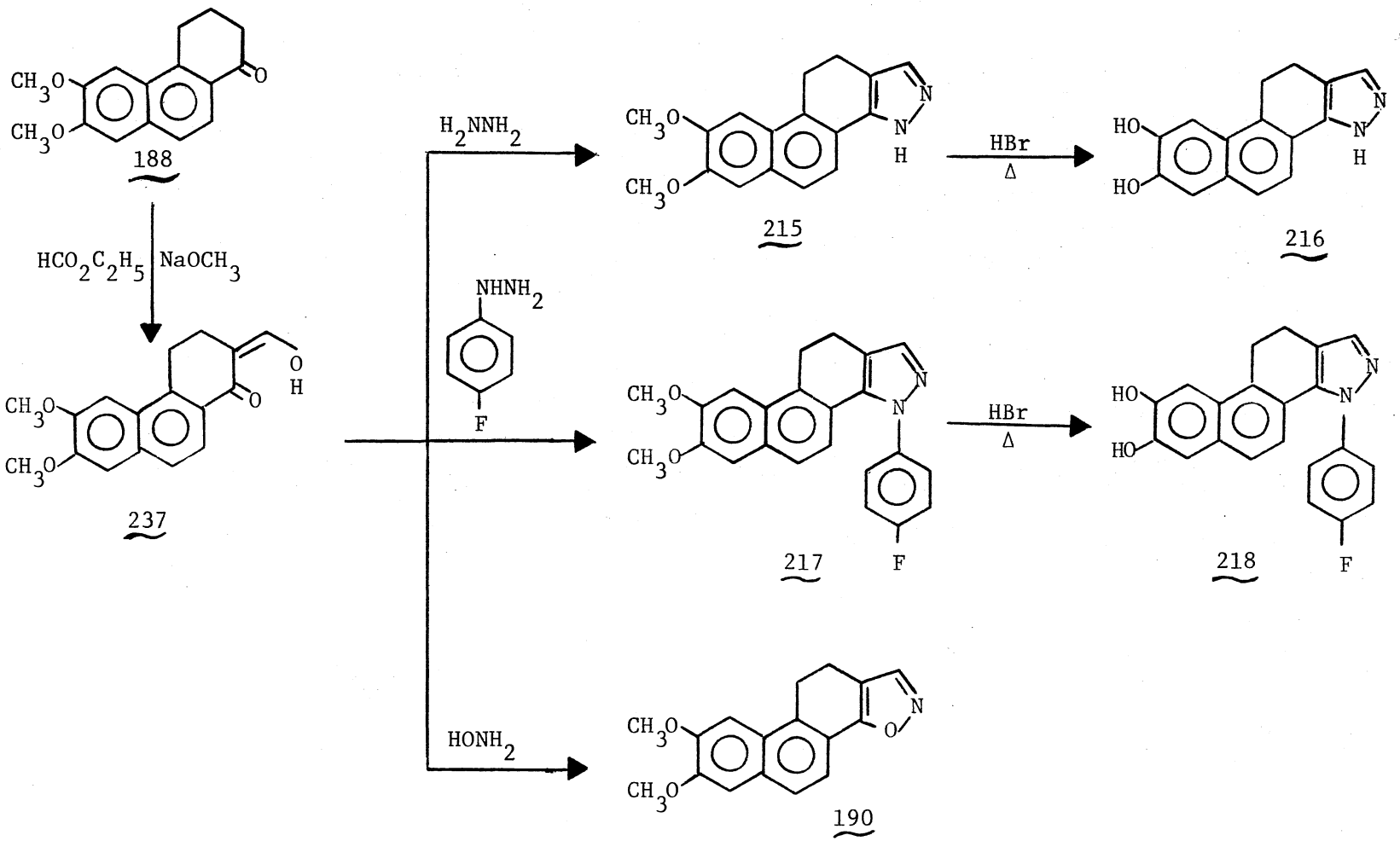


Figure 10. Synthesis of Heterocyclic Steroids

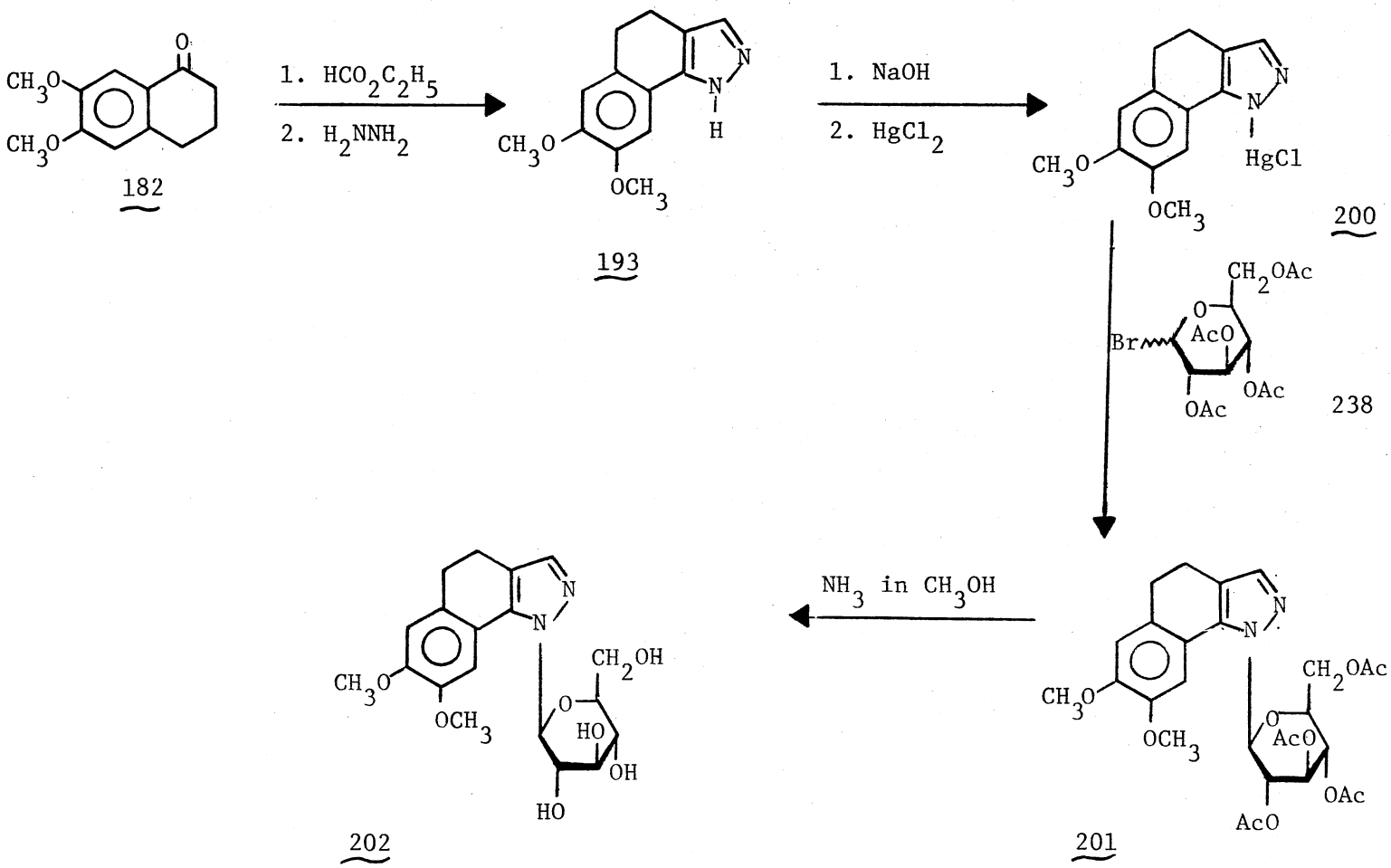


Figure 11. Synthesis of N-Glucosides From 6,7-Dimethoxy-1-tetralone

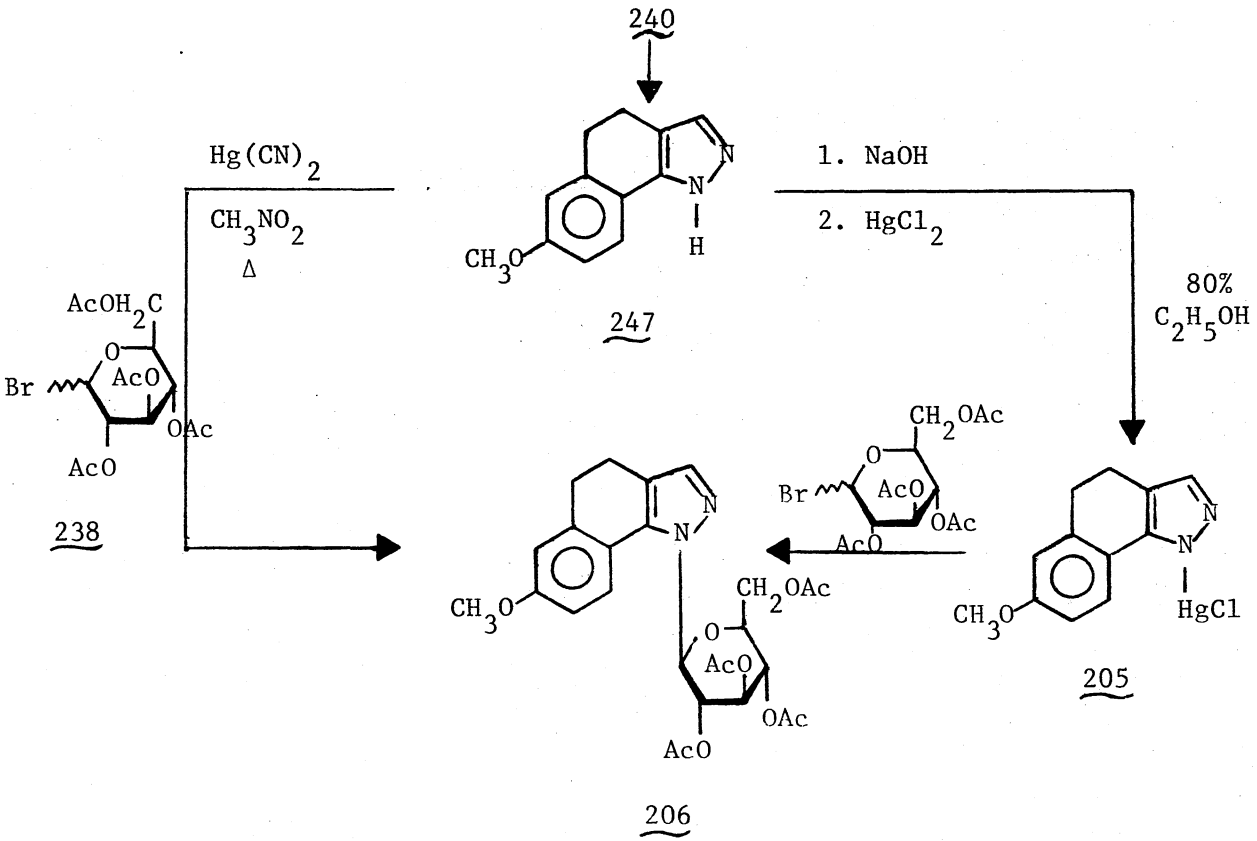


Figure 12. Synthesis of N-Glucosides From 6-Methoxy-1-tetralone

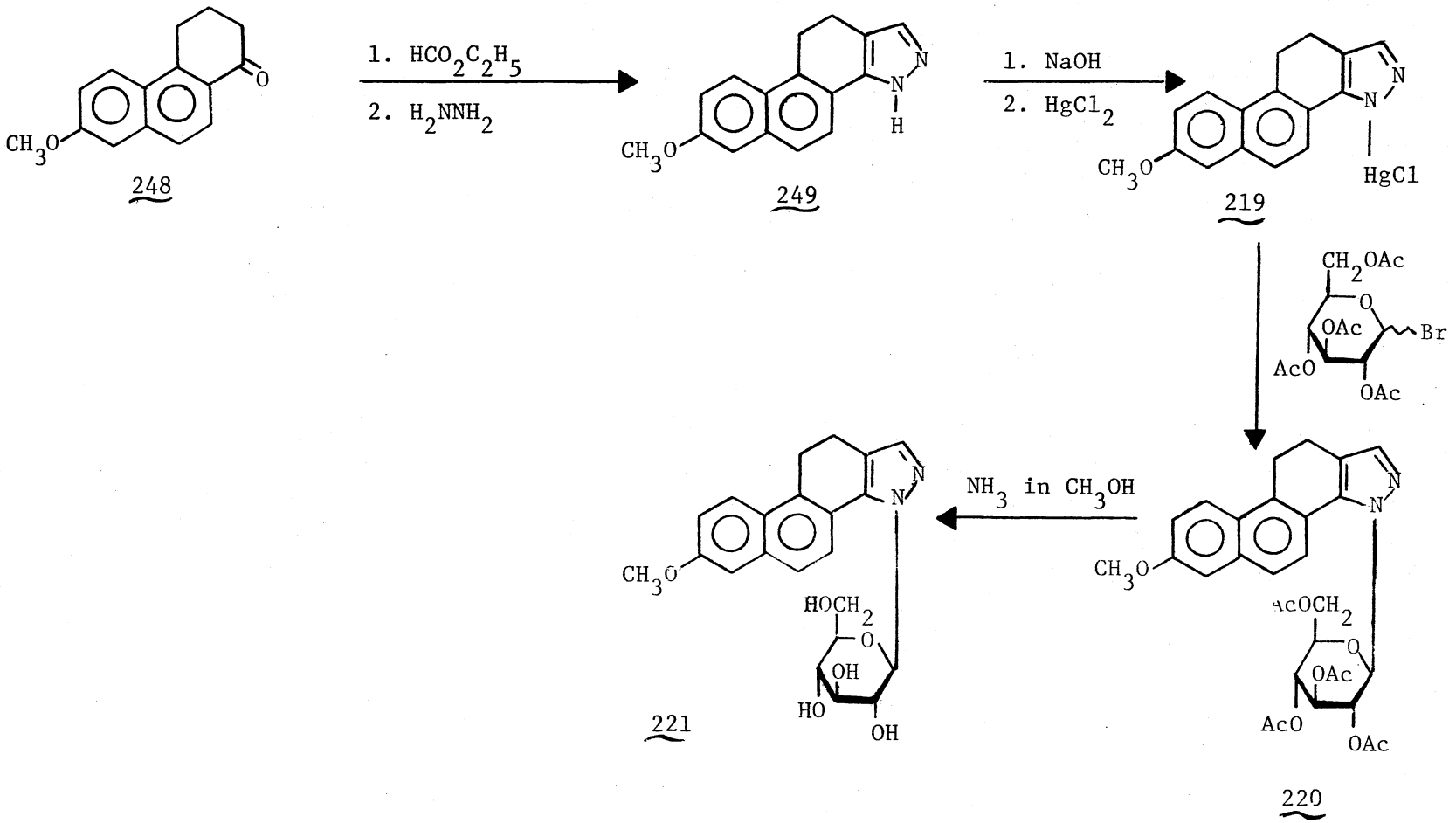
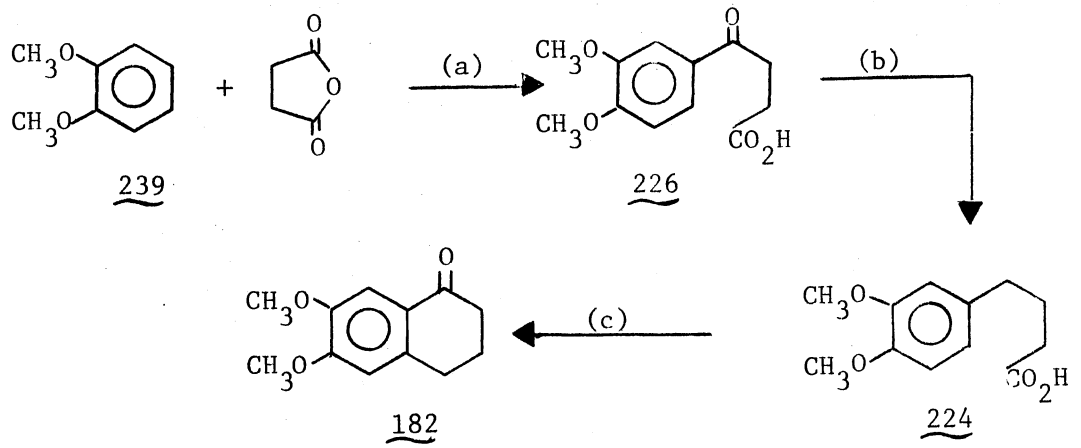


Figure 13. Synthesis of N-Glucosides From 7-Methoxy-3,4-dihydro-1(2H)phenanthrone

A key starting ketone 182 for all heterocyclic compounds synthesized in this study was obtained by several different approaches.[352] Maximization of yield of tetralone 182 via elimination of side reactions required considerable innovations and modifications of known reactions as well as the development of new techniques. The classical method of Haworth, i.e., Friedel-Crafts succinoylation of veratrole (239) and Clemmensen reduction (or Wolff-Kishner reduction) followed by acid-catalyzed cyclization of the resulting acid, gave usually an overall yield of 7-10%,[3,174,194] compared to yields in this study of 40-51% (overall):



(a) $AlCl_3$, $C_6H_5NO_2$ + $Cl_2CH\text{-}CHCl_2$, 24 hrs., room temperature.

(b) Zn(Hg)-HCl, 18-24 hrs., boiling; or $H_2N\text{-}NH_2$/KOH, $HOCH_2\text{-}CH_2OH$, 200-240°, H_3O^+.

(c) Conc. H_2SO_4, Δ; or P_2O_5, Δ.

The synthetic problems which have been commonly noted in the total synthesis of alkoxy-substitated tetralones and have contributed to poor yields can be summarized as follows:

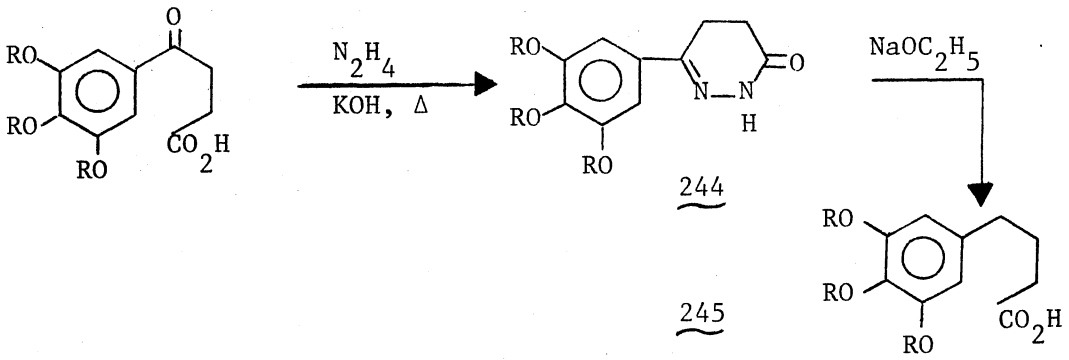
1. Partial methoxyl group cleavage in the initial acylation step caused by long reaction time (24 hours) in the presence of excess HCl gas.[186,173]

2. Partial cleavage of methoxyl groups during steam distillation of the acidic succinoylation mixture.[186]

3. Partial cleavage of methoxyl groups in the Clemmensen reduction of keto acid 226 caused by long exposure (18-24 hours) in presence of concentrated HCl.[103,172,190,264,267,276,341,352]

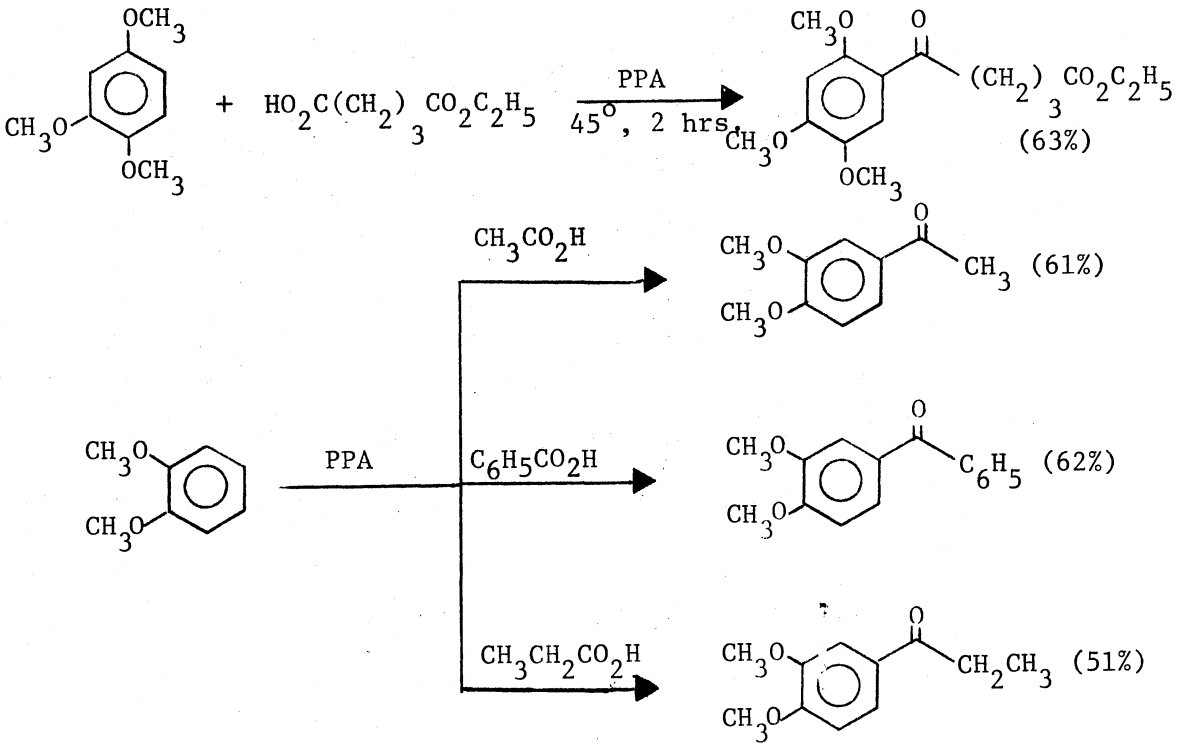
4. Partial cleavage of methoxyl groups and apparent polymerization during the cyclization by hot concentrated H_2SO_4.[3]

5. Undesirable cyclization in the Wolff-Kishner reduction method;[81,369] a pyridazinone derivative 250 was obtained as the exclusive product in a case related to our work.[175] This pyridazinone derivative 250 could be, however, converted to reduced acid 251 by treating the heterocyclic derivative with $NaOC_2H_5$.[175]

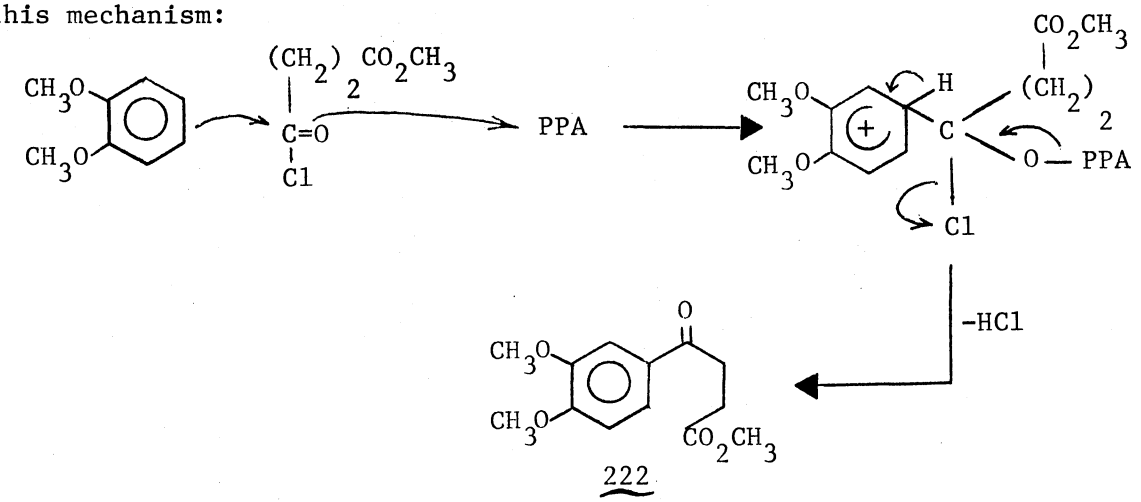


Because of these synthetic difficulties, the preparative methods to 6,7-dimethoxy-1-tetralone (182) were reinvestigated (Figure 2). Route (b) in Figure (2) gave the highest yield (51%) possible of ketone 182 in our hands. The condensation step was effected by heating a mixture of 3-carbomethoxypropanoic acid 252[84] [or its acid chloride[84] 253, which gave a slightly higher yield (15% more of 222) in this specific step], veratrole (239), and 115% PPA[366] at 40-50° for 2 hours. The condensing agent PPA has been reported to act as an acylating-type catalyst[32,250,296]

for many similar cases, among which are, for example:[13,293]



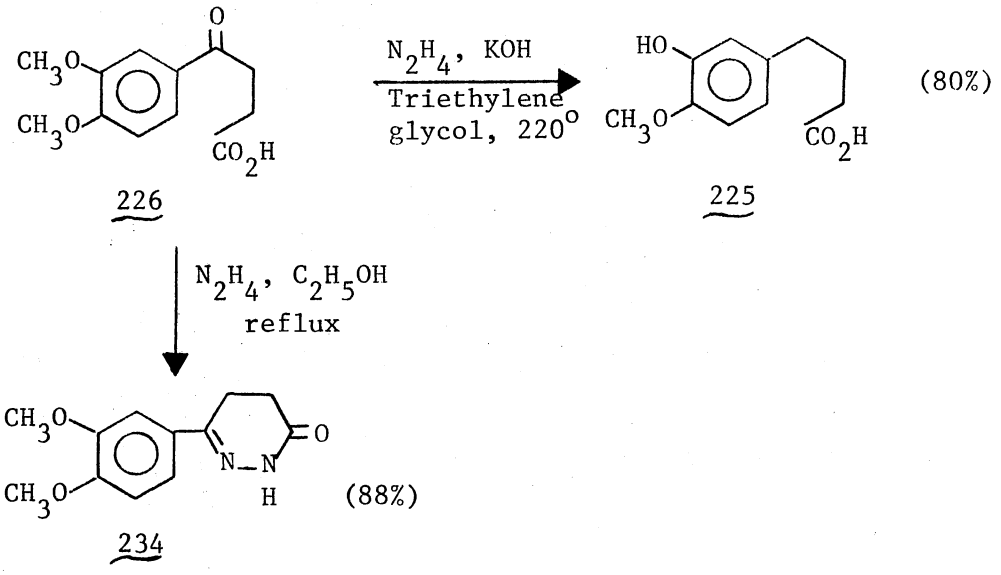
In none of those cases has any methoxy-group cleavage been reported; this renders PPA a superior acylating catalyst compared to the classical Lewis acids. In the case of veratrole, the acylation step may occur via this mechanism:



222

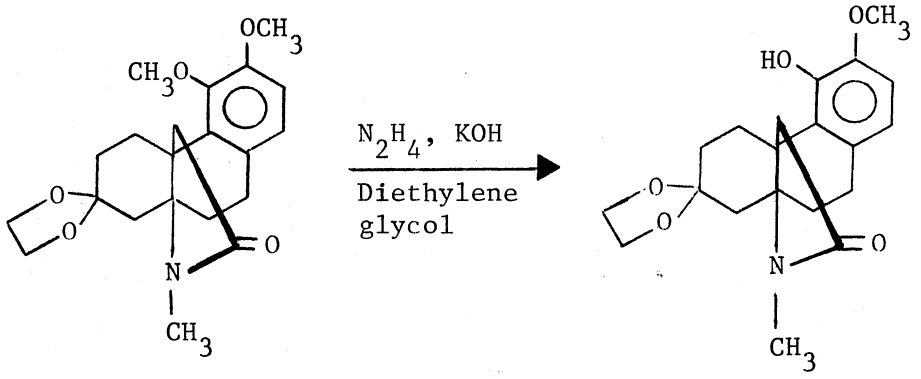
Since the Clemmensen reduction method gave only 40% yield of acid 224, the Wolff-Kishner process was tried. Triethylene glycol was used as the solvent with the intention to prevent the formation of pyridazinone

derivative 235. The carbonyl function of keto acid 229 was readily reduced but one of the methoxyl groups was cleaved under these drastic

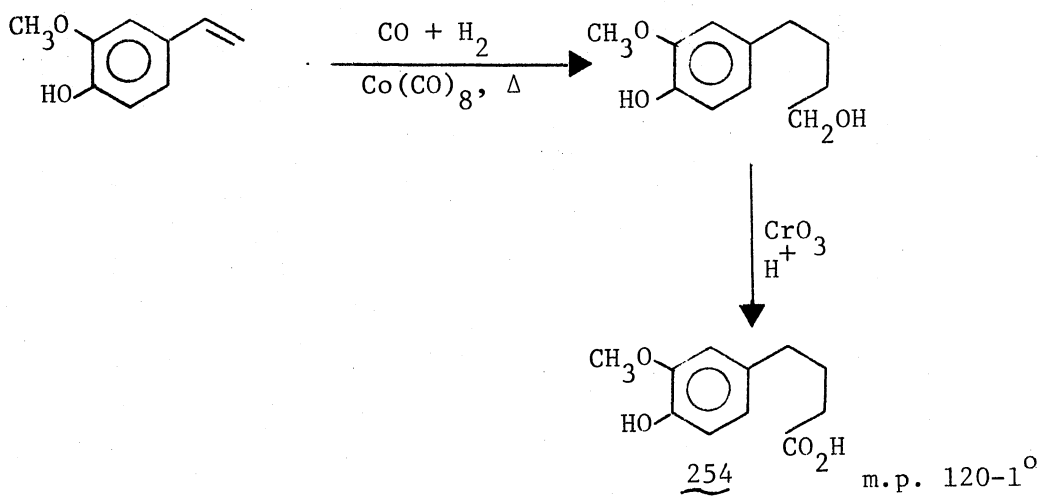


226 225 234

alkaline conditions to give hydroxy acid 225 (80%). Partial demethylation using H_2NNH_2/KOH has been occasionally used[153,204] as a standard technique for 1,2-dimethoxy compounds as shown by the example.

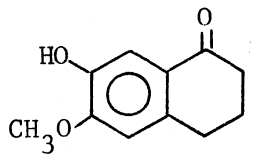


The position of the hydroxyl group in acid 225 was determined on the basis of comparison with published work[152] concerning the preparation of isomeric acid 254 as illustrated:

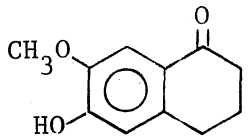


254 m.p. 120-1°

While reported[152] hydroxy acid 254 had a melting point of 120-1° our acid 225 had a melting point of 87-88°. Spectral and elemental analyses showed the presence of one OH and one OCH_3 group in our acid 225. Moreover, an attempt to cyclize the hydroxy acid 225 to the tetralone below with PPA was unsuccessful, while 254 gave a tetralone melting at 150-1°.



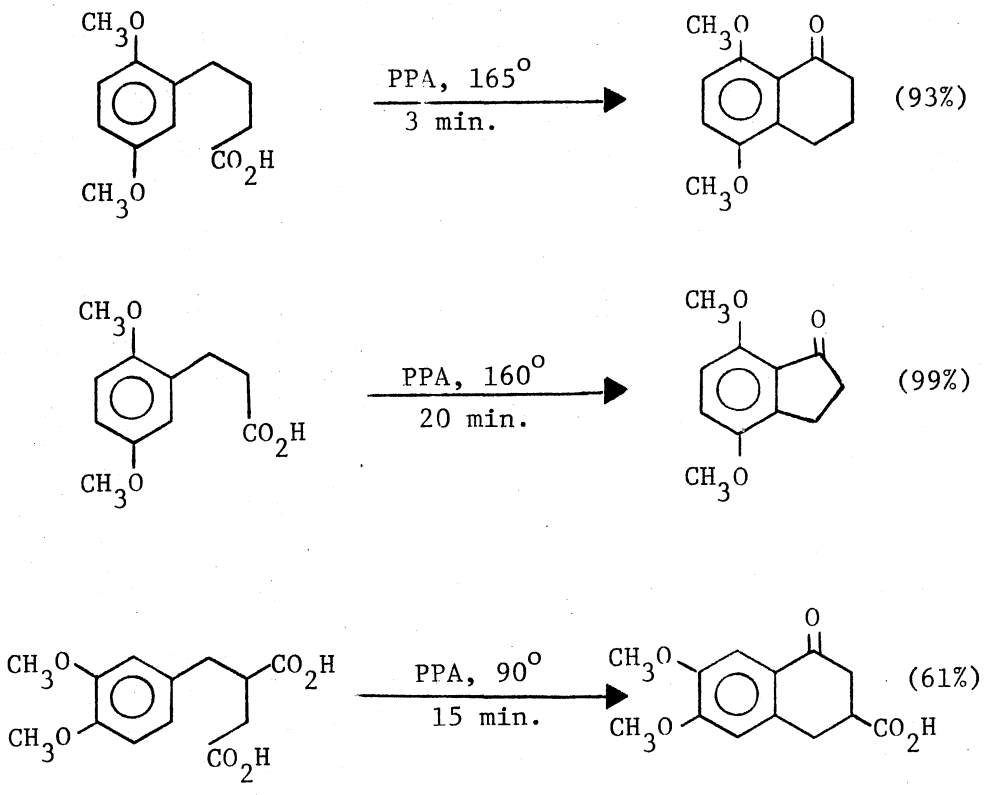
m.p. 150-1°



The reaction of keto acid 226 with 95% N_2H_4 in boiling ethanol (Figure 3) is a straightforward, high-yield reaction, giving pyridazinone 234. Structurally similar compounds have been recorded[113] recently; biological evaluation revealed high antihypertensive activity. When pyridazinone 234 was subjected to boiling 48% HBr (under N_2) for the purpose of obtaining a more water-soluble heterocyclic compound, a

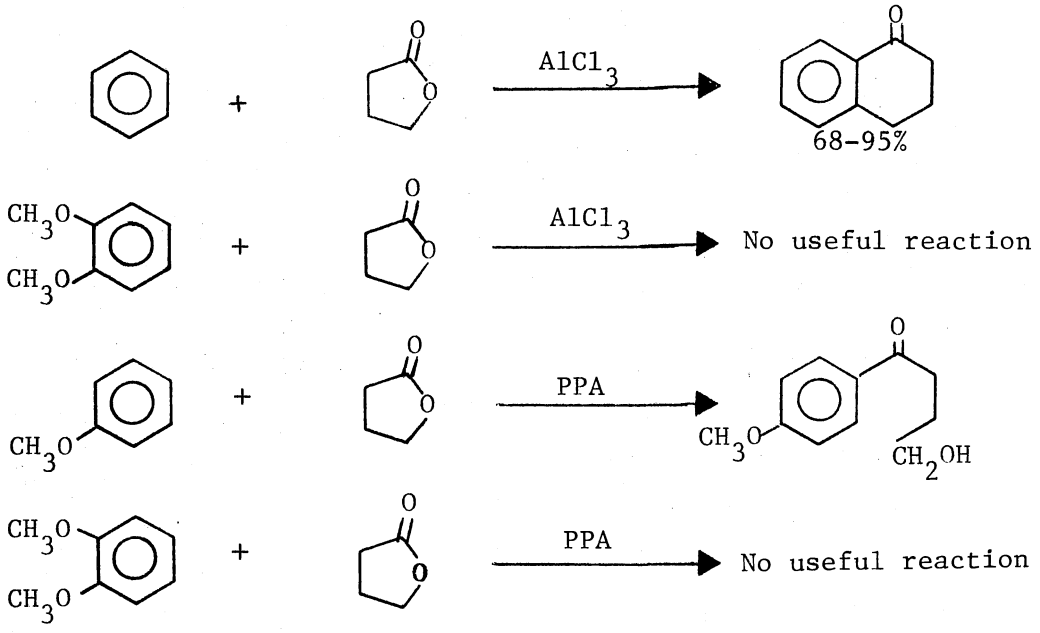
dihydroxy keto acid 227 was formed exclusively (Figure 3).

Due to the poor yields and side-reactions encountered in the Clemmensen and Wolff-Kishner reductions, a more efficient process was sought. Catalytic hydrogenation using 10% Pd-C[79,145,188] proved successful in reducing the carbonyl group in nearly quantitative yield. Polyphosphoric acid[366] was used again in the last step as a cyclizing agent (Figure 2). Many other related systems are known in literature.[134,189,239]



Our yields in this cyclization step were comparable, 82-88% from substituted butyric acid 224 to tetralone 182 (Figure 2). According to literature, PPA functions simultaneously as a protic acid, a Lewis acid,

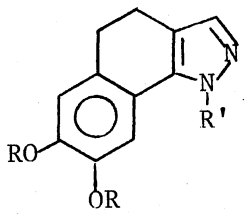
and a phosphorylating agent.[16] Although the reaction of benzene and 4-butyrolactone gave 1-tetralone (68-95%) using $AlCl_3$ as a catalyst,[304] surprisingly veratrole did not react. When $AlCl_3$ was replaced by 105% PPA, the reaction was also unsuccessful. However, anisole condensed readily with 4-butyrolactone in PPA to the corresponding keto alcohol.[191] Such random behavior in the series benzene, anisole, and veratrole toward Lewis acids defies immediate explanation.

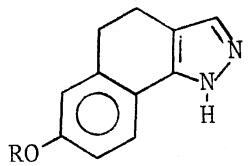


The efficiency of the commercial 115% PPA used in our study as a versatile agent is apparently due to its constituents. Polymeric acids and a certain weight percent (83.2%) of P_2O_5 had been added to H_3PO_4 to produce this PPA. Experiments (electrophilic substitution reactions run in this laboratory) using 105% PPA and the calculated amount of P_2O_5 added to produce 115% PPA did not provide an acid medium capable of initiating the above acylations.

Berlin, Durham, and co-workers[93,283] discovered that indazoles

247a and 247b demonstrate in vivo activity against a variety of microorganisms. Another major objective of our study was, in part, to obtain analogs of this model system for biological evaluation. Two vicinal methoxyl groups on positions 7 and 8 were included and were converted to hydroxyl groups. The latter should increase the water solubility of the pyrazole. N-Substituted(aryl) compounds could also provide other π systems potentially capable of forming π complexes with a conjugated group of an anticancer agent such as actinomycin D, mitomycin C, and methotrexate.





R = CH_3, R' = H (193, 72%)

R = H, R' = H (194, 50%)

R = CH_3, R' = C_6H_5 (195, 85%)

R = H, R' = C_6H_5 (196, 78%)

R = CH_3, R' = p-C_6H_4-OCH_3 (197, 52%)

R = H, R' = p-C_6H_4-OH (198, 74%)

R = CH_3, R' = p-SO_2-C_6H_4-CH_3 (199, 30%)

R = CH_3 (247a)

R = H (247b)

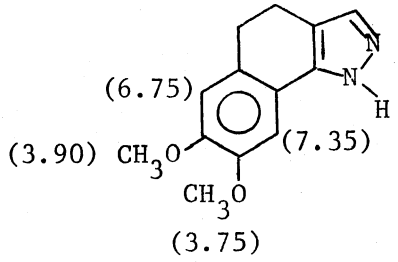
Figure 4 illustrates the synthesis of novel dimethoxy and dihydroxy pyrazoles 193 through 199 from the starting ketone 182.

The action of ethyl formate in the presence of methoxide ion on tetralone 182 produced a 1,3-dicarbonyl compound. The latter exists mainly in the enolic form 232 as evidenced by spectral data (see IR

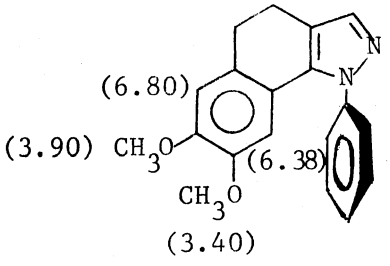
Plate IX and NMR Plate LVI) and the formation of a dark green color with $FeCl_3$. Hydroxymethylene ketone 232 cyclized readily with 95% H_2NNH_2 to give unsubstituted pyrazole 193 (80%). Yields varied from 30-85% for substituted hydrazines, depending on the stability of the hydrazine itself (see Table II). Aqueous 48% HBr cleaved the methoxyl groups on positions 7 and 8 and gave diols 194, 196 and 198 in yields of 50-70% (Table II, Figure 4).

Cleavage of the methoxyl groups to the hydroxyl functions may occur simultaneously or stepwise. A monomethyl ether intermediate has not been isolated in this study since an excess of HBr reagent and prolonged reaction times were both employed.

While alkylhydrazines usually give rise to a mixture of N-1 and N-2 substituted pyrazoles (see Chapter I, p. 17), arylhydrazines yield a specific product, the N-1 derivative.[102] As mentioned before, this may be due to the difference in the nucleophilicity of the two N atoms in the two hydrazines. It was evident (via NMR studies of the cyclization of hydroxymethylene ketone 232 to pyrazole 195) that the phenyl group is undoubtedly located on N-1 of pyrazole 195.



193



195

(Numbers in parentheses are δ values in p.p.m. from TMS).

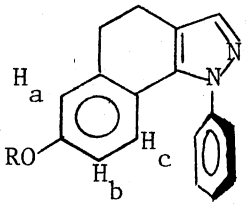
Upfield shifts of the protons on C(9) and OCH_3 on C(8) can only be reasonable if the phenyl ring is on N(1) in such a way that it shields both the neighboring proton on C(9) and OCH_3 group on C(8) (see Plate LXIII). The NMR spectra of 196 was measured in DMSO-d_6 (Plate LXIV, Table VIII) and in pyridine-d_5, and showed the following features.

(a) The two CH_2 groups coalesce in one large singlet peak.

(b) The aromatic region of the spectrum is complicated (after excluding those peaks belonging to residual protons in pyridine or the aromatic protons of the original molecule). Measuring the spectrum at sweep width 50 MHz did not separate the singlet peaks (integration = 4 H).

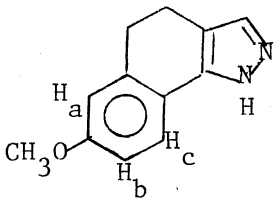
No clear conclusion could be drawn as to the reason for coalescence of the two methylene protons except that it may be a solvent-dependent phenomenon. Possibly the complexity of the downfield region is due to some sort of solute-solvent interaction via hydrogen bonding. DMSO and pyridine are both strong hydrogen-acceptor solvents.

The novel 4,5-dihydro-7-methoxy-1-phenyl-1H-benz[g]indazole (203) and 4,5-dihydro-1-phenyl-1H-benz[g]indazol—7-ol (204) were prepared for NMR analysis (Figure 8) as well as for biological screening. Two



R = CH_3, 203
= H, 204

δ_{H_a,H_b,H_c} = 6.40-6.55

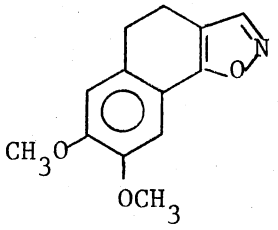


247

δ_{H_a,H_b,H_c} = 6.51-7.74

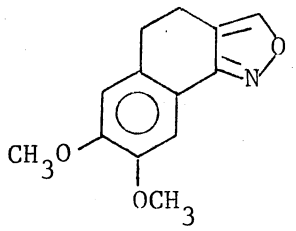
doublets for protons (H_b) and (H_c) of indazole 203 experienced some shielding effect due to the steric positioning of the benzene ring on N-1. This diamagnetic anistropic effect was not found for the same protons of the N(1) substituted indazole 247. The values are included here for comparison ($DCCl_3$). With no exception all N-1-aryl substituted pyrazole derivatives 193-199 showed this diamagnetic shielding effect. Thus, at least one aromatic proton lies above the plane of benzene ring.

Two previously unknown isomeric isoxazoles 185 and 186 were prepared from 6,7-dimethoxy-1-tetralone (182) in an attempt to determine if a structure-activity relationship existed in going from pyrazoles to isoxazoles. 4,5-Dihydro-7,8-dimethoxynaphth[2,1-d]isoxazole (185) was obtained from the hydroxymethylene ketone 232 by the action of hydroxyl-



185

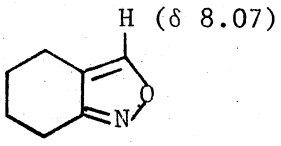
[2,1-d] isomer



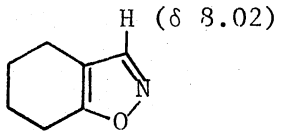
186

[1,2-c] isomer

amine hydrochloride in acetic acid (Figure 5). If the reaction was conducted in pyridine, however, the isomeric 4,5-dihydro-7,8-dimethoxynaphth[1,2-c]isoxazole (186) resulted. These findings agree with reports in the literature[37] for somewhat analogous systems. A difference of only 0.05 ppm had been reported between the chemical shifts of the heterocyclic protons of isomers 255 and 256.

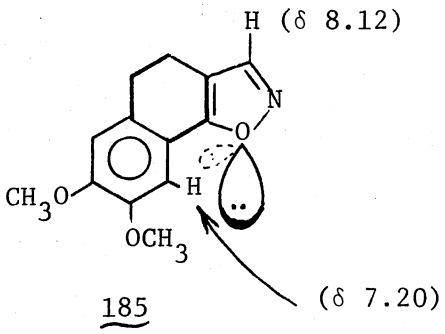


255



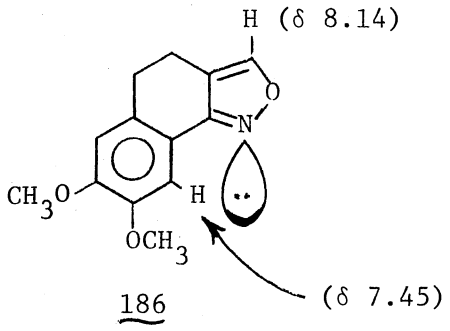
256

In the case of our isoxazoles, an even smaller difference (0.02 ppm) was observed. However, a dramatic shift was observed in the PMR spectrum of 185 and 186 regarding the proton located on C(9) (δ 7.45



185

[2,1-d] isomer



186

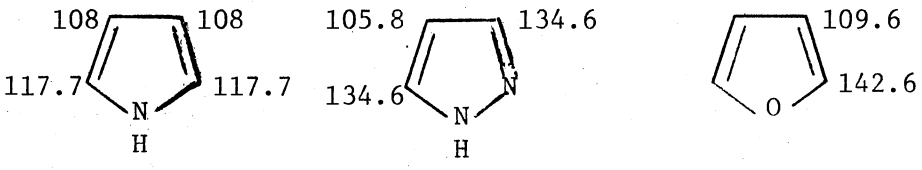
[1,2-c] isomer

ppm in the [1,2-c] isomer 186). Possibly a long-range shielding effect shifted the corresponding proton signal to δ 7.20 ppm in the [2,1-d]-isomer 185. This can be probably attributed to the close proximity of the two lone pairs of the O atom in the [2,1-d]-isomer 185. The lone electron pair on the N atom in the [1,2-d]-isomer 186 may invert rapidly but the proton on C(9) only "sees" an average shielding value which is less than the provided by the two fixed lone pairs on oxygen in the [2,1-d]-isomer.

The following suggested experiments could be instructive in making

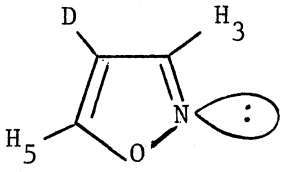
definitive the structure assignments for many isoxazoles including 185 and 186:

(1) Spectral work: (a) Determine the ^{13}CMR spectra of isomers 185 and 186. Analogous differences[132,257,321] in ^{13}C chemical shifts of simple azole compounds should be evident in ^{13}C values in ppm relative to TMS (compare related examples).

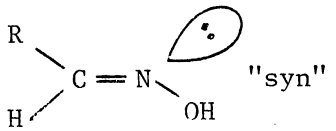


(b) Shift reagents could also be used to distinguish between the two structures such as in the case of certain pyrazole derivatives.[97]

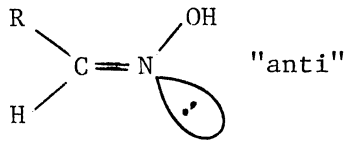
(c) Investigating the effect of the nitrogen lone pair orientation on vicinal ^{15}N-^{1}H spin-spin coupling[230] in isoxazole 257. Analogous to the two forms of oximes, isoxazole 257 was considered as an oxime locked



257



259

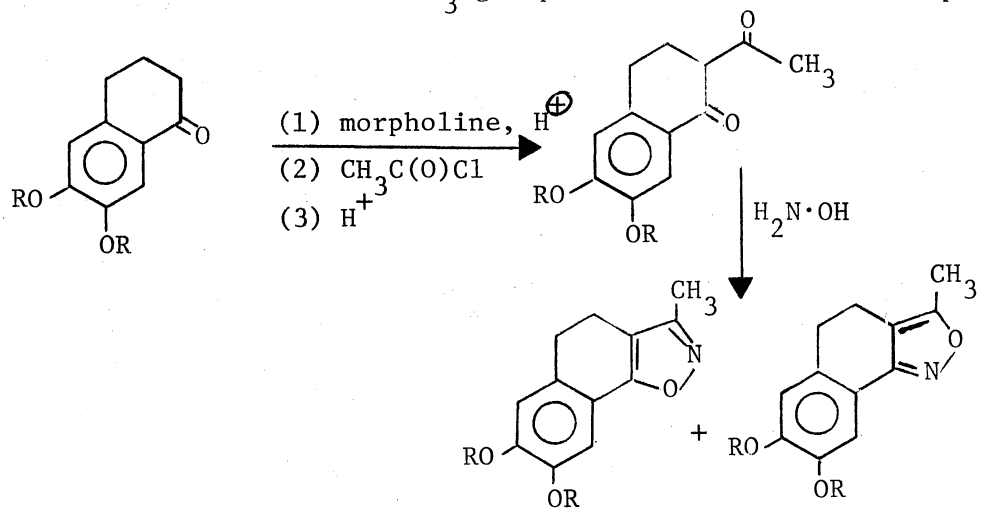


258

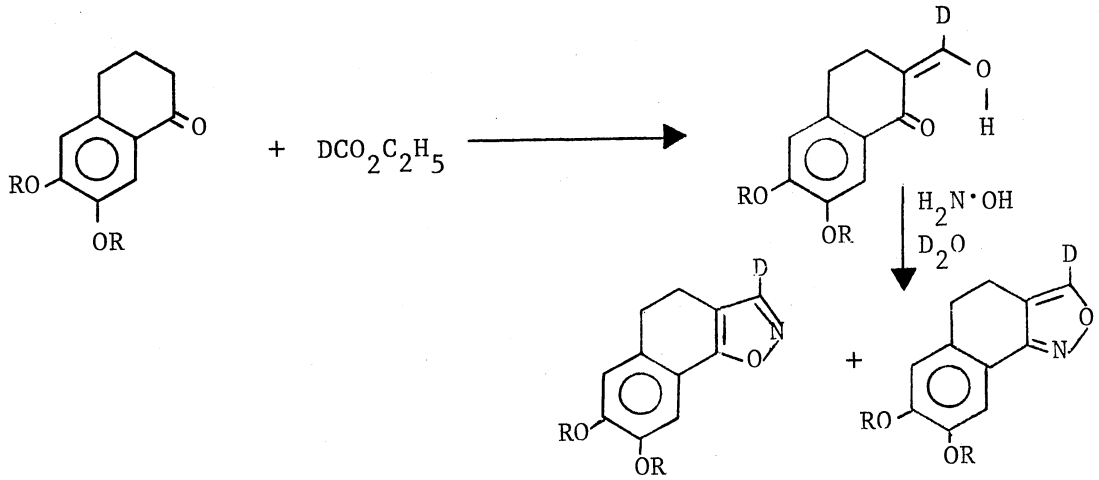
in the anti-configuration.[230] The measured $^{15}N{=}CH$ coupling for the oximes were 16 Hz (anti form 258) and 3 Hz for the syn form 259. Comparing these values with the coupling observed in compound 257 showed a splitting of 16 Hz and was also observed for $\underline{N}{=}C{-}H_3$ in 257.[230]

Consequently, with ^{15}N and FT, ^{13}CMR experiments could be devised to determine unambiguously the structure of our isoxazoles 185 and 186.

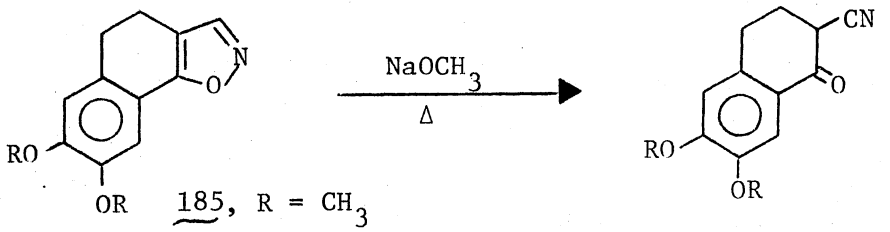
(2) Chemical and Spectral Work: To confirm assignments for H(6) and H(9), one could replace H(3) with a CH_3 group[208] and compare the chemical shift difference of CH_3 groups of the two isoxazoles produced.



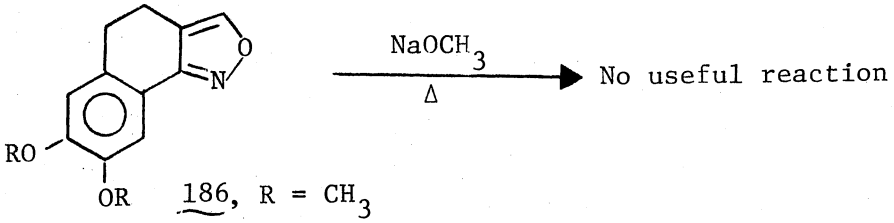
One could replace H(3) with D(3) [DCO_2H is available] and determine the position (δ value) of H(3) in both isomeric isoxazoles.



It is also possible to effect a cleavage of



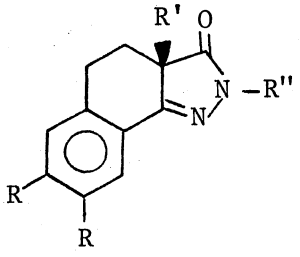
185, R = CH_3

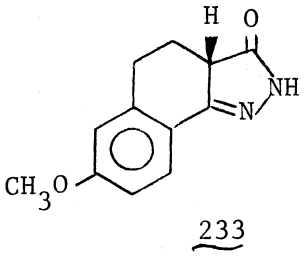


186, R = CH_3

the heterocyclic ring. Simple systems related to 185 are reported to suffer ring opening.[144,166,215,247,265,269]

It was not surprising to note that [2,1-d]isoxazole 185 was biologically active against Bacillus subtilis while the [1,2-c]-isomer 186 was inactive. Similar findings for some other isoxazole systems have been reported.[265] The screening experiments will be discussed in details at the end of this chapter.





233

R = OCH_3, R' = H, R" = H (207)

R = OCH_3, R' = H, R" = C_6H_5 (208)

R = OCH_3, R' = H, R" = p-C_6H_4F (209)

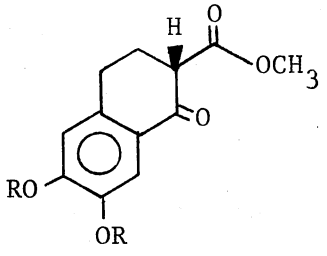
R = OCH_3, R' = CH_3, R" = H (210)

Incorporation of a carbonyl function into the heterocyclic ring of model steroidal systems have been accomplished through the preparation

of pyrazolones 207-210. This type of compounds were intentionally synthesized to provide an additional site for complexation with anti-tumor agents. The oxygen atom of the carbonyl groups could donate extra electron pairs and serve as an electron-donor.

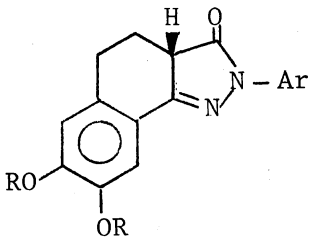
A series of pyrazolones 207-210 (Figure 6, Table IV) were prepared from the keto ester 230 precursor. This novel keto ester 230, namely, methyl 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230), was synthesized (92-96%) by the reaction of dimethyl carbonate with tetralone 182 in the presence of $NaOCH_3$. Cyclization with hydrazines to pyrazolones (Figure 6) was easily accomplished in high yields (65-92%) (see Table IV).

When arylhydrazines were used, the cyclized product formed was characterized by its IR spectrum (Plate LXXIV, and Plate LXXV). A $FeCl_3$ test was negative, i.e., no color change occurred. This suggested that the five-membered heterocyclic ring exists mainly in the keto form. A triplet in the NMR spectrum was expected at δ 3.5-3.8 ppm for the angular proton at 3a position (similar to the precursor keto ester, Plate LX) if the pyrazolone existed in the keto form.



230, R = CH_3

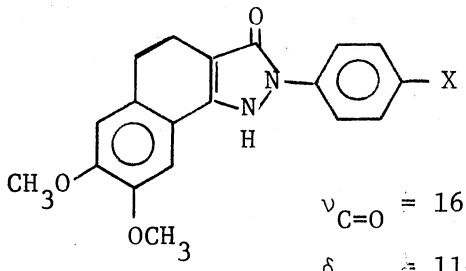
$\delta_{H(3a)}$ = 3.6 ppm



208, Ar = C_6H_5
209, Ar = p-C_6H_4F

$\delta_{H(3a)}$ = absent

This expected bridgehead proton absorption was absent in the NMR spectrum and instead a broad singlet at δ 11.10-11.15 was detected (one proton integration). This suggests that the proton resides on N-1 at low field. Accordingly, we propose the following structure for 1-N-arylpyrazolones:



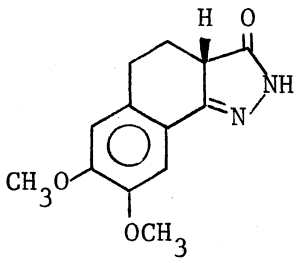
X = H,F

$\nu_{C=O}$ = 1685-1690 cm^{-1}

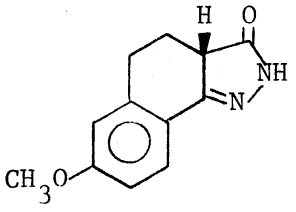
δ_{N-H} = 11-12 ppm (bs).

It seems probable that ^{13}C NMR studies of these compound would be diagnostically useful regarding hybridization of the ring carbon atoms.[132, 257]

Cyclization with unsubstituted hydrazine starting from the keto ester 230 and 241 led to the formation of pyrazolones 207 and 233 (Figure 6 and Figure 8). The absence of C=O absorption in the IR spec-

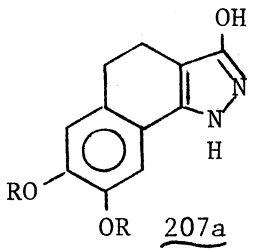


207

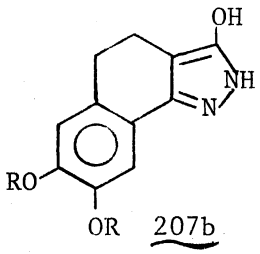


233

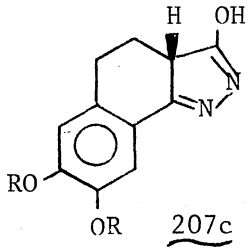
tra of those compounds and the presence of strong OH bands at 3100-3200 cm^{-1} suggested an enolic form such as 207a or 207b or 207c or 207e



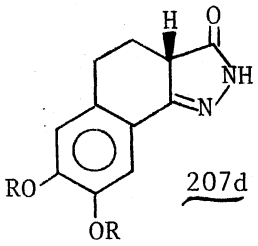
207a



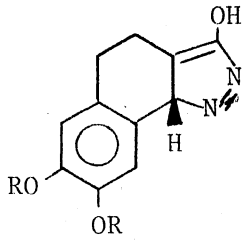
207b



207c



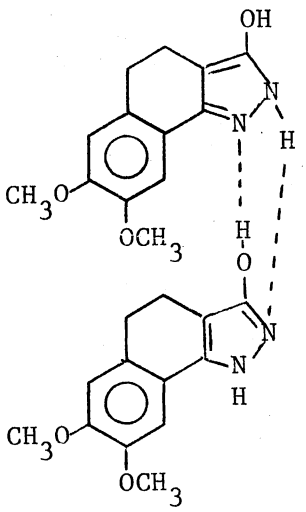
207d

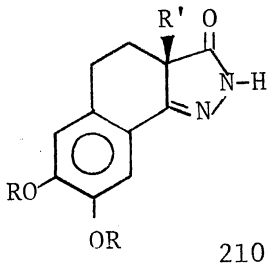


207e

(See Plate XXV and Plate XXVI). Forms 207c and 207d were ruled out on the basis of the NMR spectra. A triplet signal (one proton) was not present as in the precursor keto ester (Plate LX). Form 207e was also eliminated on the basis of NMR analysis since a singlet would be expected for the angular proton somewhere between δ 4-6; this was not observed. Forms 207a or 207b appear the most reasonable candidates for the actual structure and a $FeCl_3$ test was also positive (brownish-violet).

We suggest that form 207a predominates on the grounds that usually a double bond at the junction of bicyclic compounds are more stable than related systems with exocyclic double bonds. The literature[115,144] is, however, not consistent in this matter.[116,118,144,214,340] It is also probable that both forms, 207a and 207b, are tautomeric and thus rapidly interconvertible. This could at least account for the broad OH band (or OH and NH bands) in the IR spectrum.

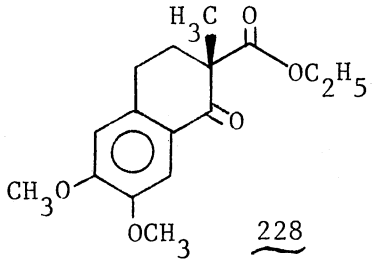




210

R = R' = CH_3

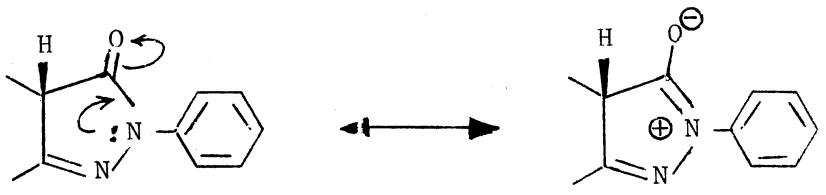
When the bridgehead position 3a was occupied by a CH_3 group, pyrazolone 210 resulted. To prepare this compound, 2,3a,4,5-tetrahydro-7,8-dimethoxy-3a-methyl-3H-benz[g]indazol-3-one (210), the first step consisted of treating tetralone 182 with excess diethyl carbonate in the presence of $NaOCH_3$ and then boiling with methyl iodide. The intermediate solid ethyl 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-oxonaphthoate (228) formed (50%) (Figure 6).



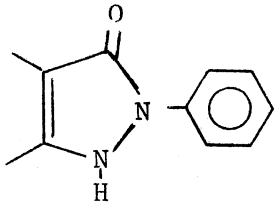
228

Cyclization with 95% hydrazine was easily accomplished to give pyrazolone 210 (82%) (Figure 6, Table IV). The IR spectrum exhibited a C=O absorption band at 1700 cm^{-1} (Plate XII) and without a broad OH band as found in structures 210 as discussed previously. The NMR spectrum (Table VIII) did agree with that structure expected for pyrazolone 210. This suggests that the 3a-methyl-substituted pyrazolone exists mainly (or exclusively) in the keto form since the possibility of enolization via the NH group is prevented.

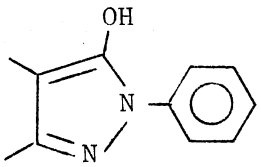
It is possible that the presence of an aryl substituent at N(2) imposes minimum steric interactions in the hybrid which may have a near planar arrangement of the O-C-N-N sequence. In view of the absence of a



signal for the bridgehead proton, the keto group for H(3a) in the PMR of 208 in DMSO-d_6, one must consider that two tautomers could exist such as (A) and (B). Unfortunately the compounds with the Ar-N group were only

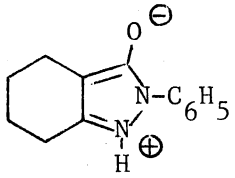


(A)

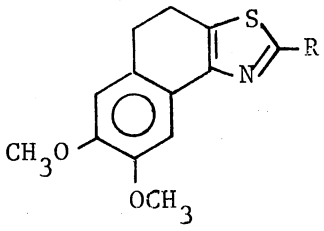


(B)

soluble in "basic" DMSO-d_6. Our work is reminiscent of the observations of others in the study of 119, the structure of which was based on an IR spectrum in a nujol mull. The IR spectrum of our Ar-N compounds (KBr pellet) showed a strong $\nu_{C=O}$ near 1680-1700 cm^{-1} like that of hydrazides. However, in DMSO-d_6 the H(3a) undoubtedly migrates to nitrogen or oxygen such as in



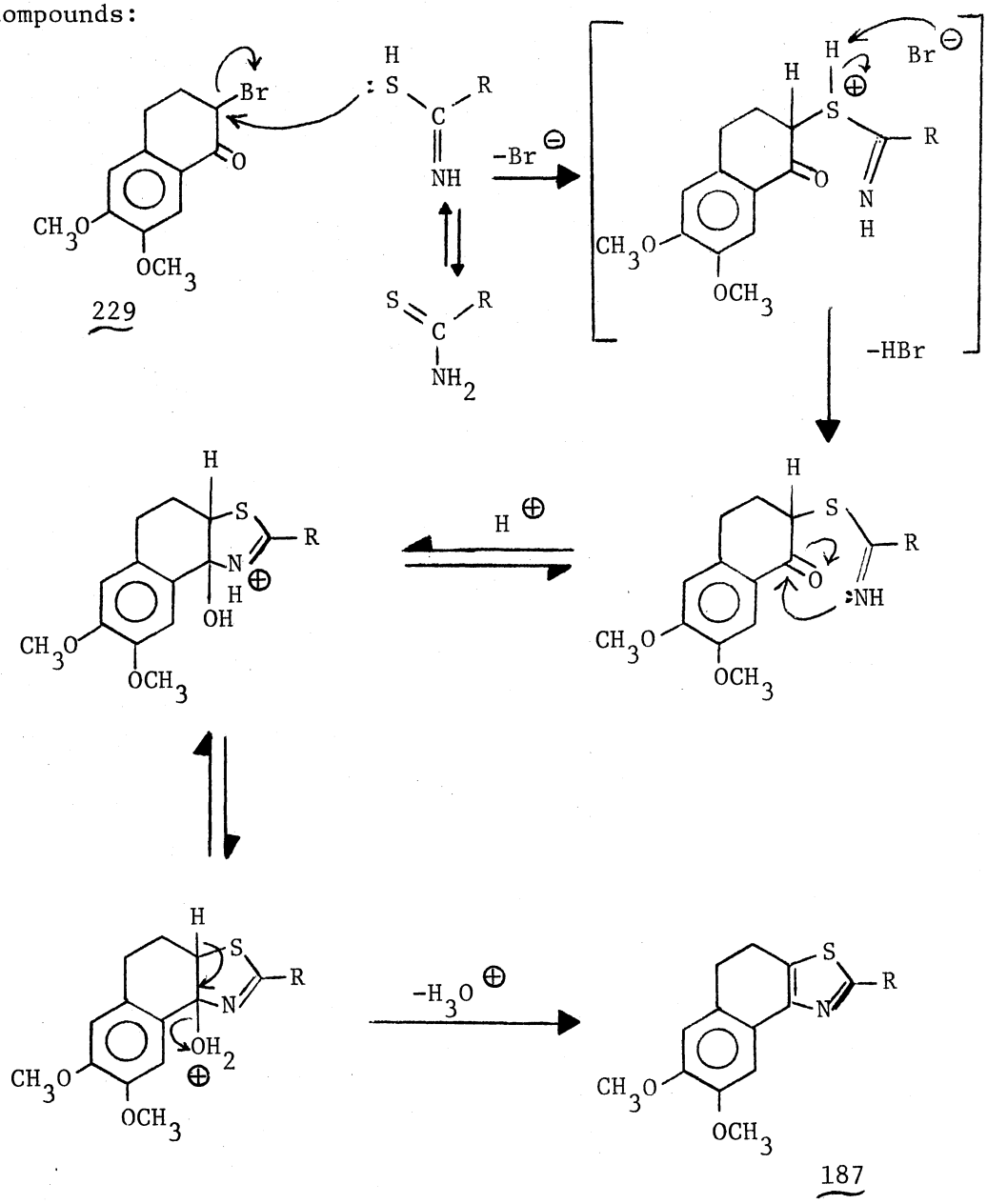
Ultraviolet spectral studies of these series of compounds might provide support for our conclusions.[131]



R = NH_2 (211)
R = NHC_6H_5 (212)
R = $NHCH_2CH{-}CH_2$ (213)
R = CH_3 (214)

The physiological importance of the thiazole ring in many compounds has been cited (see Historical). Starting from 6,7-dimethoxy-1-tetralone (182), bromo derivative 229 was prepared (60-70%) as a white solid

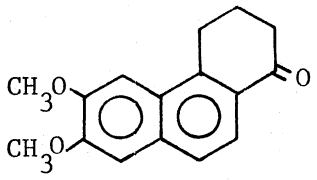
by the action of Br_2 in $HCCl_3$-C_2H_5OH medium at 0°C (Figure 7). Condensation of 2-bromo ketone 229 with thioureas gave the thiazole compounds 211 through 214. We propose this mechanism[130] for the formation of these compounds:



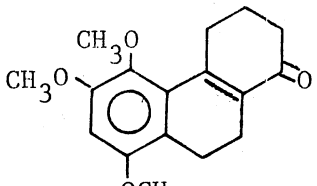
The NMR spectra of these compounds were as expected (Table VIII) except for one; that is, when R = CH_3 (Plate LXXX), the CH_2-CH_2 groups coalesced to one sharp singlet (on the 100 MHz instrument) which did

not separate at S.W. 50 MHz ($DCCl_3$). The difference of the NMR splitting patterns of the first three thiazoles 211, 212, and 213 from that of the fourth thiazole 214 (R = CH_3) is also probably due to some change in the electronic environment.

The key starting phenanthrone 188 for preparing certain heterosteroids was synthesized for the first time from tetralone 182 (30% overall yield). Other substituted phenanthrones are known and yields have been low (8-10%).[361]



188



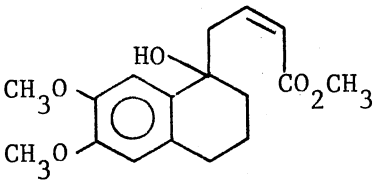
260

A literature search to December 1974 revealed 3,4-dihydro-6,7-dimethoxy-1(2H)-phenanthrone (188) had been reported[203] in 1969 (Japanese journal) as a by-product (1%) in the total synthesis of 260. NMR and the melting point of 188 were recorded.

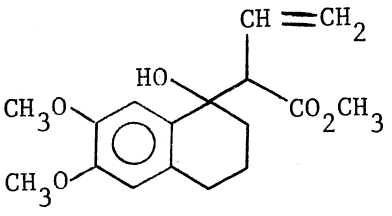
Our synthetic approach to phenanthrone 188 was based on lengthening the tetralone 182 system by four carbon atoms in one process. This was accomplished via a Reformatskii-type reaction.[351,361] Condensation of 6,7-dimethoxy-1-tetralone (182) with the Reformatskii reagent of commercial methyl 4-bromocrotonate (245) (in 3:1 C_6H_6:ether at reflux for 10-12 hours) gave the dienic ester methyl 3,4-dihydro-6,7-dimethoxy-$\Delta^{1(2H),\gamma}$ naphthalenecrotonate (235) (52%) (Figure 9).

Data on the use of various solvents to optimize a Reformatskii reaction have been published.[104] We exercised special care in the purification of all starting materials and reagents involved in the Reform-

atskii reaction. The commercial 85% methyl 4-bromocrotonate was fractionally distilled on 2.5-foot Vigreaux column and the tetralone was recrystallized and sublimed. The small-cut zinc pieces were carefully washed, amalgamated and dried. Also, the reaction was carried out under N_2 atmosphere. Despite these precautions, unchanged ketone 182 was recovered (20%) together with a high-boiling (b.p. 190-5°/1.5 mm) reddish liquid (3-4%). Repeated runs gave the same data. The high-boiling by-product has been partially characterized via IR analysis (see Experimental). The structure has been tentatively assigned as either 261a or 261b:



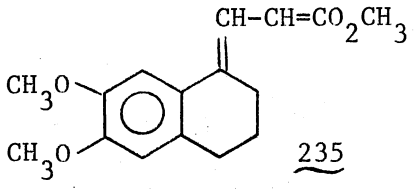
261a



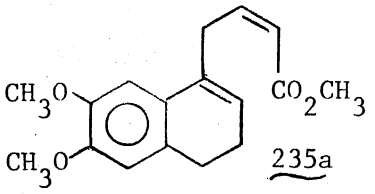
261b

Ester 261a is a conceivable intermediate resistant to dehydration which could lead to dienic ester 235. Analogs of ester 261b are not unknown in literature.[104]

The double bond in the ester 235 has been shown to be exocyclic by UV analysis and other methods[361]. Analogously, we assumed that ester 235 and not ester 235a was our product as was supported by NMR analysis. Moreover, it was concluded that ester 235 exists in the trans-trans

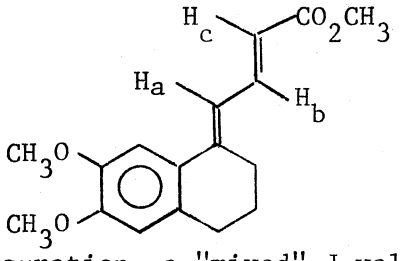


235



235a

configuration because the spin-spin coupling constant J for protons H_a, H_b, H_c had the same value (J=7 Hz). If one pair of the alkenyl protons



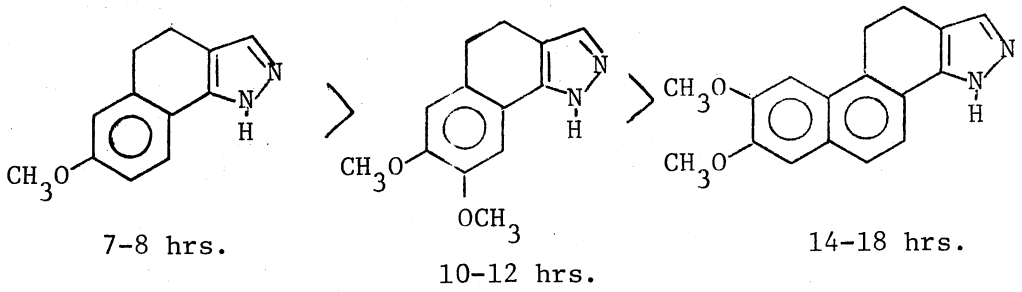
235

existed in the cis configuration, a "mixed" J value would have been expected[327]. Moreover, compound 235 was obtained as yellow-orange crystals after purification (m.p. 140-2°); the observation supports the all-trans configuration, as one might expect an all cis-isomer to exist as a liquid.

Isomerization of the dienic ester 235 to the fully aromatic ester 246 was performed (Figure 9) by using 10% Pd-C at 220-240° (under CO_2). This method has been frequently used[108,361] as a valuable procedure for dehydrogenating saturated rings with unsaturated side chains. The resulting ester was saponified directly to the naphthalenebutyric acid derivative 236. Cyclization of the latter with 115% PPA at 100° for 15-20 minutes afforded the desired phenanthrone 188 (Figure 9).

Synthesis of the heterocyclic steroid systems in our study were all initiated from the hydroxymethelene ketone 237, namely, 3,4-dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1(2H)-phenanthrone. The latter compound was prepared from the precursor ketone 188 by reaction with ethyl formate in the presence of sodium methoxide. The reaction resembles the preparation of hydroxymethylene ketone 232 (Figure 10). 10,11-Dihydro-

7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (215) was obtained (95-98%) by cyclization with 95% hydrazine. To obtain the diol 216, the dimethoxy pyrazole 221 was boiled with 48% HBr (under N_2) for 14-16 hours. Longer reaction times for the model systems was found necessary since NMR analysis of the reaction mixture after 8-12 hours showed some residual OCH_3 absorption. The order of complete ether cleavage observed was found to be:

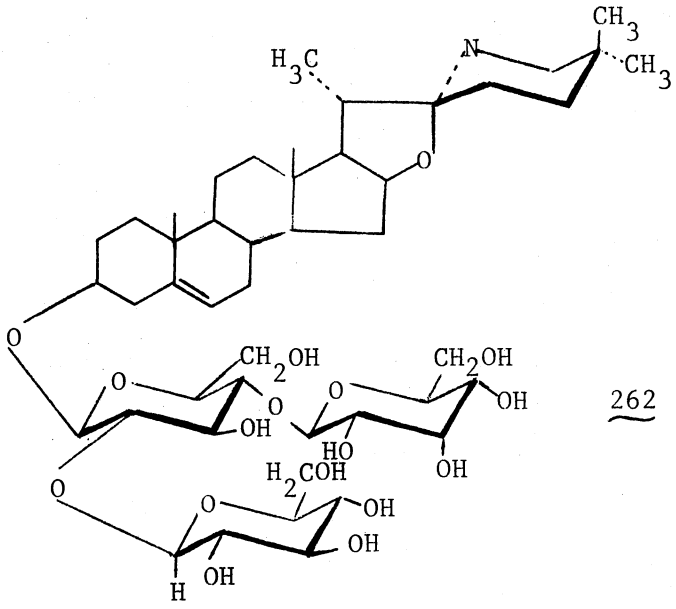


The fact that certain fluorinated chemotherapeutic agents, especially steroids,[396] have greater physiological activity than the parent non-fluorated systems prompted us to incorporate fluorine into our compound. The stability of the C-F bond, the small volume of the fluorine atom, and its highly electronegative character have resulted in unusual activity in correspondingly substituted compounds of pharmacodynamic and chemotherapeutic value.[80,91]

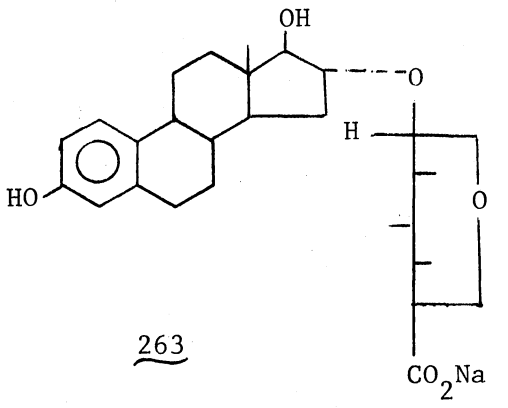
The synthesis of the p-fluorophenylpyrazole (217) was performed usually by reacting p-fluorophenylhydrazine hydrochloride with the ketone 237 in glacial acetic acid. Spectral analysis and the sharp melting point of the purified compound indicated the presence of only one compound, the N-1 substituted isomer. The reason for preferential formation of N-1 aryl compounds was discussed previously (see Page 124). Complete cleavage of methoxy groups in 217 to give the diol 218 (51%) took place in about 18 hours.

Starting from hydroxymethylene ketone 237 cyclization occurred in acetic acid with hydroxylamine hydrochloride, to give the novel isoxazolo-steroid 190 (35%) (Figure 11).

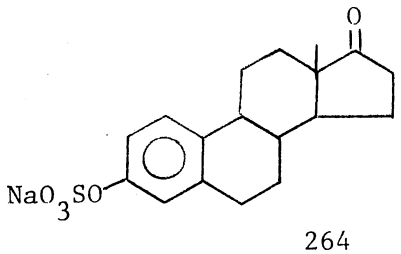
Steroidal N-glycosides are absolutely unknown in the literature. Some steroidal O-glycosides have been prepared and isolated from natural sources.[249] Indeed some have shown tumor-inhibitory activity, e.g., β-solamarin (262) isolated from Solanum dulcamara.[249] Sodium estriol glucuronide (263) and sodium estrone sulfate (264) are the only two con-



262



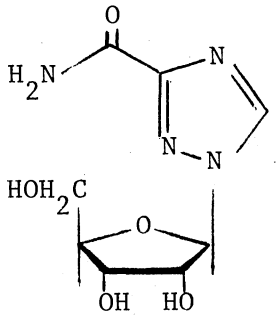
263



264

jugates isolated from natural sources. The term conjugation is applied to the process whereby an estrogen becomes chemically bound to an acid by a biological process. This action, in the case of estrone, renders the estrogen water-soluble and facilitates its transport.[257]

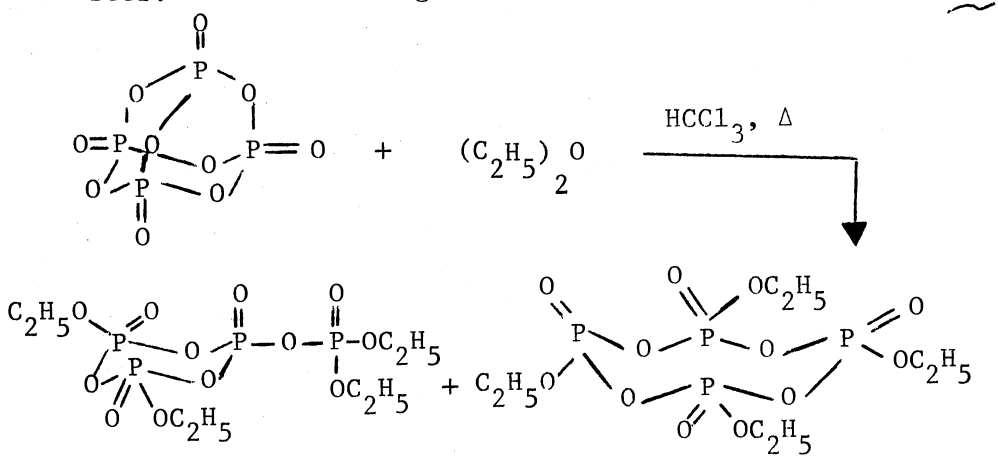
Virazole (178), a synthetic N-nucleoside analog, was discovered to be active in tissue culture against sixteen DNA and RNA viruses.[348]



178

This fact combined with our interest in synthesizing more soluble steroidal systems incorporating a sugar molecule led us to derive methods to prepare N-glucosides of 15,16-diazasteroids.

Although a silylation method[66,323] was reported to give high yields for fully aromatic indazole systems[323], isomeric N(1) and N(2) glycosides were obtained.[323] Other methods were first attempted including condensation of the free sugar and indazole in the presence of polyphosphoric ester.[312,345] Boiling a dioxane solution of indazole 247

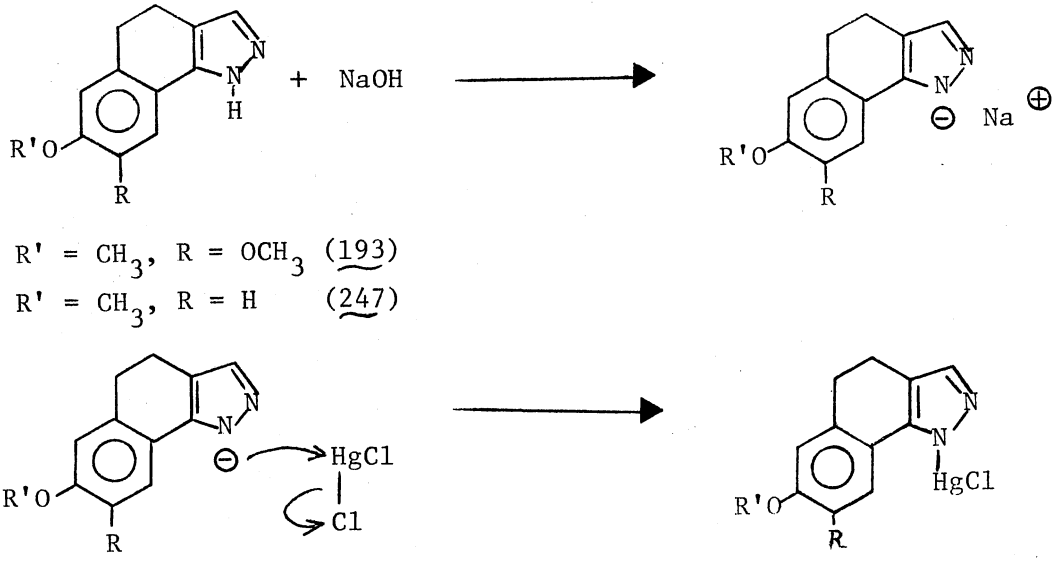


Polyphosphoric Ester (PPE)

with acetobromoglucose (238) for several hours did not effect glycosidation.[99]

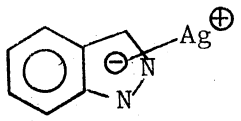
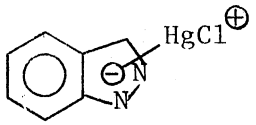
Metallation at N(1) proved applicable with all indazole systems. Direct metallation with $HgCl_2$[117] (94-100%) proved superior to that with $AgNO_3$[262] (40-60%). Recently, a method using $Hg(CN)_2$ was reported[11,397] to give higher yields. The hazard of this reaction with the involvement of HCN evolution as a by-product led us to use this method only once, despite the higher yield obtained (42% vs. 25% from $HgCl_2$).

The literature is void of any studies on the nature of the metal-heteroatom bond. We therefore assume that the metallation reaction could proceed most probably by the following pathway.

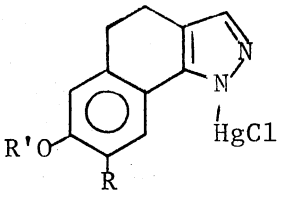
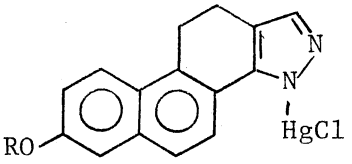


R' = CH_3, R = OCH_3 (193)
R' = CH_3, R = H (247)

The negative charge on N(1) could be delocalized over the heterocyclic ring stabilizing the aromatic π-electron system. Thus many authors prefer to denote similar structures by this formula:

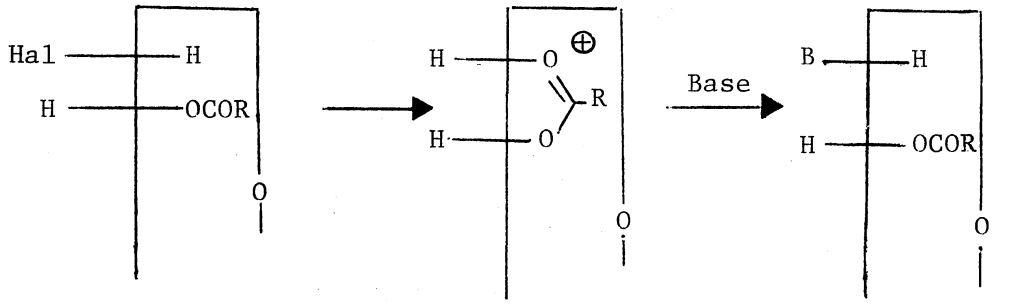
Quantitative yields of the chloromercurio derivative were realized for our compounds which could be stored at room temperature for months with no apparent decomposition. The following chloromercurio derivatives were prepared (Figures 11, 12, and 13).

$R' = CH_3$, $R = OCH_3$ (200), 100%; $R = CH_3$ (219), 100%;

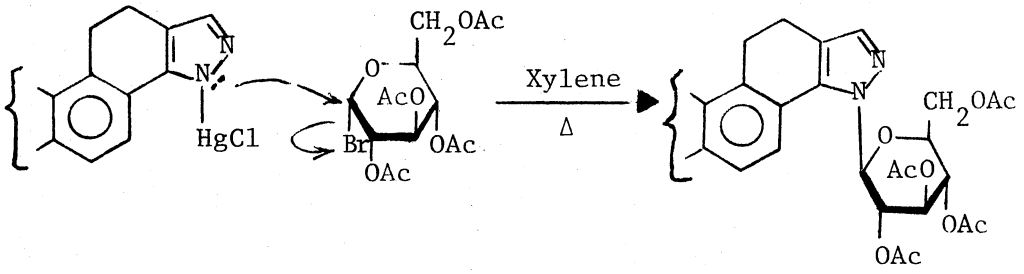
$R' = CH_3$, $R = H$ (205), 94%.

As a general procedure, the chloromercurio derivative was condensed with the commercially available acetobromoglucose (238) (see Figures 11, 12, and 13) in boiling xylene. It may be that the heterogeneous nature of this kind of reaction accounts for the lack of publications on mechanistic pathways. The only mechanistic picture suggested for aceto-halo sugar reactions with some N-heterocycles[38] involved a double inversion to explain the retention of configuration observed on C(1) of the sugar molecule.

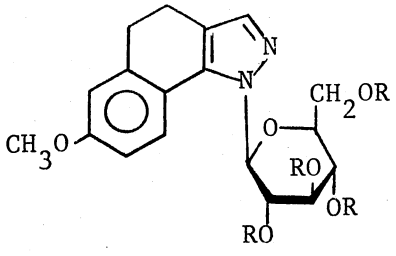


α-acetohalosugar intermediate B = base

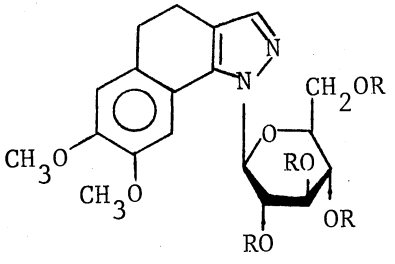
Possibly the reaction of the mercurio derivative with the halo sugar proceeds *via* an S_N2-type displacement since inversion of an anomeric carbon atom has been reported[192,34] in similar systems. Consequently, we propose a very tentative mechanism.



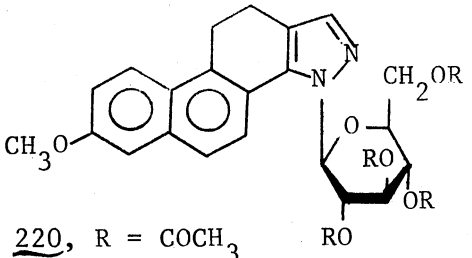
N-Glucoside derivatives 201, 202, 206, 220, and 221 were made from the chloromercurio derivatives 200, 205 and 219, respectively.



206, R = $COCH_3$



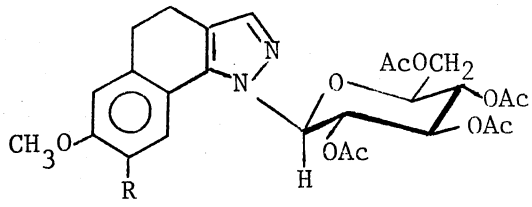
201, R = $COCH_3$
202, R = H



220, R = $COCH_3$
221, R = H

Methanolic ammonia has sometimes been the reagent of choice in carbohydrate chemistry for removing the acetate residues on the sugar moiety of nucleosides.[370,404] We successfully employed this reagent to deblock two N-glucosides to form crystalline 202 and 221. One deblocked N-glucoside from 206 (R=H) was obtained in a syrupy form and could not be crystallized (Figure 12).

An attempt was made to assign a partial configuration of the glucose residue in our compounds 201, 202, 206, 220 and 221. NMR analysis in different solvents was carried out. The chemical shift value of the anomeric H(1) of α-acetobromoglucose (238) was δ 6.62 ppm (J=2Hz). Glucosides 201 and 206 ($DCCl_3$) showed this signal at δ 5.65 with J=2Hz.



201, R = OCH_3
206, R = H

The chemical shift of the heterocyclic proton at δ 7.95 did not change with two solvents ($DCCl_3$ and DMSO-d_6). This solvent-induced shift has been reported[131] and employed[11] to determine the site of glycosidation in similar systems. However, the shift from δ 6.62 to δ 5.55 of H(1) of the sugar moiety suggested a β-configuration [trans H(1), H(2)][11] for one system.

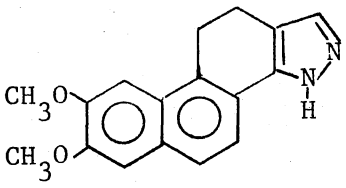
Also, the coupling constant $J_{1,2}$ would be expected to be larger in the N-glucoside than the $J_{1,2}$ in α-bromo sugar.[253] That was not observed in the J values of the two molecules 201 and 206. This does not, however, totally preclude the possibility of having a β-configuration at C(1) since a few exceptions of higher $J_{1,2}$ values of already known β-configuration have been reported.[342] Measurement of the specific

rotation (α) of both the starting material and the halo sugar may be appropriate to determine the configuration at C(1) of the sugar moiety. An inversion of the sign of (α) might indicate inversion of configuration, say, from α-halosugar to β-N-glycoside.

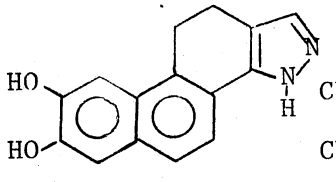
Biological Activity

A cooperative program between Professor Durham (Microbiology) and Professor Berlin (Chemistry) has permitted a fruitful collaboration especially with respect to rapid evaluation of activity of compounds on the growth of microorganisms and the human tumor cell live KB. The primary screen was growth alteration of Bacillus subtilis. If the inhibition was positive at a concentration of 91 μg/ml of test compound, additional testing was done with Pseudomonas fluorescens and KB cells before employing mice. Although inhibition of growth of KB cells is not mandatory for a compound to be of chemotherapeutic significance in humans, it is one of the best and relatively inexpensive screens available.

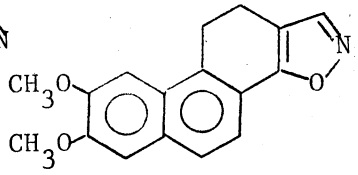
Preliminary data on 215 revealed complete inhibition of B. subtilis



215



216

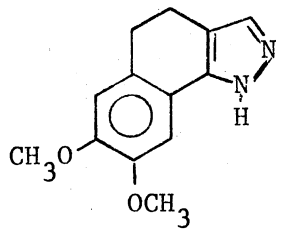


190

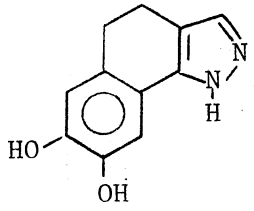
(in glucose medium) at 91 μg/ml (24 hours) but no effect was observed with Ps. fluorescens, or KB cells. In contrast, diol 216 showed no inhibition of B. subtilis or Ps. fluorescens. The isoxazole analog 190

did inhibit (91 μg/ml) B. subtilis growth up to 10 hours.

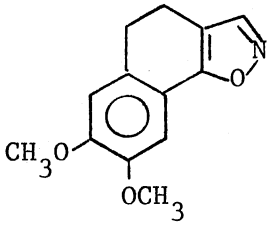
The small model systems 193, 194, and 185 showed striking inhibition of growth in certain instances. Pyrazole 193 inhibited B. subtilis



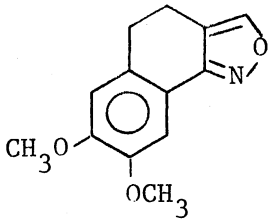
193



194



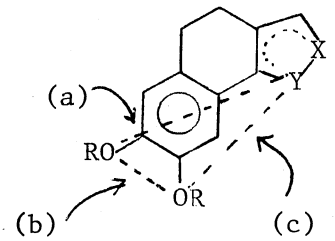
185



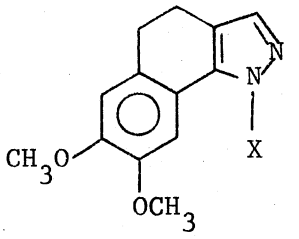
186

growth overnight and KB cells (at 50 μg/ml, 69% inhibition of cell growth resulted). Diol 194 completely inhibited B. subtilis after 5 hours and up to 23 hours at 91 μg/ml in DMSO. The following procedure was found appropriate for the preparation of a solution of the test compound: 5.0 mg. of compound was added to 0.5 ml. of DMSO + 4.5 ml. of H_2O; 0.5 ml. of this aqueous DMSO solution was added to 5.0 ml. glucose minimal, and then incubate with 0.2 ml. of culture with 5.7 ml. total

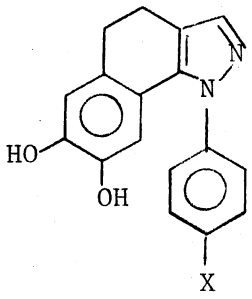
volume. Ps. fluorescens was also inhibited by diol 194; this is unique among the families of compounds we have studied. Most important was the finding that 194, at 12.5 μg/ml, completely inhibited growth of KB cells. This result is of sufficient value that 194 has been put into a program with leukemic mice. Preliminary studies using mice bearing L-1210 have shown a T/C ratio of 1.14 at 1 mg/mouse. L-1210 is a transplantable acute lymphoblastic leukemia grown in BDF_1 mice. Analysis using higher concentrations of these has yet to be completed. In contrast, the model isoxazole 185 inhibited B. subtilis growth overnight but only at high concentrations; Ps. fluorescens was unaffected. Isomeric isoxazole 186 did not inhibit B. subtilis or Ps. fluorescens. Thus, the position of the N atom appears crucial for activity. One current theory for activity in heterocycles is the distance between heteroatoms in a polycyclic system and two other hetero atoms, with one such atom being located in the first ring.[90] Possibly the charge transfer ability or hydrogen-bonding propensity are highly dependent upon size, electronegativity, and hybridization of the Y atom in the hypothetical system shown. Distances (a), (b), and (c) may be crucial for binding to the cell membrane, critical metabolites, or other primary compounds vital to cell function.



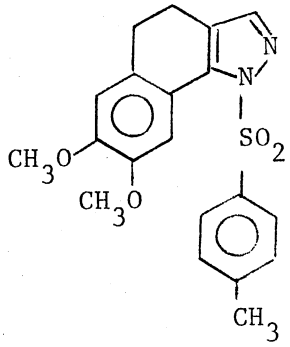
Substitution on nitrogen, in general, reduced activity of 195, 196 or 198. Although in glucose medium B. subtilis was inhibited (in DMSO)



X = H, 195
X = p-$CH_3OC_6H_4$, 197
X = 2,3,4,6-glucose-tetraacetate, 201



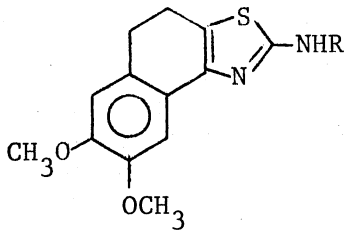
X = H, 196
X = OH, 198



199

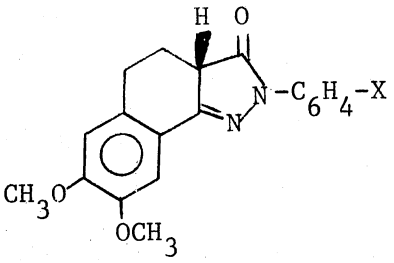
by 197 (X = p-$CH_3OC_6H_4$) at 91 µg/ml., Ps. fluorescens was unaffected and KB cells were not affected up to concentration of 250 µg/ml of 197. The glucose tetraacetate derivative 201 did not affect either microorganism. Diol 194 inhibited B. subtilis, at 91 µg/ml for 10 hours while 198 showed no inhibition. The tosyl derivative 199 was void of any activity at the primary concentration.

Replacing other atoms in the five-membered ring as in 211, 213, and 207 altered activity sharply. Inhibition of B. subtilis at 25 µg/ml by 211 in DMSO was observed and KB cells were inhibited completely at 150 µg/ml. The allyl derivative 215 is still in the primary screen. Interestingly neither of the N-aryl compounds 208 and 209 showed inhibition of B. subtilis or Ps. fluorescens. It was shown previously (Page 132) that pyrazolones 208 and 209 underwent tautomerization easily in DMSO. Coincidentally, the activity test was also performed in aqueous DMSO solution. The N-H analog 207 has yet to be tested. However, the mono-



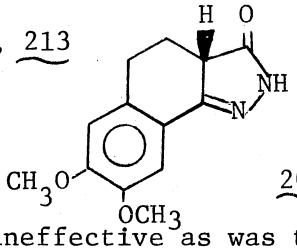
R = H, 211

R = $-CH_2CH=CH_2$, 213



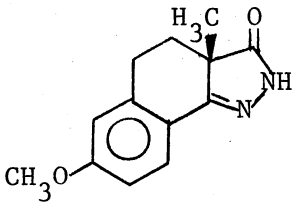
X = H, 208

X = p-F, 209

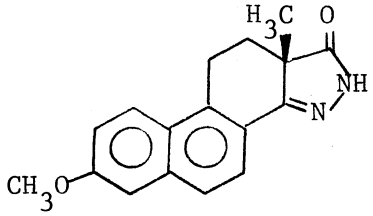


207

methoxy derivative 265 was ineffective as was the larger compound 266.

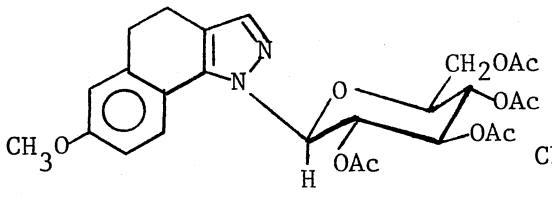


265

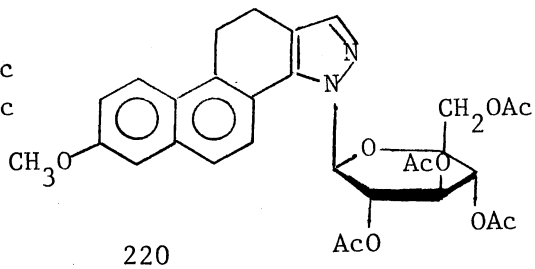


266

With only one methoxyl group and substituting nitrogen with the tetracetate derivative of acetoglucose gave the remarkably potent system 206. Complete inhibition of B. subtilis for 24 hours was observed, as was also recorded with Ps. fluorescens.



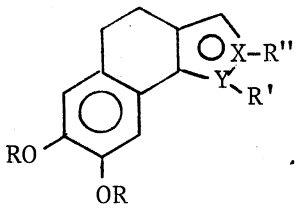
206



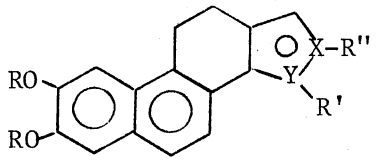
220

Moreover, at 50 μg/ml. of 206, KB cell growth was terminated. A recent clinical isolate of Staphylococcus aureus, shown to be oxacillin-resistant[50] (the organism proved fatal to a young female patient at Georgia Medical College Hospital in 1974), was also inhibited at 91 μg/ml. This organism is particularly resistant to penicillin-type antibiotics and infections involving it are therefore difficult to treat. Compounds such as 206 may result in improved chemotherapeutic agents able to combat such drug-resistant organisms. Screening of the steroidal system 220 is still in progress.

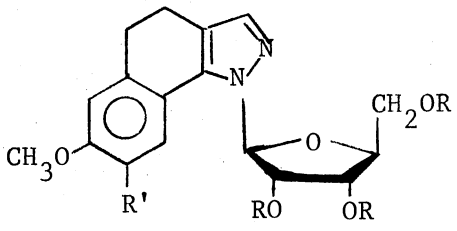
In summary, our work has uncovered several valuable clues to structure-activity relationships in the families of compounds represented by 267 and 268. Construction of new related compounds such as 269-276



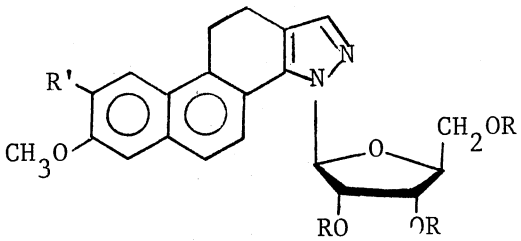
267



268



R = H, R' = H, 269;
R = H, R' = OCH_3, 270;
R = $COCH_3$, R' = H, 271;
R = H, R' = H, 272.

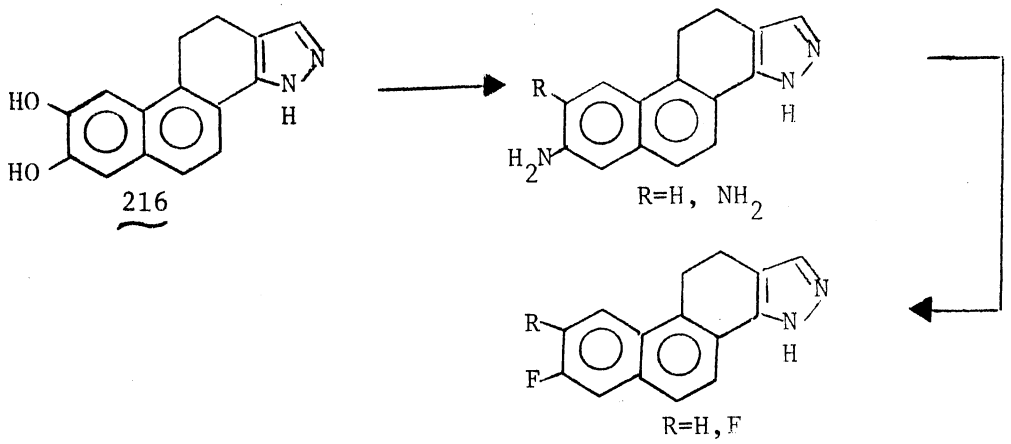


R = H, R' = H, 273;
R = H, R' = OCH_3, 274;
R = $COCH_3$, R = H, 275;
R = H, R' = OCH_3, 276.

could well provide improved activity against growth of bacterial and culture systems and therefore in humans. The incorporation of a sugar residue could be most fruitful. It is known that nucleotides do not

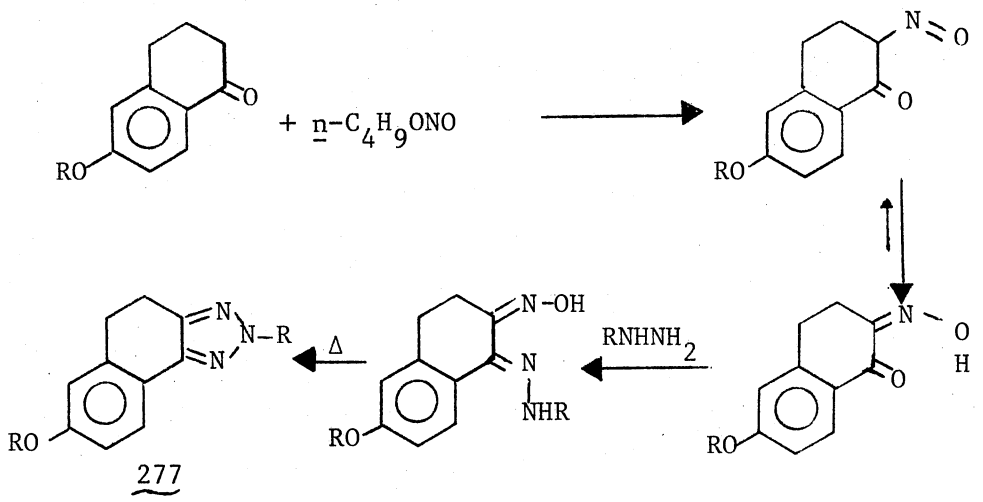
pass through some membranes in contrast to nucleosides, which do permeate.[280] Thus, there is precedent for the idea that a sugar moiety can facilitate membrane penetration and possibly carrying heterocycles other than nucleotide bases into a cell.

Diol 216 did not inhibit B. subtilis growth while indazole 190 was highly active against this organism. Presumably, a slight change in structure, trying to preserve all atomic distances between heteroatoms, may prove worthy of investigation. Analogous to a procedure applied by Hecker (1962)[176] and Evans (1964)[133] and Morrow[284] the following scheme is suggested for the synthesis of a fluorine derivative.



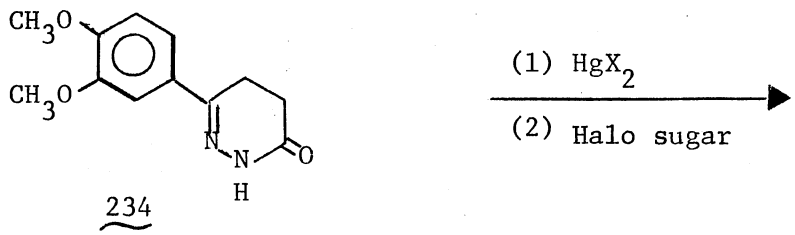
216

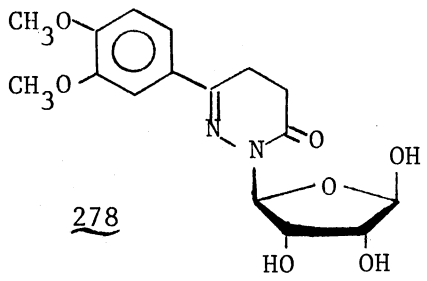
Whether or not the pyrazole and [2,1-d]isoxazole in the heterocyclic steroids are vital to the activity of these families could be investigated. For instance, 1,2,3-triazoles[48] of the type 277 could be examined and thus provide insight as to the influence of carbon versus nitrogen or activity in the small ring. A proposed sequence is:

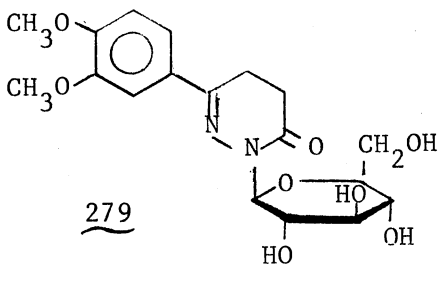


Actually, very few examples of those triazolosteroids have been found in literature.[122]

Numerous examples have been published[168,404] in which a sugar residue is attached to one N atom of a heterocyclic compound. Most of these cases included a pyrimidine or purine ring system.[404] No examples were found, however, attempting the glycosidation of pyridazinones. Our available compound 234 could introduce a novel mimic of nucleoside molecules 278 and 279, the activity of which is unknown:







Mass spectral data for most model compounds and heterosteroid systems are provided in Tables IX-XI. Relatively little such data have been recorded for heterosteroids. Quite possibly the use of mass spectrometry to detect traces of such steroids in in vitro systems could be instructive as to the mechanism and rate of breakdown to products. Except for certain hydroxy derivative 198, 202, 221 and 227, the M^+ is the m/e of highest intensity. Obviously, considerable interpretation is needed here for rapid and accurate structural analysis.

TABLE IX

INTENSE IONS IN MASS SPECTRA (70 eV) OF SOME MODEL HETEROSTEROIDS AND THEIR PRECURSORS

Cpd.	Vacuum (mm)	Probe Temp. (^{o}C)	Source Temp. (^{o}C)	m/e (% RI)
193	2.6×10^{-6}	110	230	189(17), 203(12), 217(49%), 229(62), 230(100).
194	2.3×10^{-6}	150	230	50(9), 52(13), 63(12), 155(23), 174(25), 175(20), 200(20), 201(40), 202(100), 203(13).
197	4×10^{-6}	40	200	37(4), 91(7), 109(9), 168(6), 206(4), 321(26), 336(100).
198	8×10^{-6}	50	190	17(83), 18(87), 31(15), 32(37), 43(100), 58(10), 149(26), 167(23), 279(38).
207	2.2×10^{-6}	185	200	77(17), 101(17), 111(30), 145(20), 162(22), 175(30), 203(17), 217(10), 231(31), 246(100).
208	5×10^{-6}	110	210	29(5), 39(17), 51(42), 63(20), 64(17), 65(14), 75(9), 77(79), 91(20), 103(25), 115(50), 128(20), 131(24), 145(71), 161(29), 189(38), 294(45), 322(100).

TABLE IX (Continued)

Cpd.	Vacuum (mm)	Probe Temp. (^{o}C)	Source Temp. (^{o}C)	m/e (% RI)
210	3.4×10^{-6}	90	220	151(90), 161(26), 176(28), 189(40), 201(18), 217(13), 245(19), 260(100).
185	7.8×10^{-6}	60	220	78(21), 90(47), 103(30), 121(13), 130(12), 150(29), 160(17), 170(13), 178(17), 189(9), 202(10), 216(23), 230(9) 231(100).
186	4×10^{-6}	60	200	57(15), 69(8), 150(44), 202(18), 231(100).
211	2.8×10^{-6}	80	210	63(7), 115(11), 134(10), 175 (12), 176(12), 177(11), 204 (11), 217(12), 219(25), 247 (47), 260(15), 261(38), 262 (100), 263(56), 264(19).
213	4.6×10^{-6}	105	200	39(20), 43(31), 56(39), 107 (100), 119(67), 202(4), 302 (18).
214	3.6×10^{-6}	105	205	34(7), 215(14), 246(25), 261 (100).

TABLE IX (Continued)

Cpd.	Vacuum (mm)	Probe Temp. (^{o}C)	Source Temp. (^{o}C)	m/e (% RI)
231	3×10^{-6}	60	200	15(2), 39(7), 51(7), 63(9), 77(15), 91(7), 92(12), 107(9), 150(95), 151(11), 179(47), 220(100).
229	3.6×10^{-6}	65	205	39(14), 51(27), 63(47), 77(42), 91(35), 103(23), 115(34), 131 (23), 150(32), 171(16), 177 (43), 178(100), 206(36), 284 (31), 286(29).
230	3.8×10^{-6}	90	240	50(3), 89(4), 91(50), 115(22), 135(5), 177(39), 197(43), 232 (30), 264(100).
225	2.8×10^{-6}	70	225	45(3), 87(8), 65(8), 77(14), 91(9), 94(15), 107(11), 122 (21), 137(65), 150(93), 210 (100).
227	2.2×10^{-6}	135	250	27(42), 45(41), 52(20), 63(48), 81(20), 109(41), 137(100), 161 (8), 192(22), 210(28).

TABLE X

INTENSE IONS IN MASS SPECTRA (70 eV) OF SOME HETEROSTEROIDS AND THEIR PRECURSORS

Cpd.	Vacuum (mm)	Probe Temp. (^{o}C)	Source Temp. (^{o}C)	m/e (% RI)
188	2×10^{-6}	110	200	114(12), 153(6), 180(16), 185 (17), 200(14), 228(13), 241 (13), 256(100).
236	4×10^{-6}	100	200	77(3), 114(5), 115(23), 127(10), 128(21), 139(11), 141(11), 157 (23), 183(22), 187(25), 201 (100), 202(14), 214(15), 274 (78).
215	3.4×10^{-6}	125	200	140(18), 194(17), 237(18), 280(100), 281(18).
216	1×10^{-5}	280	200	103(24), 126(43), 152(19), 197(16), 205(23), 224(42), 252(100).

TABLE XI

INTENSE IONS IN MASS SPECTRA (70 eV) OF SOME PYRAZOLO N-GLUCOSIDES

Cpd.	Vacuum (mm)	Probe Temp. (°C)	Source Temp. (°C)	m/e (% RI)
202	3.5×10^{-6}	150	220	171(10), 186(29), 215(21), 230(100), 392(5).
206	4×10^{-6}	110	210	43(66), 81(20), 97(18), 109 (74), 115(17), 169(67), 185 (19), 200(100), 213(25), 229 (27), 255(15), 530(5).
220	3×10^{-6}	100	230	27(24), 42(27), 43(100), 50 (65), 91(41), 96(41), 115(21), 250(18), 580(10).
221	3×10^{-6}	185	250	235(8), 249(6), 250(100), 263(5), 412(6).

CHAPTER III

EXPERIMENTAL[a-f]

The reactions described in this chapter were performed several times on various scales with slight variations in procedure. The following are representative descriptions of the procedures employed.

Preparation of 3-Carbomethoxypropanoic Acid[84] (252) and 3-Carbomethoxypropanoyl Chloride[84] (253). A mixture of 300 g. (3.0 moles) of succinic anhydride (Eastman Organic) and 121.6 g. (3.8 moles, 145.5 ml.) of absolute methanol (Mallinckrodt Co.) in a one-liter, round-bottomed flask was heated at reflux on a steam bath. After about 30 minutes, the

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[a]Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

[b]Proton magnetic resonance spectra were determined on a Varian XL-100 (15) high resolution spectrometer operating at 100.1 MHz with tetramethylsilane (TMS) as the internal standard.

[c]Infrared spectra were determined on a Beckman IR-5A spectrophotometer as films on sodium chloride plates or as potassium bromide pellets.

[d]Microanalysis were performed by Galbraith Laboratories, Knoxville, Tennessee, and by Instranal Laboratory, Inc., Rensselaer, New York.

[e]High resolution mass spectra were obtained on a CEC 21-110 B double-focusing mass spectrometer.

[f]Commercially available reagents were used without further purification unless otherwise stated. Polyphosphoric acid was obtained from FMC Corporation, Inorganic Chemical Division, New York, New York, by the gracious aid of Mr. J. P. Cassidy.

mixture was swirled until all the solid dissolved. The flask was then half-immersed in a steam bath for an additional 30 minutes. Excess methanol was removed by distillation on a rotary evaporator, and residual liquid was poured into a large evaporating dish which was cooled in a shallow pan of cold water. As the half ester 252 crystallized, it was stirred and scraped off the dish in order to prevent formation of a hard solid cake. The sample was dried to constant weight in a vacuum oven at 40^{o}/25 mm. The yield was 400 g. (98%).

To 66.0 g. (0.05 mole) of the half ester 252, 119.0 g. (1.0 mole) of thionyl chloride (Fisher Scientific Co.) was added in one batch, and the mixture was heated (40^{o}) for 4 hours. The excess thionyl chloride was distilled at aspirator pressure, and the crude acid chloride 253 was distilled at reduced pressure; (b.p. 65^{o}/3 mm.) yield 70 g. (93%) of pure 253 (lit.[84], b.p. 93^{o}/18 mm., 90-93% yield).

Preparation of Methyl 4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoate (222).[114] Method A. 1,2-Dimethoxybenzene (Aldrich Chemical Co.) (27.0 g., 0.2 mole) was stirred with 3-carbomethoxypropanoic acid (40 g., 0.3 mole) in 200 g. of 115% PPA (FMC Corp.) at $45-50^{o}$ for one hour and was then left overnight at room temperature. The dark-brown reaction mixture was poured onto one liter of ice-water. The yellowish product obtained solidified upon standing in ice-water for several hours with occasional stirring. The crude product was collected by suction filtration and washed with excess cold water, 5% $NaHCO_3$ solution, and then with water until the filtrate was neutral to pH paper. The crude air-dried ester 222, which was recrystallized from 50% aqueous ethanol, weighed 35.0 g. (64.5%), m.p. $89-90^{o}$ (lit.[114] m.p. 90^{o}).

Method B. A solution of 1,2-dimethoxybenzene (13.8 g., 0.1 mole)

and 3-carbomethoxypropanoyl chloride (31.0 g., 0.2 mole) was added in small portions with vigorous stirring to 230 g. of 115% PPA contained in a beaker pre-warmed to 40-50°. A gas was evolved, presumably HCl. Stirring was continued for 1 hour and the reaction mixture was left for 2 hours at room temperature until the gas evolution ceased. The dark-violet, viscous reaction mixture was poured onto approximately one kilogram of crushed ice and worked up as in Method A above. The yield of ester 222 was 19.9 g. (80%). IR and NMR spectra (Plates II and XLIX) support the proposed structure of 222.

Preparation of Methyl 4-(3 ,4 -Dimethoxyphenyl)butanoate (223). A solution of 10 g. (0.04 mole) of methyl 4-(3 ,4 -dimethoxyphenyl)-4-oxobutanoate (222) in 150 ml. of glacial acetic acid was hydrogenated at about 60° with 2 g. of 10% palladium on charcoal catalyst (Matheson Co.) at 40 psi in a Parr apparatus. The reaction mixture was cooled and filtered through a filter cake of Celite in a medium-sized, sintered glass funnel. The filter cake was washed with 20 ml. of ether, and the solvents were removed on a rotary evaporator to yield crude ester 223 (9.1 g., 96%) as a light yellowish oil. An analytical sample was obtained by distillation, b.p. 152-4°/0.1 mm.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.54; H, 7.56.

Found: C, 65.36; H, 7.60.

IR and NMR spectra (Plates III and L) support the proposed structure for 223.

Preparation of 4-(3 ,4 -Dimethoxyphenyl)butanoic Acid (224).[174]

Method A. Methyl 4-(3 ,4 -dimethoxyphenyl)butanoate (223) (23.8 g., 0.1 mole) was boiled with 250 ml. of 10% KOH for 6 hours (under N_2). The cold hydrolyzate was extracted with ether (2 x 100 ml.), and the aque-

ous layer was cooled in ice and acidified with excess conc. cold HCl. Ether extraction (3 x 100 ml.) gave a solution which was evaporated to yield 4-(3 ,4 -dimethoxyphenyl)butanoic acid (224) (13.7 g., 62%), m.p. 58-59°, from hexane (lit.[174] m.p. 58-60°). IR (Plate IV), NMR (Plate LI).

Method B. 1,2-Dimethoxybenzene (55.2 g., 0.40 mole) and succinic anhydride (Eastman Organic) (40 g., 0.40 mole) were dissolved with mechanical stirring in 200 ml. of 1,1,2,2-tetrachloroethane (Aldrich Chemical Co.) and 50 ml. of nitrobenzene (Fisher Scientific Co.). The resulting mixture was cooled to 0-5°. Reagent-grade, anhydrous $AlCl_3$ (Fisher Scientific Co.) (60.0 g., 0.45 mole) was added in small portions over a period of 2 hours keeping the temperature between 5-10°. Stirring was continued (24 hours) at room temperature with the exclusion of moisture ($CaCl_2$ tube). The dark, bluish-violet reaction mixture was decomposed by the addition of 200 ml. of ice-cold 10% HCl, and the mixture was steam-distilled. The aqueous mixture in the distilling flask was filtered hot. The crude product, which crystallized on cooling, was removed by suction filtration. The keto acid thus obtained was purified by dissolution in a boiling 5% NaOH solution which was treated with Nuchar, filtered, cooled, and acidified with excess 6 N HCl. The crude keto acid 226 precipitated and was recrystallized from H_2O; m.p. 158° (lit.[174] m.p. 159-160°). The yield was 52.0 g. (54%).

The keto acid prepared was reduced catalytically in glacial acetic acid. Thus, 10 g. (0.04 mole) of the acid 226 in 150 ml. of glacial acetic acid and 1.0 g. of 10% Pd-C were shaken at about 60° at 40 psi of H_2 pressure in a Parr apparatus for about 40 minutes [theoretical uptake of H_2 (pressure drop of ca. 7.5 lbs) was observed]. The catalyst was

removed using Celite, and the acetic acid solution was concentrated (rotary evaporator) to about 15 ml. The concentrate was then poured onto to 500 ml. of ice-water to precipitate pure acid 224; yield 9.0 g. (97%), m.p. 58-60° (lit.[174] m.p. 58-60°).

Keto acid 226 was also obtained by the saponification of keto ester 222. Thus keto ester 222 (10.0 g., 0.04 mole) was boiled with 100 ml. solution of 10% NaOH for 4 hours. After cooling in ice, 6 N HCl was added dropwise with stirring to give an acid (pH = 1-2) medium. The white precipitate obtained was collected by suction filtration, washed with water and air dried. Crude keto acid 226 was recrystallized from H_2O; m.p. 158-159° (lit.[174] m.p. 159-160°). The yield of pure keto acid 226 was 79% based on keto ester 222.

Preparation of 3,4-Dihydro-6,7-dimethoxy-1[2H]-naphthalenone[174] (182). 4-(3 ,4 -Dimethoxyphenyl)butanoic acid (4 g., 0.018 mole) was added in small portions with stirring to 50 g. of 115% PPA pre-warmed to 70-75°. Heating and stirring was continued for 10-15 minutes. An additional 30 g. of PPA were added, and the mixture was stirred (10 minutes) while warming at 70-75°. The brown, viscous mixture was cooled, poured onto 250 ml. of ice-water and stirred, a process which initiated solidification. The product was moved by suction filtration and washed successively with H_2O, saturated $NaHCO_3$ solution, and H_2O again. After drying, crude ketone 182 was recrystallized from n-heptane to give 3.65 g. (83%) of 182; m.p. 99-100° (lit.[174] m.p. 99-100°). IR and NMR spectra; (Plates VIII and LV) supported the proposed structure for 182.

Attempted Synthesis of 6,7-Dimethoxy-3,4-dihydro-1[2H]-naphthalenone Using (A) $AlCl_3$ or (B) PPA in One Step: Method A.[304] 1,2-Dimethoxybenzene (veratrole) (Aldrich Chemical Co.) (34.5 g., 0.25 mole) and 4-

butyrolactone (Aldrich Chemical Co.) (21.5 g., 0.25 mole) were placed in a three-necked flask equipped with a condenser (capped with $CaCl_2$ tube), a mechanical stirrer, and a wide-bore rubber tube leading to a 250-ml. Erlenmeyer flask. The Erlenmeyer flask was charged with reagent-grade anhydrous $AlCl_3$ (Fisher Scientific Co.) (66.75 g., 0.50 mole) and mounted on the 3-necked flask. The $AlCl_3$ was added during a period of 2 hours with stirring. The reaction mixture turned grey and some gas (HCl) was evolved. After all the catalyst was added, the mixture was heated on steam bath (1 hour) with continuous stirring. The reaction mixture was cooled and poured onto ice-water drenched with about 100 ml. of dil. HCl. The mixture was extracted twice with 100 ml. of ether, and the ether layer was dried ($MgSO_4$). The ether was filtered and evaporated to give a colorless oil. The oily material was made strongly alkaline by adding 20 ml. of 1 N NaOH, and the resulting solution was extracted with ether. The ether layer was washed (H_2O), dried ($MgSO_4$), and concentrated. An IR spectrum of the product obtained from the ether extraction was identical with that of 1,2-dimethoxybenzene.

Method B. Use of Polyphosphoric Acid. PPA [105% (FMC Corp.), 40 g.] was placed in 250 ml. Erlenmeyer flask and heated to 90° on a steam bath. Veratrole (14 g., 0.1 mole) and 4-butyrolactone (9.0 g., 0.1 mole) were added immediately in one batch with stirring. Heating was continued (15 minutes) followed by the addition of 20 g. of cold PPA. The reaction mixture was rewarmed on a steam bath at 90° (3 hours). During that time, the color changed from light pink to light brown. Left to cool overnight the reaction mixture was poured onto ice-water. From the resulting mixture there was deposited an oil. The aqueous mixture was then extracted with ether. The ether layer was washed with

saturated $NaHCO_3$ solution, H_2O, NaOH (1 N), and H_2O and was then dried ($MgSO_4$). An IR spectrum of the product from evaporation of the ether showed unchanged veratrole.

Preparation of 4-(3 -Hydroxy-4 -methoxyphenyl)butanoic Acid (225). 4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoic acid (226) (7.14 g., 0.03 mole) was boiled with 3 ml. of 85% hydrazine hydrate (Fisher Scientific) and 4.5 g. of solid KOH in 30 ml. of triethylene glycol (Aldrich Chemical Co.) in standard apparatus with a condenser. After 1 hour, the condenser was removed and the dark-brown mixture was allowed to boil to 220° for 20 minutes. The condenser was reattached and the mixture was boiled (3 hours). After cooling to room temperature, the reaction mixture was acidified (conc. HCl) and extracted with ether (2 x 100 ml.). The ether was washed successively with H_2O, Na_2CO_3 solution (10%), and H_2O and was then dried (Na_2SO_4). The ether was filtered from Na_2SO_4 and evaporated (rotary evaporator) to yield 5.05 g. (80%) of a solid, m.p. 75-77°. Recrystallization of the crude acid 225 from ether-petroleum ether (30-60°) and sublimation at 80°/5 x 10^{-4} mm. gave a product melting at 87-88°. IR and NMR spectra (Plates VII and LIV) suggested that the product had one methoxyl and one hydroxyl group (acid 225) and was not the acid 224 expected from this Wolff-Kishner reduction. A sample of the sublimed product was submitted for microanalysis:

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67.

Found: C, 63.17; H, 6.60.

IR and NMR spectra (Plates VII and LIV) supported the proposed structure for 225.

Reduction of 4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoic Acid (226) to 4-(3 ,4 -Dimethoxyphenyl)butanoic Acid (224) by Clemmensen Reduction: A

modified Clemmensen procedure[267] was used to reduce acid 226 to acid 224. Conc. HCl (6.0 ml.) and H_2O (150 ml.) were added with stirring for 5 minutes to 120 g. (1.8 g. at.) of mossy zinc and 12 g. (0.05 mole) of $HgCl_2$. The aqueous solution was decanted and 150 ml. of fresh H_2O were added. The amalgamated zinc was transferred to a 500 ml., 3-necked, round-bottomed flask to which were added 175 ml. of conc. HCl and 50 g. (0.21 mole) of 229 (the keto acid) in 120 ml. of toluene. The reaction mixture was boiled with vigorous stirring (mechanical) (24 hours) with addition of 50 ml. of conc. HCl every 8 hours. The reaction mixture was then cooled and diluted (200 ml. of H_2O). The toluene layer was separated and saved and the aqueous layer was extracted with ether (2 x 100). The ether and toluene solutions were combined, washed with water, Na_2CO_3 solution (5%), and H_2O and then dried ($MgSO_4$). Evaporation of the organic solvents (rotary evaporator) gave a heavy viscous syrup, slightly brown in color. When crystallization from $HCCl_3$/petroleum ether failed, a TLC analysis using silica gel plates and CH_3OH:$HCCl_3$ [1:9] as the solvent was performed. It showed a two-component-mixture indicating a side reaction had occurred which was believed to be the formation of the substituted butanoic acid 225 (contains one OH and one OCH_3 group). Spectral analysis (NMR and IR) were suggestive of the presence of a mixture.

An aqueous mixture of the previous product, therefore, was made alkaline (20% NaOH)and treated with excess $(CH_3O)_2SO_2$ (100 g.). The reaction mixture was extracted with ether (3 x 100 ml.). The solution was washed with H_2O, with 0.5 N HCl, and with H_2O to neutrality (pH paper). Evaporation of ether gave 18.0 g. (40%) of the expected acid 224. This experiment was repeated four times on different scales and

the yield of 80% claimed in the literature[267] was never attained.

Attempted Cyclization of the Mixture Resulting From Clemmensen Reduction of Acid 224 Using 105% PPA; Attempted Preparation of Ketone 182. The mixture (8 g.) from the previous experiment was added with stirring to 20 g. of 105% PPA preheated to 90°. Stirring was continued (20 minutes), keeping the temperature between 85-90°. The reaction mixture was then cooled and poured onto 200 ml. of ice water. When solidification did not occur after several hours of cooling and stirring, the aqueous reaction mixture was extracted with ether (2 x 100 ml.). The ether layer was washed with water, 10% NaOH (to remove phenolic compounds), H_2O, and dried (Na_2SO_4). The ether solution was filtered from Na_2SO_4 and evaporated to dryness. A resulting brown oil did not crystallize from many different solvents. A chloroform solution of the oily product was passed through a 2 x 50 ml. neutral alumina column but the 6 fractions collected were all identified by spectral (IR and NMR) analysis to be unchanged starting material.

Cyclization of Acid 224 to Ketone 182 Using 95% H_2SO_4.[174] A mixture of 4 g. (0.02 mole) of acid 224 and 8 ml. of 95% H_2SO_4 in a 100-ml. Erlenmeyer flask was heated on a steam bath for 0.5 hour with stirring. The reaction mixture, which turned dark violet, was cooled, diluted with 200 ml. of cold H_2O (carefully) and extracted with ether (3 x 50 ml.). The ether layer was washed (H_2O, sat. $NaHCO_3$ solution, H_2O) and dried (Na_2SO_4) and concentrated. Recrystallization of the residue from petroleum ether (40-60°) gave 0.4 g. of the ketone 182 (11%), m.p. 96-99° (lit.[174] m.p. 99-100°). Characterization by NMR spectrum (Plate LV, Table VIII) and IR spectrum (Plate VIII) supported the structure of tetralone 182.

Catalytic Hydrogenation of the Keto Acid 226 to Give Acid 224 Using 10% Pd-C.[79,145,188] In a 500-ml., pyrex pressure flask were placed 10 g. (0.04 mole) of the keto acid 226 dissolved in 100 ml. of glacial acetic acid containing 1.5 g. of 10% Pd-C catalyst (Matheson Co.). The experiment was run in a Parr apparatus at 40 psi of H_2 and about 60° [using an external heat lamp (Westinghouse, 150W)] to warm the flask while shaking. After the theoretical uptake of H_2 pressure drop (ca. 7.5 lbs.) was observed, the reduction was stopped and the reaction flask was cooled. The catalyst was filtered through a Celite cake. Concentration of the clear filtrate to about 15 ml. (rotary evaporator) gave a liquid which was poured onto 200 of ice-water. A white precipitate was filtered out and the yield was 8.4 g. (90%), m.p. 58-60° (lit.[174] m.p. 58-60°). The acid 224 was sufficiently pure to use in the following synthetic step, i.e., the cyclization to the tetralone 182. IR and NMR spectral data (Plates IV and LI) supported the structure proposed for acid 224.

Preparation of 6-(3 ,4 -Dimethoxyphenyl)-4,5-dihydro-3[2H]-pyridazinone (234). A solution of 1.0 g. (0.004 mole) of the keto acid 235 in 50 ml. of 95% ethanol was boiled with 1 ml. of 95% H_2NNH_2 for 30 minutes. The resulting yellowish solution was evaporated to half its original volume and left to cool. A crystalline product separated out and was filtered out; weight 0.95 g. (93%), m.p. 168-170°. Recrystallization from 95% alcohol gave pure pyridazinone 234, a sample of which was submitted to microanalysis:

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: N, 11.96.

Found: N, 12.01.

IR and NMR spectra (Plates V and LII) supported the proposed struc-

ture for 234.

Attempted Reaction of 3-Carbomethoxypropanoic Acid[84] (252) With Veratrole Using 105% PPA. 1,2-Dimethoxybenzene (veratrole) (65.0, 0.49 mole) was mixed with 3-carbomethoxypropanoic acid[84] (252) (65.0 g., 0.5 mole) at room temperature. The mixture was then added in small portions over a period of 2 hours to 690.0 g. of 105% PPA[366] prewarmed to 50°. The reaction mixture was heated to 80-90° for 15 minutes, cooled to room temperature and poured onto about one kilogram of crushed ice. An oily layer separated on the top of the water mixture when all the ice melted, but solidification, as expected, did not occur. After the oil had been distilled (b.p. 84-86°/10 mm.), NMR and IR spectra analysis showed unchanged veratrole (see Table VIII).

Preparation of 3-Protocatechuoylpropanoic Acid (227). This experiment was originally planned for preparation of the dihydroxy derivative of 6-(3 ,4 -dimethoxyphenyl)-4,5-dihydro-3[2H]-pyridazinone (234) via reaction of the latter with 48% aqueous HBr. The procedure resulted, however, in the formation of another compound, the keto acid 227.

Thus, pyridazinone 234 (6.0 g., 0.026 mole) was boiled (under N_2) with 100 ml. of 48% HBr for 9 hours with magnetic stirring. A straw-yellow color developed and soon changed to deep purple and finally to deep brown. The reaction solution was cooled under N_2 overnight. Filtration was then carried out to remove the brownish-black precipitate that separated on cooling. The aqueous mother liquor was concentrated (rotary evaporator) to one-fourth of its original volume. After storage under a hood for 3 days, the solution deposited additional solid. Dissolving the combined two solid products in about 20 ml. of 5% NaOH gave a grey-colored solution. Acidification of that alkaline solution

with 6 N HCl (while cooling) yielded a greyish-white, crude keto acid 227. Recrystallization (95% alcohol) gave 0.9 g. (16% based on 234) of somewhat purified acid m.p. 190-1°. Sublimation at 180-190°/10^{-4} mm. gave a pure, colorless sample of 227, m.p. 194-5°:

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.10; H, 4.76.

Found: C, 57.31; H, 5.03.

IR and NMR spectra (Plates VI and LIII) were in agreement with the proposed structure of keto acid 227.

Preparation of 3,4-Dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1-(2H)-naphthalenone[83] (232). A solution of 7.0 g. (0.09 mole) of ethyl formate (Eastman Organic) in 50 ml. of dry benzene was added to a cooled (10 to 15°) suspension of sodium methoxide (4.8 g., 0.09 mole) in 75 ml. of dry benzene under N_2. While the mixture was magnetically stirred, a solution of 9.0 g. (0.044 mole) of 6,7-dimethoxy-1-tetralone (182) in benzene was added at one time. Only a small amount of yellow precipitate separated after about 20 minutes, but the quantity of precipitate increased sharply after 1 hour of stirring. The reaction mixture was left at room temperature for 30 minutes and was then hydrolyzed with 300 ml. of ice-water. The organic layer was separated and washed with H_2O, washed with 5% NaOH solution, and then washed with H_2O. The combined aqueous extracts were washed (ether), and the ether was discarded. The aqueous extracts were cooled (ice) and acidified (excess 6 N HCl). The yellowish product, which was obtained upon acidification, was filtered out and weighed (after drying) 7.8 g. (76%). The hydroxymethylene ketone 234 was recrystallized from hexane, m.p. 157-9° (lit.[83] m.p. 157-9°). IR and NMR spectra (Plates IX and LVI) supported the proposed structure for 232.

Preparation of 4,5-Dihydro-7,8-dimethoxy-1H-benz[g]indazole (193). To a magnetically stirred mixture of 232 (7 g., 0.03 mole) in 125 ml. of methanol in a 250 ml. flask was added 5 ml. (0.15 mole) of 95% hydrazine (Fisher Scientific Co.) under N_2. A clear brown solution developed as soon as the hydrazine was added. The reaction was slightly exothermic, as a few droplets of methanol condensed on the condenser. The reaction mixture was stirred (3 hours) whereupon a large amount of a yellow precipitate appeared and increased with time. The reaction mixture was left at room temperature for 1 hour and was then poured onto 600 ml. of ice-water. A yellow crystalline product was removed by filtration and air-dried. The yield was 5 g. (72%); m.p. of a sample recrystallized from dilute, aqueous alcohol (ca. 75%) was 178-180°. Sublimation of the recrystallized indazole at 160°/0.05 mm. gave an analytical sample, m.p. 179.5-180°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.08; N. 12.12.

Found: C, 67.90; H, 6.16; N, 12.25.

IR and NMR spectra (Plates XIV and LXI) were consistent with the proposed structure for 193.

Preparation of 4,5-Dihydro-1H-benz[g]indazole-7,8-diol (194). Indazole 193 (4 g., 0.02 mole) was boiled with 150 ml. of aqueous 48% HBr for 10 hours under N_2. The dark-brown reaction mixture was cooled to room temperature whereupon shiny, pinkish needles separated out. The needles were removed by filtration and redissolved in 50 ml. of 10% NaOH solution. The alkaline solution was filtered and neutralized (cooled 6 N HCl). The beige-colored precipitate (m.p. 276-8°) was filtered out and recrystallized (H_2O); yield of diol 194 was 2.6 g. (65%); m.p. 294-298°. An analytical sample was sublimed twice at 260°/10^{-3} mm. to

yield a flaky, brittle, white solid, m.p. 300-1°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.35; H, 4.95; N, 13.86.

Found: C, 65.51; H, 4.86; N, 13.79.

IR and NMR spectra (Plates XV and LXII) were consistent with the proposed structure of 194.

Preparation of 4,5-Dihydro-7,8-dimethoxy-1-phenyl-1H-benz[g]indazole (195). 2-(Hydroxymethylene)-6,7-dimethoxy-1-tetralone (232)(1.5 g., 0.006 mole) was dissolved in 50 ml. of glacial acetic acid in a 100-ml., round-bottomed flask. Phenylhydrazine (2.0 g., 0.018 mole) (Fisher Scientific Co.) was added to the solution, and the mixture was gently boiled with magnetic stirring (under N_2). The dark-reddish mixture was concentrated (rotary evaporator) to about one-fourth volume of its original volume. When the reaction mixture was poured onto 500 ml. of ice-cold water, a light-brown, gummy product (crude 195) formed. Solidification was effected by decanting the acidic, supernatant liquid and adding an equal volume of fresh, ice-cold water with stirring and trituration. Indazole (crude) 195 was filtered out on a small Hirsch funnel, washed generously with cold water, and air dried. Recrystallization (twice) (95% C_2H_5OH) gave 1.75 g. (85%) of pure 195, m.p. 125-126°:

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.51; H, 5.88; N, 9.15.

Found: C, 74.10; H, 6.28; N, 9.25.

IR and NMR spectra (Plates XVI and LXIII) supported the proposed structure for 195.

Preparation of 4,5-Dihydro-1-phenyl-1H-benz[g]indazole-7,8-diol (196). A suspension of 1.0 g. (0.003 mole) of 4,5-dihydro-7,8-dimethoxy-1-phenyl-1H-benz[g]indazole (195) in 40 ml. of aqueous 48% HBr (J. T. Baker Chemical Co.) was boiled gently for 7 hours under N_2. Magnetic

stirring was used. A dark-purple color developed after about 1 hour of boiling. Upon cooling (N_2), the solution deposited a pinkish-white precipitate. This precipitate was filtered out with suction. Purification of the product (presumably the hydrobromide of 196) was achieved by adding 20 ml. of 20% NaOH; undissolved impurities were removed by filtration. A grey clear filtrate was obtained which was chilled in ice and treated dropwise (with manual stirring) with 6 N HCl just to the neutral point (using a pH paper) to form a shiny white, crystalline product. When crude indazole (diol) 196 was dried in air for several hours, the shiny white precipitate turned slightly grayish-tan. The yield was 0.65 g. (78%) of crude indazole (diol) 196, m.p. 271-276°. An analytical sample sublimed at $250^{\circ}/10^{-4}$ mm., m.p. 276-278°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.38; H, 5.04.

Found: C, 73-13; H, 5.00.

Spectral measurements by IR and NMR (Plates XVII and LXIV) were consistent with the expected structure proposed for substituted indazole (diol) 196.

Preparation of 4,5-Dihydro-7,8-dimethoxy-1-(p-methoxyphenyl)-1H-benz[g]indazole (197). p-Methoxyphenylhydrazine hydrochloride (Aldrich Chemical Co.) (2.1 g., 0.012 mole) was suspended in a solution of 2-(hydroxymethylene)-6,7-dimethoxy-1-tetralone (232)(1.0 g., 0.004 mole) in 100 ml. of methanol. A solution of sodium acetate trihydrate (4.09 g., 0.03 mole) in 20 ml. of water was added to the suspension, and the reaction mixture was magnetically stirred (under N_2 - 1 hour) at room temperature. Stirring was continued for an additional 2 hours while warming the reaction gently at about 50°. The brown solution which resulted was allowed to cool to room temperature and was then diluted (300 ml. of

H_2O). Extraction of the solution was performed with ether (2 x 200 ml.). The ether layer was dried (Na_2SO_4), filtered, and evaporated to a light-brown solid. Recrystallization (n-heptane) gave 1.15 g. (86%) of pure indazole 197, m.p. 132-3°. Sublimation at 120°/10^{-3} mm. gave a product melting at 136-7°, a sample of which was submitted for microanalysis.

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33.

Found: C, 71.75; H, 6.07; N, 8.29.

IR and NMR spectra (Plates XVIII and LXV) were consistent with the structure proposed for 197.

Preparation of 4,5-Dihydro-1-(p-hydroxyphenyl)-1H-benz[g]indazole-7,8-diol (198). The appropriate indazole which we have designated as 197 (1.2 g., 0.004 mole) was suspended in 100 ml. of 48% aqueous HBr. Under an N_2 atmosphere (to prevent undesirable oxidation of the resulting polyol 197), the reaction mixture was boiled gently (3 hours) with slow magnetic stirring. When cooled overnight (N_2), the reaction mixture deposited dark-purple needles. These needles (presumably the hydrobromide of 198) were filtered out by suction, which removed excess hydrobromic acid solution, and dried. Cold 3 N NaOH (ca. 20 ml.) was added to this purple product contained in a small flask. A deep-grey, alkaline solution resulted which was carefully neutralized (ca. pH 7) with cold 6 N HCl. The faint-purple precipitate was removed by filtration under aspirator pressure. Recrystallization from aqueous ethanol (1:1) gave indazole (triol) 198, weight 0.70 g. (74%), m.p. 290-292°. An analytical sample was prepared by sublimation of recrystallized indazole (triol) 198 at 220°/10^{-4} mm., m.p. 295°.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: N, 9.52.

Found: N, 9.51.

IR and NMR spectra (Plates XIX and LXVI) were consistent with the structure given to indazole (triol) 198 .

Preparation of 4,5-Dihydro-7,8-dimethoxy-1-(p-tolysulfonyl)-1H-benz[g]indazole (199). p-Tolylsulfonyl hydrazine [1.2 g. (0.006 mole), Aldrich Chemical Co.] was added to 2-(hydroxymethylene)-6,7-dimethoxy-1-tetralone (232) (1.5 g., 0.006 mole) in 40 ml. of glacial acetic acid. The solution was shaken manually for 4-5 minutes and then boiled under reflux for 2 hours under N_2. A wine-red solution resulted. This was cooled to room temperature and then poured onto about 300 ml. of ice-water with stirring. A yellow solid formed and was filtered out. The melting point determined showed a wide range and suggested an impure or amorphous material. When the solid was allowed to dry in air, some noticeable decomposition occurred on the filter paper giving oily products. Thus, the remaining solid was transferred quickly to 40 ml. of 95% ethanol and stored to permit slow evaporation. Crystallization took place after 3-4 hours and crude tosyl indazole 199 was collected by filtration; weight 0.6 g. (26%), m.p. 178-181° (decomp.). Recrystallization from 95% ethanol and subsequent sublimation ($160^{\circ}/10^{-4}$ mm.) gave the tosyl indazole 199, m.p. 185-187°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: N, 7.29; S, 8.33.

Found: N, 7.36; S. 8.38.

IR and NMR (Plates XY and LXVII) spectra support the structure of tosyl indazole 199 proposed here.

Preparation of 4,5-Dihydro-7-methoxy-1-phenyl-1H-benz[g]indazole (203). Phenylhydrazine [(3.0 g., 0.028 mole), Aldrich Chemical Co.] was dropped into a solution of 2-(hydroxymethylene-6-methoxy)-1-tetralone in 40.0 ml. of glacial acetic acid. The reddish-brown solu-

tion was boiled and magnetically stirred (3 hours) under N_2. It was then concentrated to one-fifth original volume (rotary evaporator) to give a dark-red, viscous syrup. When the syrup was poured onto ice-cold water (ca. 400 ml.), a gummy light-brown residue formed. After the residue stood in ice-water several hours (with occasional changes of water above the gummy residue and then trituration), solidification was effected. In order to crystallize the amorphous, brown solid obtained, about 20 ml. of 95% ethanol was added and the suspension was warmed to effect solution. Crystalline indazole 203 was obtained as light-brown prisms; 1.81 g. (93.8%), m.p. 103-5°. An analytical sample was sublimed (100°/5 x 10^{-4} mm.) and melted at 105-106°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: N, 10.14.

Found: N, 10.25.

Both IR and NMR spectra (Plates XXI and LXVIII) supported the structure proposed for substituted indazole 203.

Preparation of 4,5-Dihydro-1-phenyl-1H-benz[g]indazol-7-ol (204).

4,5-Dihydro-1-phenyl-7-methoxybenz[g]indazole (203) prepared above (1.0 g., 0.004 mole), was suspended in 50 ml. of 48% aqueous HBr (J. T. Baker Chemical Co.). The suspension was boiled under N_2 for 8 hours with magnetic stirring. Bright-purple needles were collected by filtration after the HBr reaction mixture had been allowed to cool to room temperature under N_2. This product was worked up like previous ones. To free the indazole from its purple hydrobromide, the needles were taken up in 20 ml. of 30% NaOH solution and the solution was cooled. Upon acidification (cold 6 N HCl) to just the neutral point (pH paper), a white-to-grey precipitate was formed. Suction filtration separated the crude substituted indazole product 204. It was dried in air to con-

stant weight and sublimed ($200^{o}/10^{-3}$ mm., weight-0.75 g., 72%), m.p. 238-240°. Characterization by spectral analysis using IR (Plate XXII) and NMR (Plate LXIX) supported the proposed structure of N-substituted indazole 204.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.69.

Found: C, 77.84; H, 5.19; N, 10.79.

Preparation of Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthoate (241). Dimethyl carbonate (Aldrich Chemical Co.) was distilled from NaH and stored over molecular sieve [Linde type 3A (1/16"), Matheson, Coleman and Bell]. In a 250-ml., three-necked flask was placed 90.0 g. (1.0 mole) of dimethyl carbonate. The flask was fitted with a mechanical stirrer and a Friedrich condenser (with N_2 inlet). To the flask were added 10.4 g. (0.2 mole) of pure sodium methoxide (Fisher Scientific Co.) and 17.6 g. (0.1 mole) of 6-methoxy-1-tetralone (240). The mixture was boiled (4 hours) with mechanical stirring. During that period the reaction mixture developed a shiny pink color. It was cooled and 50 ml. of CH_3OH was added to dissolve some of the precipitate formed. Hydrochloric acid (6 N) was added dropwise to the cooled mixture until it was just slightly acidic (ca. pH 6.5). Excess methanol was evaporated on a rotary evaporator to leave a light pink-colored solid, m.p. 76-79°. This crude ester recrystallized from 95% ethanol (m.p. 89-90°) gave 20.5 g. (87.5%) of pure keto ester 241 (lit.[117] 88-89°).

Preparation of 2,3a,4,5-Tetrahydro-7-methoxy-3H-benz[g]indazol-3-one (233). To 4.0 g. (0.017 mole) of keto ester 253 was added 100 ml. of anhydrous methanol (Mallinckrodt) in which the amount of ester was only partially soluble. Hydrazine [95% (Eastman Organic)(5.0 g., 0.16 mole)] was added to the ester 241 in methanol, and the reaction was in-

itiated by stirring the mixture magnetically with boiling under N_2. Boiling was continued for 12 hours. A straw-yellow colored solution resulted after only 1 hour of boiling. The resulting solution was concentrated to one-fourth of the original volume. Cold water (ca. 250 ml.) was added with stirring whereupon a white precipitate separated. Suction filtration removed the precipitate, which was allowed to air-dry to constant weight. Thus crude indazolone 233 was obtained, 3.0 g. (82%), as a white product; m.p. 218-220°. Recrystallization (50% aqueous ethanol) afforded pure, colorless needles m.p. 219-220°. Sublimation at 200°/10^{-4} mm. gave a sample melting at 220-1°. IR analysis (Plate XXV) showed no carbonyl band, which indicates this compound exists predominantly in the enol form (see Results and Discussions Chapter). NMR (Plate LXXII) and mass spectral data support the proposed structure for indazolone, or more correctly indazolenol, 233, in the media examined. A specimen of the sublimed sample was submitted for microanalysis. The following results were obtained:

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: N, 12.96.
Found: N, 13.00.

Preparation of Methyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230). The procedure was essentially the same as for the keto ester 241 prepared above. In a 250-ml., three-necked flask was placed 90.0 g. (1.0 mole) of dimethyl carbonate (Aldrich Chemical Co.), (which was previously distilled from NaH and stored over molecular sieve). The flask was equipped with a mechanical stirrer and a Friedrich condenser with N_2 inlet. Reagent grade sodium methoxide [(Fisher Scientific Co.)(10.0 g., 0.2 mole)] was added to dimethyl carbonate followed by 10.0 g. (0.048 mole) of 6,7-dimethoxy-1-tetralone (182).

The mixture was boiled (4 hours) with mechanical stirring. The color of the reaction mixture was greyish-tan initially and then changed to deep pink and finally to purple. Methanol (about 50 ml.) was added to dilute the solid suspended in the reaction medium which was rendered slightly acidic by the addition of 6 N HCl dropwise. Residual reactants and solvents were removed by evaporation (aspirator). Crude keto ester 230 was collected from the evaporation flask by dispersing in water and filtering it out. After drying, the crude ester weighed 11.7 g. (93%) and was pink in color, m.p. 129-132°. Recrystallization (95% alcohol) gave pure keto ester 230 (11.0 g., 92%), m.p. 139-140°. Sublimation at 130°/10^{-4} mm. afforded a colorless sample of the keto ester 230; m.p. 140-141°. IR and NMR spectra (Plates XIII and LX) support the structure of 230.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.64; H, 6.06.

Found: C, 64.09 H, 5.94.

Preparation of 2,3a,4,5-Tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one (207). The procedure was similar to that described for indazolone 233. Thus, 1.0 g. (0.004 mole) of methyl 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (203) and 2.5 g. (0.063 mole) of 95% H_2N-NH_2 (Matheson Co.) and 2 drops of glacial acetic acid were boiled (2 hours) in 30 ml. of anhydrous methanol (under N_2). Evaporation of most of the excess organic solvents and pouring the concentrate into cold water (ca. 250 ml.) gave a white, crude indazolone 207. Recrystallization (95% alcohol) gave pure, colorless indazolone 207; 0.9 g. (91.5%), m.p. 258-260° (decomp.). Sublimation (240°/0.01 mm.) afforded a highly pure substance, m.p. 265° (decomp.). Again, as in the case of the monomethoxy derivative 233, IR analysis (Plate XXVI) of this product 207 showed no carbonyl band; the NMR spectrum (Plate LXXIII) showed no signal for

angular H signal at position 3.85. This strongly suggested the compound, like 233, existed mainly in the enolic form. Mass spectral data confirmed the structure proposed for the product 207 of this experiment;

M.S. Calcd. for $C_{13}H_{14}N_2O_3$: m/e 246.100435 (M^+).

Found: m/e 246.105069 (M^+).

Calcd. for fragment $C_{13}H_{14}N_2O_2$: m/e 230.105521.

Found: m/e 230.102257.

Preparation of 2,3a,4,5-Tetrahydro-7,8-dimethoxy-2-phenyl-3H-benz[g]-indazol-3-one (208). Methyl 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230) (1.0 g., 0.004 mole) was dissolved in 30 ml. of absolute methanol and 2 drops of glacial acetic acid. The solution was placed to a 100-ml., round-bottomed flask to which was added 2.0 g. (0.019 mole) of phenylhydrazine (Matheson Co.). Heating was initiated and the solution was boiled for 2 hours with magnetic stirring (under N_2). A reddish-brown solution resulted; this was cooled and concentrated to about one-fourth of the original volume. While concentrating on a rotary evaporator, an orange-red crystalline solid separated out. Suction filtration isolated those crystals from the methanolic solution. The crude crystalline product (indazolone 208) weighed 1.18 g. (92%); m.p. 198-200°. Recrystallization (95% ethanol) gave material melting at 200-201°. Sublimation (200°/10^{-3} mm.) gave a solid, m.p. 202°. Spectral analysis [IR and NMR (Plates XXVII and LXXIV)] showed that the structure proposed for indazolone 208 was correct.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: N, 8.69.

Found: N, 8.55.

Preparation of 2-(p-Fluorophenyl)-2,3a,4,5-tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one (209). In a 100-ml., round-bottomed flask with

a condenser and a magnetic stirrer was placed a solution of 1.0 g. (0.004 mole) of methyl 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230) in 50 ml. of 95% ethanol. To that solution was added a suspension of p-fluorophenylhydrazine hydrochloride [Aldrich Chemical Co. (1.3 g., 0.008 mole)] in 10 ml. of 95% ethanol containing 2 ml. of 10% acetic acid. Sodium acetate trihydrate (1.0 g., 0.008 mole) was added to the previous mixture. The reaction mixture was boiled (under N_2) for 2 hours. The reddish-brown solution initially formed turned to yellow after about 0.5 hour of boiling. Concentration of the reaction solution to about one-half of the original volume resulted in formation of some crystalline substance. Those crystals of crude indazolone 209 were filtered out and dried; weight, 0.86 g. (65%). Crude indazolone 209 was recrystallized from 95% ethanol; m.p. 243-244°. An analytical sample was sublimed at 210°/10^{-4} mm., m.p. 244-5°.

Anal. Calcd. for $C_{19}H_{17}N_2O_3F$: N, 8.23; F, 5.60.

Found: N, 8.14; F, 5.48.

Spectral analysis [(IR and NMR) Plates XXVIII and LXXV] were also in excellent agreement with the proposed structure of indazolone 209.

Preparation of 2,3a,4,5-Tetrahydro-7,8-dimethoxy-3a-methyl-3H-benz[g]indazol-3-one (210). Diethyl carbonate (Aldrich Chemical Company) (100 g. 0.847 mole, distilled from NaH) was mixed with 6,7-dimethoxy-1-tetralone (182) (5.0 g., 0.024 mole.) and $NaOCH_3$ (4.2 g., 0.048 mole.) in a 250-ml., three-necked flask equipped with a mechanical stirrer and a Friedrich condenser. The reaction mixture was boiled under N_2 (2.5 hours) during which time the color changed from dark purple to brown. Enough methanol (ca. 150 ml.) was added to dissolve the precipitate formed after allowing the reaction mixture to cool to room temperature.

To the previous solution in methanol (which had a light-brown color) was added reagent CH_3I (Fisher Scientific Co.) (9.0 g., 0.063 mole). Stirring was initiated at room temperature and was continued for 18 hours followed by gentle boiling (1 hour). The reaction mixture was allowed to cool and was neutralized with 2 M acetic acid. Concentration on a rotary evaporator gave a brown syrup. This solidified during trituration with hot hexane (several times) and cooling. The amorphous solid obtained from the hexane extract was filtered and crystallized (95% ethanol), m.p. 74-76°; weight of pure ester 228 was 3.3 g. (46%). A sample was recrystallized again (95% ethanol) and sublimed at 70°/0.001 mm. Mass spectral analysis gave the following data.

M.S. Calcd. for $C_{16}H_{20}O_5$: m/e 292.125911 (M^+).

Found: m/e 292.131064 (M^+).

IR and NMR spectra (Plates XII and LIX) supported the proposed structure 228.

Ethyl 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-oxo-2-naphthoate (228) (1.2 g., 0.004 mole) obtained above was dissolved in 15 ml. of anhydrous methanol and treated with 3 g. (0.094 mole) of 95% hydrazine. The reddish-brown solution obtained was stirred under N_2 with gentle heating (2 hours). Cooled to room temperature and diluted with about 150 ml. of ice-cold water, the reaction mixture deposited a nearly pure solid. Filtration of that solid and air drying yielded 0.85 g., (82% based on 228) of indazolone 210, m.p. 215-218°.

An analytical sample was sublimed at 200°/0.005 mm. and was submitted for microanalysis:

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: N, 10.77.

Found: N, 10.59.

IR and NMR spectra (Plates XXIX and LXXVI) were in agreement with the expected structure for 210.

Preparation of 2-Methyl-6,7-dimethoxy-1-tetralone (231). Sodium ethoxide (8.0 g., 0.12 mole) (Aldrich Chemical Co.) was suspended in 150 ml. of denatured ethanol and transferred into a 100-ml., round-bottomed (N_2). To that suspension was added 1.5 g. (0.007 mole) of methyl 1,2,3,-4-tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230) which was followed by the addition of 14.0 g. (0.1 mole) of CH_3I. An exothermic reaction occurred as soon as the reactants were stirred magnetically. A brown solution resulted. The mixture was stirred (17 hours) at room temperature (under N_2). An additional amount of sodium ethoxide (2.0 g., 0.03 mole) was added, and the reaction was boiled for 0.5 hour and then stirred for an additional 4 hours at room temperature. It was acidified with dil HCl (6 N) to pH 6-6.5. Excess solvents were evaporated (aspirator pressure) and the residue was suspended in water and extracted with ether (2 x 50 ml.). Ether was evaporated after the solution had been dried (Na_2SO_4). A yellowish-white solid was obtained, m.p. 110-113°. This compound was recrystallized (hot hexane), m.p. 114-115°; yield 0.8 g. (52%). An NMR spectrum (Plate LVII) and an IR spectrum (Plate X), together with mass spectral analysis, proved that the product was 2-methyl-6,7-dimethoxy-1-tetralone (231). A sublimed (100°/10^{-4} mm.) sample gave the following mass spectral data:

M.S. Calcd. for $C_{13}H_{16}O_3$: m/e 256.109937 (M^+).

Found: m/e 256.108282 (M^+).

Calcd. for fragment $C_{13}H_{12}O_2$: m/e 200.083724.

Found: m/e 200.083825.

Preparation of 4,5-Dihydro-7,8-dimethoxynaphth[2,1-d]isoxazole

(185). A solution of $HONH_2 \cdot HCl$ (1.0 g., 0.14 mole) and sodium acetate trihydrate (1.0 g., 0.007 mole) in 5 ml. of water was added to a solution of 2-(hydroxymethylene)-6,7-dimethoxy-1-tetralone (232)[83] (2.0 g., 0.086 mole) in 25 ml. of glacial acetic acid. The combined solutions were boiled (1 hour) under N_2. The reaction mixture was cooled to room temperature whereupon shiny, golden needles separated out. The needles were filtered out with a suction funnel (aspirator pressure) and washed with 80% acetic acid and then with cold water, and dried; m.p. 186-189°. Recrystallization from 50% CH_3CO_2H afforded 1.7 g. (84%) of pure 185, m.p. 189-190°. An analytical sample was prepared by subliming a specimen of the recrystallized isoxazole at 160°/0.025 mm.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.62; N, 6.06.

Found: C, 67.71; H, 5.75; N, 5.98.

IR and NMR spectra (Plates XXIII and LXX) were consistent with the proposed structure of 185.

Preparation of 4,5-Dihydro-7,8-dimethoxynaphth[1,2-c]isoxazole (186). A mixture of 2-(hydroxymethylene)-6,7-dimethoxy-1-tetralone (232)[83] (2.0 g., 0.086 mole), $HONH_2 \cdot HCl$ (1.0 g., 0.14 mole) in 2 ml. of water, and 8 ml. of pyridine was boiled under N_2 (3 hours). A dark-green color developed quickly in the solution at reflux. The reaction mixture was allowed to cool overnight whereupon a brownish, crystalline solid separated out. It was filtered and allowed to dry in air; crude yield was 0.8 g. This solid was an isomeric mixture[166] of the two isoxazoles 185 and 186 which was separated as follows: The crude mixture was partitioned between 200 ml. of ethyl acetate and 100 ml. of 1 N HCl solution. The organic layer was washed twice with 30 ml. of 1 N HCl and 30 ml. of saturated sodium chloride solution; it was then dried (Na_2SO_4). Solvents

were removed using a rotary evaporator. The residue was redissolved in 100 ml. of dry THF (from NaH) containing 0.7 g. (0.012 mole) of $NaOCH_3$. The resulting reddish solution was stirred at room temperature (1 hour) using a magnetic stirrer. The reaction mixture was then washed with 50 ml. of saturated NaCl solution, 20 ml. of 2% NaOH solution, and then with 100 ml. of H_2O. Drying the organic layer ($MgSO_4$) and concentrating it on a rotary evaporator gave crude 186 as a light brown solid. Recrystallization from C_2H_5OH-H_2O (9:1) gave 0.5 g. (38%) of pure 186, m.p. 176-178°. A sample sublimed at 160°/10^{-2} mm.

Anal. Calcd. for $C_{13}H_{13}NO_3$: N, 6.06.

Found: N, 6.12.

IR and NMR spectra (Plates XXIV and LXXI) supported the proposed structure for 210. Mass spectral data obtained were:

M.S. Calcd. for $C_{13}H_{13}NO_3$: m/e 231.089537 (M^+).

Found: m/e 231.088599 (M^+).

Calcd. for fragment $C_{12}H_{12}NO_2$: m/e 202.086798.

Found: m/e 202.087017.

Calcd. for fragment $C_9H_{10}O_2$: m/e 150.068075.

Found: m/e 150.068382.

Attempted Cleavage of the Methoxyl Groups of 4,5-Dihydro-7,8-dimethoxynaphth[2,1-d]isoxazole (185) by 48% Aqueous HBr. Isoxazole 185 (1.2 g., 0.006 mole) was boiled under N_2 with 50 ml. of 48% aqueous HBr for 5 hours. A brown solution resulted and was left to cool overnight. This solution was diluted with 100 ml. of cold H_2O and extracted with ether (2 x 100 ml.). The ether layer was washed with saturated $NaHCO_3$ solution (50 ml.) and then water and was finally dried ($MgSO_4$). Filtration of the solution removed the drying agent and the clear solution was

concentrated to a brown oil; weight 0.2 g. The identity of the oil was not examined further since a spectral analysis (IR and NMR) did not support the presence of the expected dihydroxy compound. It was assumed that HBr had cleaved the isoxazole heterocyclic ring, presumably to give the corresponding 2-cyano-1-tetralone[215].

Preparation of 2-Bromo-3,4-dihydro-6,7-dimethoxy-1(2H)naphthalenone (229). A solution of 10.3 g. (0.05 mole) of 6,7-dimethoxy-1-tetralone (182) in 100 ml. of chloroform-ethanol medium (1:1) was placed in a three-necked, 250-ml. flask. A mechanical stirrer, a Friedrich condenser (with N_2 inlet) and a dropping funnel were fitted to the flask. Reagent-grade bromine [(Fisher Scientific Co.)(8.8 g., 0.055 mole)] was dissolved in 10 ml. of pure $HCCl_3$, and the solution was charged in the dropping funnel. The reaction flask was cooled in ice-bath and the dropwise addition of Br_2 solution proceeded in 50 minutes. A yellow precipitate began first to appear after about 1 hour of stirring at room temperature. That yellow precipitate disappeared in solution with further stirring, which was allowed to continue for an additional 3 hours. Washing the resulting solution (dark-yellow to light-brown) successively with H_2O, with saturated aqueous $NaHSO_3$, and with H_2O and finally drying ($MgSO_4$) it gave a clear and almost colorless solution. Evaporation of the organic solvents (rotary evaporator) gave a brown syrup. Trituration of that syrup with $HCCl_3$- ether (1:4, v/v) yielded 8.5 g. (60%) of crude bromo ketone 229, m.p. 103-5°. Sublimation of the recrystallized bromo ketone 229 at 110°/0.1 mm. afforded a highly pure product melting at 107-8°.

Anal. Calcd. for $C_{12}H_{13}O_3Br$: C, 50.53; H, 4.56.

Found: C, 50.19; H, 4.59.

Spectral measurements (NMR and IR data Plates XI and LVIII) supported the structure proposed for the bromo ketone 229.

Preparation of 2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (211). The procedure of Doorenbos[122] was modified. To a solution of the bromo ketone 229 (2.0 g., 0.007 mole) in 75 ml of $HCCl_3$-C_2H_5OH (1:1) was added 3.0 g. (0.039 mole) of reagent-grade thiourea (J. T. Baker Chemical Co.). The mixture was boiled with magnetic stirring (under N_2) for 6.5 hours. The clear solution that resulted was cooled under N_2 overnight. Unchanged thiourea (ca. 1.0 g., 0.013 mole) precipitated out upon cooling and was removed by filtration. Evaporation of the filtrate to complete dryness (rotary evaporator) resulted in the formation of a white solid (presumably the hydrobromide of thiazole 211). Dissolution of the white solid in 250 ml. of 95% ethanol and treatment with about 15-20 ml. of cold 2 N KOH (until pH 10-11) gave another white precipitate (thiazole 213) which was collected by suction filtration. The crude thiazole 211 obtained, weight 1.2 g. (65%), melted at 228-230°. Sublimation of a sample at 190-200°/0.01 mm., surprisingly, resulted in a color change from white to a bright yellow. The yellow, crystalline compound melted at 235-7°; the proposed structure for thiazole 211 was supported by IR, elemental, and NMR analysis (see Plates XXX and LXXVII).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: N, 10.68.

Found: N, 10.64.

Preparation of 2-Anilino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]-thiazole (212). 2-Bromo-6,7-dimethoxy-1-tetralone (229) (1.8 g., 0.063 mole) was dissolved in 50 ml. of $HCCl_3$-C_2H_5OH (1:1) in a 100-ml., round-bottomed flask attached to a condenser. N-Phenylthiourea [(Eastman Or-

ganic) 1.0 g., 0.066 mole] was added and the resulting mixture was stirred magnetically and boiled for 6 hours under N_2. The slightly yellowish solution was cooled and then evaporated completely to dryness on a rotary evaporator. The white solid obtained was dissolved in cold ethanol (ca. 25 ml.). A solution of 2 N KOH was added dropwise with cooling, whereupon a shiny white precipitate separated out (crude thiazole 212). Filtration and drying in air yielded 1.9 g. (90%), m.p. 174-177°. IR and NMR spectra (Plates XXXI and LXXVIII) supported the presented structure of thiazole 212. A sample sublimed at 160°/10^{-4} mm.; m.p. 180-181°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: N, 8.58.

Found: N, 8.85.

Preparation of 2-(Allylamino)-4,5-dihydro-7,8-dimethoxynaphtho-[1,2-d]thiazole (213). N-Allylthiourea [(1.5 g., 0.0013 mole), Eastman Organic] was dissolved in 50 ml. of mixed $HCCl_3$-C_2H_5OH (1:1). To that solution was added 2.0 g. (0.007 mole) of 2-bromo-6,7-dimethoxy-1-tetralone (229), and the resulting solution was boiled under N_2 for 16 hours. A slightly yellow but clear solution developed. The solution was cooled to room temperature overnight under N_2 with continuous magnetic stirring. After evaporation to remove all solvents (rotary evaporator), a yellow, viscous oil formed. Cold 95% ethanol (ca. 25 ml.) was added to that oil and triturated for a few minutes. A white precipitate appeared when the flask was allowed to cool in ice-bath. Water was added to dilute the ethanolic mixture (ca. 20 ml.), and the mixture was made alkaline (excess cold 2 N KOH). By reducing the volume of the resulting alkaline solution to about half volume (rotary evaporator) and cooling in an ice-bath for several hours, a grayish-tan precipitate was obtained. Crude

thiazole 213 weighed 2.3 g. (95%), m.p. 85-87°.

IR and NMR spectra (Plates XXXII and LXXIX) were consistent with the proposed structure for thiazole 213. Sublimed thiazole 213 (100°/ 5 x 10^{-4} mm.) melted at 88-90°. Mass spectral data were:

M.S. Calcd. for $C_{16}H_{18}N_2O_2S$: m/e 302.136820 (M^+).

Found: m/e 302.136094 (M^+).

Preparation of 4,5-Dihydro-7,8-dimethoxy-2-methylnaphtho[1,2-d]-thiazole (214). Thioacetamide [(3.0 g., 0.041 mole), Eastman Organic] was added to a solution made from dissolving 2.0 g. (0.007 mole) of 2-bromo-6,7-dimethoxy-1-tetralone (229) in 75 ml. of chloroform-ethanol (1:1). Magnetic stirring was initiated, and the solution was boiled for 10 hours under N_2. A change of color was observed during the time of boiling, from clear colorless to clear yellow. Upon cooling under N_2 and evaporating to dryness, some odor of H_2S was detected (presumably due to the side reaction between HBr in the medium and excess thioacetamide). A white solid was obtained from the evaporation process and was washed by decanting with 10 ml. of H_2O (to remove inorganics). After dissolving the solid in hot 95% ethanol and adding a cold solution of 2 N KOH (ca. 10 ml.) (followed by the addition of about 25 ml. of cold water), a shiny, white precipitate was produced. This crystalline material, thiazole 214 (1.6 g., 88%), melted at 140-141°. An analytical sample sublimed (130-140°/5 x 10^{-4} mm.) and then melted at 140-141°.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.37; H, 5.75; N, 5.36; S, 12.26.

Found: C, 64.11; H, 5.84; N, 5.24; S, 12.12.

Characterization by spectral analysis (IR and NMR, Plates XXXIII and LXXX) supported the structure of thiazole 214 given.

Preparation of Methyl 3,4-Dihydro-6,7-dimethoxy-$\Delta^{1(2H),\gamma}$-naphtha-

lenecrotonate (235). In a one-liter, three-necked flask equipped with a Friedrich condenser (with N_2 inlet), a mechanical stirrer and a 250-ml. pressure-equalizing separatory funnel, was placed 75 g. (1.15 g. at.) of zinc pieces. The Zn pieces were previously cut from Zn ribbon (J. T. Baker Chemical Company) into strips about ¼ x ¼ cm., washed with dil. HCl for 2-3 minutes, rinsed with water, acetone, ether and then dried in an oven above 150° for 2-3 hours. To the activated zinc covered with 150 ml. of dry benzene (dried over sodium) was added 4 g. (0.015 mole) of $HgCl_2$. The suspension was mechanically stirred for 10 minutes at room temperature, warmed with continuous stirring under N_2 for 20 minutes, and allowed to cool to room temperature. After this had stood for 30 minutes at room temperature, a solution of 40.0 g. (0.223 mole) of methyl 4-bromocrotonate (245)(Aldrich Chemical Co.) (fractionally distilled at 109°/22 mm.) in 100 ml. absolute ether (dried over Na) and sublimed 6,7-dimethoxy-1-tetralone (182) (61.8 g., 0.3 mole) in 300 ml. of dry benzene were added all at once. A crystal of iodine was then added. The mixture was boiled under reflux with mechanical stirring for 1.5 hours. The reaction mixture, which began to acquire a greenish color (after about 10 minutes of boiling) soon changed to deep yellow after another 15 minutes and finally to orange (after another 20 minutes) and then to brick red which persisted throughout the remaining reaction period. After 1.5 hours of stirring and boiling, an additional 15 g. (0.084 mole) of the bromo ester 245 was added followed by 25 g. (0.382 g. at.) of the activated zinc and a crystal of iodine. Boiling was continued for an interval of 1.5 hours, and the above addition process (with the same amounts of chemicals) was repeated twice. Thus, a total of 150 g. of Zn (2.3 g. at.), 85 g. (0.475 mole) of methyl 4-bromo-

crotonate (245), and 61.8 g. (0.3 mole) of ketone 182 were used in this experiment. After the last addition was completed, the reaction mixture was allowed to boil with continuous stirring overnight (under N_2). The reaction mixture was cooled and diluted to twice its volume with cold water. Then 150 ml. of 2 N HCl was added. The organic layer was separated and the aqueous layer was extracted with benzene (2 x 100 ml.). The deep orange-colored organic extracts were combined, washed with H_2O, and dried ($CaCl_2$). Evaporating most of the solvents on a rotary evaporator and allowing the deep-orange, oily product to stand at room temperature in an open beaker under hood resulted in formation of an orange-colored, crystalline product. The solid was filtered using a medium-sized, sintered glass funnel and washed with some dry ether to give 42 g. (48.6%) of ester 235, m.p. 136-9°. Recrystallization from 95% ethanol and subsequent sublimation at 130°/5 x 10^{-4} mm. yielded a bright yellow sample, m.p. 142-3°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94.
Found: C, 70.67; H, 7.28.

IR and NMR spectra (Plates XXXIV and LXXXI) were consistent with the structure proposed for 235.

Concentration of the benzene-ether filtrate from the orange crystalline product 235 (rotary evaporator) and vacuum distillation gave a viscous, yellowish distillate (180-190°/1.5 mm.) which solidified immediately (11-12 g., ca. 5-6% recovery); m.p. 95-97°. IR and NMR analysis indicated the solid was unchanged 6,7-dimethoxy-1-tetralone (182).

Another oily fraction was also collected at 190-195°/at 1.5 mm. during the same fractional distillation. This oil (yield was ca. 2.09 g.) did not solidify but turned red upon standing for 2-3 days. IR

analysis showed the presence of a hydroxyl group. Further identification was not attempted. It is believed that the side product is either alcohol-ester 261a or 261b.

Preparation of 6,7-Dimethoxy-1-naphthalenebutanoic acid (236). A mixture of 12.2 g. (0.043 mole) of recrystallized ester 235 and 3.0 g. of 10% Pd-C (Matheson Co.) was heated in a carbon dioxide atmosphere to 220-250° for 1.5-2 hours. After cooling under CO_2, ether was added (ca. 50 ml.), and the catalyst was filtered off using a medium-sized, sintered glass funnel. Ether was evaporated (rotary evaporator) to give the crude intermediate methyl 4-(6,7-dimethoxy-1-naphthyl)butanoate (246); weight 10.0 g. (83% yield based on 235). Crude isomerized ester 246 was not purified further but saponified directly to the corresponding acid 236. Thus, crude ester 246 (10.0 g., 0.035 mole) was placed in a 250 ml., round-bottomed flask and dissolved in 100 ml. of methanol. To this methanolic solution was added a solution of 3.2 g. (0.057 mole) of KOH in 30 ml. of water. This mixture was boiled, under N_2, for 3-4 hours using a Friedrich condenser and a magnetic stirrer. Cooling the hydrolyzate (a dark-brown solution) in ice and acidification with excess cold 6 N HCl precipitated crude 6,7-dimethoxy-1-naphthalene butanoic acid (236) as an off-white solid. Crude acid 236 was removed by filtration from the aqueous acidic solution, washed several times with water until neutral to pH paper, and air dried. Recrystallization from H_2O afforded pure, colorless needles of acid 236, m.p. 132-133°; yield 9.1 g. (95% based on ester 246 and 76% based on ester 235). An analytical sample of acid 235 was prepared by subliming the recrystallized product at 120-130°/10^{-4} mm., m.p. 135°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.07; H, 6.57.

Found: C, 69.89; H, 6.68.

IR and NMR spectral analyses (Plates XXXV and LXXXII) supported the suggested structure of acid 236.

Preparation of 3,4-Dihydro-6,7-dimethoxy-1[2H]-phenanthrone (188). Polyphosphoric acid (150 g., 115%) was heated to 90-100° in a 600-ml. beaker. Heating was momentarily halted, and acid 236 (20.0 g., 0.073 mole) was added in small portions while stirring the PPA mixture with a thermometer. Stirring was continued for 10-15 minutes followed by an addition of another 50 g. of PPA; the mixture was reheated to 110°. A deep greenish-brown, viscous mixture resulted, and this was cooled to room temperature with continuous stirring. That deep-colored syrup was poured onto about 800 ml. of ice-water. Crude 6,7-dimethoxy-3,4-dihydro-1-[2H]-phenanthrone (188) obtained as a grey precipitate was filtered out by suction and washed generously with water, saturated aqueous $NaHCO_3$ solution, and finally with water until the filtrate was neutral to pH paper. The residue obtained was extracted (500 ml. of n-heptane) in a Soxhlet apparatus for 48 hours. Pure ketone 188 separated out in the hot heptane as the extraction proceeded. Pure ketone 188 (11.3 g.) was obtained by filtering the cooled heptane suspension. However, another crop (4.8 g.) of ketone 188 was collected by evaporating the heptane mother liquor for a total yield of the beige-colored ketone 188 of 15.4 g. (83%); m.p. 198-200°. Sublimation of the sample at 160°/5 x 10^{-4} mm. gave highly pure ketone 188; m.p. was 210-211° (lit.[203] 215-215.5°). Mass spectral data obtained were:

M.S. Calcd. for $C_{13}H_{16}O_3$: m/e 220.109937, (M^+).

Found: m/e 220.108976, (M^+).

Calcd. for fragment: $C_{12}H_{13}O_3$: m/e 205.086463.

Found: m/e 205.085130.

Calcd. for fragment: C_6H_5: m/e 77.039123.

Found: m/e 77.037689.

IR and NMR spectra (Plates XXXVI and LXXXIII) combined with MS data were sufficient evidence for the proposed structure of ketone 188.

Preparation of 3,4-Dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1(2H)-phenanthrone (237). In a 500-ml., round-bottomed flask was placed a solution of 6,7-dimethoxy-3,4-dihydro-1[2H]-phenanthrone (188) (8.0 g., 0.03 mole) in 250 ml. dry benzene. Sodium methoxide (Fisher Scientific Co.) (3.8 g., 0.07 mole) was suspended in 50 ml. of dry benzene and added to the ketone solution in benzene. Ethyl formate (Eastman Organic) (6.0 g., 0.07 mole) was added to the previous mixture, and the reaction was initiated by mechanical stirring at room temperature under N_2. After 1 hour of stirring, a gelatinous precipitate began to form which made stirring somewhat difficult. Enough dry benzene (ca. 100 ml.) was added to redissolve some of the gelatinous precipitate and to facilitate the agitation. Stirring was continued (24 hours) at room temperature under N_2. Ice-water (ca. 800 ml.) was used to hydrolyze the reaction product; the benzene layer was separated. The benzene solution was added to about 200 ml. of fresh water and the two layers were extracted with ether (2 x 150 ml.). The alkaline, aqueous layer was saved. The organic phase was washed with about 50 ml. of 5% NaOH. Combining the alkaline washings and the extracts gave a solution which was cooled and made acidic (pH = 1-2) by adding excess 6 N HCl. A finely divided, yellow precipitate was formed and was isolated by suction filtration. The solid 237 obtained was air-dried for 2 days to constant weight. This

experiment afforded 8.3 g. (94%) of crude hydroxymethylene ketone 237, m.p. 145-147°, which was sufficiently pure to use in to the next synthetic step, i.e., cyclization to the corresponding pyrazole. Subliming a specimen of this hydroxymethylene ketone 237 at 120-130°/3 x 10^{-3} mm. gave pure 237 as a yellow, crystalline product, m.p. 147-8°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.83; H, 5.63.

Found: C, 71.74; H, 5.73.

NMR and IR spectral data (Plates XXXVII and LXXXIV) were indicative of the correctness of the structure proposed for 237.

Preparation of 10,11-Dihydro-7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (215). 2-(Hydroxymethylene)-6,7-dimethoxy-1-phenanthrone (237) (4.0 g., 0.014 mole) was dissolved in 250 ml. of methanol in a 500-ml. round-bottomed flask. Magnetic stirring was used to agitate the solution under N_2. To that solution was added 6 ml. of 95% H_2N-NH_2 (Eastman Organic) whereupon a clear, wine-red color developed. The temperature rose to about 35° and then dropped to room temperature during about 30 minutes of stirring. Stirring was continued (4 hours) at room temperature under N_2. During that period a golden-yellow, fine precipitate (which increased with time) began to appear in the stirred reaction mixture. Filtration by suction using a medium-sized, sintered glass funnel removed the precipitate from the methanolic mixture; weight of crude pyrazole 215 was 2.40 g., m.p. 273-5°. The yellowish, methanolic filtrate was evaporated (rotary evaporator) to complete dryness. Suspending the yellowish, fine residue obtained in about 150 ml. of cold water and filtering that suspension by suction (using a sintered glass funnel) furnished a second crop (1.5 g.), m.p. 272-5°, of crude pyrazole 215 as a fine, straw-yellow colored product. Thus a total yield of pyrazole

215 was 3.9 g. Recrystallization from THF-benzene afforded 3.7 g. (97%) of pure pyrazole 215, m.p. 276-7°. A doubly sublimed sample (270°/10^{-4} mm.), m.p. 277.5°, was submitted for analysis.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.86; H, 5.71; N, 10.00.

Found: C, 72.81; H, 5.77; N, 10.06.

Spectral NMR and IR analyses (Plates XXXVIII and LXXXV) were consistent with the structure proposed for 215.

Preparation of 10,11-Dihydro-3H-phenanthro[1,2-c]pyrazole-7,8-diol (216). Recrystallized pyrazole 215 (3.0 g., 0.011 mole) was suspended in 100 ml. of 48% aqueous HBr solution. In standard apparatus, the reaction mixture was boiled for 8 hours (under N_2) with magnetic stirring. A purple-to-brown color in the solution resulted after about 1 hour of boiling. The reaction mixture was allowed to come to room temperature gradually under N_2. A deep purple solid (presumably the hydrobromide of 216) precipitated; it was removed by suction filtration. That solid was suspended in about 30 ml. of cold water, and the resulting mixture was made strongly alkaline (addition of 15-20 ml. of 30% NaOH solution). This alkaline solution was deep-grey in color and was filtered from suspended impurities through a glass-wool plug. The filtrate was cooled in ice, and 6 N HCl was added dropwise just to the neutralization point (pH = 7). A grey-white, crude pyrazole (diol) 216 was formed and was filtered out. Recrystallization from 50% aqueous alcohol afforded 2.0 g. of 216 (74% based on 215) as a white, microcrystalline product; m.p. 295-8°. A sample of the pyrazole (diol) 216 was sublimed at 280°/5 x 10^{-4} mm. and was again recrystallized from 50% aqueous alcohol, Nuchar being used to remove traces of colored impurities. Finally, the sample was resublimed at 280°/5 x 10^{-4} mm. to give pure pyrazole (diol) 216

melting at 324-6°. Microanalysis and gave the following results:

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.33; H, 4.76; N, 11.11.

Found: C, 70.97; H, 4.50; N, 11.07.

IR and NMR spectra (Plates XXXIX and LXXXVI) furnished a further proof for the structure 216.

Preparation of 10,11-Dihydro-1-(p-fluorophenyl)-7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (217). p-Fluorophenylhydrazine hydrochloride [(0.6 g., 0.002 mole), Aldrich Chemical Co.] was mixed with sodium acetate trihydrate [(0.5 g., 0.002 mole) Mallinckrodt] in 20 ml. of acetic acid and 5 ml. of water. The mixture was shaken manually for 2-3 minutes and added to a solution of hydroxymethylene ketone 237 (1.0 g., 0.004 mole) in 30 ml. of acetic acid. Heat was applied to boil the reaction mixture (red) for 2.5 hours under N_2. Most of the acetic acid was removed on a rotary evaporator. After the suspension in cold water was cooled for several hours, crude pyrazole 217 separated out. Filtered from water and dried, the crude pyrazole 217 weighed 0.45 g. (64%); m.p. 195-7°. IR and NMR (Plates XLI and LXXXVIII) analysis support the structure proposed for 217. Sublimation (180°, 10^{-4} mm.) gave a colorless pure product; m.p. 197-8°.

Anal. Calcd. for $C_{23}H_{19}N_2O_2F$: N, 7.49; F, 5.08.

Found: N, 7.40; F, 5.01.

Preparation of 10,11-Dihydro-1-(p-fluorophenyl)phenanthro[1,2-c]-pyrazole-7,8-diol (218). Hydrobromic acid [48% aqueous solution, 50 ml. (J. T. Baker Chemical Company)] was used to cleave the two methoxyl ether linkages in pyrazole 217. Boiling (under N_2) 0.8 g. (0.002 mole) of the pyrazole 217 in the acid for 17 hours gave a brownish-purple solution. Upon cooling this deposited a fine deep burgundy-colored powder.

Filtration removed the powder which was air dried. The purple powder was dissolved in alkali (NaOH, 2 N, about 15 ml.) to give a deep-grey solution. Using a glass-wool plug, the strongly alkaline solution was filtered from undissolved impurities. Neutralization (pH paper) while cooling in an ice-bath using 6 N HCl gave a grey-tan precipitate; this was collected by cooling the solution in a refrigerator and filtration of the solid obtained by suction filtration. Crude pyrazole (diol) 218 thus obtained weighed 0.35 g. (51%), m.p. 248-252°. Purification by sublimation gave a colorless product, pyrazole (diol) 218; m.p. 256-8°.

Anal. Calcd. for $C_{21}H_{15}N_2O_2F$: N, 8.09; F, 5.50.

Found: N, 8.10; F, 5.42.

Spectral analysis (IR and NMR, Plates XLII and LXXXIX) gave support for the suggested structure for pyrazole (diol) 218.

Preparation of 10,11-Dihydro-7,8-dimethoxyphenanthro[2,1-d]isoxazole (190). Hydroxymethylene ketone 237 (1.3 g., 0.005 mole) was boiled with a mixture of $HONH_2 \cdot HCl$ (0.8 g., 0.012 mole) and sodium acetate trihydrate (0.8 g., 0.006 mole), all suspended in 25 ml. of acetic acid and 3 ml. of water. Boiling of the mixture was allowed to continue for 1.5 hour with gentle magnetic stirring (N_2). A brown color developed on boiling. This brown solution was cooled to room temperature and 10 ml. of water was added. The flask then was stored in a refrigerator for 12 hours. Shiny golden-yellow crystals separated out upon cooling. Filtration by suction removed these crystals (crude isoxazole 190) from the acidic solution; the crystals were washed (cold water) and dried. The acidic mother liquor gave a second crop of crude isoxazole 190 upon dilution with water until turbidity began to persist; the mixture was chilled at 0°C. The second crop was darker in color than the first

product, and after washing with cold water and drying, the total yield amounted to 1.20 g. (85%), m.p. 192-193°. IR and NMR spectra (Plates XL and LXXXVII) were consistent for the structure of isoxazole 190. A sample of isoxazole 190 sublimed at 180°/10^{-3} mm., m.p. 194-195°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.60; H, 5.34.

Found: C, 72.52; H, 5.40.

Preparation of 1-β-D-Glucopyranosyl-4,5-dihydro-7-methoxy-1H-benz-[g]indazole Tetraacetate (ester) (206). The modified procedure[118] for the chloromercurio derivative was used in this experiment. (A): Preparation of the chloromercurio derivative of 4,5-dihydro-7-methoxy-1H-benz-[g]indazole (205): A solution of indazole 247 (5.0 g., 0.025 mole) in 150 ml. of hot 50% ethanol containing an equivalent of NaOH (1.0 g., 0.025 mole) was treated with one equivalent of $HgCl_2$ (6.79 g., 0.025 mole). The latter was previously dissolved in 50 ml. of boiling 95% ethanol. A white precipitate formed immediately. After cooling to room temperature, the white precipitate was collected by suction filtration using a medium-sized, sintered glass funnel. The solid was washed with cold water and with 5 ml. of cold, 95% ethanol and finally with 25 ml. of cold ether. After drying 2 days under a hood, the product had a constant weight. This experiment gave 8.6 g. (88%) of chloromercurio indazole 205. In order to maximize the yield, the mode of addition of reactants was reversed to prevent the formation of R_2Hg which could conceivably reduce the yield of chloromercurio indazole 205. Thus in a second run the alkaline-ethanolic solution of indazole 247 (same quantities as before) was added dropwise to a boiling ethanolic solution of $HgCl_2$. By use of this simple reverse addition, the yield of chloromercurio derivative was almost quantitative; 9.7 g. (98%).

(B): Condensation of chloromercurio indazole 205 with tetra-O-acetyl-α-D-glucopyranosyl bromide (238): A suspension of chloromercurio indazole 205 (4.0 g., 0.009 mole) in 400 ml. of dry xylene (dried over sodium) was stirred vigorously by a magnetic stirrer for 10-15 minutes. About 100 ml. of xylene was distilled off azeotropically to remove traces of water. The distillation apparatus was protected by a $CaCl_2$ tube. Tetra-O-acetyl-α-glucopyranosyl bromide (238) (4.0 g., 0.0098 mole) was added into the cooled, xylene suspension of chloromercurio indazole 205. Another 100 ml. of xylene was azeotropically distilled from the suspension with vigorous magnetic stirring. The distillation condenser was disconnected and the reaction mixture was boiled for 3 hours and allowed to cool overnight (all under N_2). Filtration by suction removed the dark-brown, inorganic by-products from the xylene solution. Evaporation of the xylene solution was effected (rotary evaporator) and light-brown syrup was obtained. Dissolving that syrup in chloroform and allowing it to stand overnight in a refrigerator resulted in formation of a precipitate (inorganic by-products and unchanged reactants). Gravity filtration of the chloroform solution was carried out. Remaining mercury salts and complexes were removed by washing the chloroform solution with water, with 30% NaI solution, and again with water. A dried ($MgSO_4$) solution was passed through a neutral alumina column (2 x 60 cm.) which was eluted with $HCCl_3$. There were afforded almost colorless fractions. Evaporation of the $HCCl_3$ from various fractions (rotary evaporator) resulted in the isolation of an amber-colored syrup. Trituration with hot hexane initiated solidification. Crystallization occurred after several washings with hot hexane followed by the addition of cold ether. An off-white, crystalline

product N-glycoside 206 was obtained; weight 1.4 g. (25% based on 247), m.p. 148-150°. Recrystallization from petroleum ether (b.p. 30-60°)/ diethyl ether (1:2) afforded a colorless product, m.p. 155-156°. A sample of a sublimed product (140°/2 x 10^{-4} mm.) melted at 159-160°.

Anal. Calcd. for $C_{26}H_{30}N_2O_{10}$: C, 58.87; H, 5.66; N, 5.28.
Found: C, 59.03; H, 5.60; N, 5.25.

IR and NMR (Plates XLIII and XCI) data agreed well with the structure proposed for N-glucoside 206.

(C): Cleavage of the Acetate Groups in 206; Formation of the deacetylated N-glucose derivative of 4,5-dihydro-7-methoxy-1H-benz[g]indazole: Anhydrous methanol [(Mallinckrodt)(250 ml.)] was placed in 500-ml., round-bottomed flask chilled in an ice-salt bath. Ammonia gas from a commercial lecture-bottle (Matheson Co.) was bubbled into the cooled methanol for about 2 hours to effect saturation. Blocked N-glycoside 206 (0.9 g., 0.002 mole) was transferred into the methanolic ammonia solution and the flask was stoppered. The reaction flask was stored (24 hours) in a refrigerator (ca. 5°C.) and for another 24 hours at room temperature (ca. 23°C.). Excess methanol and ammonia were evaporated (rotary evaporator); a yellowish-brown syrup was obtained. Acetamide (a by-product) was removed by washing the syrup with 1 ml. $HCCl_3$ and 10 ml. of hot hexane. Purification was accomplished by allowing a chloroform solution of the syrup to pass through a neutral alumina column (2 x 50 cm.) and then eluting with methanol. Solidification did not occur by evaporating of the organic solvents to dryness. Trituration with cold CH_3OH-$(C_2H_5)_2O$ (1:9) and boiling in excess ether (ca. 250 ml.) followed by slow evaporation of the ether solution at room temperature did not initiate crystallization. Many attempts

were made using various solvents and combination of solvents, all being unsuccessful in giving a crystalline product. The crude syrup (in $HCCl_3$) was again caused to pass through a column of neutral alumina (4 x 50 cm.) which was washed thoroughly with $HCCl_3$. The $HCCl_3$ fractions were evaporated separately and again attempts at crystallization were resumed. However, they were also unsuccessful. The only proof that the compound was the free sugar-pyrazole came from NMR and IR analyses of the syrup. These spectra were very similar to those obtained on the dimethoxy analog. The latter was successfully recrystallized.

N-Glycosidation Using $Hg(CN)_2$[11,397]. The procedure used was similar (but with modifications) to that of Yamaoka.[397] 4,5-Dihydro-7-methoxy-1H-benz[g]indazole (247) (2.0 g., 0.011 mole) was dried by azeotropic distillation of its solution in nitromethane (Fisher Scientific Co.). About 50 ml. of distillate was collected from an original volume of about 250 ml. of nitromethane. The remaining nitromethane solution was cooled; the acetobromoglucose (232) (6.15 g., 0.015 mole) was added cautiously followed by 5.0 g. (0.037 mole) of anhydrous $CaSO_4$ (commercial-grade "Drierite"). To this mixture was added 2.7 g. (0.01 mole) of $Hg(CN)_2$ (Ventron), and the reaction mixture was vigorously stirred by a magnet and allowed to boil for 4 hours under N_2. Filtration was carried out while the mixture was still hot with a medium-mesh, sintered glass funnel (150 ml. capacity). Warm CH_3NO_2 (ca. 20 ml.) was used to wash the residue in the funnel. Combining the original filtrate and washings and evaporating all the nitromethane (rotary evaporator) gave a light-brown syrup. Chloroform (about 100 ml.) was added to the syrup in the evaporating flask, which was then stored in a refrigerator

for 1 day. Complex Hg and Ca salts deposited upon cooling the solution and were filtered out and discarded. The clear, amber-colored chloroform filtrate was washed with H_2O, with 30% NaI, and with H_2O; it was dried ($MgSO_4$) and evaporated to a very viscous straw-yellow syrup. Repeated trituration of the syrup with petroleum ether (b. 40-60°) with cooling in ice-bath gave a pasty, off-white product. Cold ether was added dropwise during the trituration; the pasty product in petroleum ether solidified and was filtered out and dried (23 g., 42%); m.p. 158-160°. Spectral analyses (NMR and IR, Plates XLIII and XCI) were in agreement with the proposed structure of acetylated N-glycoside 206. Mixed m.p. determination with the product of the $HgCl_2$ method showed no appreciable depression in m.p. (150-155°).

Preparation of 1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole (202). (I): The chloromercurio derivative of pyrazole 200: A suspension of pyrazole 193 (5.0 g., 0.02 mole) in 100 ml. of 50% aqueous ethanol was boiled to complete solution. One equivalent of NaOH (0.8 g., 0.02 mole) was added to that boiling solution. While hot, this alkaline solution was added dropwise to another boiling solution made from dissolving $HgCl_2$ (5.43 g., 0.02 mole) in 50 ml. of 95% ethanol. A creamy-white precipitate formed at once. This mixture was heated for an additional 3 to 4 minutes to complete digestion; heat was stopped, and the flask was cooled under a hood. A white precipitate (chloromercurio derivative 200) was collected by suction filtration in a sintered glass funnel (medium-pored, 150 ml. capacity). Crude chloromercurio compound 200 was allowed to dry thoroughly in air under a hood for many hours; 9.3 g. (100%).

(II): Chloromercurio compound 200 (9.3 g., 0.02 mole) was further

dried azeotropically by distillation with xylene. Thus a suspension of the chloromercurio derivative 200 in 300 ml. of dry xylene (dried over Na) was stirred vigorously and distilled until about 70-80 ml. of xylene had been collected. The residual xylene suspension was cooled and the acetobromoglucose (238) (8.2 g., 0.02 mole) was added. Distillation was resumed to dehydrate the mixture. There was collected another 70-80 ml. of xylene as distillate. Boiling was then continued in the residual xylene mixture (under N_2) for 14 hours with vigorous magnetic stirring. Cooled to room temperature, the reaction mixture deposited solid, presumably some brown inorganic complexes as by-products. The latter were removed by filtration and the xylene solution (yellow in color) was evaporated to a brown syrup which was dissolved in chloroform (approximately 30 ml.). Undissolved substances (presumably some sort of inorganic compounds) were filtered out. Washing the chloroform solution free of excess Hg salts was accomplished with H_2O, 30% NaI solution, and H_2O consecutively; the final solution was dried ($MgSO_4$). Passing the dried solution through a neutral alumina column (4 x 60 cm) and evaporating the chloroform gave a honey-colored syrup. Trituration with petroleum ether (b.p. 30-60°) and adding a few ml. of cold diethyl ether gave 7.4 g. (66%) of N-glycoside acetate 201, m.p. 142-146°. Sublimation at 150-160°/5 x 10^{-3} mm. gave a colorless glycoside acetate 201, m.p. 170-171°.

Anal. Calcd. for $C_{27}H_{32}N_2O_{11}$: N, 5.00.

Found: N, 4.97.

IR and NMR spectra (Plates XLIV and XCII) support the structure for N-glycoside acetate 201.

(III): Removing the acetate moieties on N-glycoside 201 with

NH_3/CH_3OH: The tetraacetyl compound 201 (3.0 g., 0.006 mole) was added to 250 ml. of methanol saturated with ammonia gas at 0° for 2 hours. The resulting yellowish solution was stored in a refrigerator for 24 hours and for another 24 hours at room temperature. Excess NH_3 and CH_3OH were volatilized on a rotary evaporator to leave a syrupy residue. This was washed with 5 ml. of hot hexane and 2 ml. of $HCCl_3$ to remove acetamide the main, by-product of hydrolysis. The resulting syrupy compound was purified on a neutral alumina column (70 x 3 cm.). The eluent $HCCl_3$ was evaporated to leave an oil which solidified after trituration several times with a methanol-ether mixture. Recrystallization (ether) gave a solid (m.p. 162-165°), yield 1.0 g. (45.6% based on acetate 201 and 30% based on pyrazole 193). The sugar-pyrazole product 202 did not sublime. Therefore, one recrystallization (ether) of a sample was considered (m.p. 163-165°) pure to submit for analysis and spectral characterization. IR and NMR spectra (Plate XLV and XCIII) agreed with the structure for free N-glycoside 202.

Anal. Calcd. for $C_{19}H_{24}N_2O_7$: N, 7.14.

Found: N, 6.87.

Preparation of 1-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole Tetraacetate (ester) (220). (A): Chloromercurio derivative (219): 10,11-Dihydro-7-methoxy-3H-naphth[1,2-g]indazole (249) (1.5 g., 0.006 mole) was dissolved in 200 ml. of boiling 80% ethanol. One equivalent of NaOH (0.24 g., 0.006 mole) was added to the previous solution, which was boiled for five minutes. This solution was added dropwise to 2.0 g. (0.0073 mole) of $HgCl_2$ dissolved in 25 ml. of boiling 95% ethanol. An immediate white precipitate appeared. This was cooled and filtered out with a medium-sized sintered glass funnel.

The precipitate was washed successively with cold water, cold ethanol, and finally ether and dried in air, yield 2.91 g. (100%).

(B): N-Glycosidation of the chloromercurio derivative: a suspension of chloromercuriopyrazole 219 (3.4 g., 0.007 mole) in 400 ml. of dry xylene (dried over sodium ribbon) was distilled to remove water azeotropically. About 100 ml. of xylene was distilled, and the mixture cooled to room temperature. Tetra-O-acetyl-α-D-glucopyranosyl bromide (4.1 g., 0.01 mole) was added to the cooled xylene suspension. Another 100 ml. of xylene was added and the suspension was again distilled with vigorous magnetic stirring. The reaction mixture was boiled 8 hours (N_2 atmosphere). A brown precipitate was filtered off from the cooled reaction mixture and discarded (this was presumably some inorganic by-products). Xylene was completely evaporated by using a hot water bath and rotary evaporator. Chloroform was added (about 50 ml.) to redissolve the syrup obtained. Another fine brown solid inorganic complex was removed by filtration. The chloroform filtrate was washed with H_2O, 10% NaI, and H_2O successively, and dried ($MgSO_4$). Purification of the solution was carried out by passing it through a neutral alumina column (3 x 50 cm.). Chloroform was also used as the eluent. Evaporation of the chloroform left a light-yellowish syrup which crystallized via trituration using first boiling hexane and then cold ether. The technique also involved boiling the syrup in hexane; the solution was cooled and ether was then added while chilling in ice-bath and stirring vigorously; yield was 2.1 g. (52%), m.p. 110-114°. Recrystallization from hexane-ether gave pure, white N-glycoside 220, m.p. 116-7°.

IR and NMR (Plates XLVI and XCIV) were consistent with the structure proposed for N-glycoside 220.

(C): A methanolic ammonia solution effected hydrolysis of the acetylated N-glycoside 220. Anhydrous methanol (Mallinckrodt) (ca. 200 ml.) was placed a in 500-ml., round-bottomed flask which was cooled in ice-sodium chloride bath. Ammonia gas from a commercial lecture bottle (Matheson Gas Co.) was bubbled very slowly into the cooled methanol for about 2 hours to effect saturation. Blocked N-glycoside 220 (1.5 g., 0.0026 mole) was added to the saturated methanolic ammonia, and the flask was stoppered tightly. The flask in that condition was kept for 24 hours at about 5^{o} (refrigerator temperature) and for another 24 hours at room temperature. Excess methanol and excess NH_3 were removed by evaporation (rotary evaporator). A honey-like residue was obtained. Washing the residue with 5 ml. of hot hexane followed by 2 ml. of $HCCl_3$ was performed in order to remove acetamide (by-product). The syrup was evaporated until free from solvents and triturated with anhydrous CH_3OH until solidification occurred. Thus, crude deblocked N-glycoside 221 melted at 210-212^{o} and weighed 0.15 g. [14% based on 220, 7.3% based on pyrazole 249]. Sublimation ($200^{o}/10^{-4}$ mm.) gave a highly pure compound, m.p. 219^{o}-220^{o}. IR and NMR analysis (Plates XLVII and XCV) agree well with the structure proposed for N-glycoside 221.

Anal. Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.08; H, 5.82; N, 6.80.
Found: C, 64.35; H, 5.86; N, 6.84.

Attempted Condensation of D-Glucose With 7-Methoxy-4,5-dihydro-1H-benz[g]indazole (247) Using Polyphosphoric Ester (PPE):[312,345] An attempt to condense the title compound using PPE according to the method of G. Schramm[312,345] (1962) was not fruitful. Thus indazole 247 (3 g., 0.017 mole) was dissolved with magnetic stirring in 100 ml. of DMF [water content (0.1-0.2%) was necessary according to Schramm[312,345]].

Concentrated HCl (ca. 1.2 ml.) was added to the solution. PPE (10 g.) prepared according to Schramm[312,345] was added in one lot. Anhydrous D-glucose [1.5 g., 0.008 mole (Mallinckrodt)] was dissolved in 70 ml. of DMF and added dropwise to the acidic (pH 3) indazole solution. The solution was heated at 50-60° in an oil bath for 22 hours with continuous magnetic stirring. DMF was distilled off with a rotary evaporator and the moist residue was brought to pH 7 (pH paper) with 5% NH_4OH solution. A solid precipitated but it was identified by m.p., mixed m.p., NMR, and IR as unchanged indazole 247 recovered material (2.85 g.).

An Attempted One-step Synthesis of N-Glycoside of 7-Methoxy-4,5-dihydro-1H-benz[g]indazole (247) With Acetobromoglucose (238) in Dry Dioxane: Indazole 247 (1.5 g., 0.008 mole) was dissolved in 40.0 ml. of dry dioxane, and the solution was mixed with 1.0 g. (0.003 mole) of acetobromoglucose.[99] The resulting mixture was boiled for 2 hours under N_2. A solid substance (crystalline, off-white) appeared in the reaction flask. This was filtered off after cooling the reaction mixture to room temperature. This solid, m.p. 270-3° (decomp.), was presumed to be the hydrobromide of 247. Dioxane was removed (rotary evaporator) whereby a white solid deposited on the inside walls of the evaporation flask. Ether (20 ml.) was added and the suspension was filtered. Comparing the m.p. of the crude product (150-155°) and mixed m.p. with the starting indazole (pure m.p. 162-164°, mixed m.p. 158-160°) made it evident that reaction had not taken place. This was supported by an NMR analysis of the recovered indazole (78.5%). This experiment might usefully be repeated on a larger scale with higher-boiling aprotic solvents like DMSO or DMF.

The Reaction of 6,7-Dimethoxy-1-tetralone (182) and 95% hydrazine

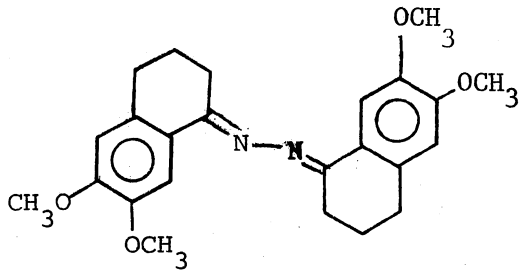
in Methanolic Sodium Methoxide Medium; the Isolation of an Unknown Compound: 6,7-Dimethoxy-1-tetralone[174] (182) (4.12 g., 0.02 mole) was dissolved in 100 ml. of absolute CH_3OH containing 1.35 g. (0.025 mole) of sodium methoxide (reagent grade, Fisher Scientific Co.). The mixture was boiled for 3 hours under N_2 and allowed to cool. More CH_3OH (ca. 30 ml.) was added to dissolve the precipitate and the clear light-brown solution was stored in the refrigerator (1 day). Hydrazine [(95%, 3.0 g., 0.094 mole), Eastman Organic] was added to the cold reaction solution which was warmed to 60° (1 hour). It was cooled to room temperature and stored in the hood and exposed to air for slow evaporation of solvent [CH_3OH and excess reactants (H_2NNH_2)]. Acidification with HCl (6 N) was done dropwise to a neutral pH (pH paper). A brown oil settled out; this was extracted with benzene (2 x 50 ml.) and then ether (1 x 25 ml.). The organic solutions were combined, washed with H_2O, and dried ($MgSO_4$). Evaporation of solvents gave an oily product which when triturated with cold 95% ethanol solidified. There was obtained a bright-yellow crystalline product, m.p. 218-220°. Recrystallization from THF-C_2H_5OH (95%) yielded a canary-yellow, crystalline compound, m.p. 220-2°; weight 1.5 g. Microanalysis gave the following results:

Anal. Calcd. for $C_{26}H_{30}N_2O_2$: C, 69.44; H, 6.88; N, 6.45.

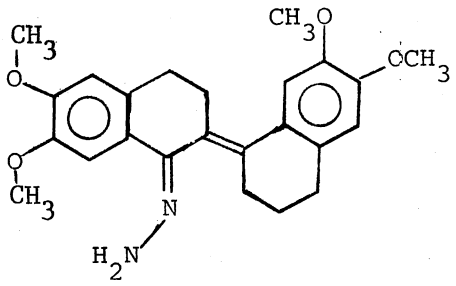
Found: C, 69.28; H, 6.49, N, 6.29.

Two strong contenders for the structure of this unknown solid were (a) and (b), both of which had the identical calculated analyses. Spectral data were as follows: IR(KBr), cm^{-1}, 1570-1580 (C=C or C=N), 1240-1250 (C-O); NMR ($DCCl_3$), 2 singlets (2H), δ 6.60 and 7.84 (ArH), 2 singlets (6H), δ 3.88 and 3.90 (ArO CH_3), 2 multiplet (6H), δ 1.95 and 2.80 ($CH_2CH_2CH_2$); MS, m/e (M^+) 408.

Structures (a) or (b) were thus considered to be possible candidates for the unknown compounds. Both have a molecular weight of 408.



(a)



(b)

There was no H-D exchange (with D_2O) in the NMR spectrum, however, to support (b). Furthermore, from the integration of the NMR spectrum of the compound, (a) might be expected to give a pattern consistent with a symmetrical anti isomer. Isomer (b) would not be expected to give such a spectral pattern. Thus, taken on the whole, the data supported structure (a).

Reaction of Veratrole, 3-Carbomethoxypropanoic Acid and 115% PPA at 100°: Veratrole (239) (138.0 g., 1.0 mole) was mixed with 3-carbomethoxypropanoic acid[84] (242) (198.0 g., 1.5 mole) and the mixture was added to 500 g. of 115% PPA.[366] Manual stirring was used while the viscous reaction mixture was warmed to 80-90°. Stirring became more facile as the temperature rose. A deep-violet color developed upon heating and persisted throughout the 2-hour period allowed for the reaction at 90-100°. The reaction mixture was cooled with continuous stirring to room temperature and poured onto about 2 kg. of crushed ice. Vigorous stirring resulted in the deposition of an oily substance which soon solidified to a white precipitate. The precipitate changed, after

several hours of cooling in the aqueous acidic medium, to a gummy material. Water was decanted and the gummy material was washed carefully by $NaHCO_3$ solution and then with water until neutral (pH paper). Ethanol (95%, ca. 200 ml.) was added to the gummy product and the mixture was triturated several minutes in the cold. This formed a crystalline precipitate. The product was filtered and recrystallized from boiling 95% ethanol, m.p. 220-2°. The undissolved substance, obtained from the ethanol recrystallization, was recrystallized from acetone, m.p. 128-130°. The ratio of products by weight was 1:5. Mass spectral analysis of the ethanol fraction (m.p. 220-222°) gave an m/e 340 (M^+), while the acetone fraction (m.p. 128-130°) gave an m/e 252 (M^+). Both compounds had C=O absorption bands in the IR spectrum at 1739 cm^{-1} and were very similar. Since both compounds appeared to give identical NMR spectra, the two products may only be different crystalline forms. Further studies to identify that unusual reaction of hot 115% PPA with veratrole and 3-carbomethoxypropanoic acid were terminated at that stage. The compound of m/e 252 (M^+) was, of course, not methyl 4-(3 ,4 -dimethoxyphenyl)-4-butanoate (222) but we cannot rule out a 1,2,3-substituted benzene analog.

Condensation of Hydroxymethylene Ketone 232 With Methylhydrazine; Formation of Isomers: In similar fashion to the condensation of hydroxymethylene ketones with substituted arylhydrazines, this experiment was carried out using methylhydrazine. The hydroxymethylene compound 232 (1.6 g., 0.007 mole) was dissolved in 50 ml. of CH_3OH and 2 drops of acetic acid were added. To that solution was added 8.0 ml. (8.4 g., 0.183 mole) of 98% CH_3NHNH_2 (Aldrich Chemical Co.), and the mixture magnetically stirred and boiled (3 hours) under N_2. Concentration to dry-

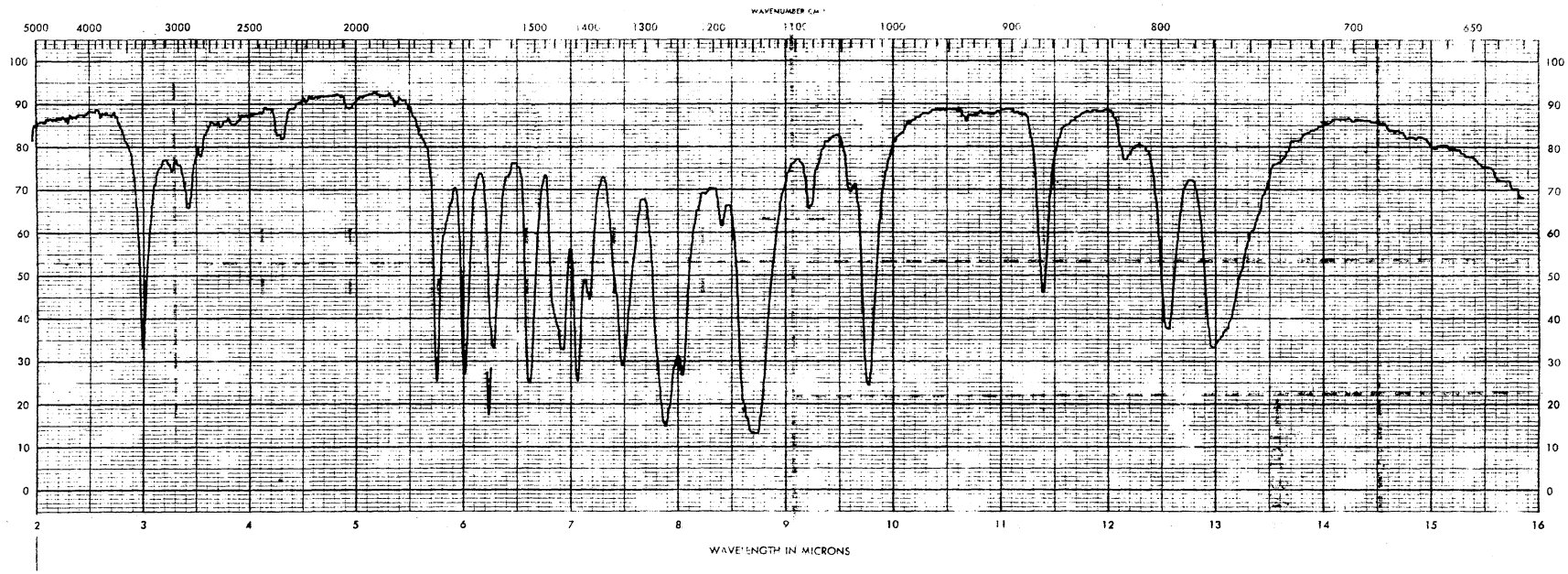
ness (rotary evaporator) gave a crude product (creamy-white) which was recrystallized from 50% C_2H_5OH; weight 1.45 g. (ca. 85%), m.p. 90-105°. Sublimation (100°/10^{-4} mm/Hg) gave a pure material (lighter in color) but the m.p. was unchanged. NMR analysis revealed four $O\underline{CH}_3$ (singlets 12 protons) at δ 3.7-3.95. An obvious conclusion was that an 1-N methyl and 2-N isomeric mixture of methyl pyrazoles was present. No attempt was made to separate the isomers or study the mixture further.

Attempted Bromination of the Allylic Position of Alkene 242 by Bromine in the Presence of Light. In a 250-ml., round-bottomed flask fitted with a condenser, a dropping funnel and a thermometer was placed a solution of alkene 242 (5.0 g., 0.029 mole) in 20 ml. of pure CCl_4. Bromine [(reagent-grade, Fisher Scientific Co.); 4.6 g., 0.058 mole] was dissolved in 50 ml. of pure CCl_4, and the solution was charged to the dropping funnel. The source of light used in this experiment was a 150-watt, frosted, tungsten lamp (Westinghouse Electric Corporation). The reaction was initiated by adding the bromine solution dropwise into the magnetically stirred CCl_4-alkene solution with the light directed at the reaction flask. The bromine color disappeared during the addition period (1 hour). A few droplets of CCl_4 condensed as the temperature rose to about 60-70°. Evaporating the CCl_4 solvent (after 2 hours) from the colorless solution yielded a crystalline product. Recrystallization from 95% ethanol gave a highly pure bromo compound (2.5 g.), m.p. 122-3°. An NMR analysis of the bromo compound showed a multiplet (centered at δ 7.6) corresponding to five aromatic protons; a singlet at δ 3.89 due to $ArO\underline{CH}_3$ (with 3 protons); and a singlet at δ 2.6 due to $Ar\underline{CH}_3$ (with 3 protons) (CCl_4). Mass spectral data showed M^+ at a m/e = 251. It was concluded that a single bromine atom was introduced in one

position. However, dehydrogenation of the 3,4-positions possibly had taken place (presumably via a bromination-dehydrobromination process). Apparently, two simultaneous undesired side-reactions occurred and no further studies of the process were conducted.

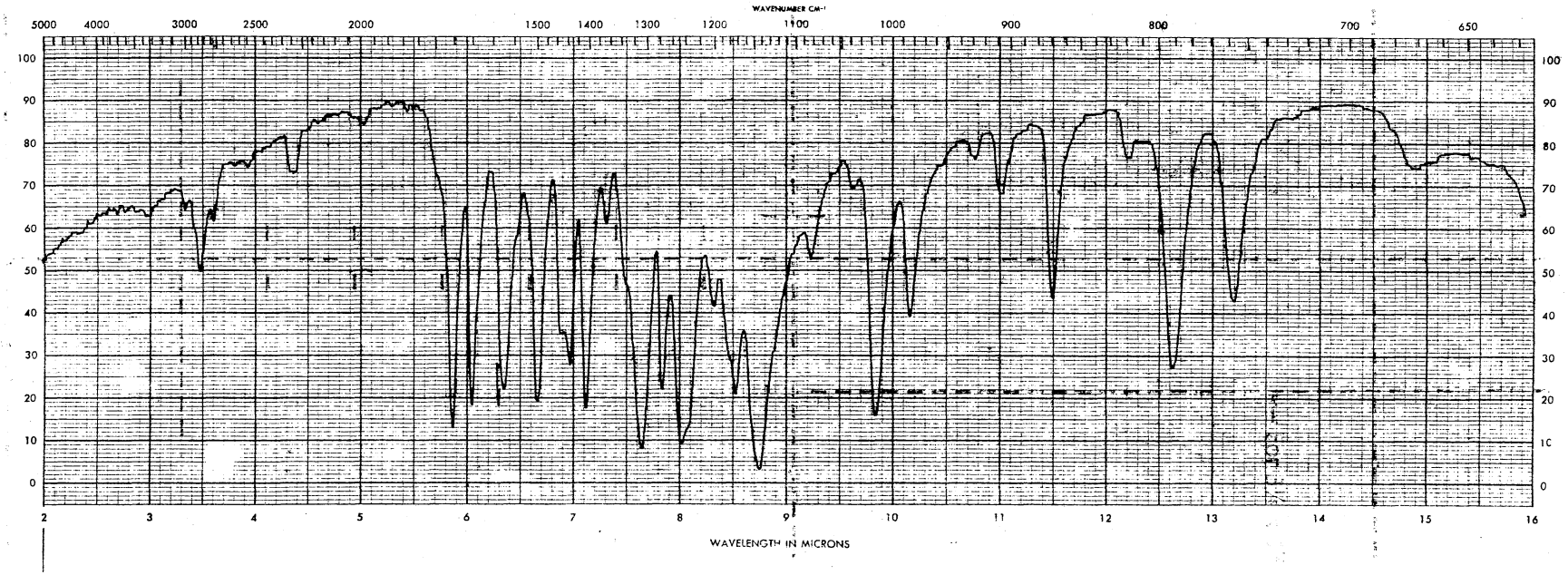
Preparation of 6-Methoxy-1-methyl-3,4-dihydronaphthalene[53] (242). The procedure was a modification of that of Bhattacharyya[53]. Thus, 6-methoxy-1-tetralone (240) (50.0 g., 0.312 mole) was dissolved in 200 ml. of a solution of dry benzene-dry ether (3:1). This solution was added dropwise (under N_2) to a Grignard reagent prepared from 57.0 g. (0.400 mole) of CH_3I and 9.7 g. of pure Mg (0.400 g. at.) in 200 ml. of dry ether. After all the ketone had been added, the reaction mixture was stirred (3 hours) at room temperature (under N_2). A white complex precipitated out after boiling the reaction mixture for 1 hour. Stirring was allowed to continue overnight at room temperature. Cold concentrated H_2SO_4 (ca. 20 ml.) was dropped in cautiously with continuous stirring while the reaction flask was cooled in an ice-bath. Decomposition with cold water (ca. 100 ml.) was performed by careful addition using a dropping funnel (and mechanical stirring). Cold water was allowed to drip into the mixture until most of the white complex disappeared. The organic layer was separated, and the aqueous layer was extracted with benzene. Combining the organic solutions and washing successively with H_2O, saturated $NaHCO_3$, and H_2O and then drying ($MgSO_4$) and evaporating the solvents gave an amber-colored oil (crude alkene 242). Distillation of that crude alkene at 85-90°/0.2 mm. (lit.[53] b.p. 128-30°/6 mm.) gave a slightly yellowish liquid; weight 28 g. (52%). IR and NMR spectra were indicative of the presence of alkene 242.

PLATE I



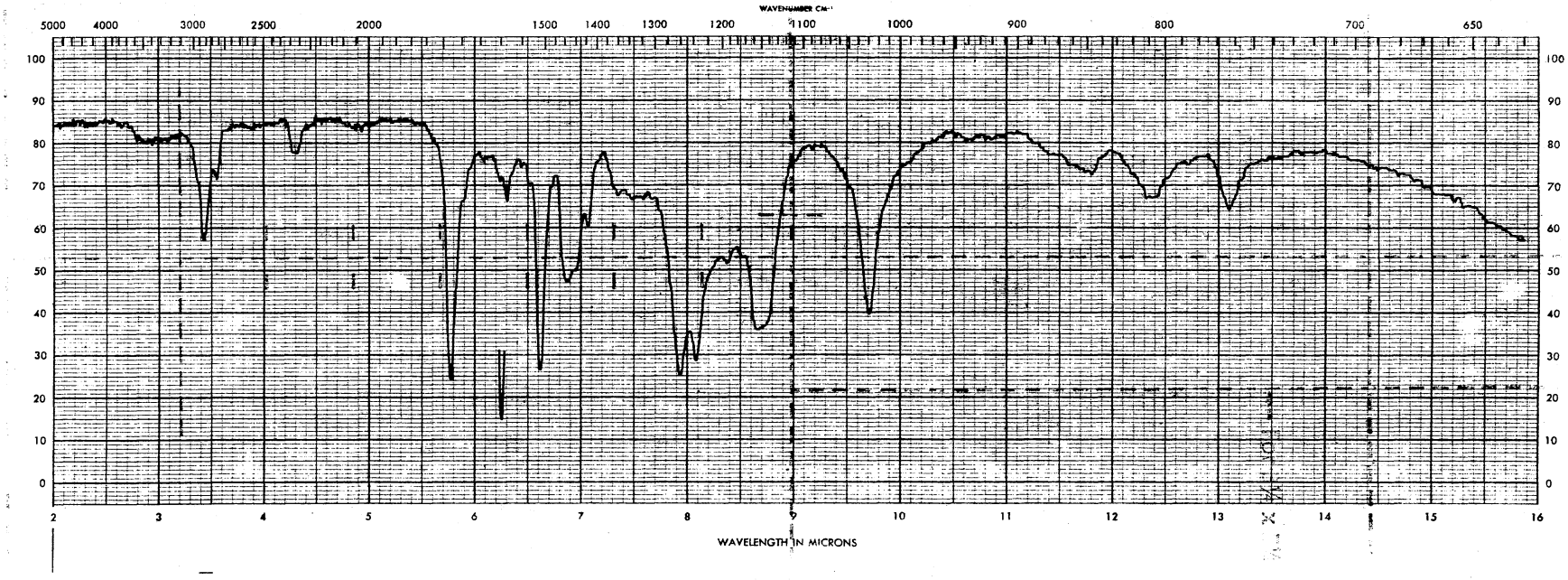
4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoic Acid (226), KBr Pellet

PLATE II



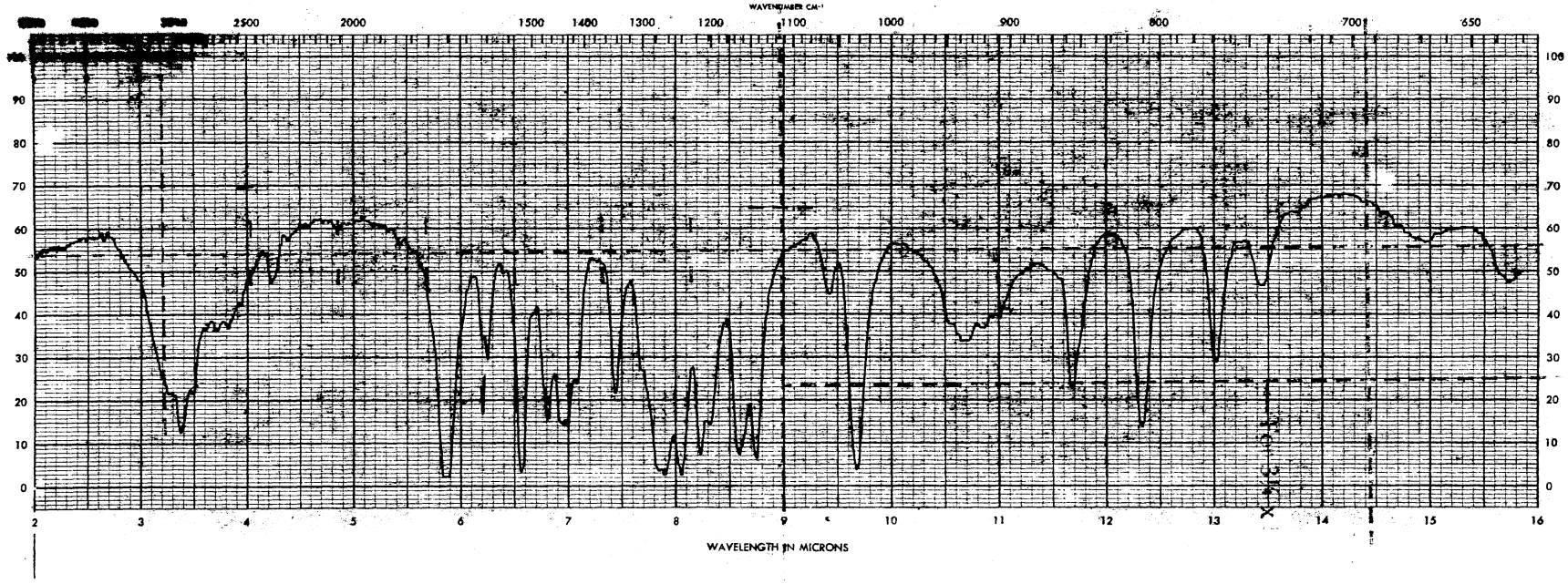
Methyl 4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoate (222), KBr Pellet

PLATE III



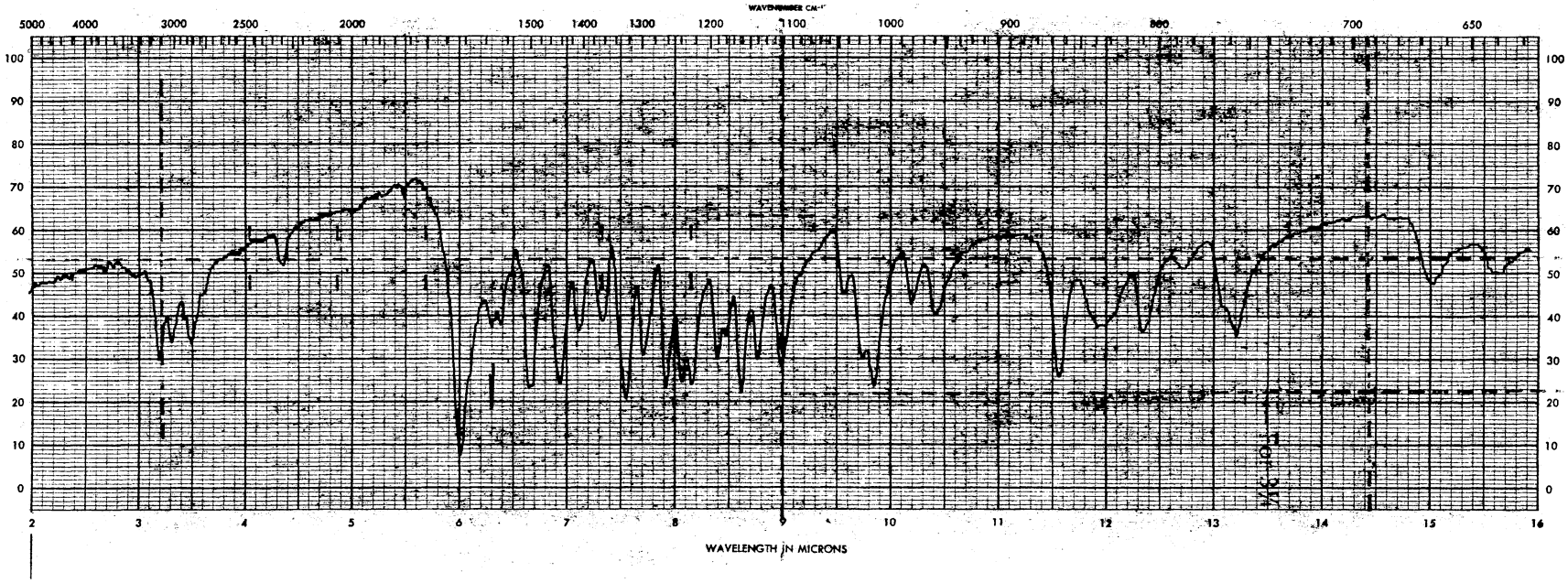
Methyl 4-(3 ,4 -Dimethoxyphenyl)butanoate (223), Film on NaCl Plates

PLATE IV



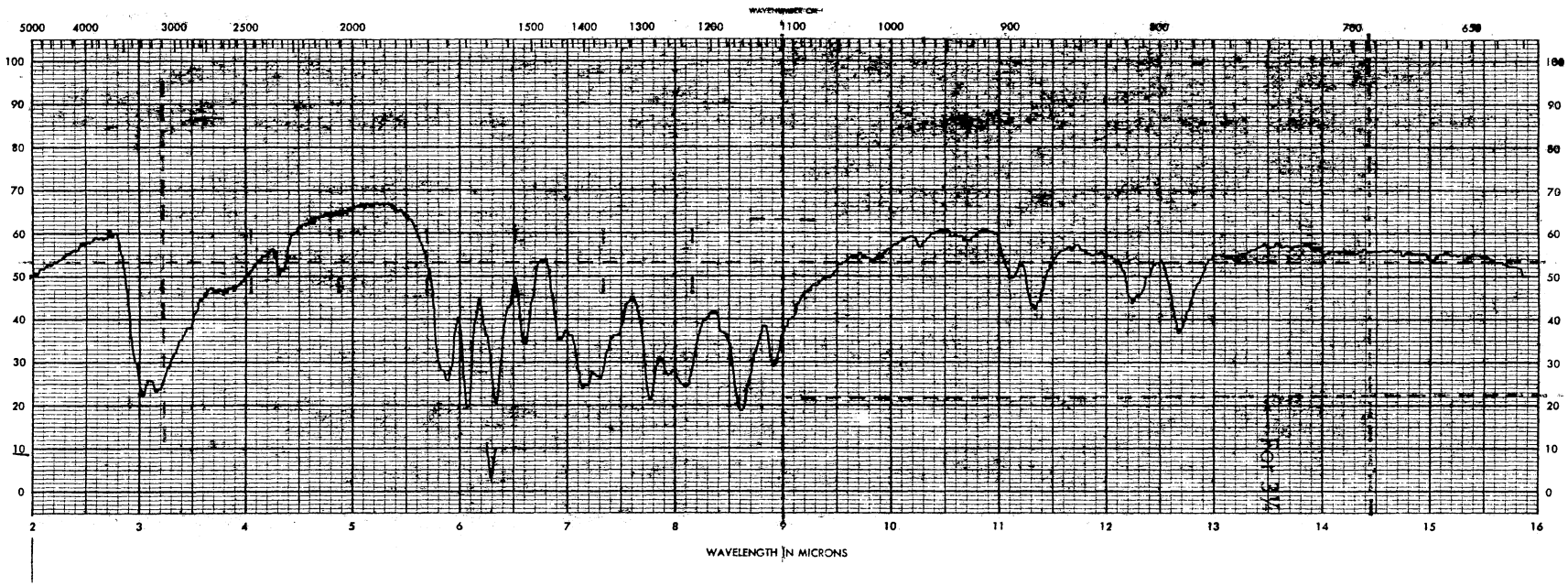
4-(3 ,4 -Dimethoxyphenyl)butanoic Acid (224), KBr Pellet

PLATE V



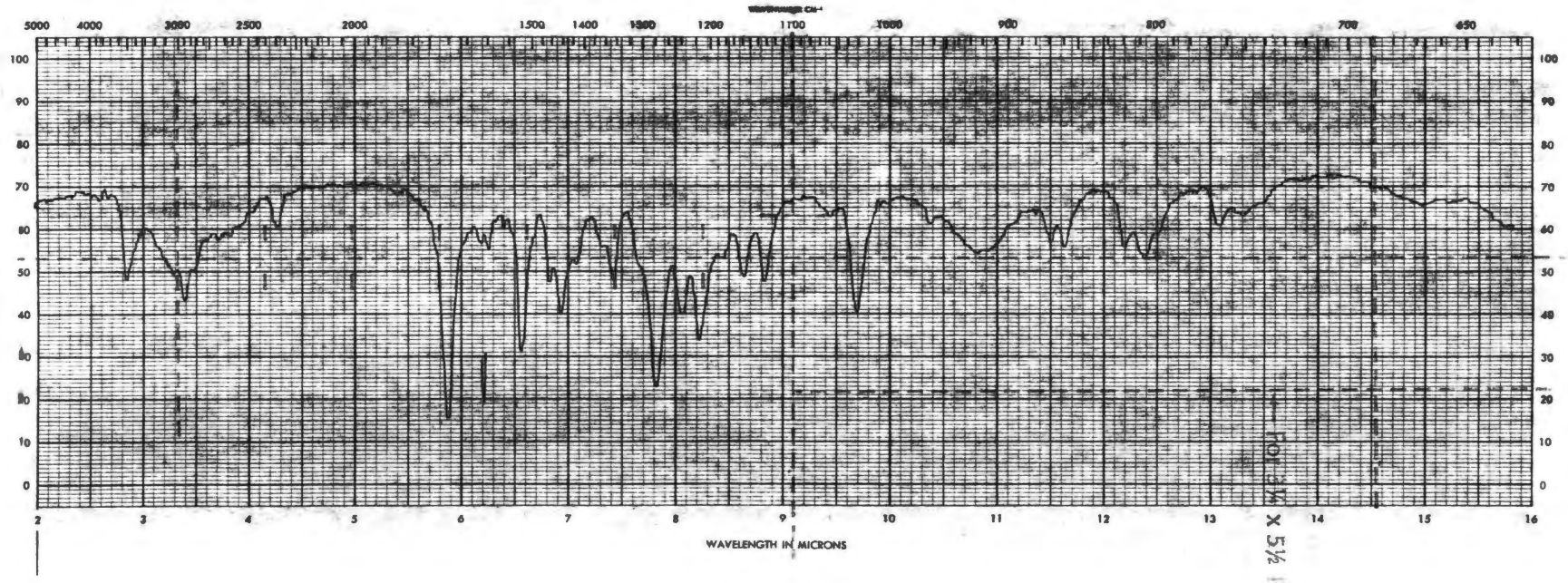
6-(3,4-Dimethoxyphenyl)-4,5-dihydro-3(2H)-pyridazinone (234), KBr Pellet

PLATE VI



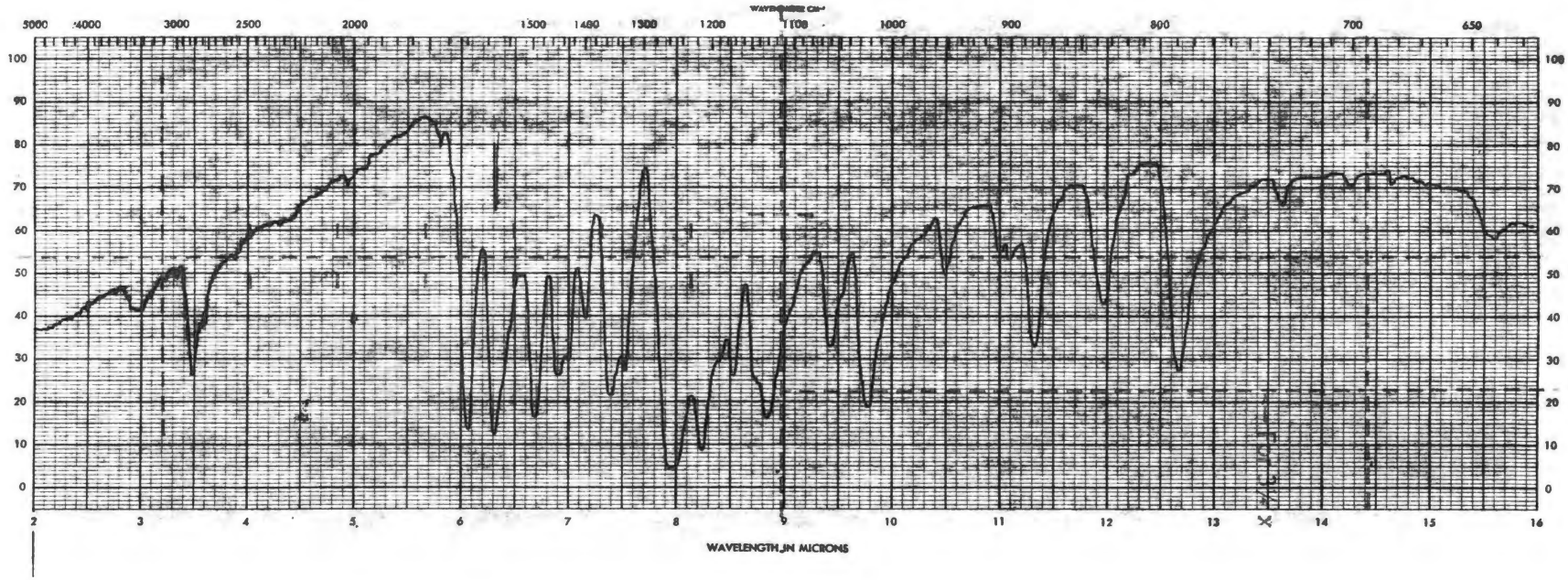
3-Protocatechuoylpropionic Acid (227), KBr Pellet

PLATE VII



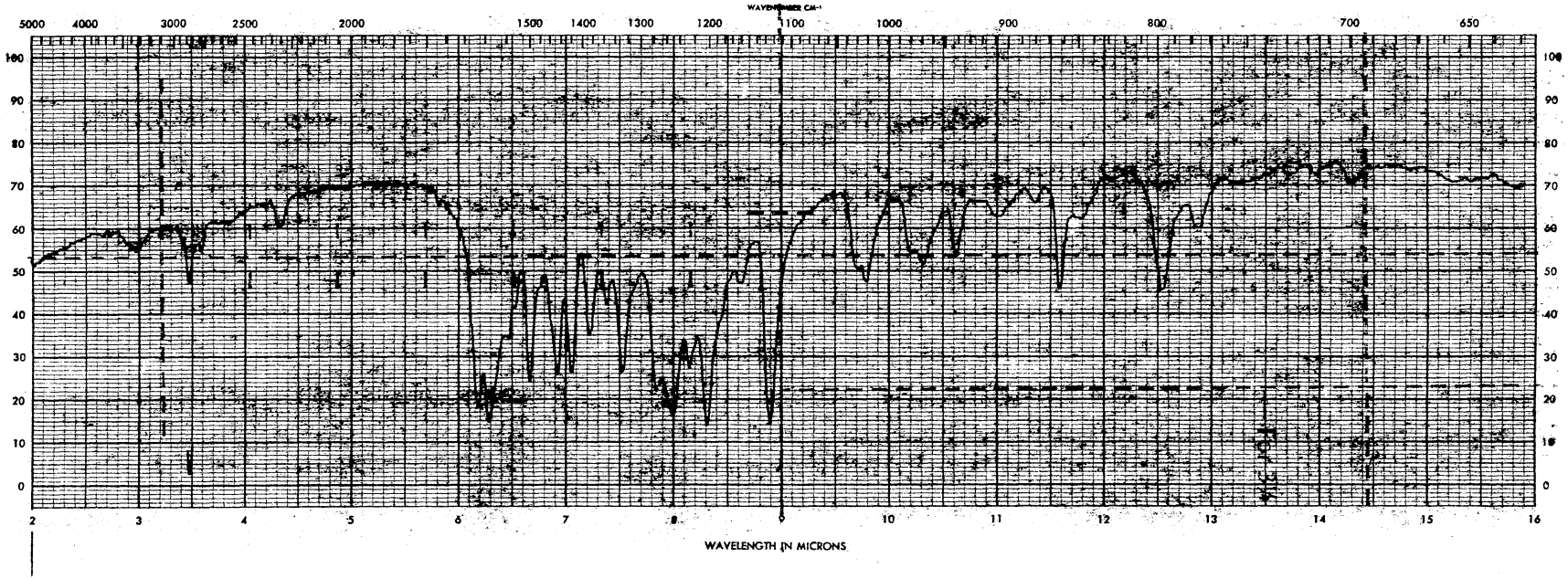
4-(3-Hydroxy-4-methoxyphenyl)butyric Acid (225), KBr Pellet

PLATE VIII



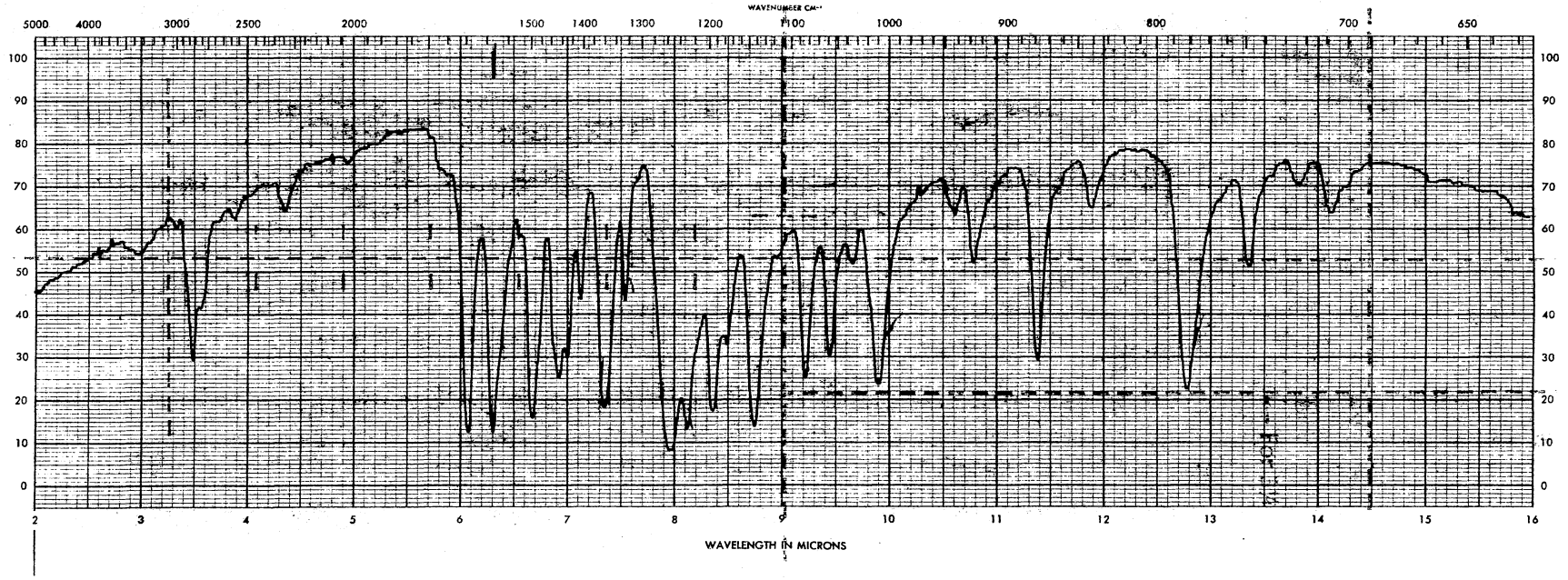
3,4-Dihydro-6,7-dimethoxy-1(2H)-naphthalenone (182), KBr Pellet

PLATE IX



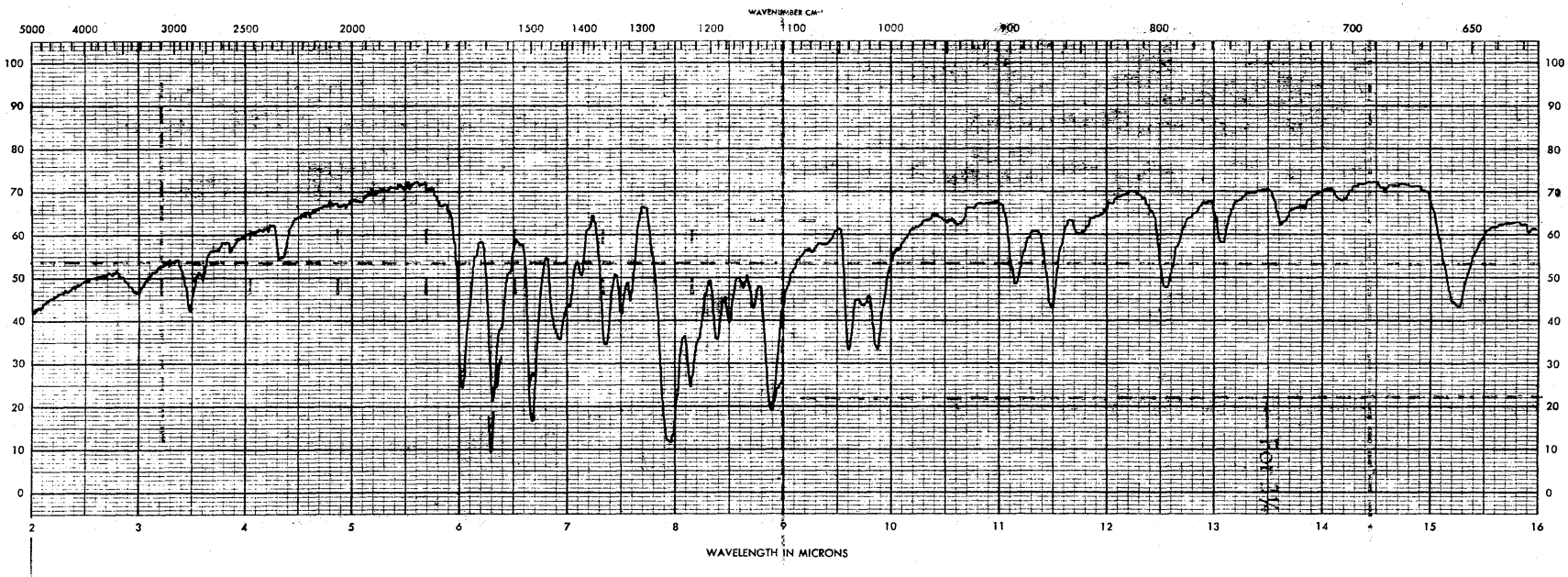
3,4-Dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1(2H)-naphthalenone (232), KBr Pellet

PLATE X



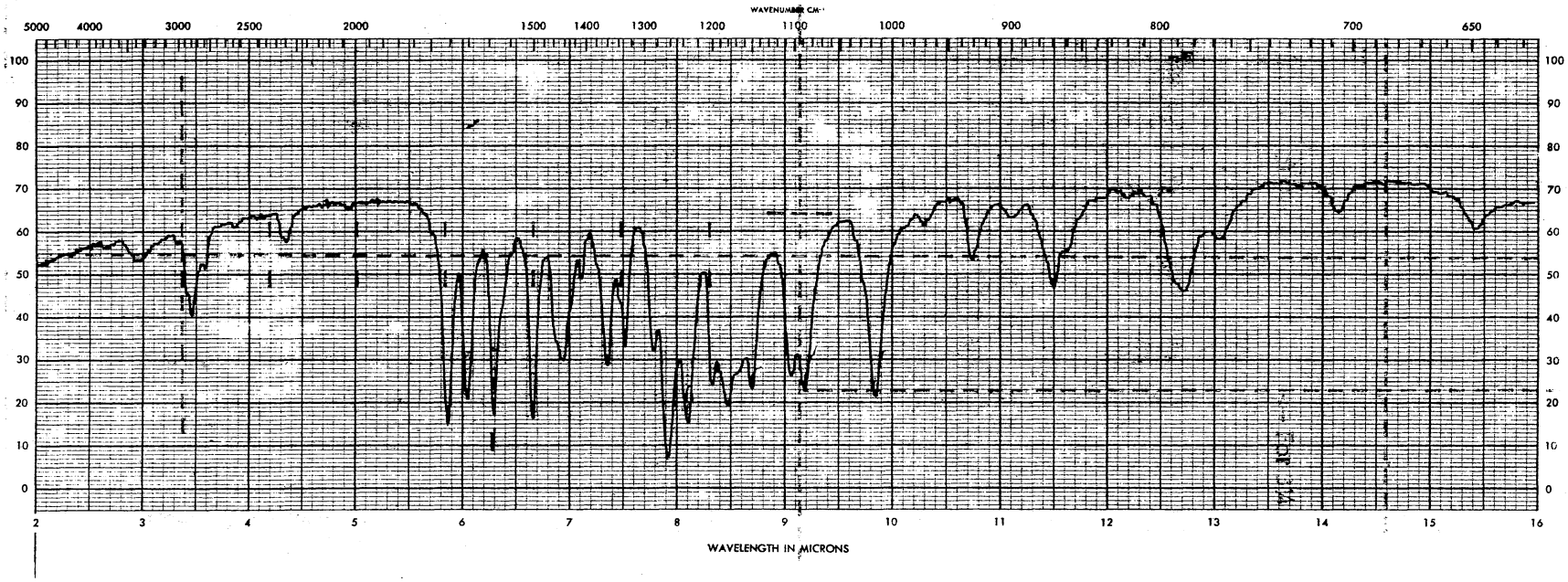
3,4-Dihydro-6,7-dimethoxy-2-methyl-1(2H)-naphthalenone (231), KBr Pellet

PLATE XI



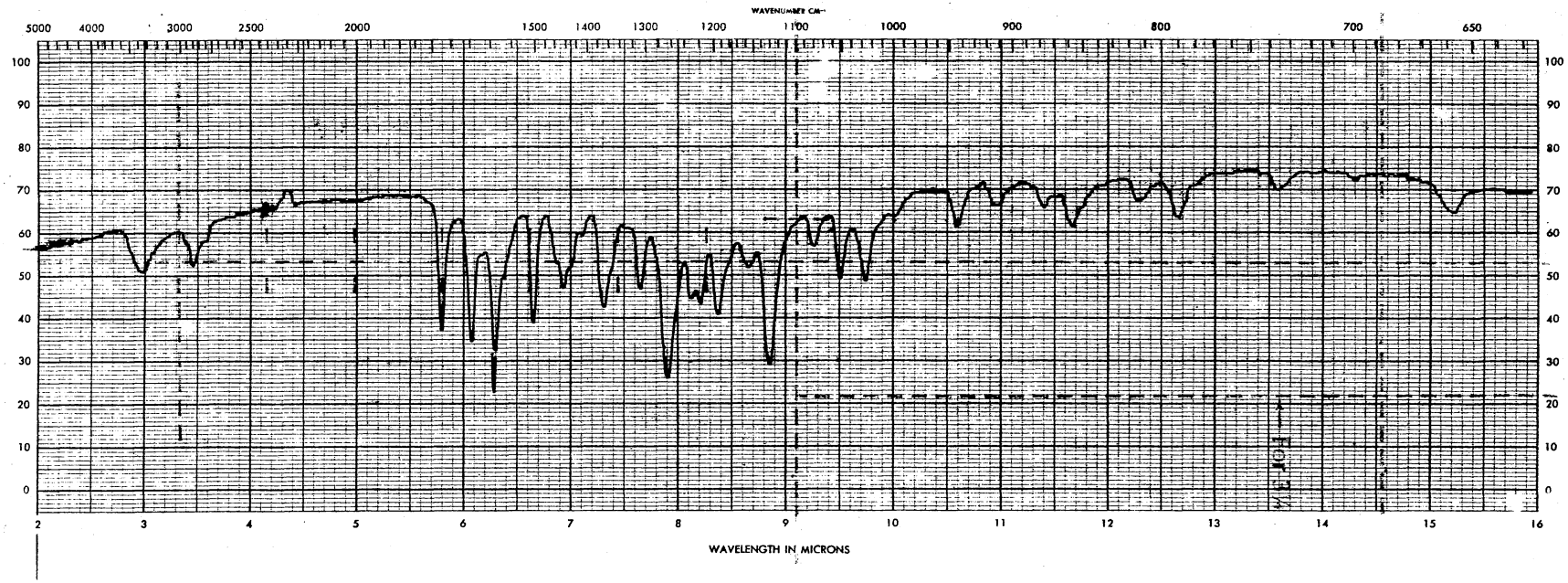
2-Bromo-3,4-dihydro-6,7-dimethoxy-1(2H)-naphthalenone (229), KBr Pellet

PLATE XII



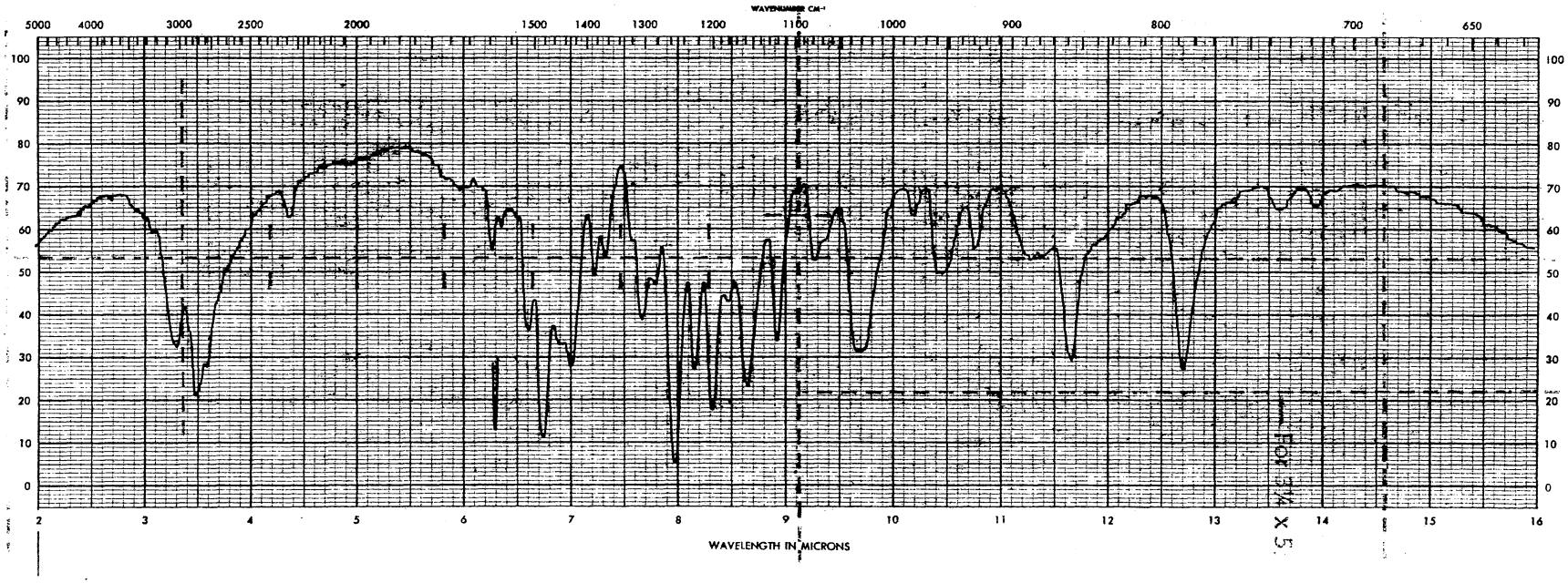
Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-oxo-2-naphthoate (228), KBr Pellet

PLATE XIII



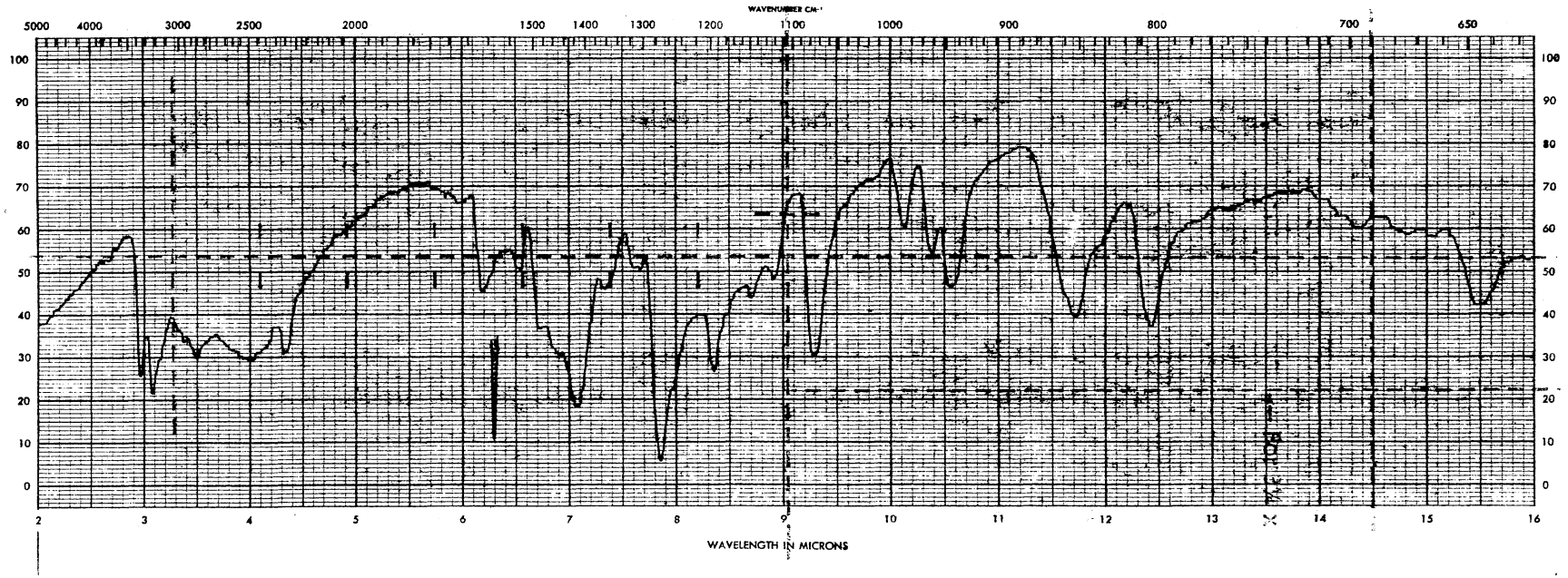
Methyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230), KBr Pellet

PLATE XIV



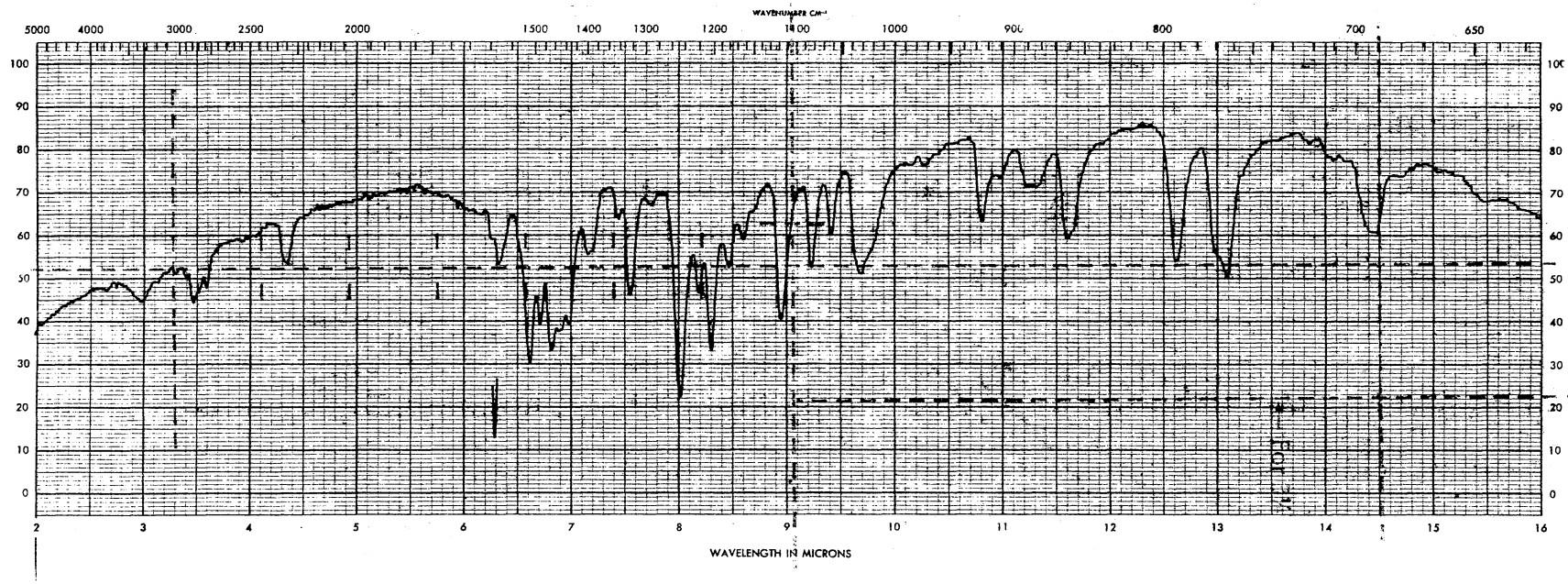
4,5-Dihydro-7,8-dimethoxy-1H-benz[g]indazole (193), KBr Pellet

PLATE XV



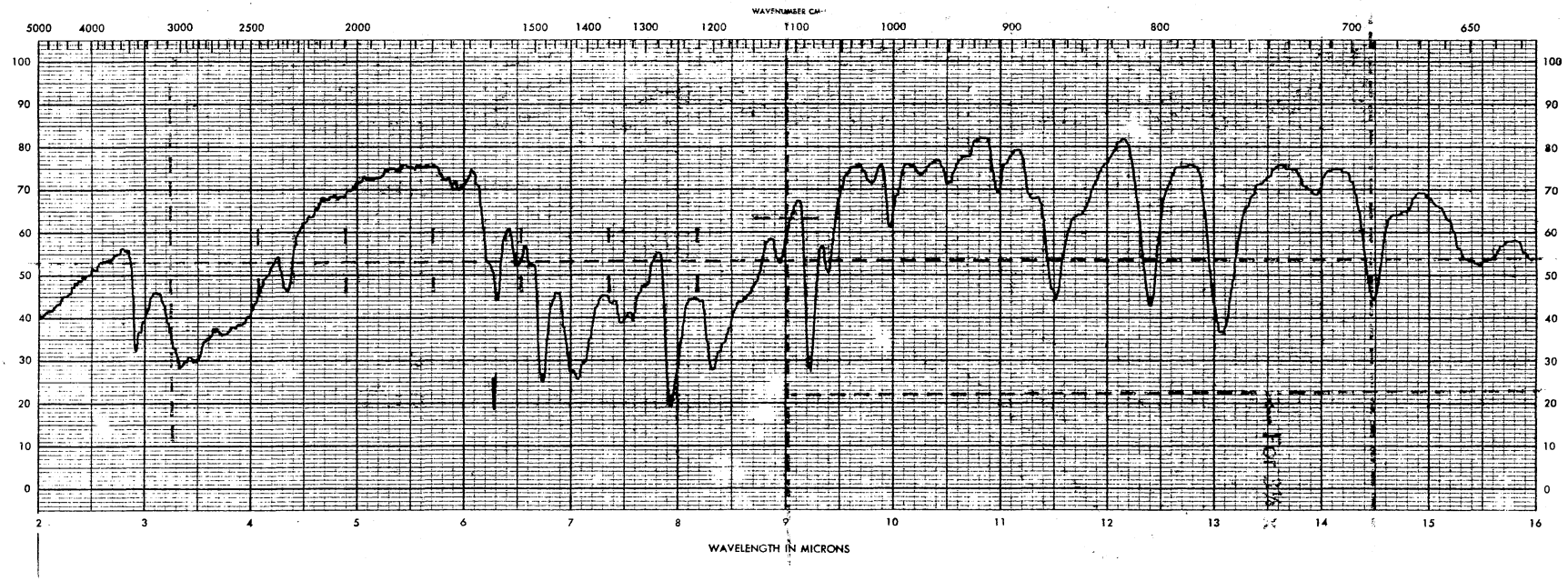
4,5-Dihydro-1H-benz[g]indazole-7,8-diol (194), KBr Pellet

PLATE XVI



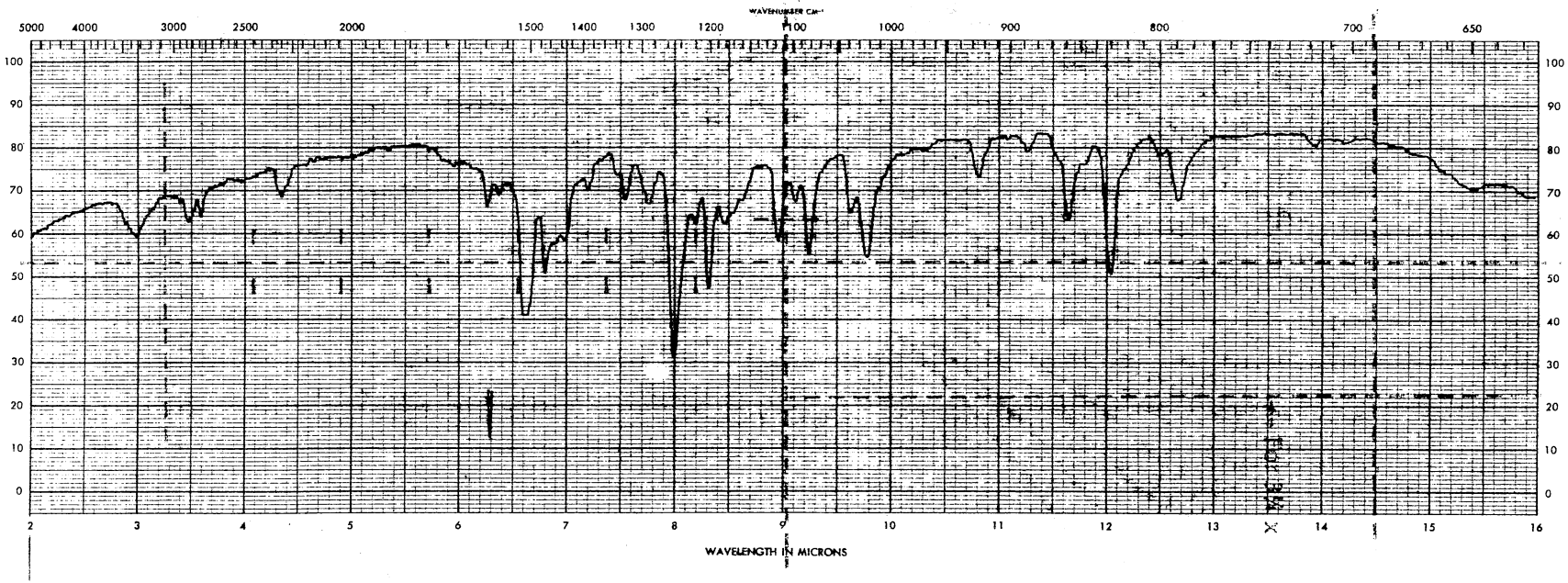
4,5-Dihydro-7,8-dimethoxy-1-phenyl-1H-benz[g]indazole (195), KBr Pellet

PLATE XVII



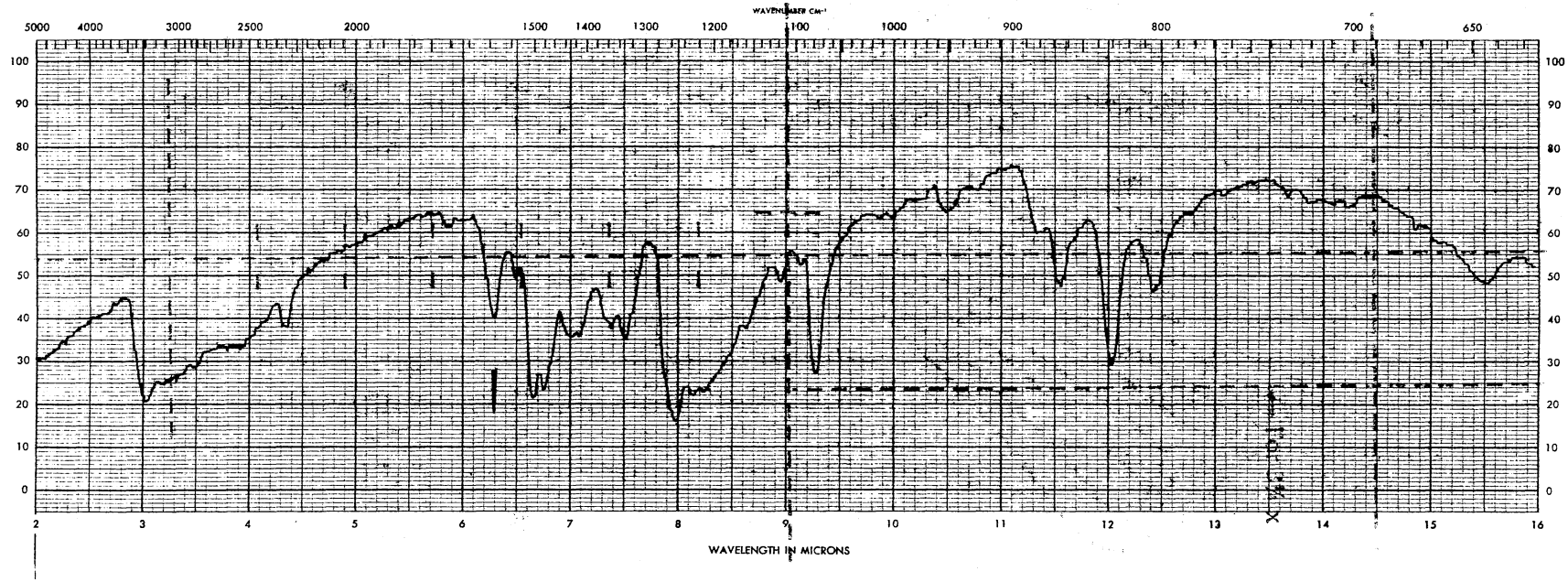
4,5-Dihydro-1-phenyl-1H-benz[g]indazole-7,8-diol (196), KBr Pellet

PLATE XVIII



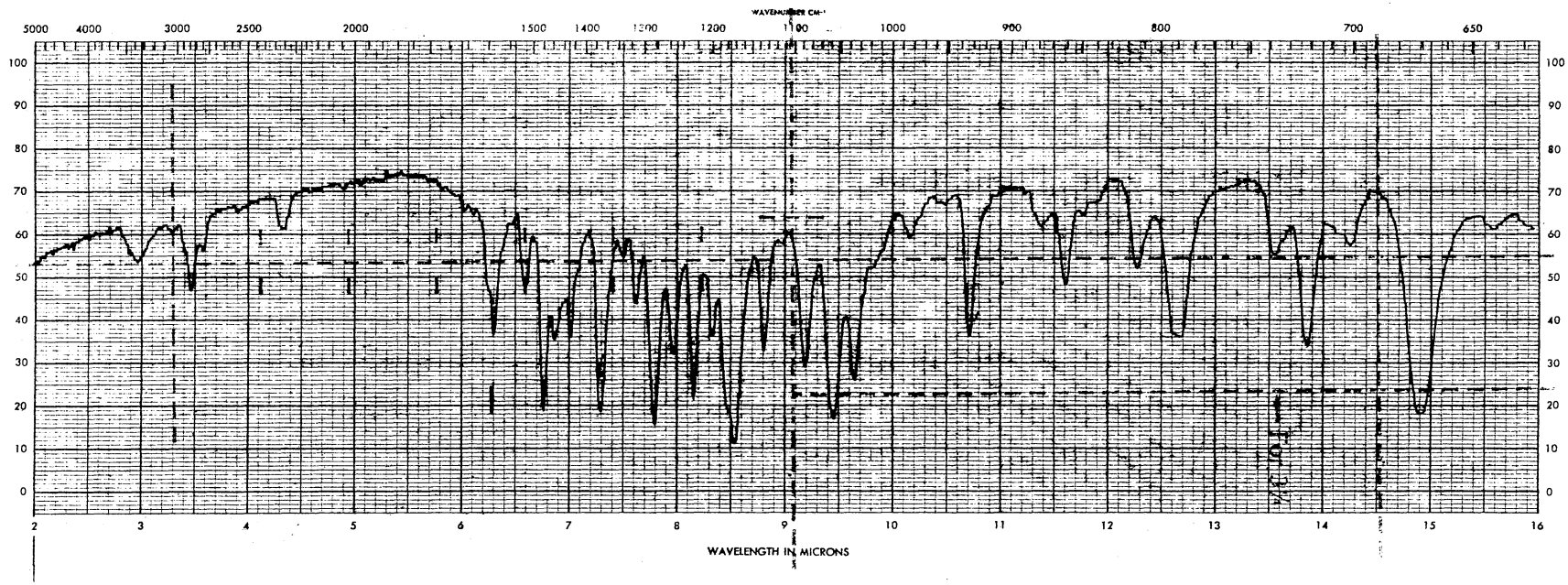
4,5-Dihydro-7,8-dimethoxy-1-(p-methoxyphenyl)-1H-benz[g]indazole (197), KBr Pellet

PLATE XIX



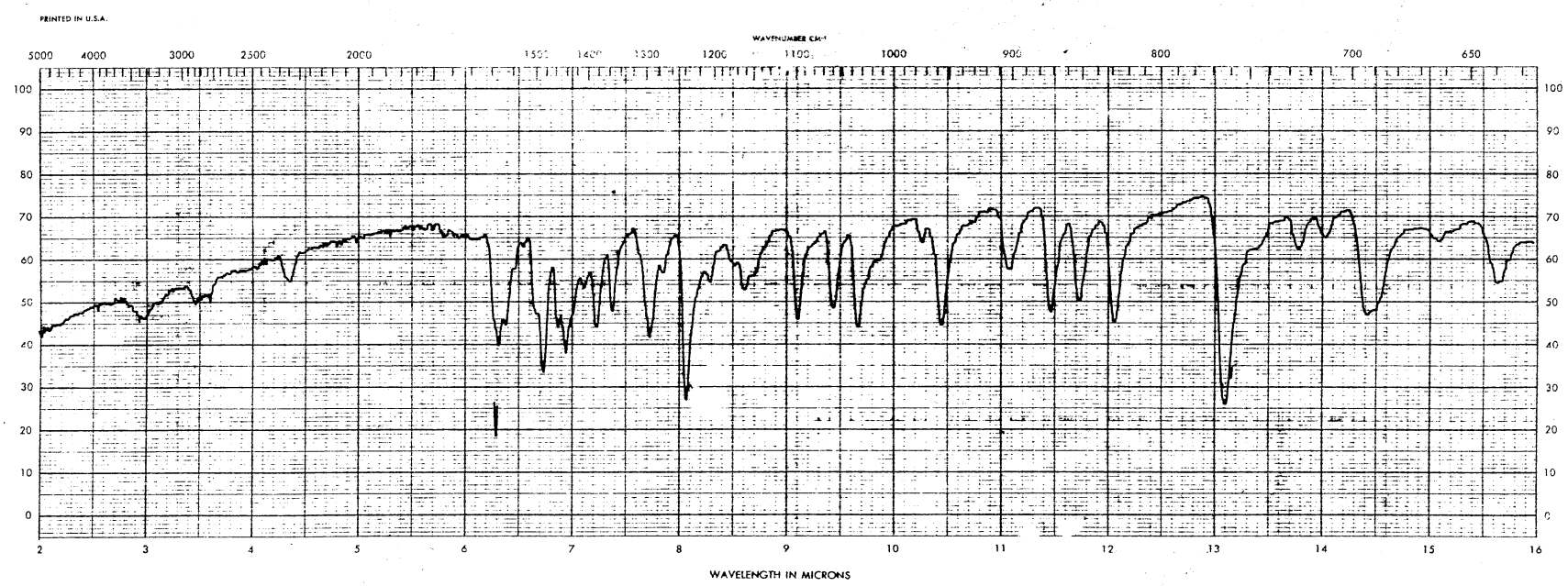
4,5-Dihydro-1-(p-hydroxyphenyl)-1H-benz[g]indazole-7,8-diol (198), KBr Pellet

PLATE XX



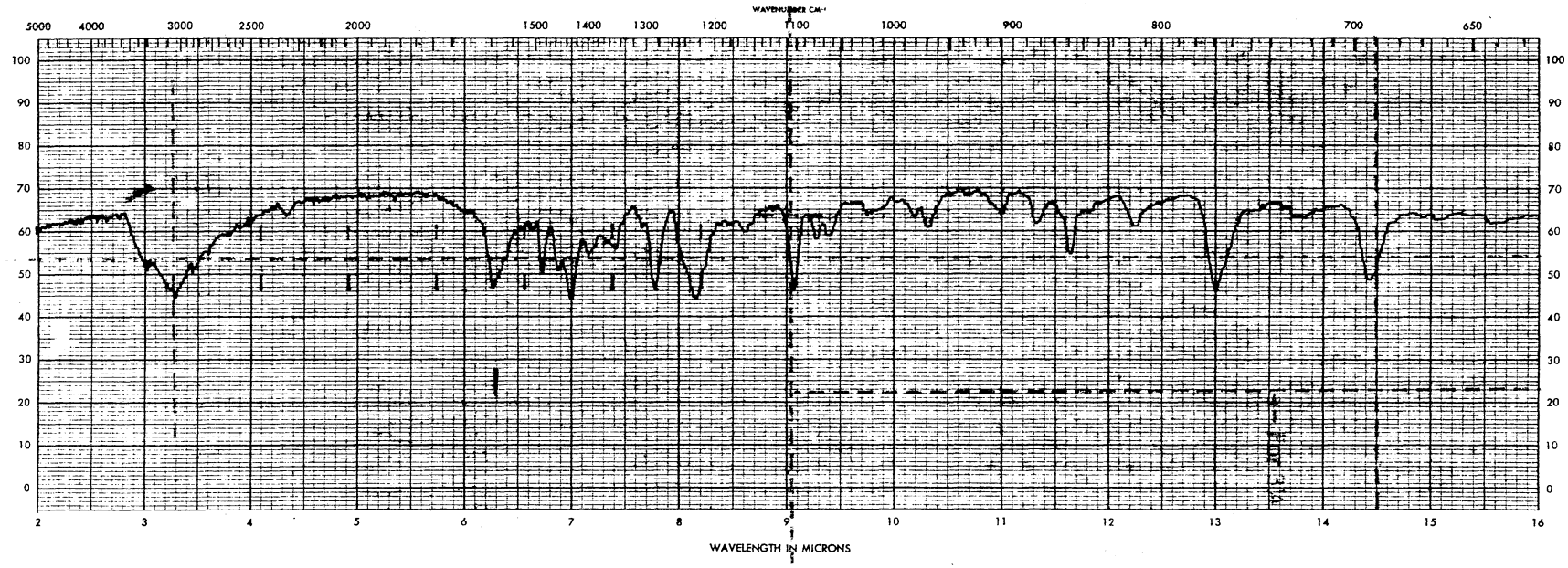
4,5-Dihydro-7,8-dimethoxy-1-(p-tolylsulfonyl)-1H-benz[g]indazole (199), KBr Pellet

PLATE XXI



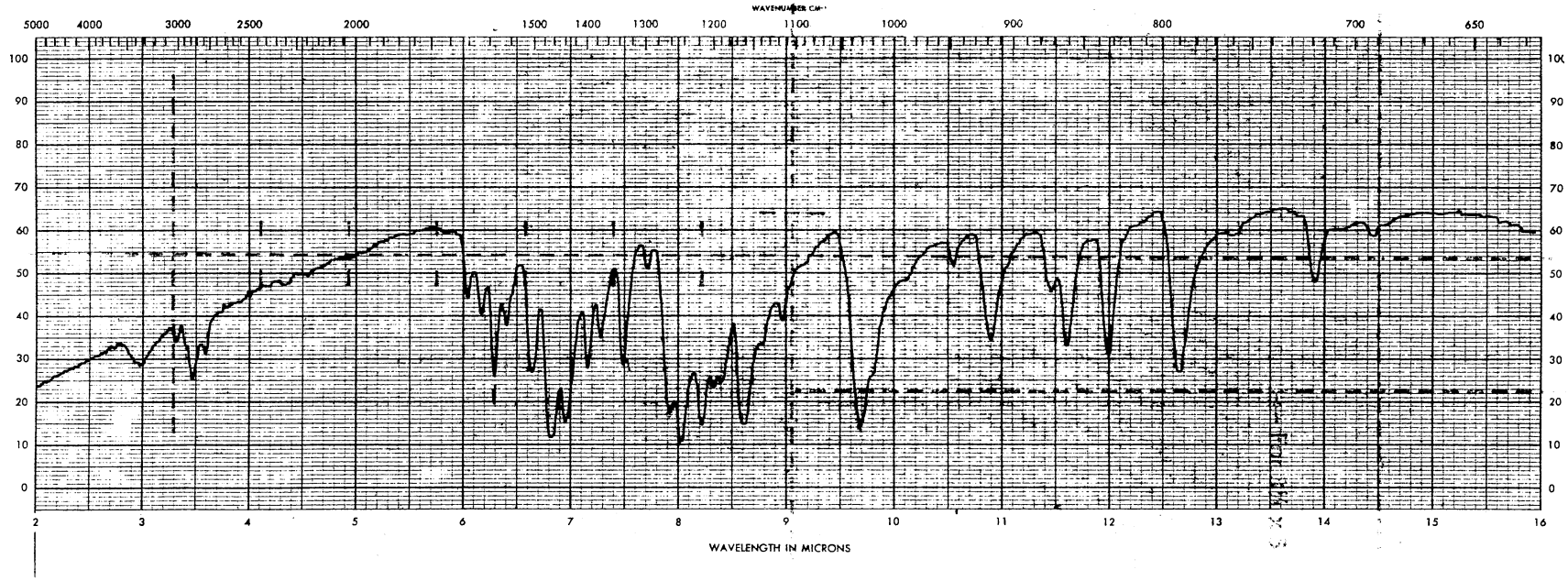
4,5-Dihydro-7-methoxy-1-phenyl-1H-benz[g]indazole (203), KBr Pellet

PLATE XXII



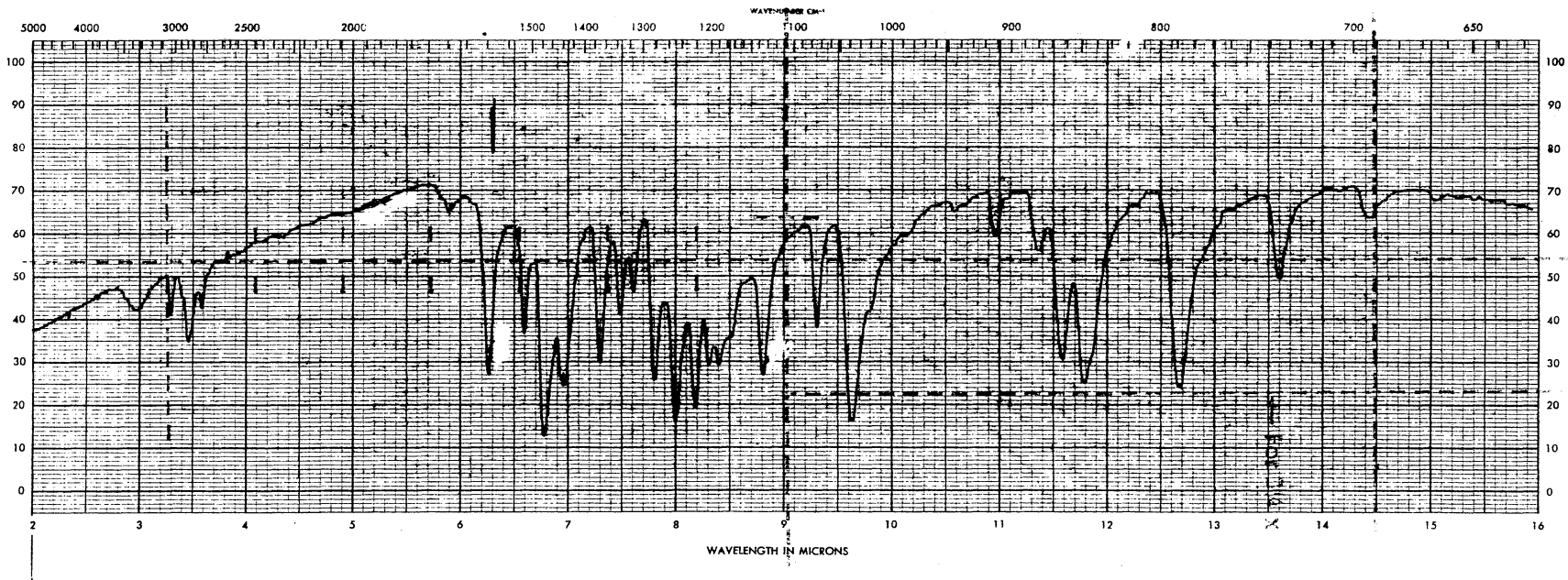
4,5-Dihydro-1-phenyl-1H-benz[g]indazol-7-ol (204), KBr Pellet

PLATE XXIII



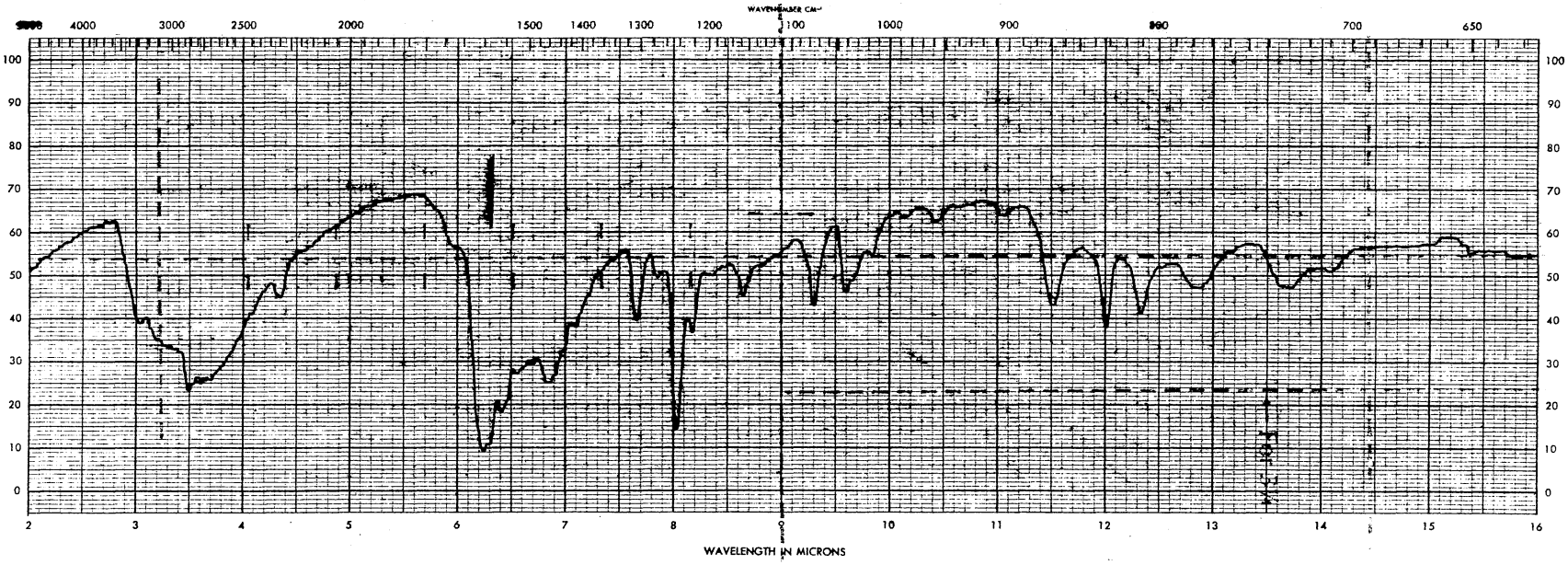
4,5-Dihydro-7,8-dimethoxynaphth[2,1-d]isoxazole (185), KBr Pellet

PLATE XXIV



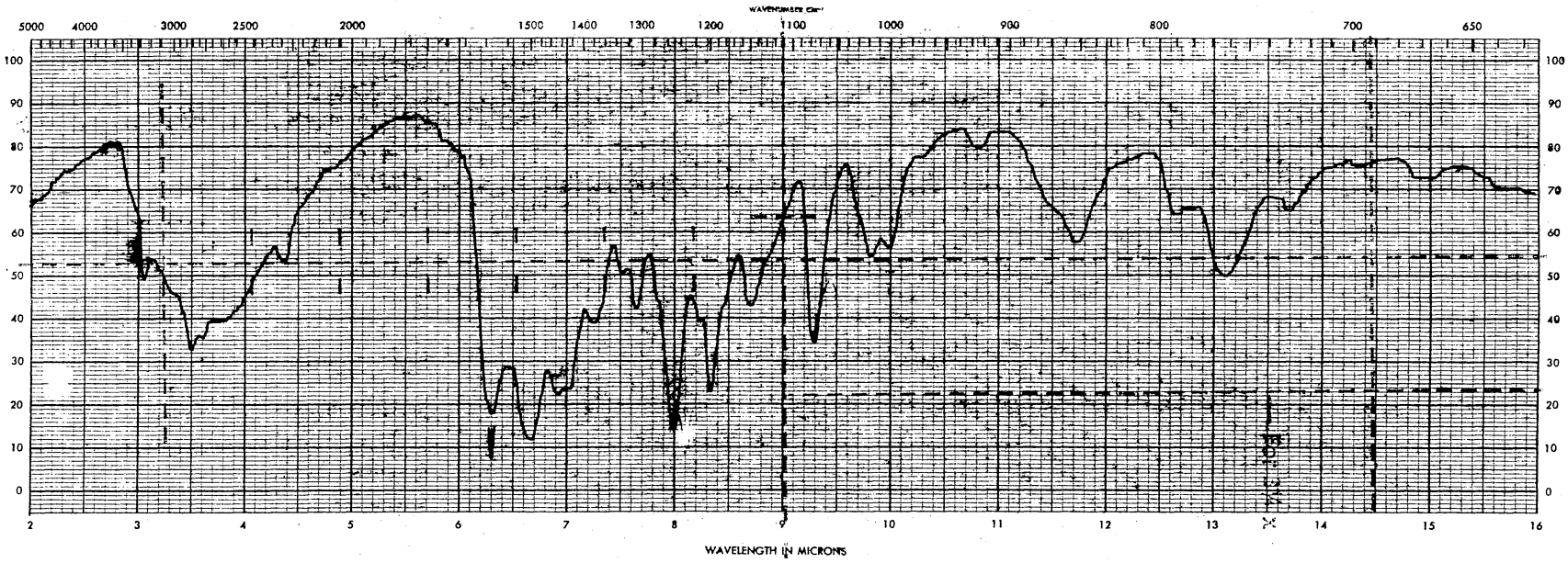
4,5-Dihydro-7,8-dimethoxynaphth[1,2-c]isoxazole (186), KBr Pellet

PLATE XXV



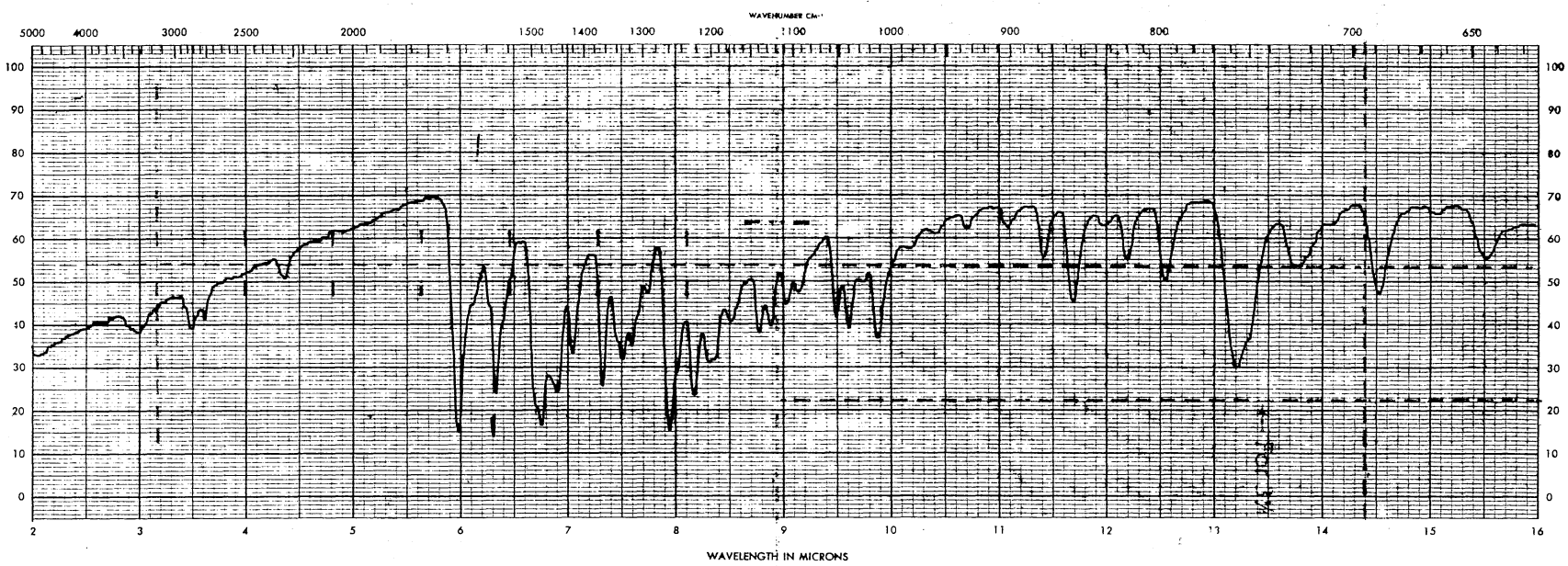
2,3a,4,5-Tetrahydro-7-methoxy-3H-benz[g]indazol-3-one (233), KBr Pellet

PLATE XXVI



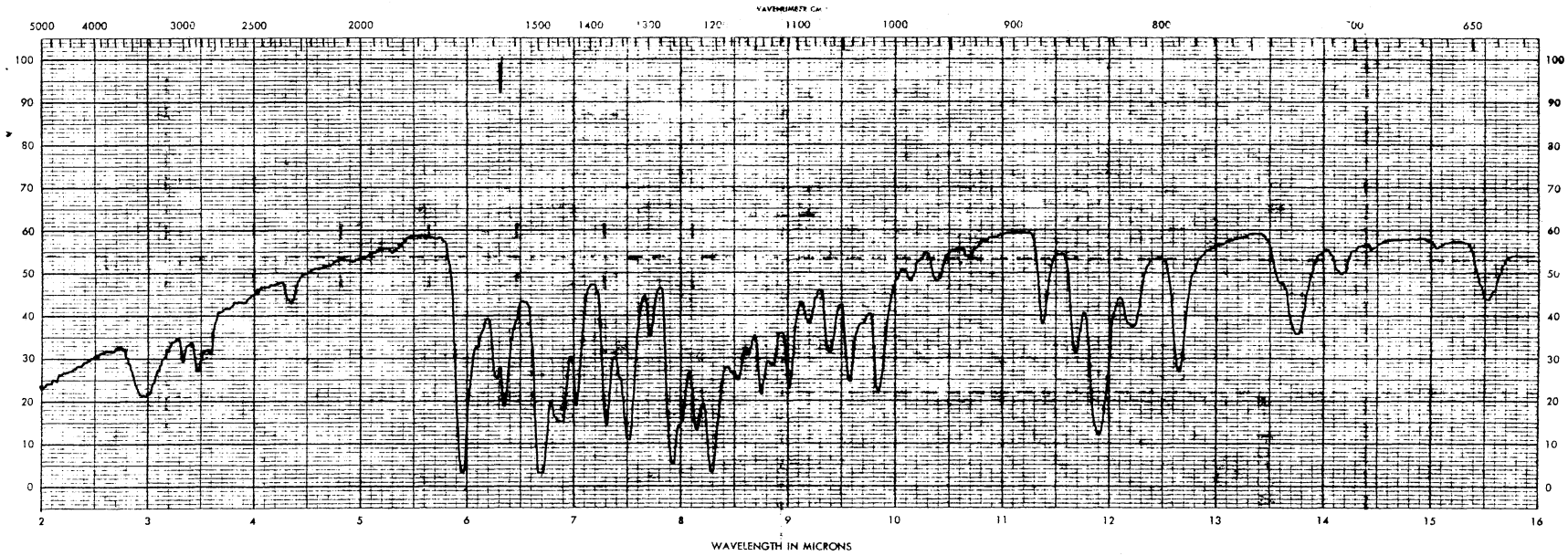
2,3a,4,5-Tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one (207), KBr Pellet

PLATE XXVII



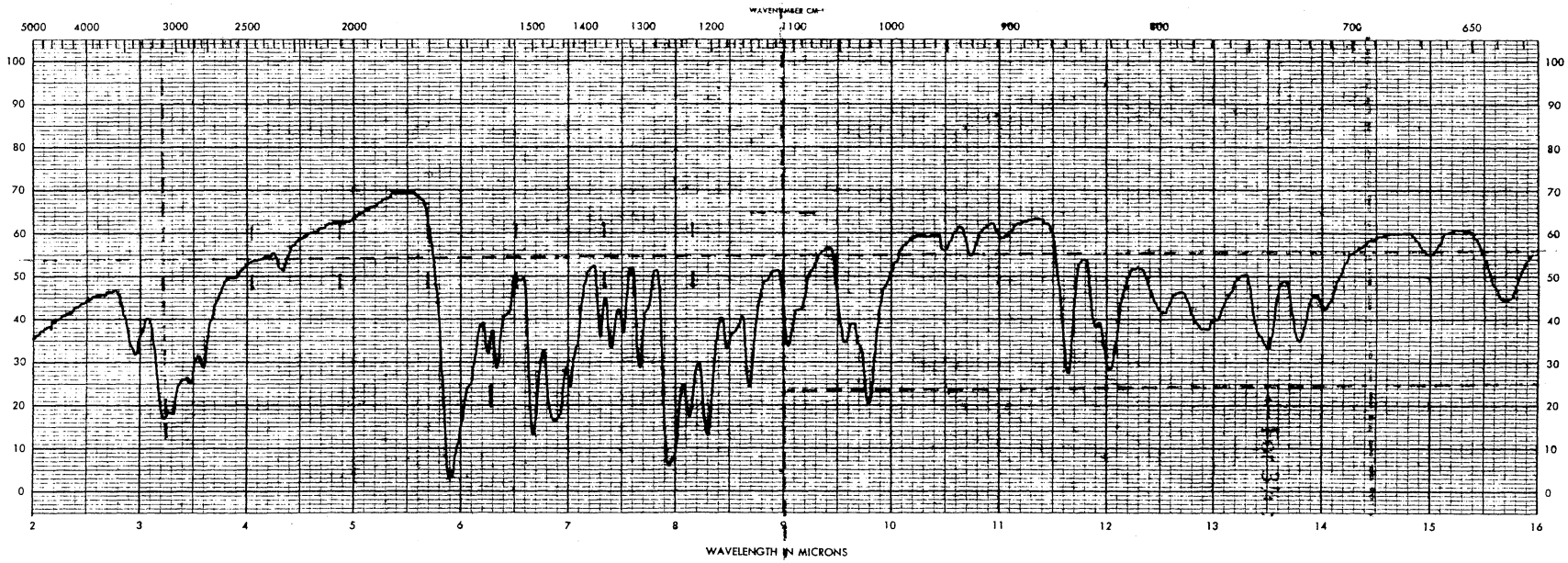
2,3a,4,5-Tetrahydro-7,8-dimethoxy-2-phenyl-3H-benz[g]indazol-3-one (208), KBr Pellet

PLATE XXVIII



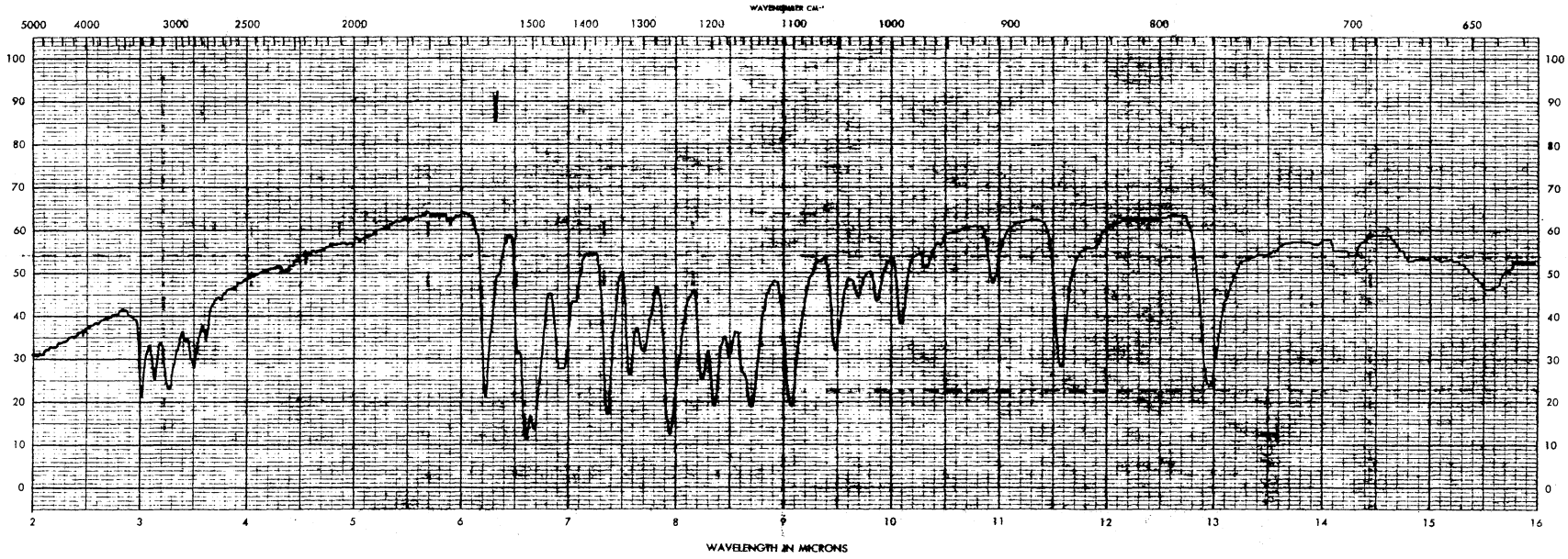
2-(p-Fluorophenyl)-2,3a,4,5-tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one (209), KBr Pellet

PLATE XXIX



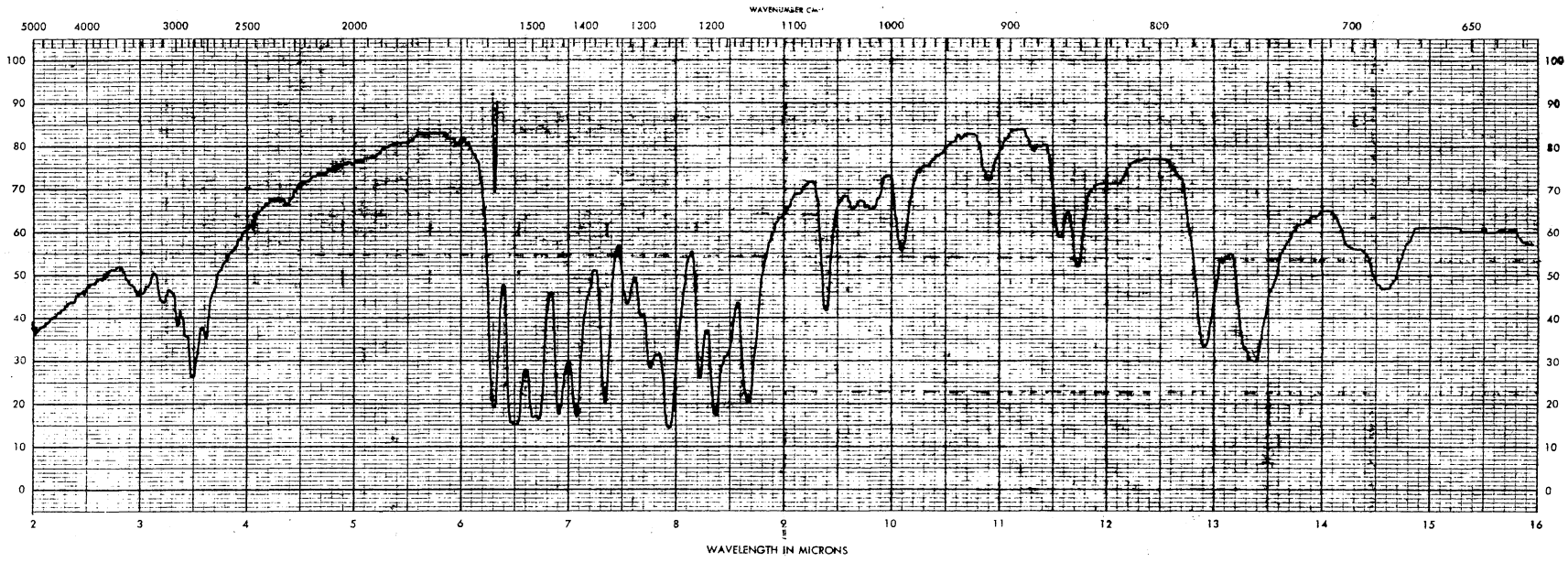
2,3a,4,5-Tetrahydro-7,8-dimethoxy-3a-methyl-3H-benz[g]indazol-3-one (210), KBr Pellet

PLATE XXX



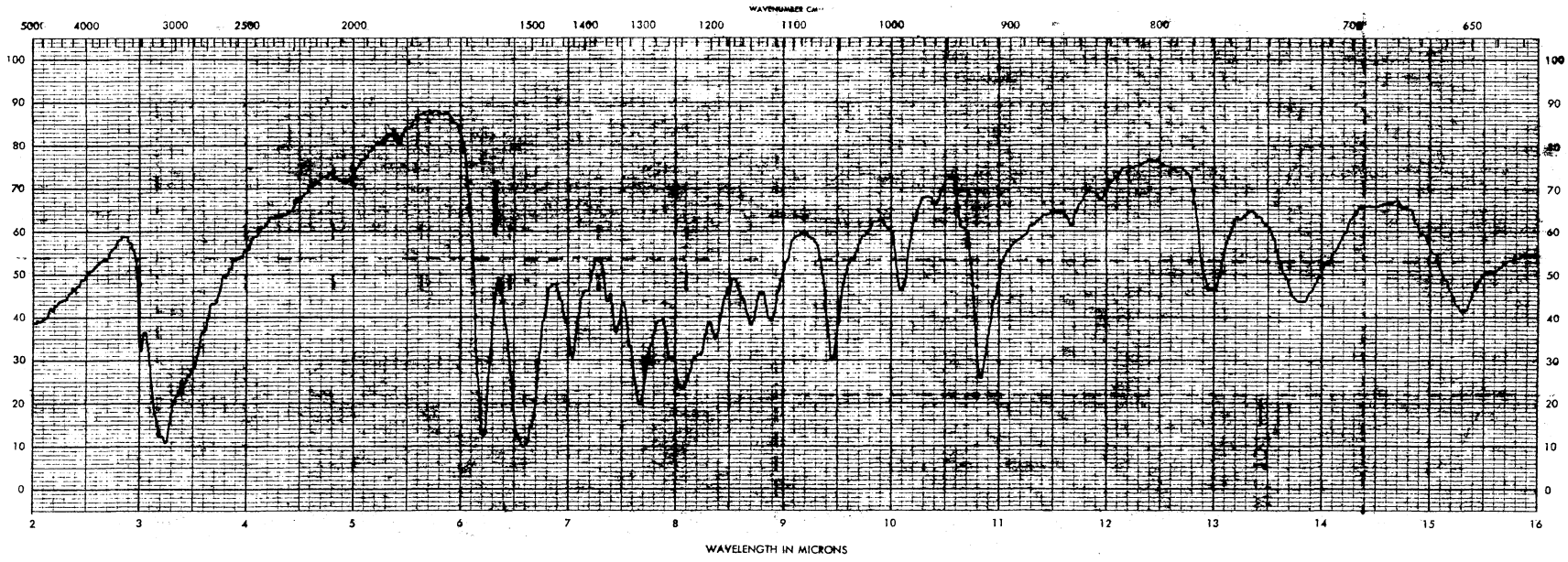
2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (211), KBr Pellet

PLATE XXXI



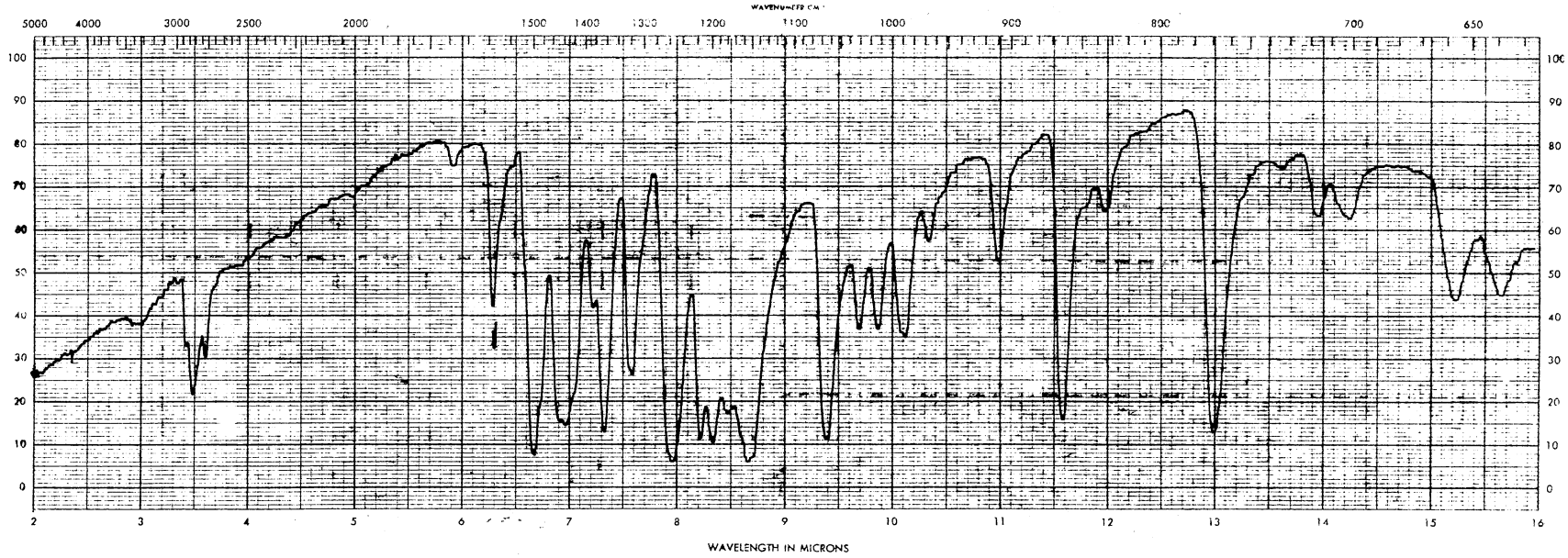
2-Anilino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (212), KBr Pellet

PLATE XXXII



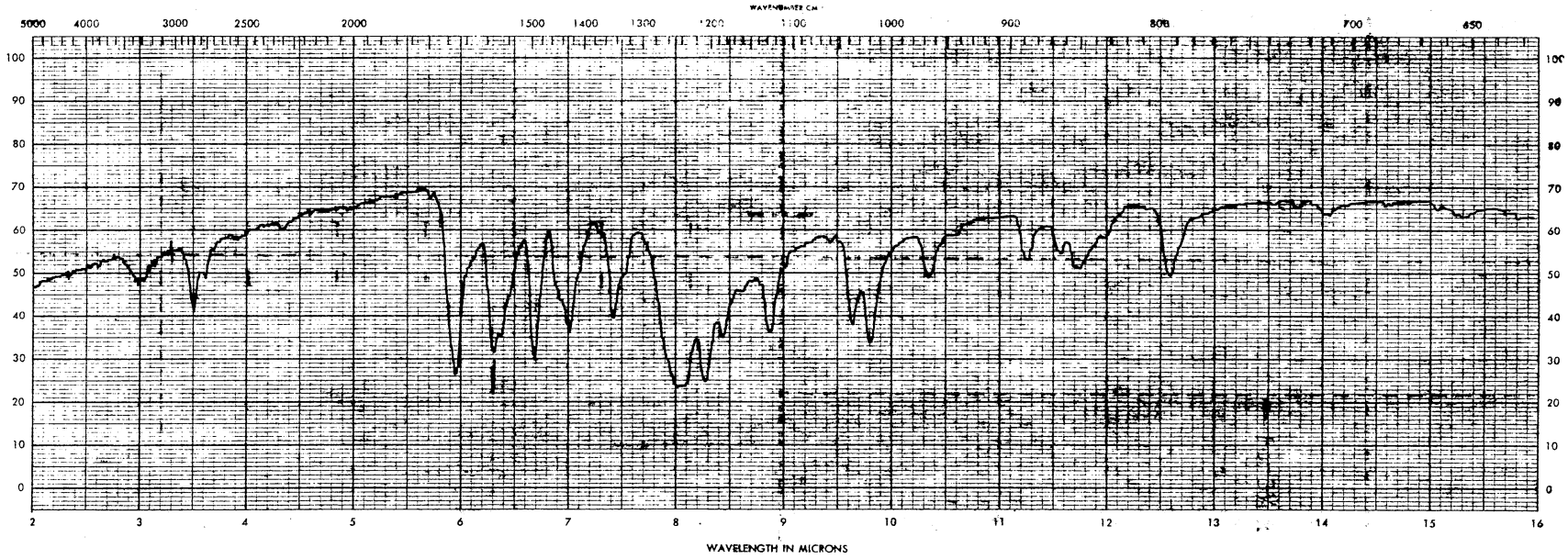
2-(Allylamino)-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (213), KBr Pellet

PLATE XXXIII



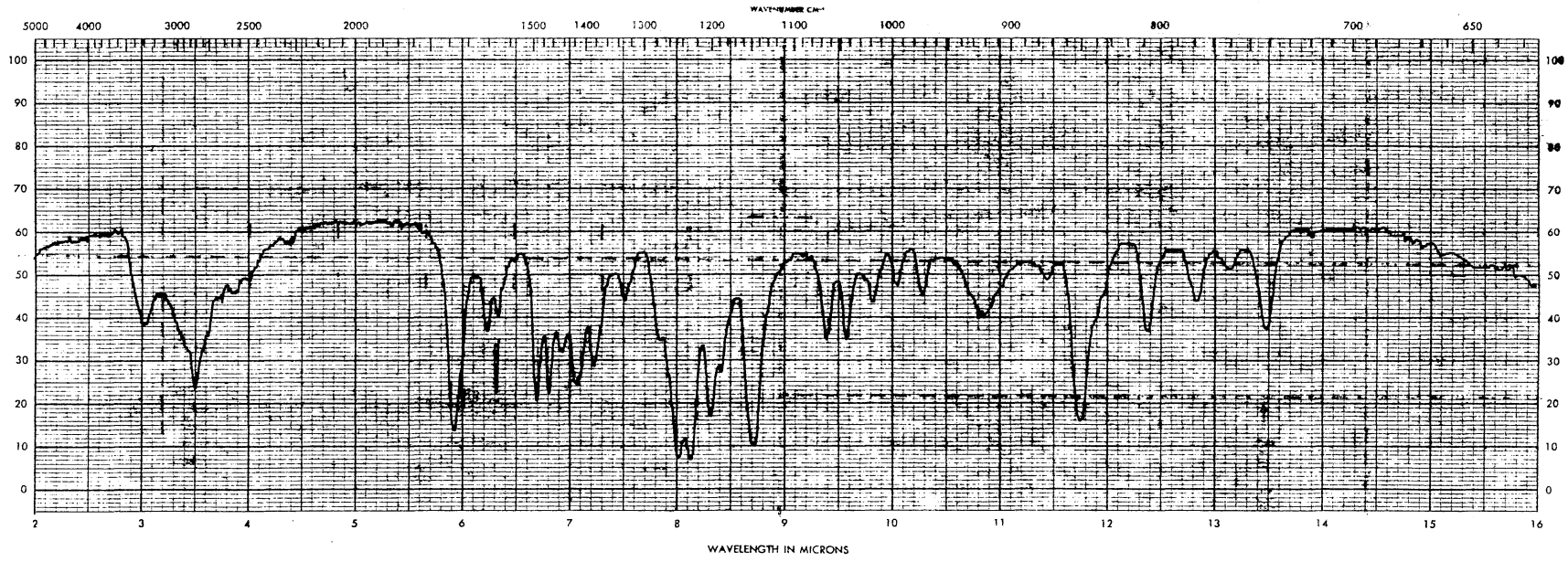
4,5-Dihydro-7,8-dimethoxy-2-methylnaphtho[1,2-d]thiazole (214), KBr Pellet

PLATE XXXIV



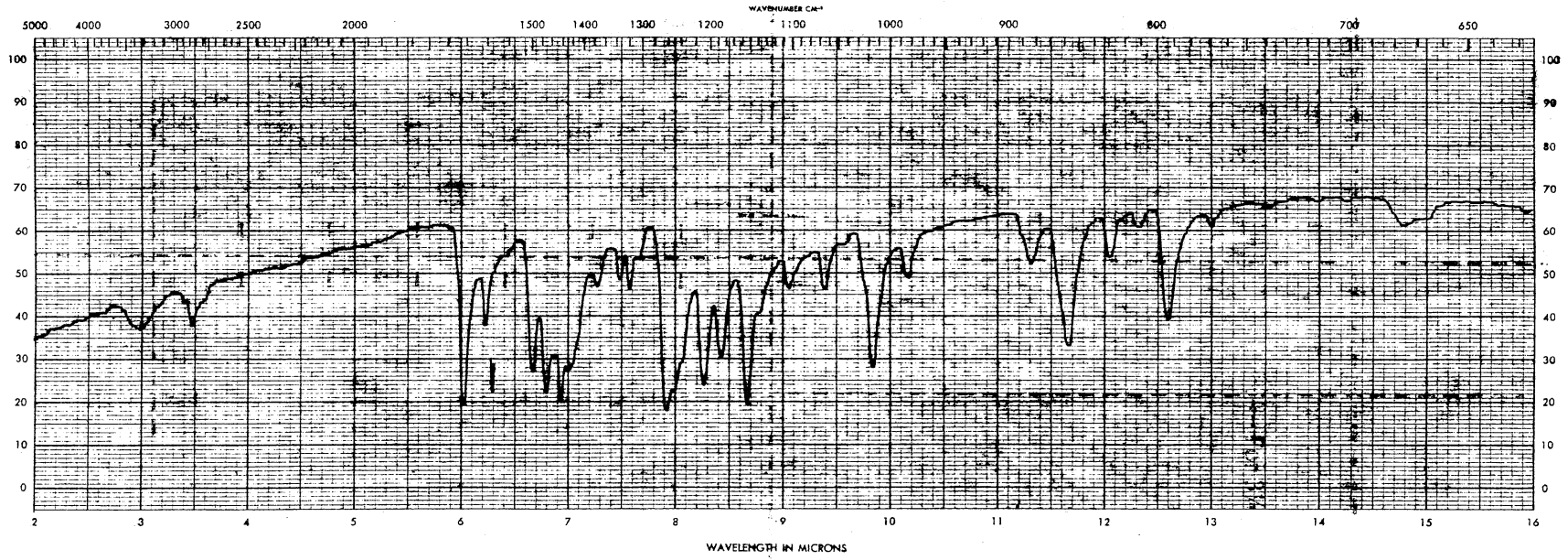
Methyl 3,4-dihydro-6,7-dimethoxy-$\Delta^{1(2H),\gamma}$-naphthalenecrotonate (235), KBr Pellet

PLATE XXXV



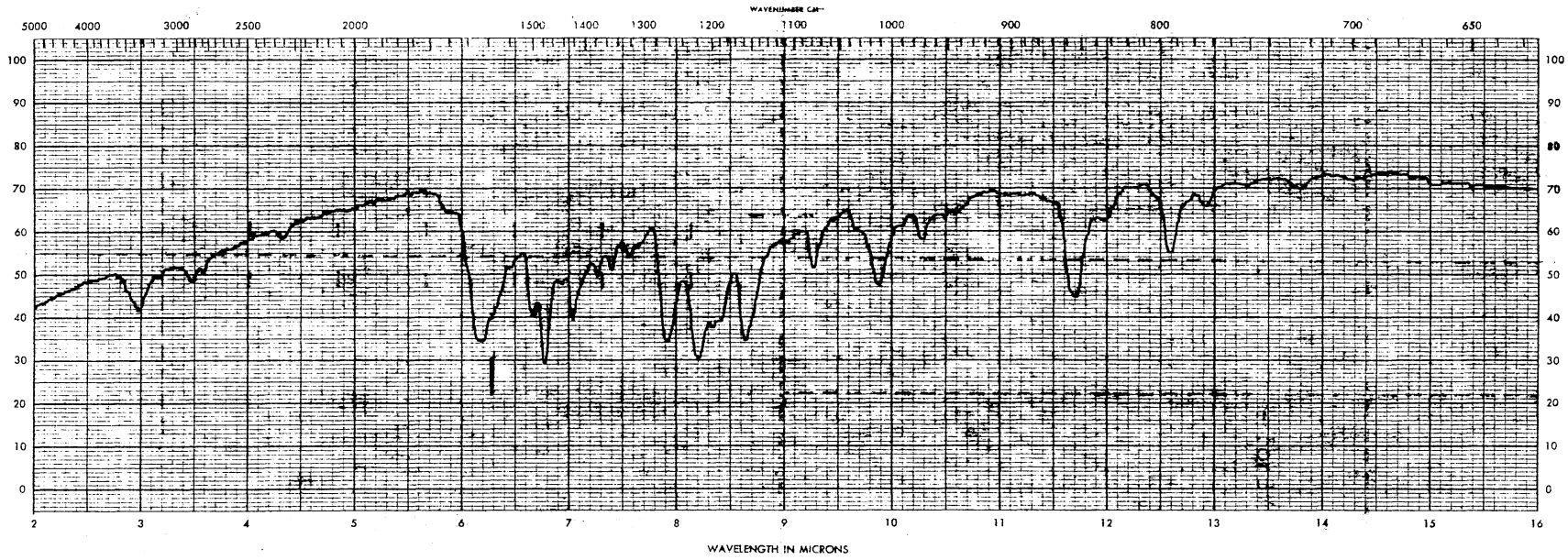
6,7-Dimethoxy-1-naphthalenebutyric Acid (236), KBr Pellet

PLATE XXXVI



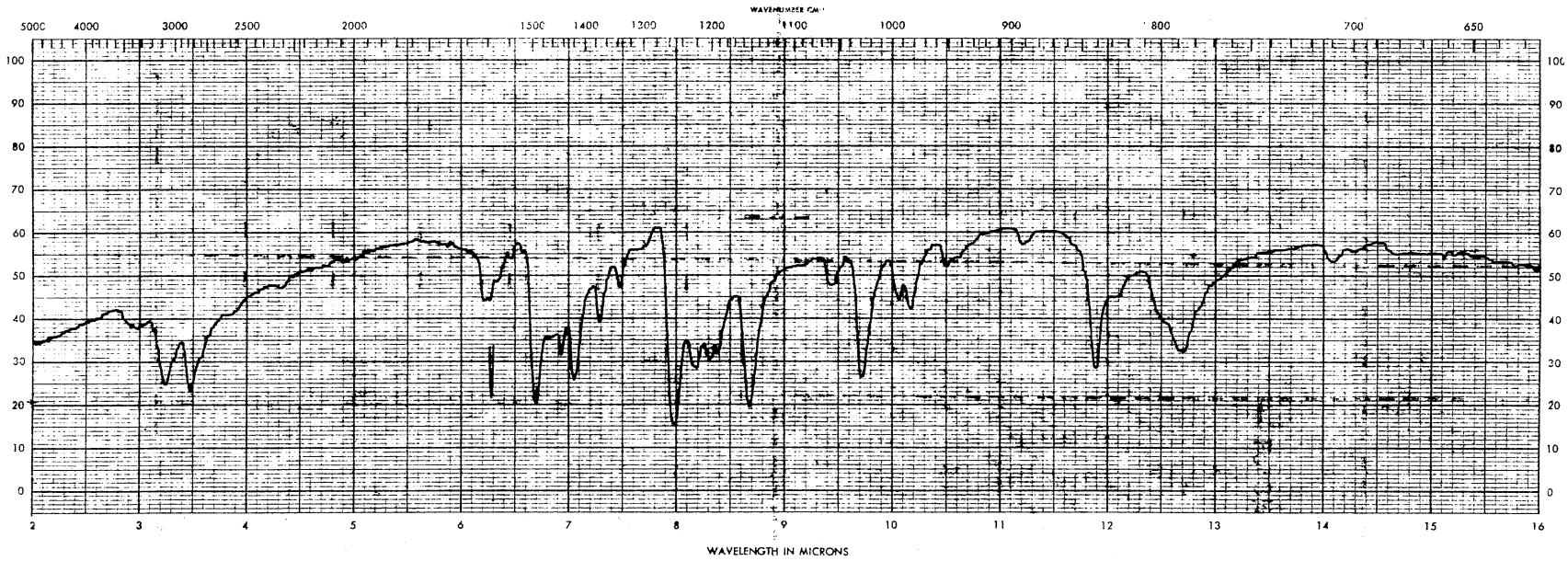
3,4-Dihydro-6,7-dimethoxy-1(2H)-phenanthrone (188), KBr Pellet

PLATE XXXVII



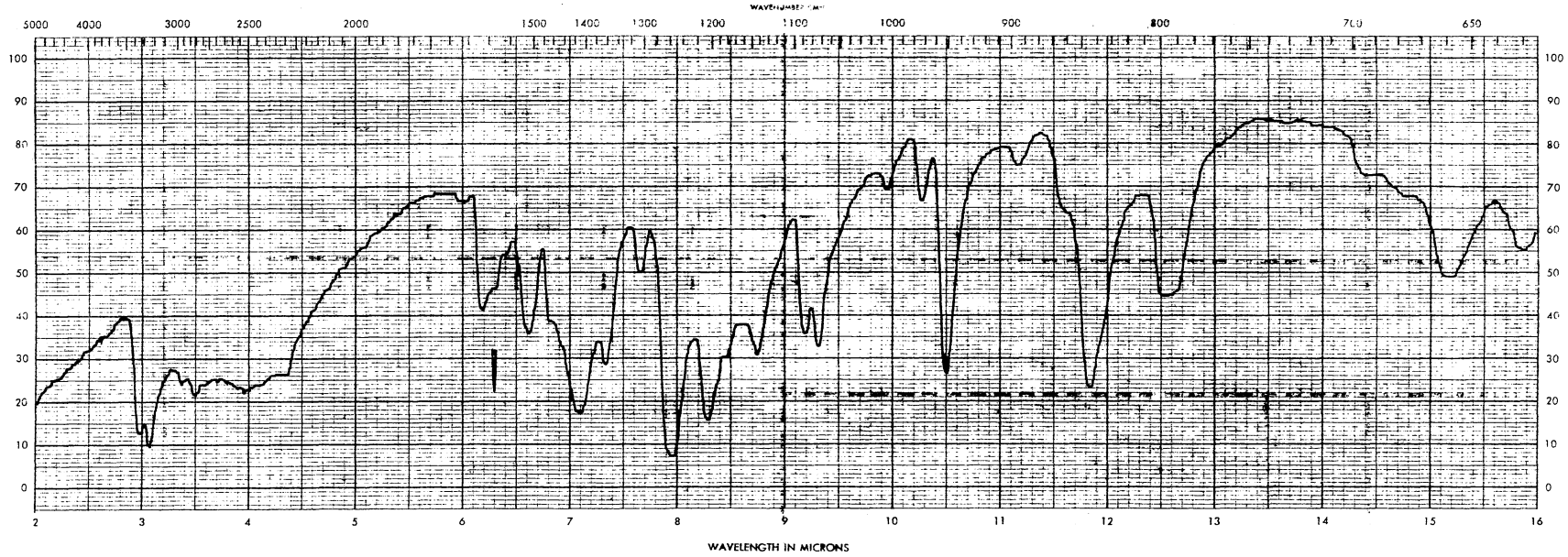
3,4-Dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1(2H)-phenanthrone (237), KBr Pellet

PLATE XXXVIII



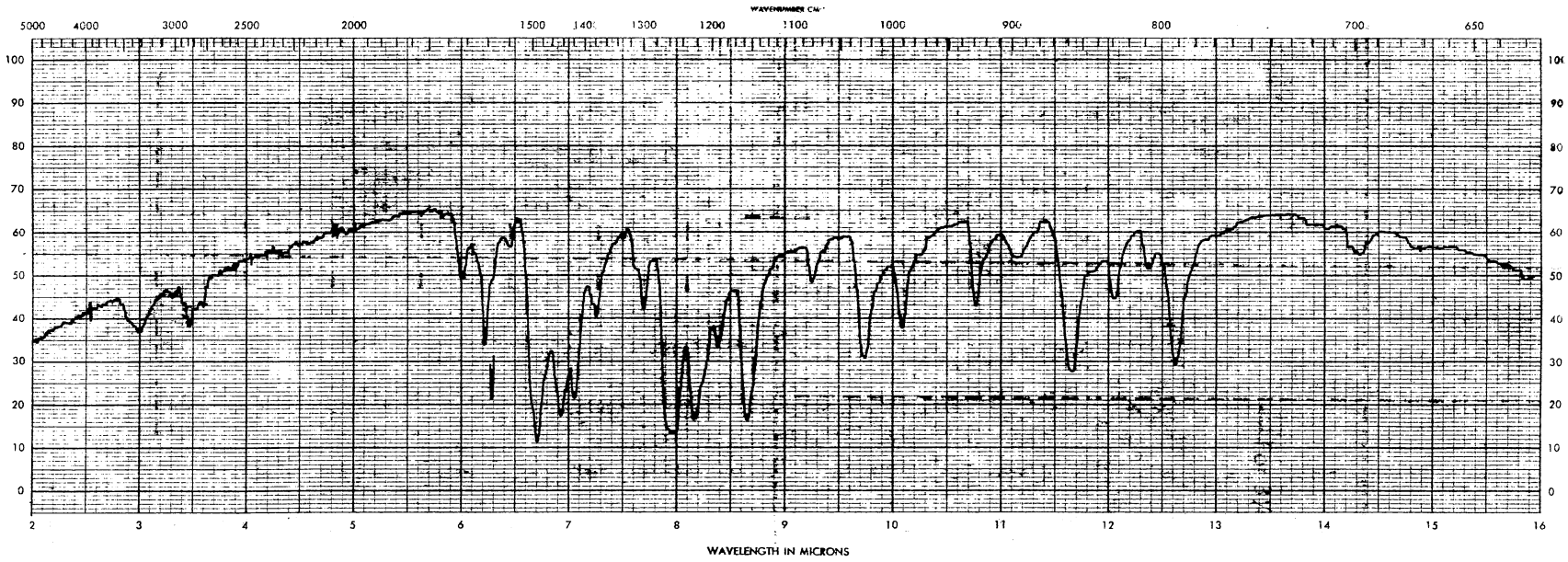
10,11-Dihydro-7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (215), KBr Pellet

PLATE XXXIX



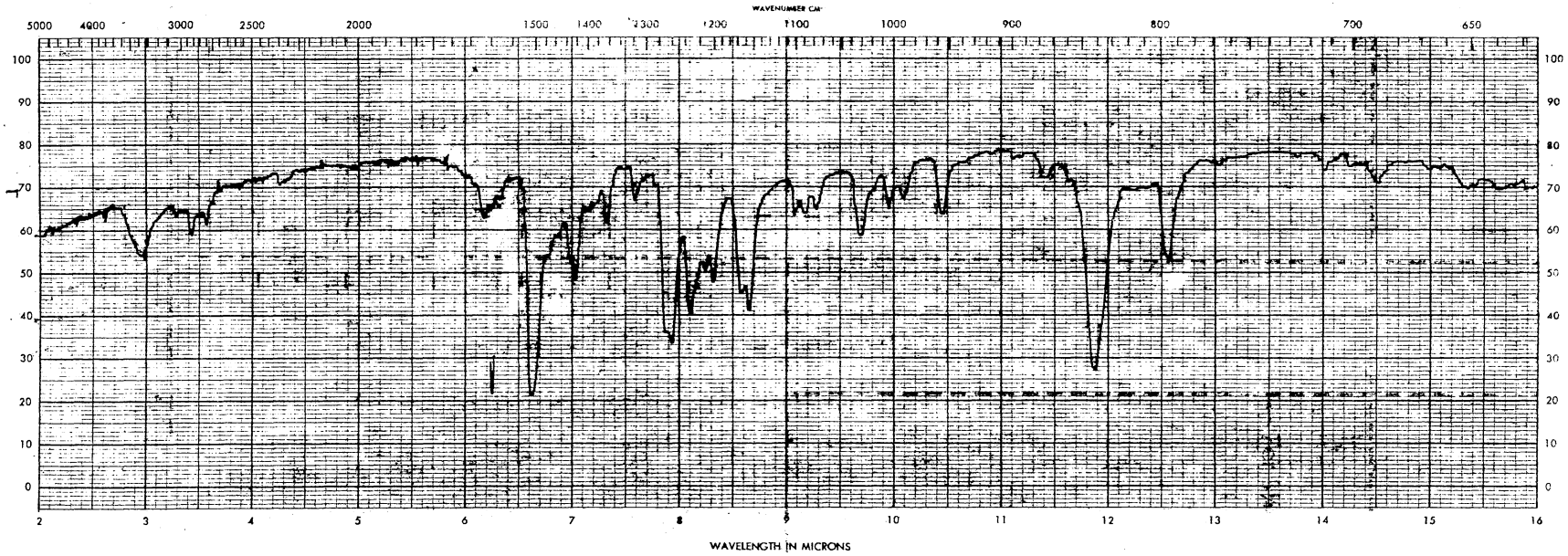
10,11-Dihydro-3H-phenanthro[1,2-c]pyrazole-7,8-diol (216), KBr Pellet

PLATE XL



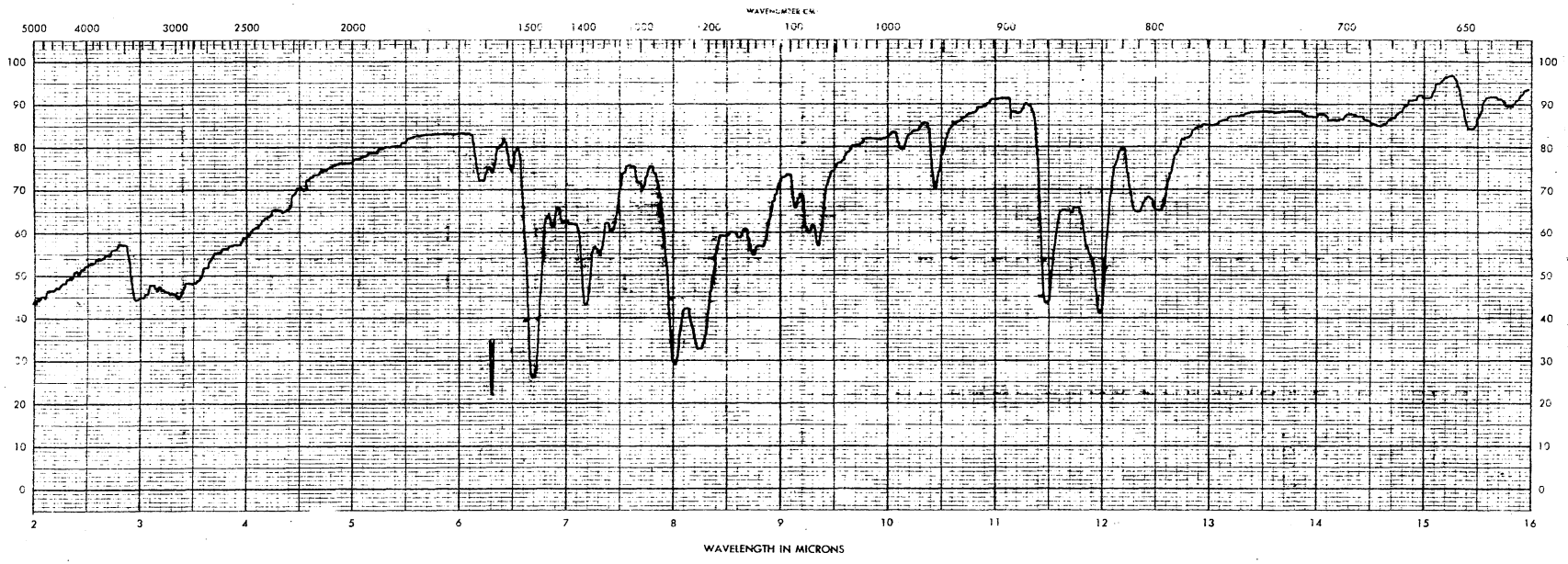
10,11-Dihydro-7,8-dimethoxyphenanthro[2,1-d]isoxazole (190), KBr Pellet

PLATE XLI



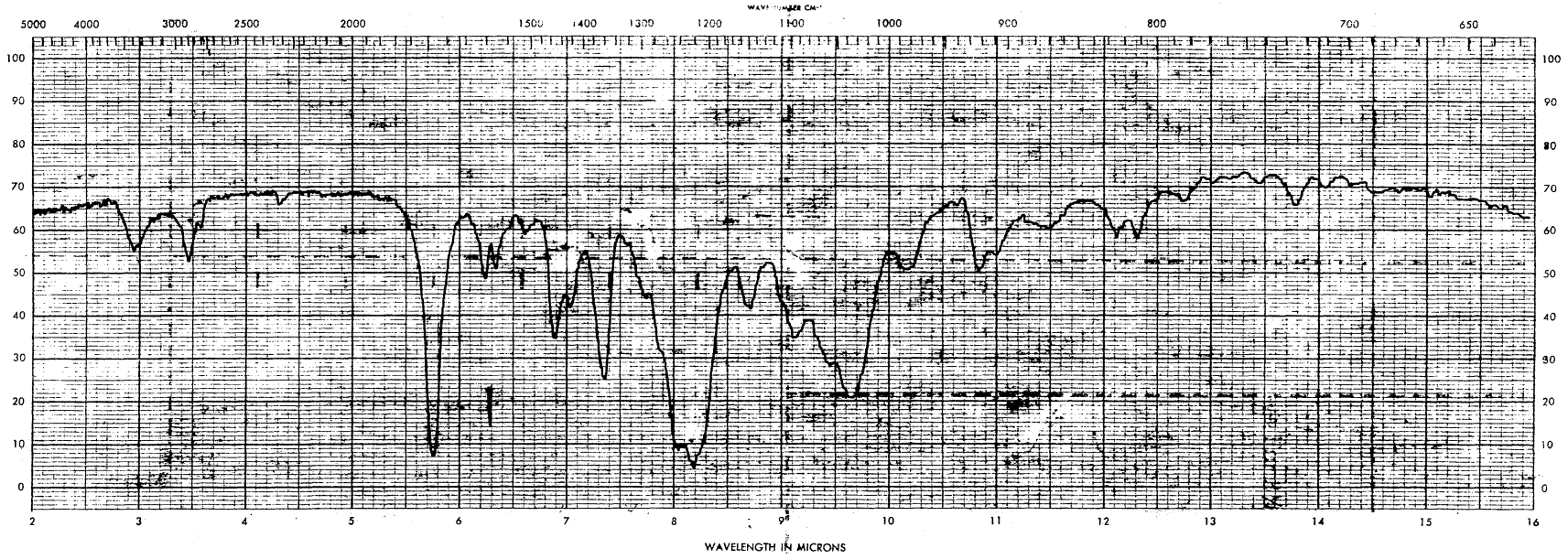
10,11-Dihydro-1-(p-fluorophenyl)-7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (217), KBr Pellet

PLATE XLII



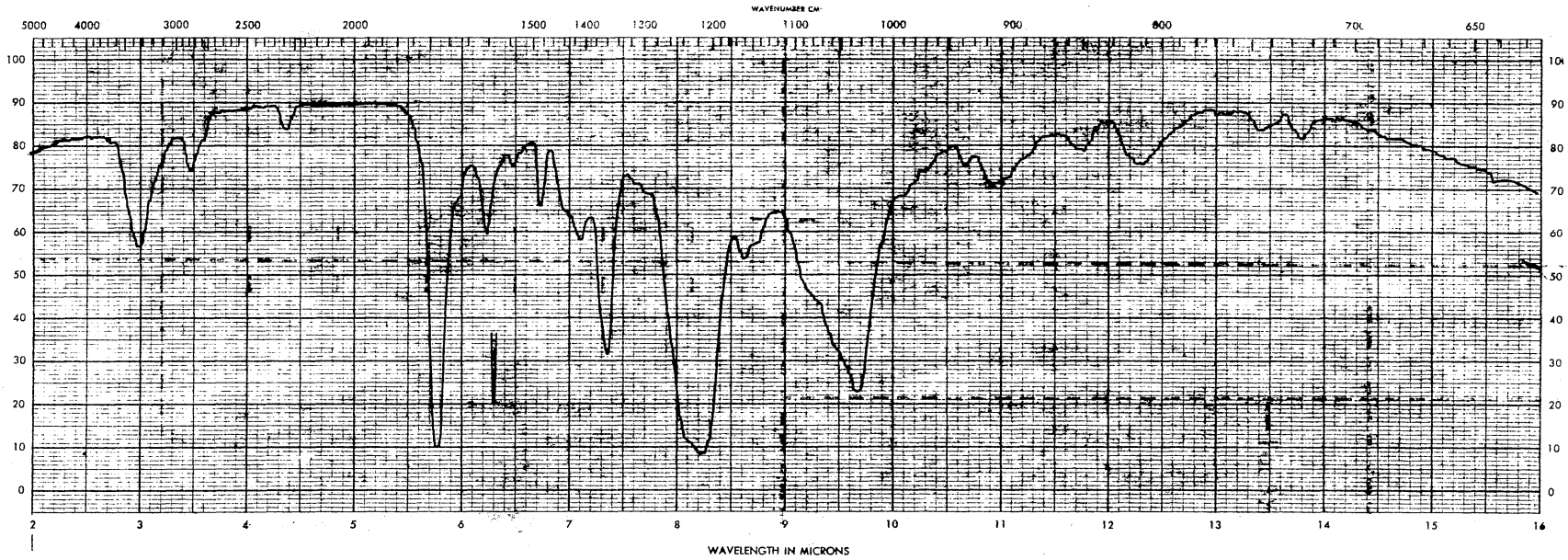
10,11-Dihydro-1-(p-fluorophenyl)-3H-phenanthro[1,2-c]pyrazole-7,8-diol (218), KBr Pellet

PLATE XLIII



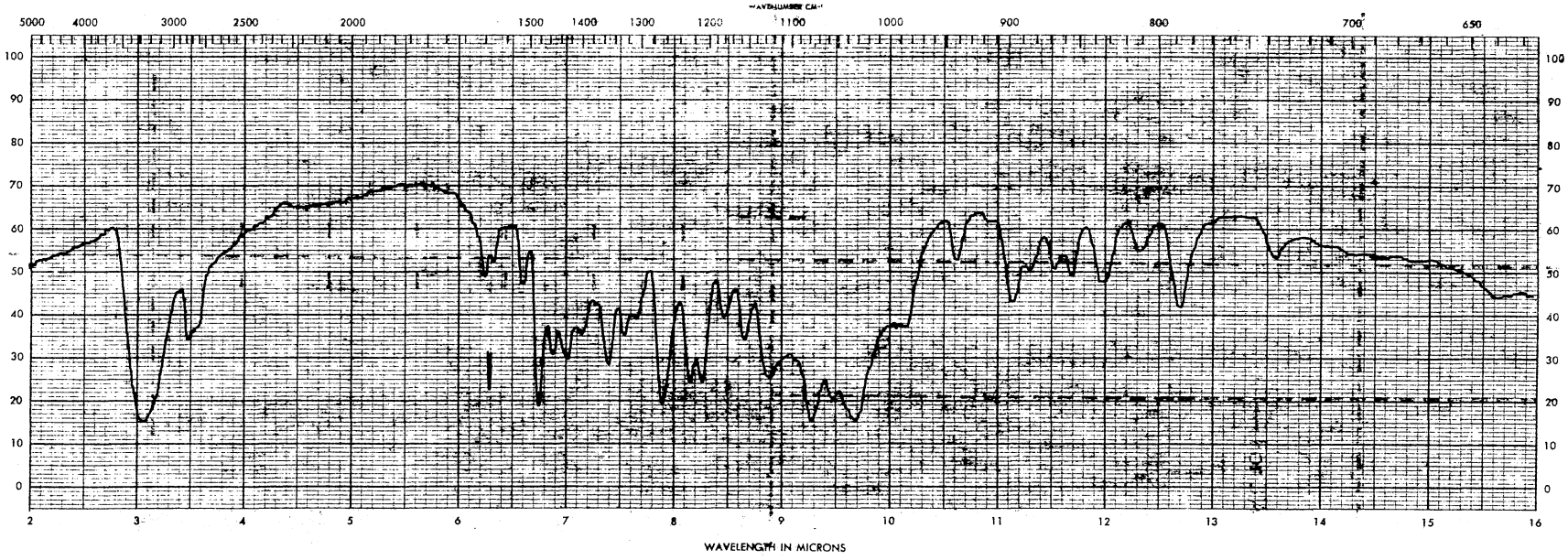
1-β-D-Glucopyranosyl-4,5-dihydro-7-methoxy-1H-benz[g]indazole Tetraacetate (ester) (206), KBr Pellet

PLATE XLIV



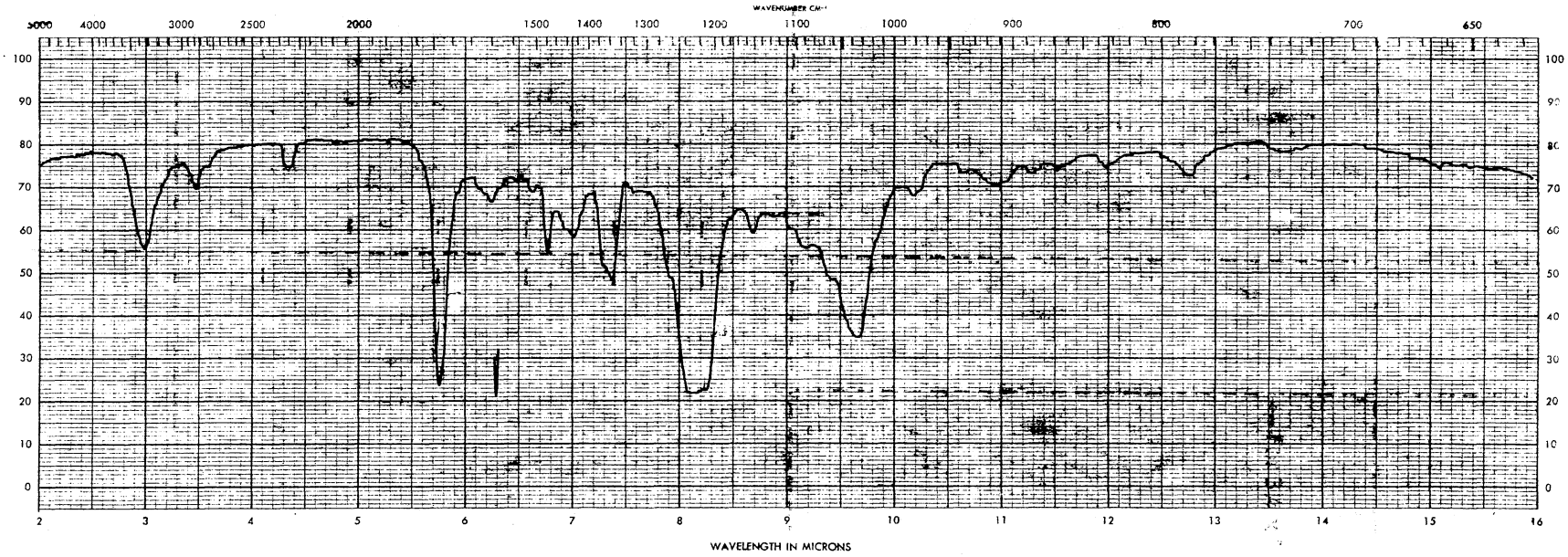
1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole Tetraacetate (ester) (201), KBr Pellet

PLATE XLV



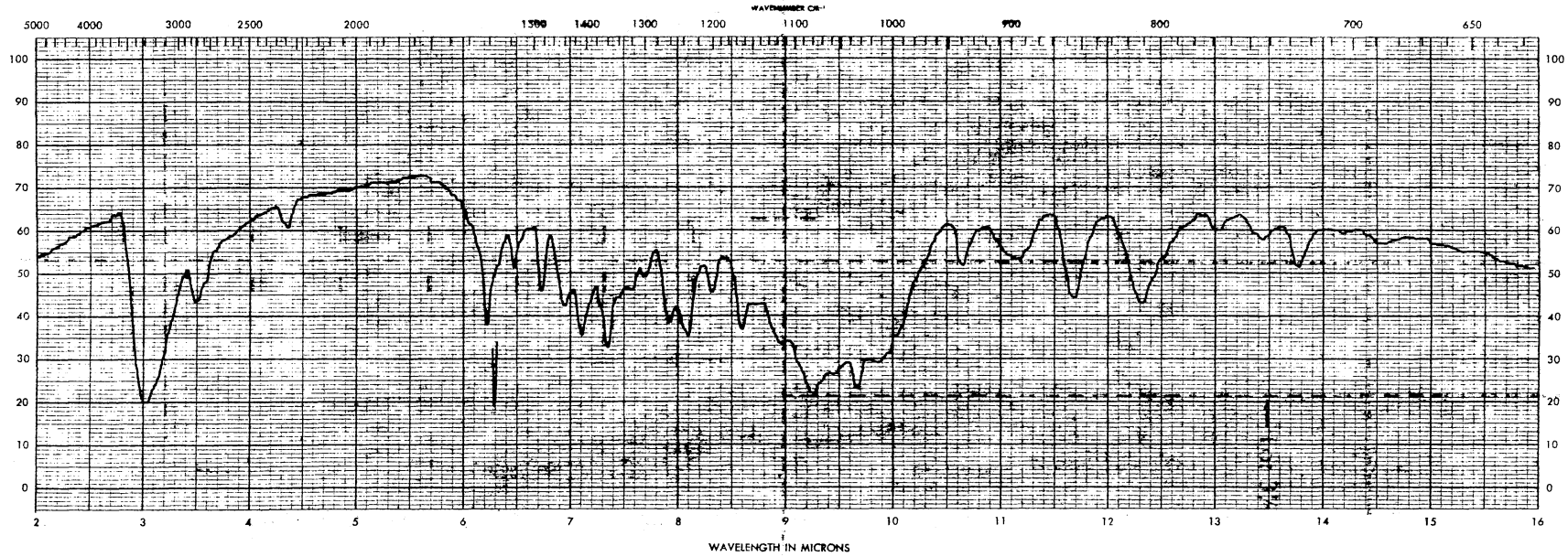
1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole (202), KBr Pellet

PLATE XLVI



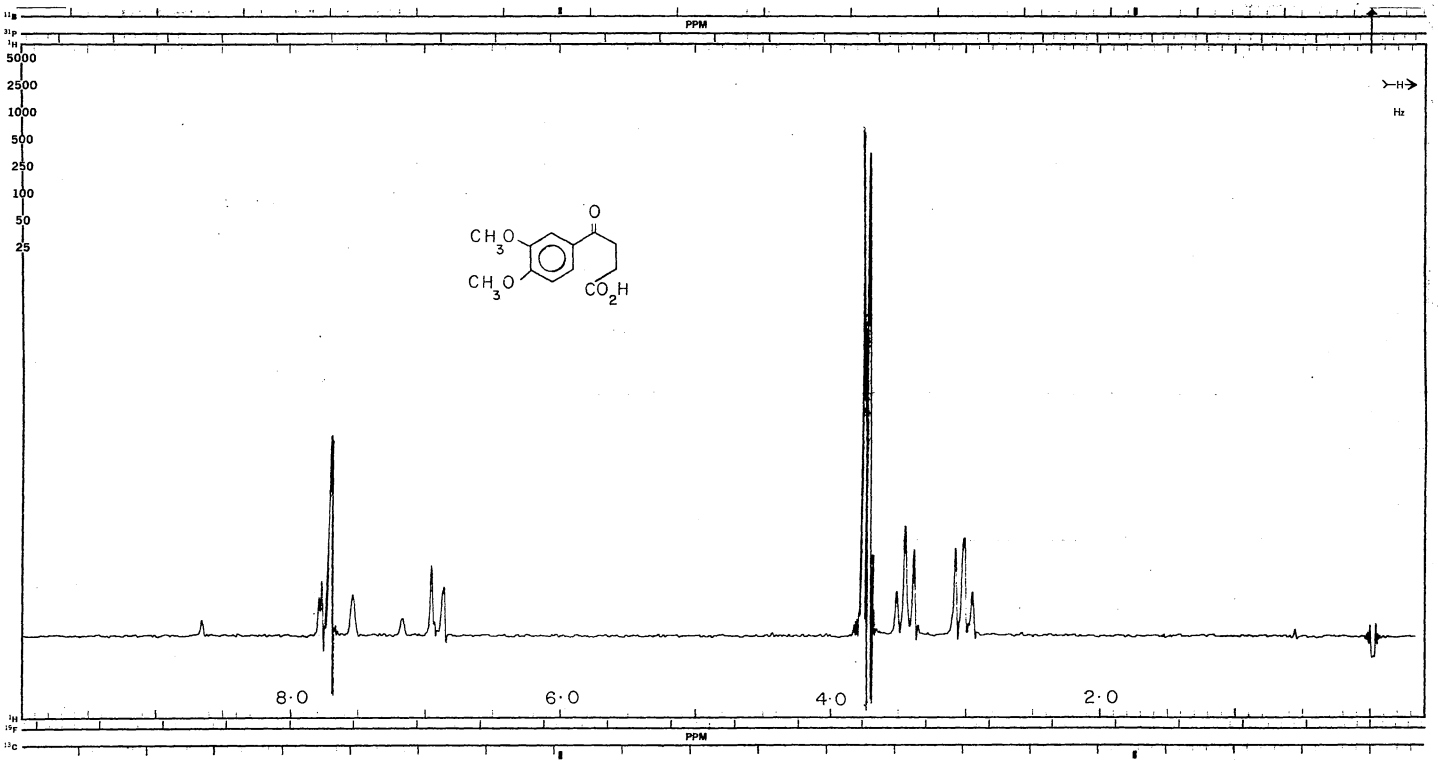
3-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole tetraacetate (ester) (220), KBr Pellet

PLATE XLVII



3-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole (221), KBr Pellet

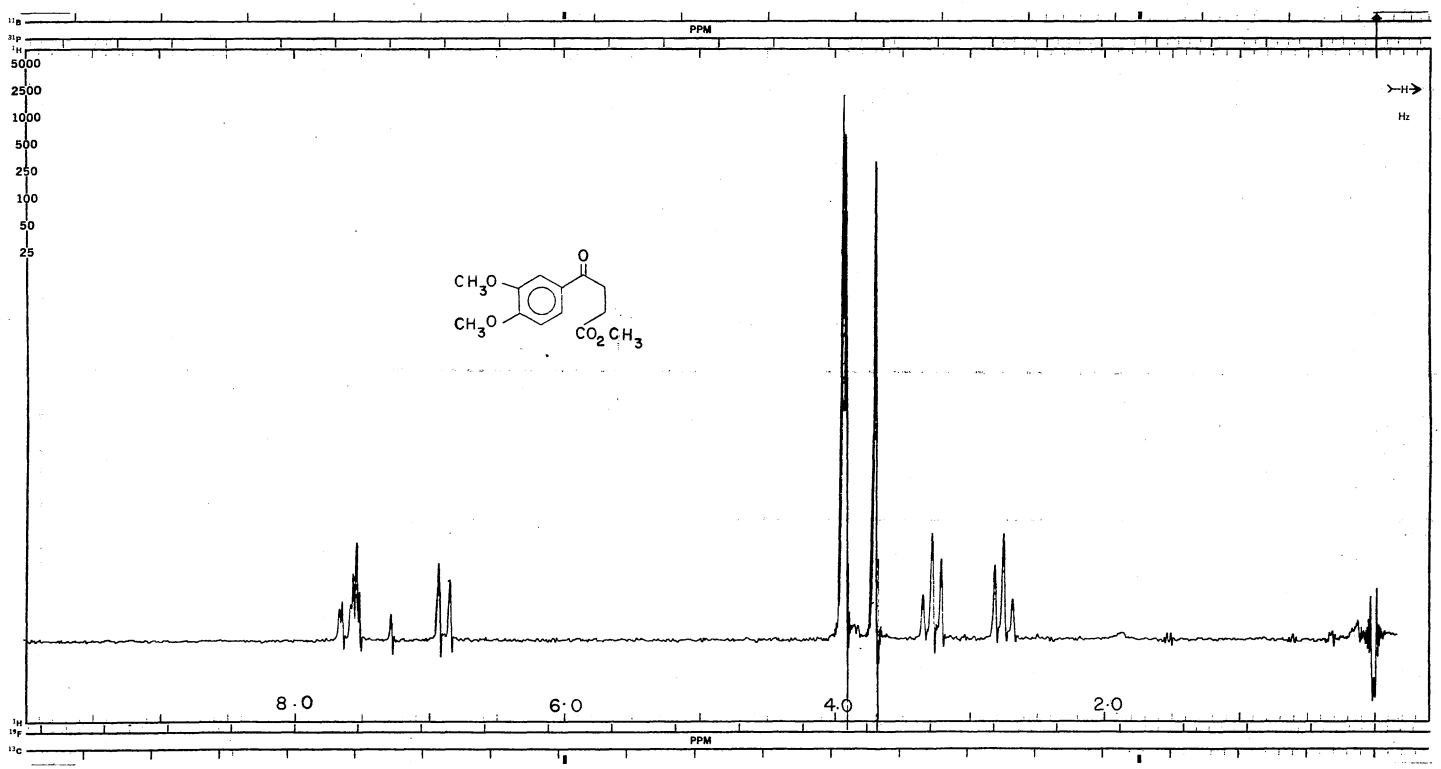
PLATE XLVIII



4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoic Acid (226)

Solvent. . . C_5D_5N	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 3.2

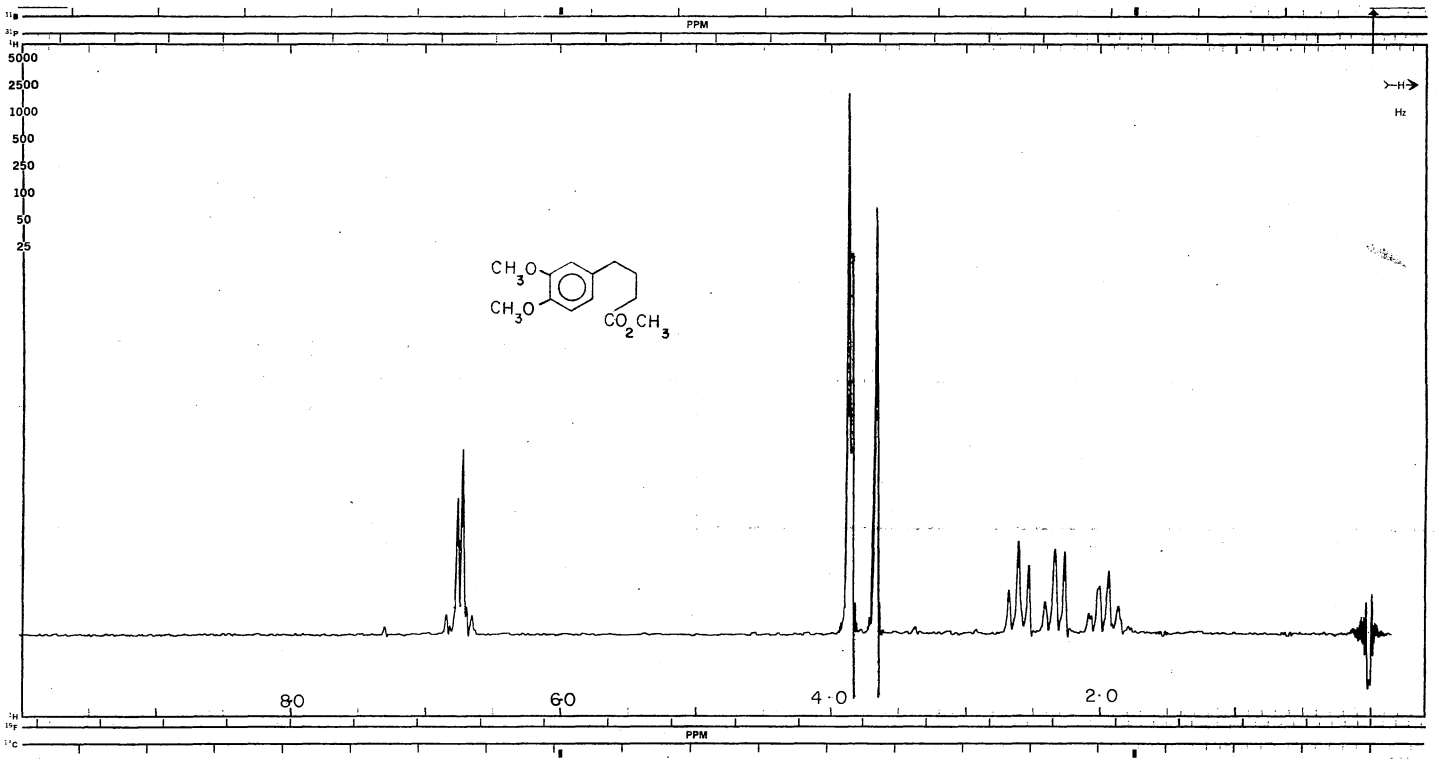
PLATE XLIX



Methyl 4-(3 ,4 -Dimethoxyphenyl)-4-oxobutanoate (222)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 64 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 3.2

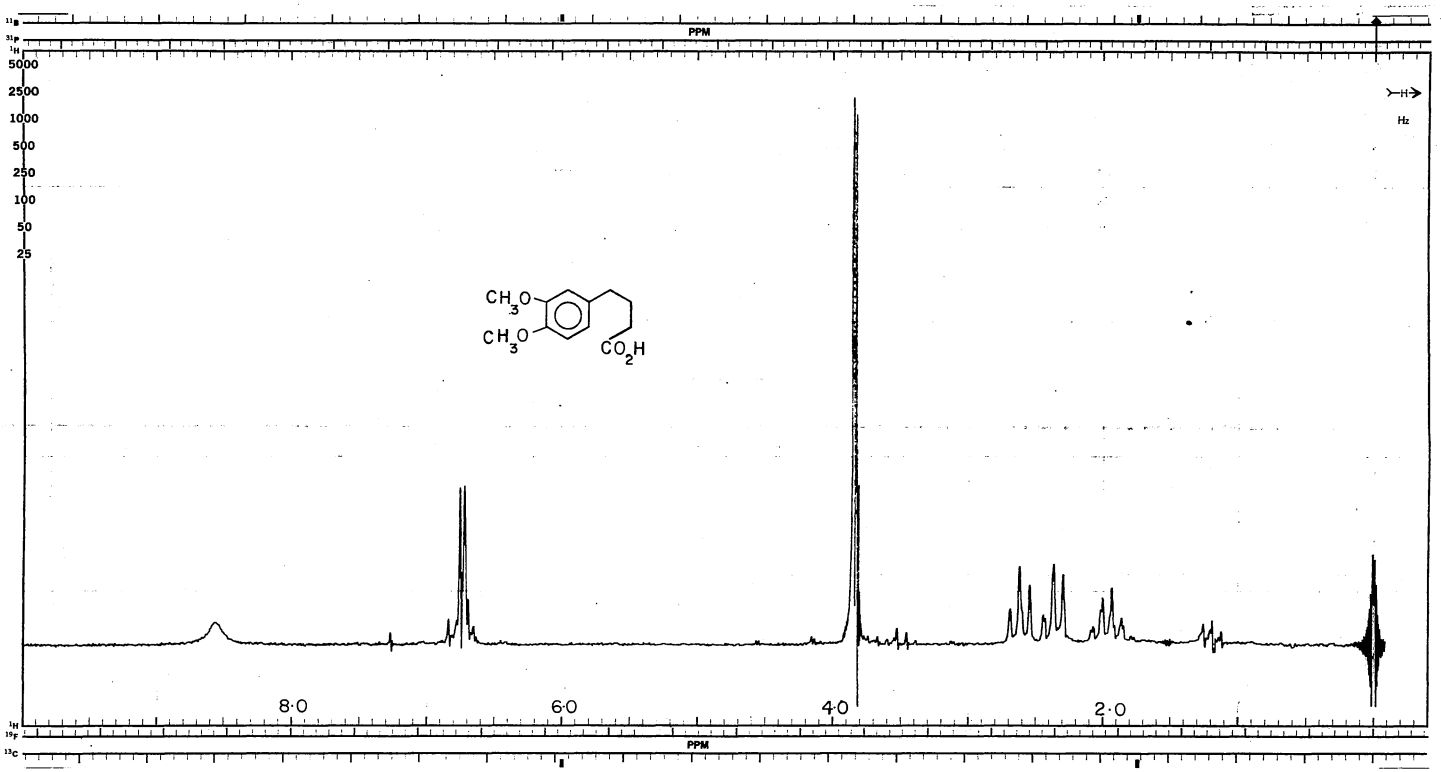
PLATE L



Methyl 4-(3 ,4 -Dimethoxyphenyl)butanoate (223)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 62 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 1.6

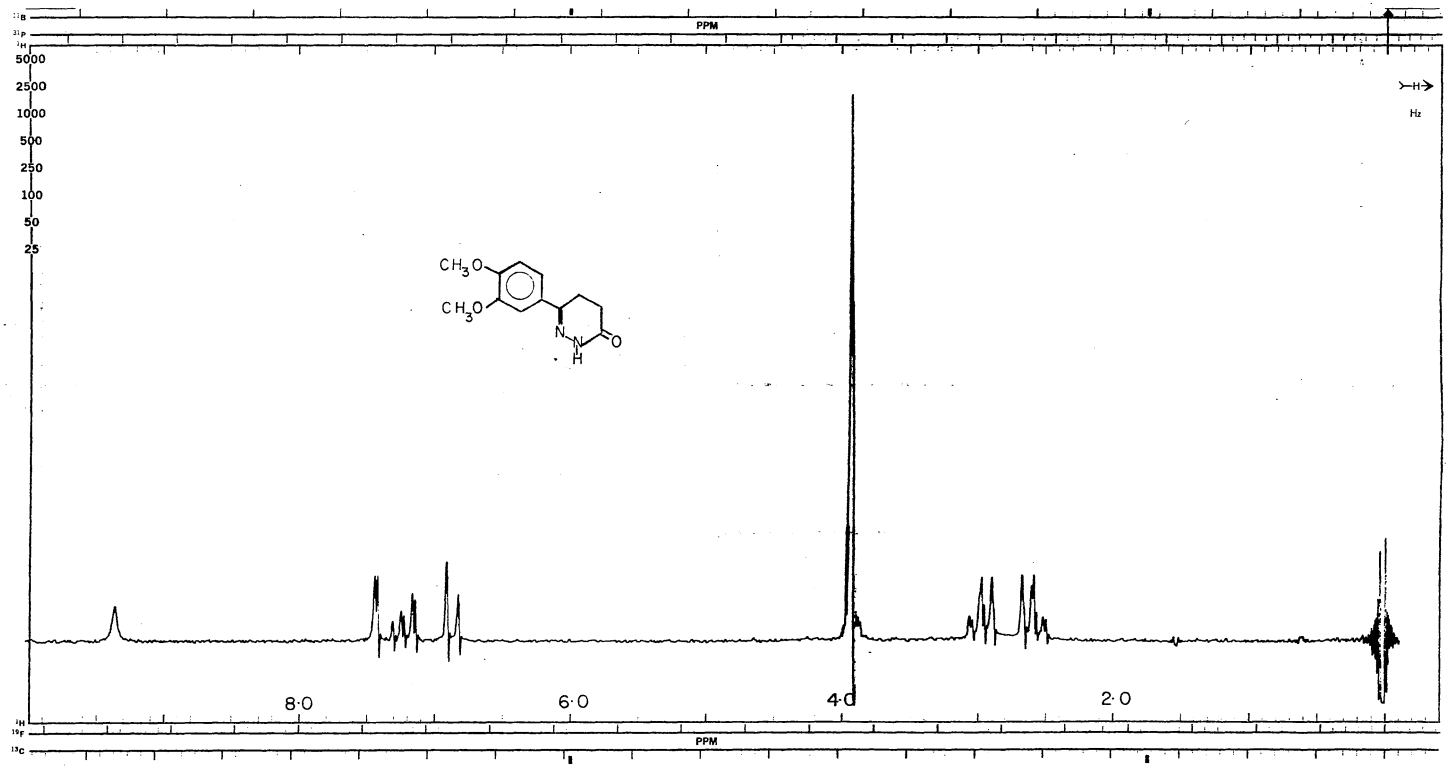
PLATE LI



4-(3 ,4 -Dimethoxyphenyl)butanoic Acid (224)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 60 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 1.6

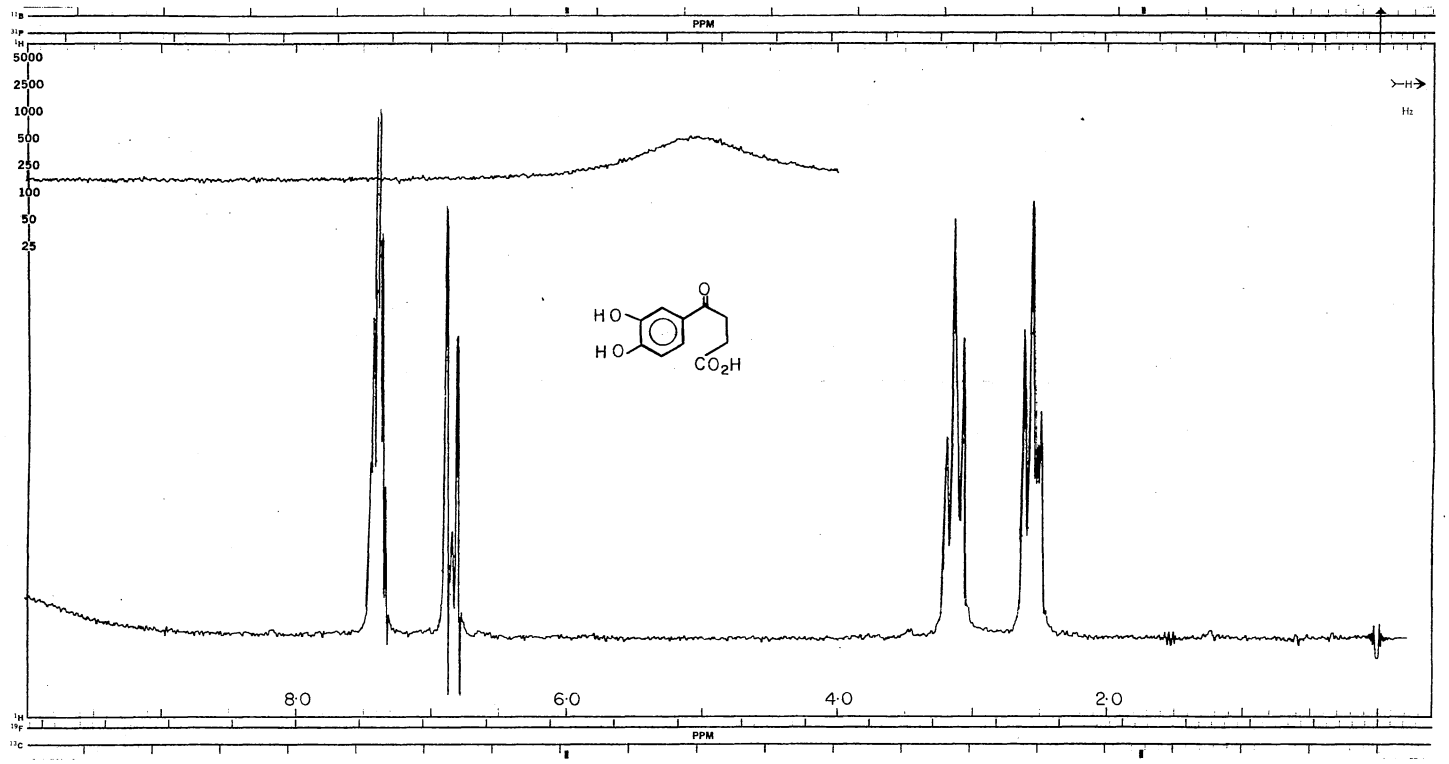
PLATE LII



6-(3,4-Dimethoxyphenyl)-4,5-dihydro-3(2H)-pyridazinone (234)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 64 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 2

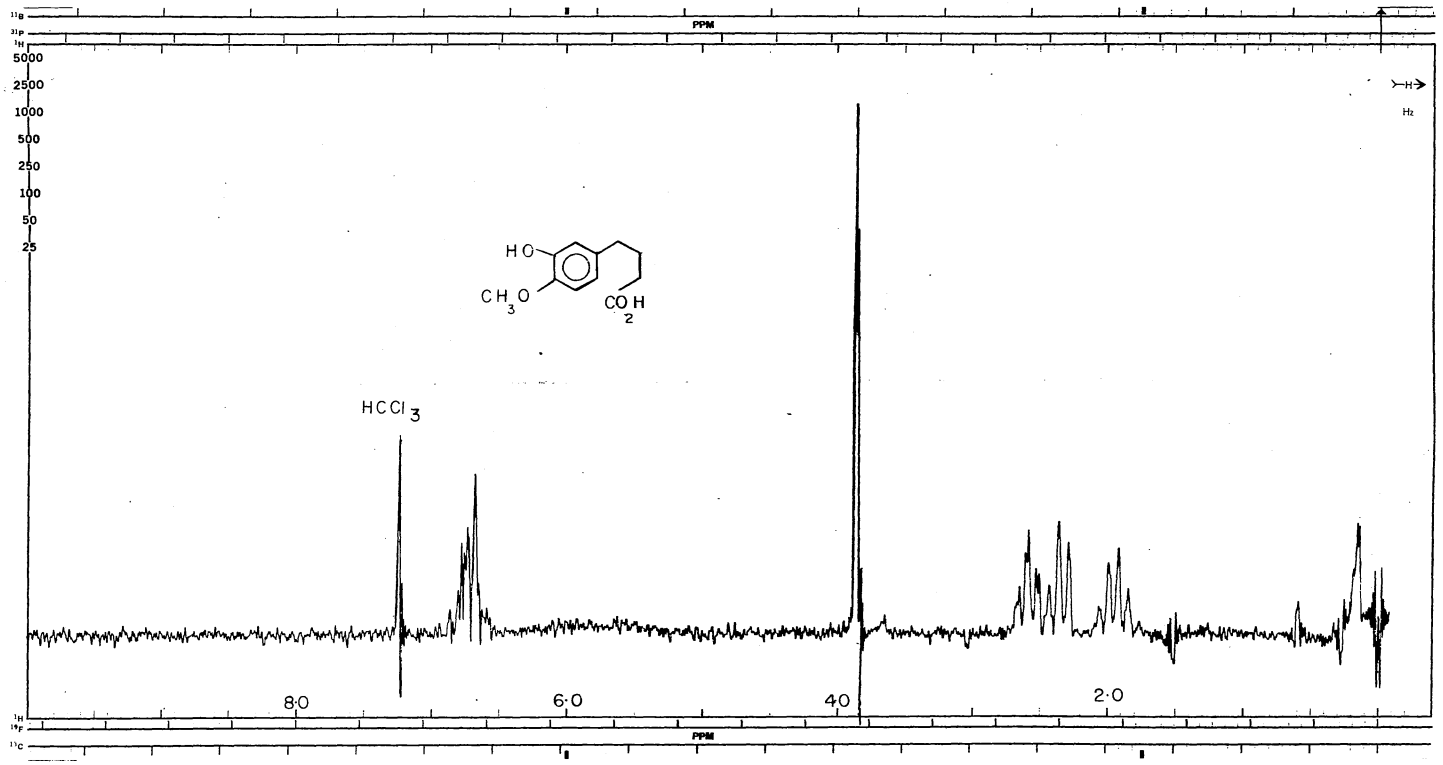
PLATE LIII



3-Protocatechuoylpropionic Acid (227)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 69 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 3.2

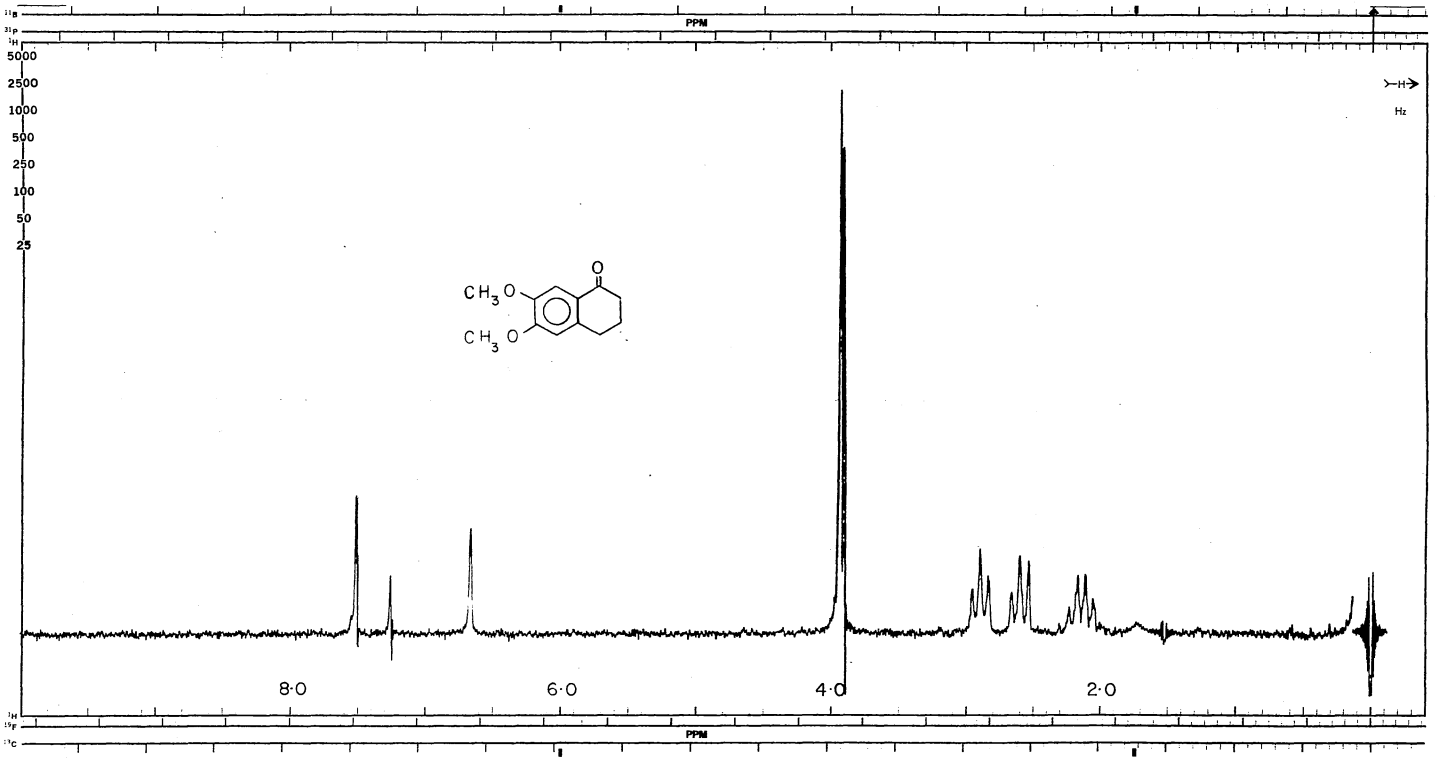
PLATE LIV



4-(3-Hydroxy-4-methoxyphenyl)butyric Acid (225)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 69 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . 12.5

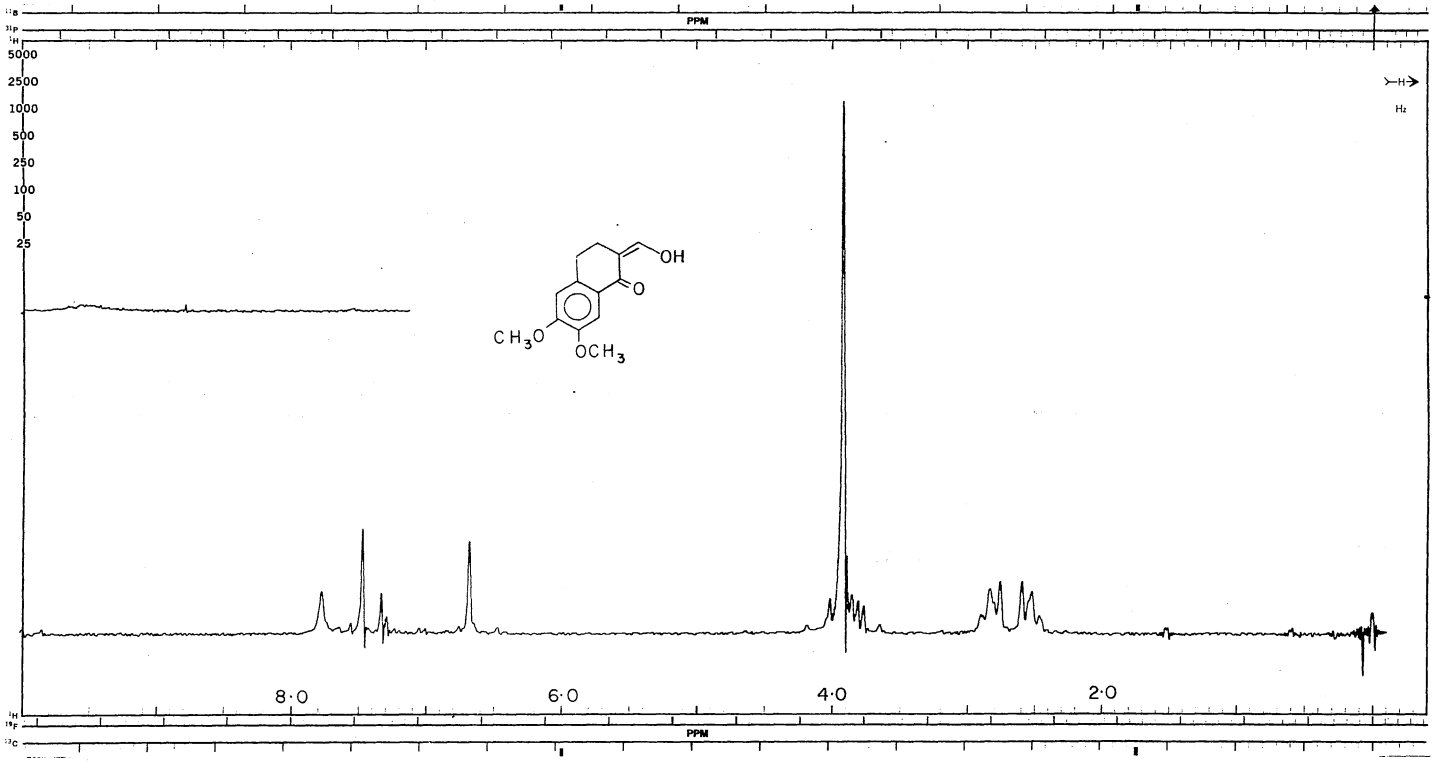
PLATE LV



3,4-Dihydro-6,7-dimethoxy-1(2H)-naphthalenone (182)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 52 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 6.3

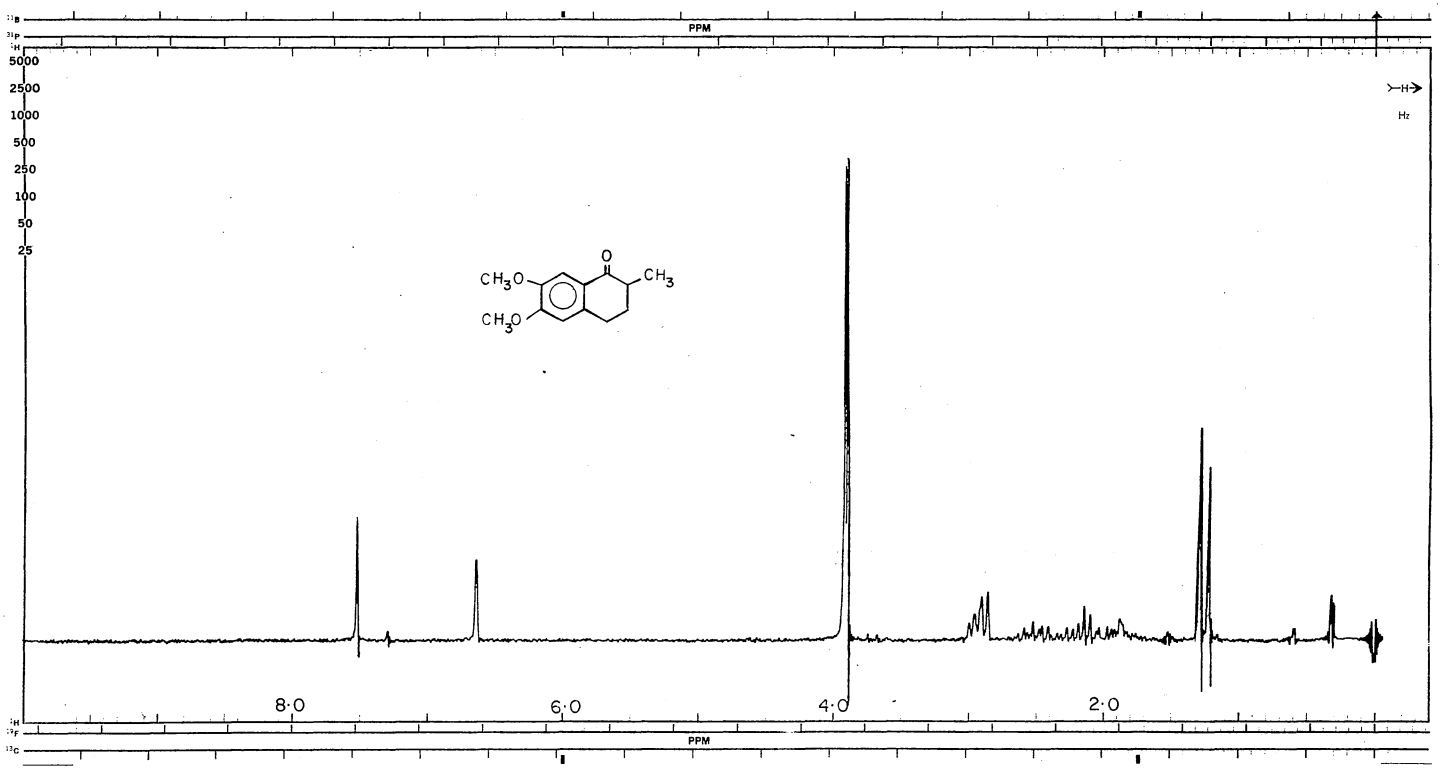
PLATE LVI



3,4-Dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1(2H)-naphthalenone (232)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 62 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 1.6

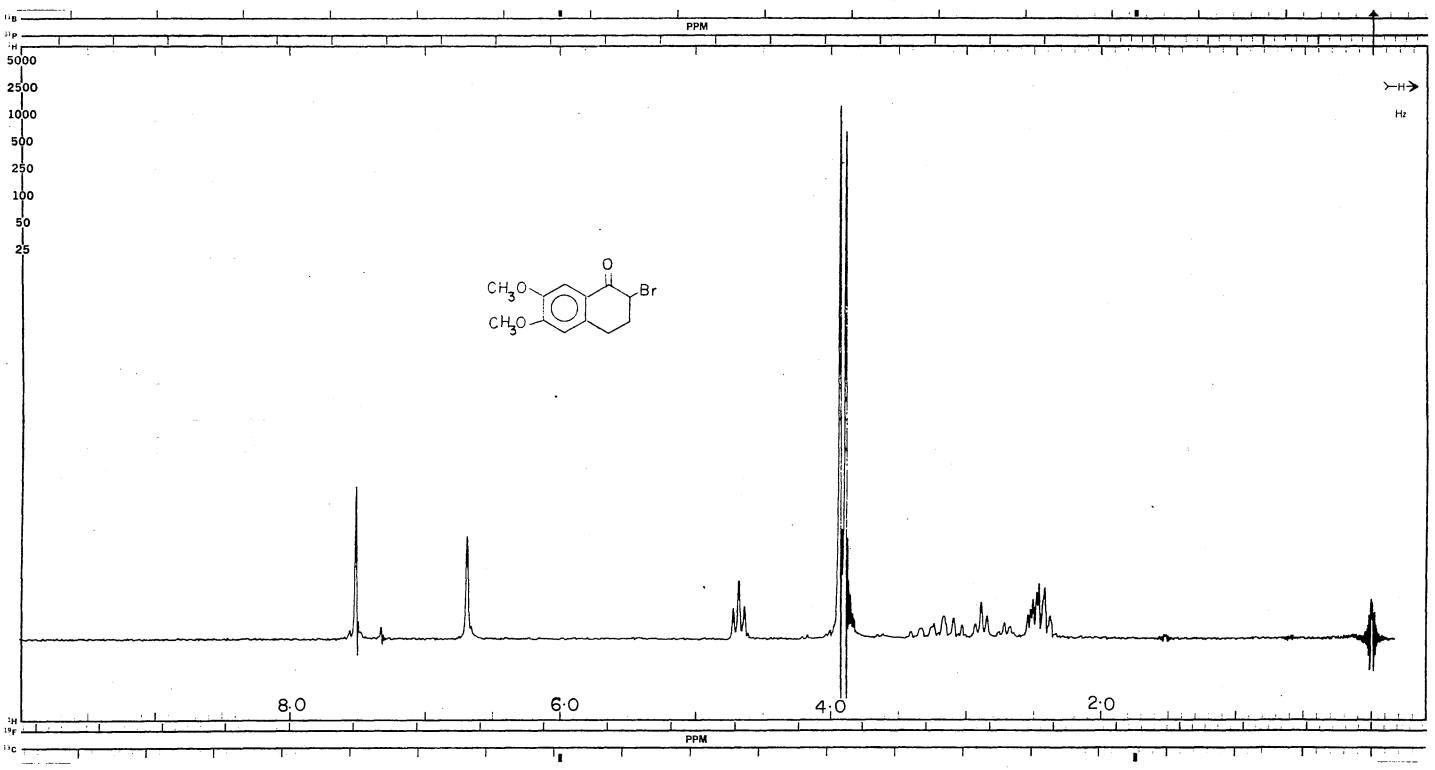
PLATE LVII



3,4-Dihydro-6,7-dimethoxy-2-methyl-1(2H)-naphthalenone (231)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 57 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.5

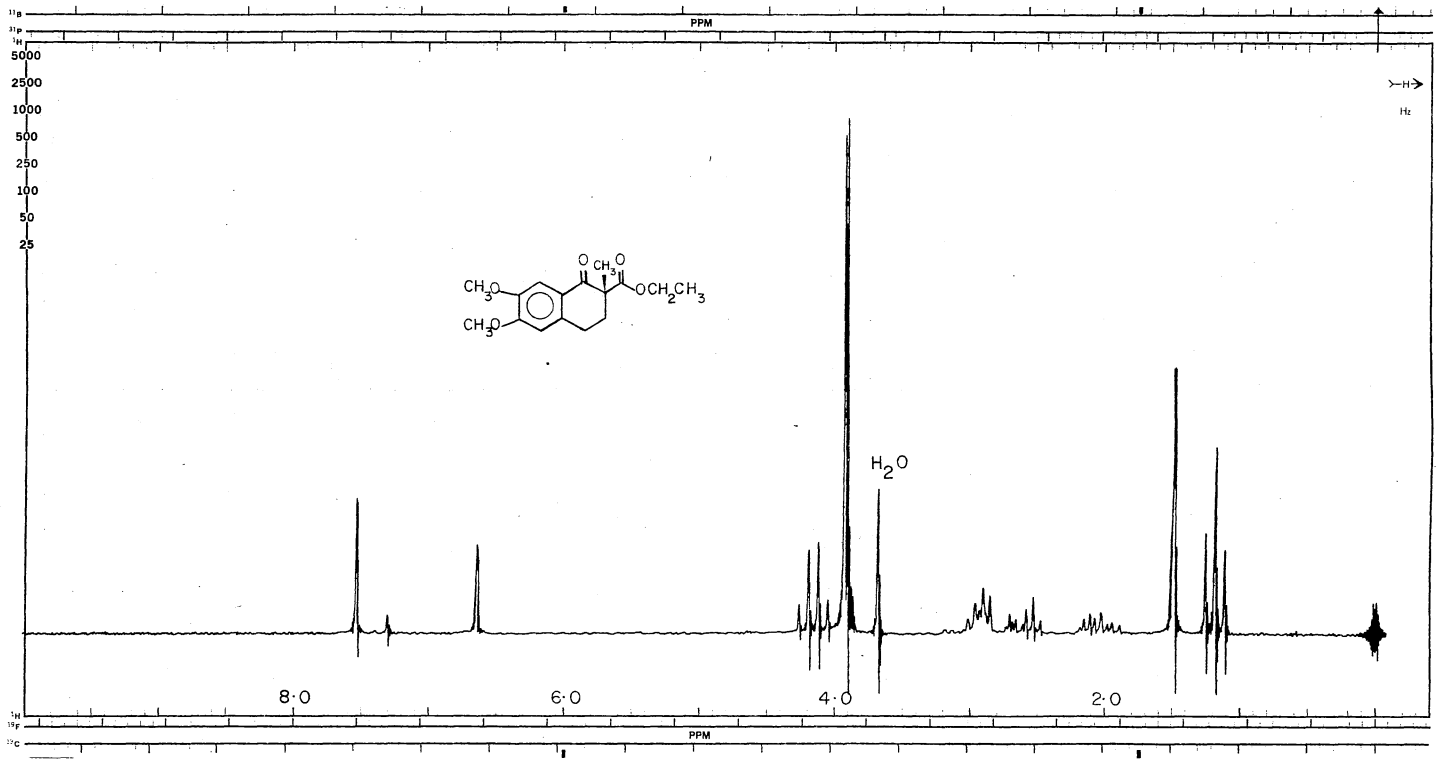
PLATE LVIII



2-Bromo-3,4-dihydro-6,7-dimethoxy-1(2H)-naphthalenone (229)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 48 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 1

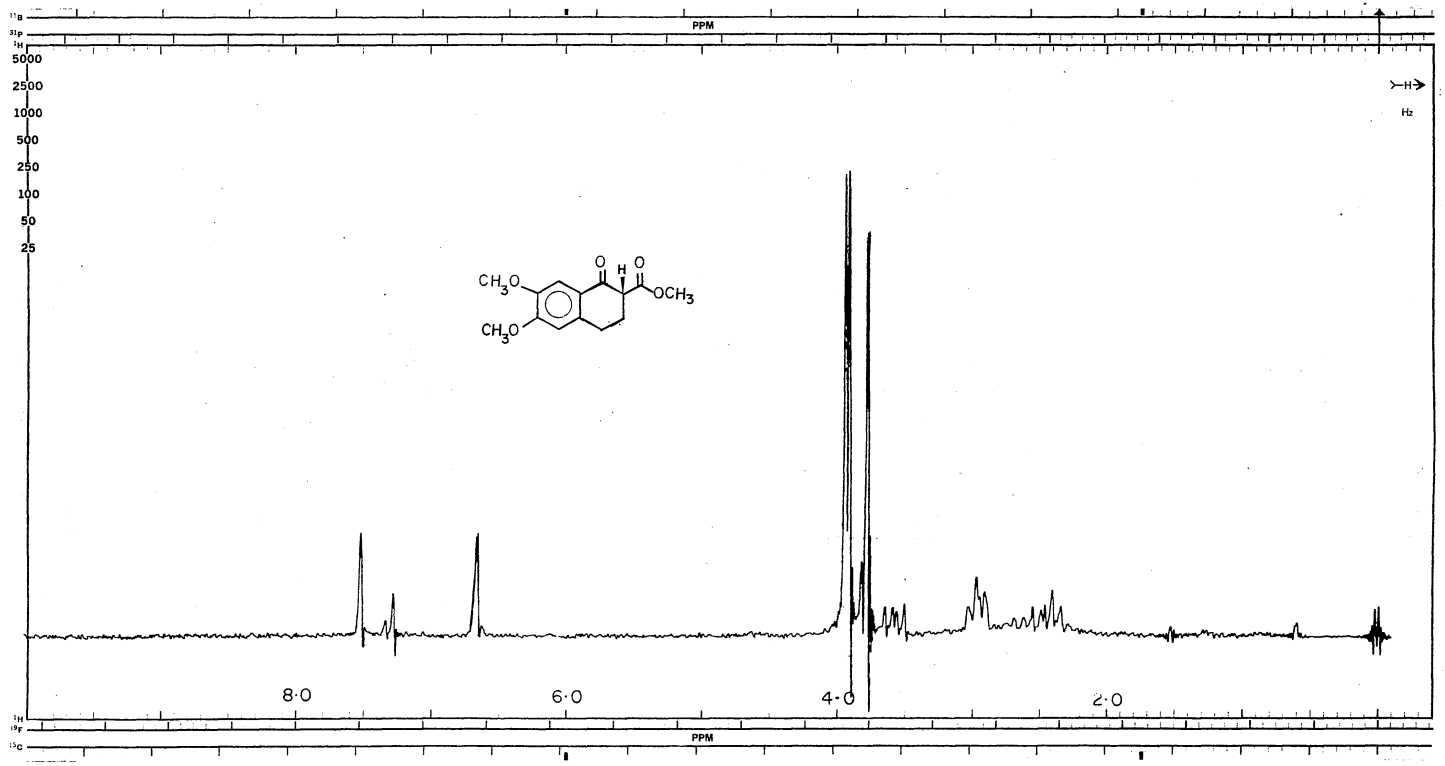
PLATE LIX



Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-oxo-2-naphthoate (228)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 66 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 1

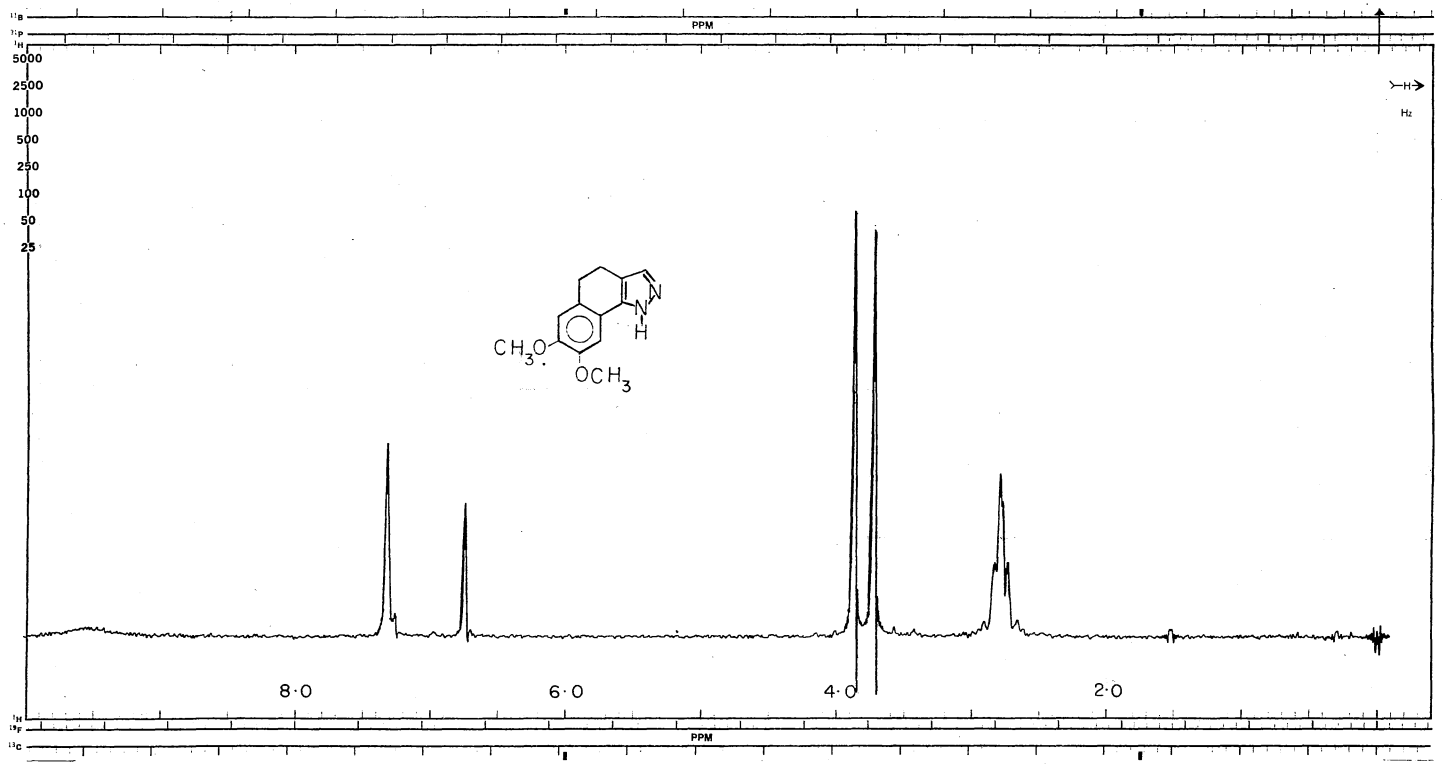
PLATE LX



Methyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-oxo-2-naphthoate (230)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 67 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 8

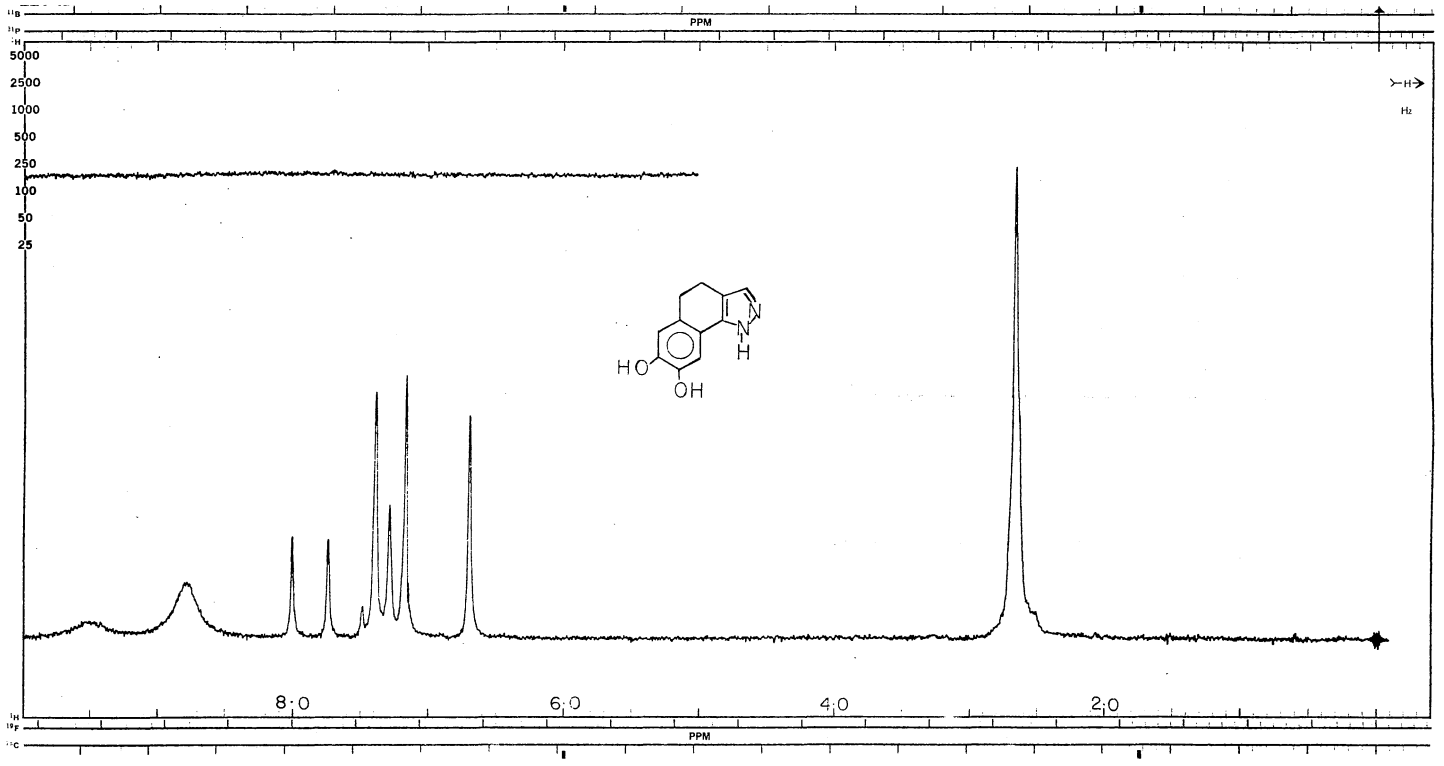
PLATE LXI



4,5-Dihydro-7,8-dimethoxy-1H-benz[g]indazole (193)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 61 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 2.5

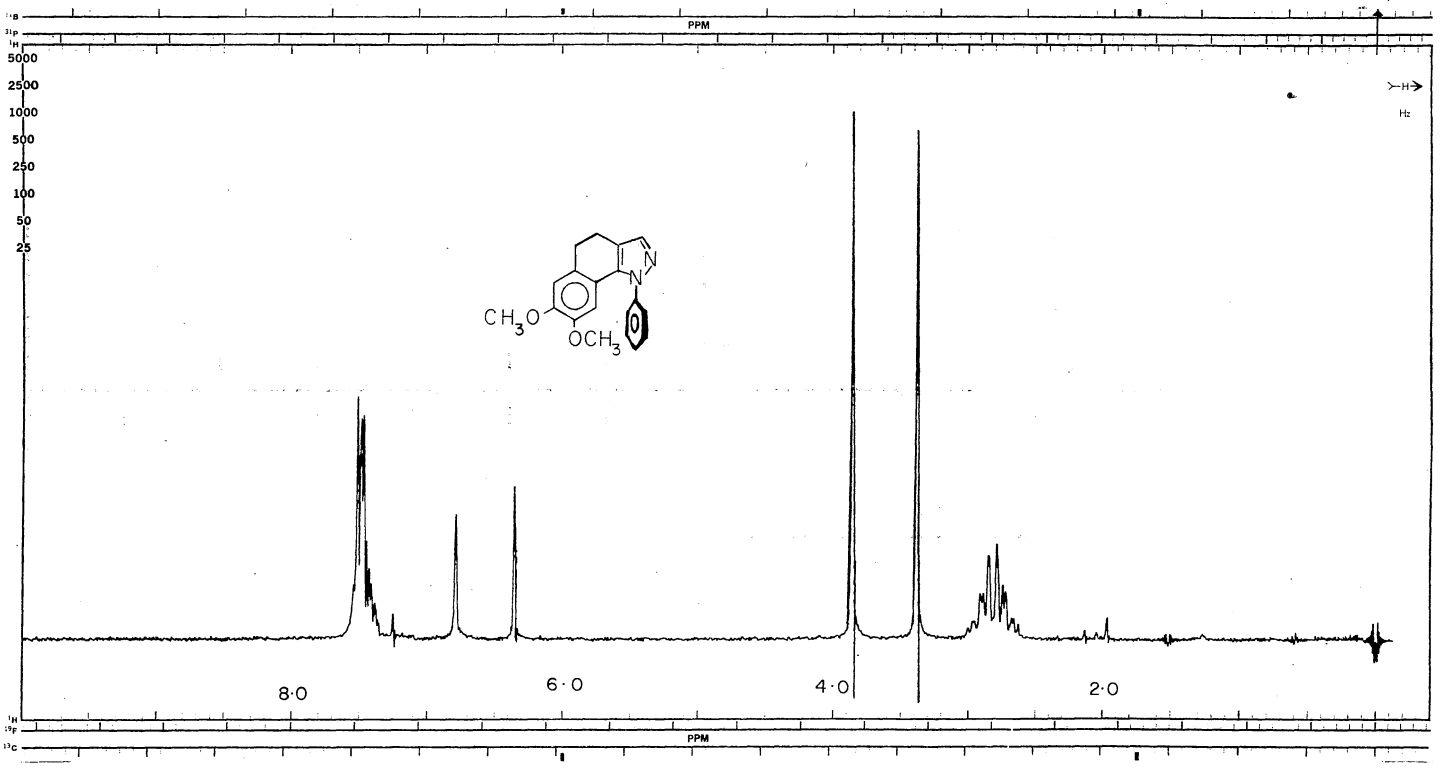
PLATE LXII



4,5-Dihydro-1H-benz[g]indazole-7,8-diol (194)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 4

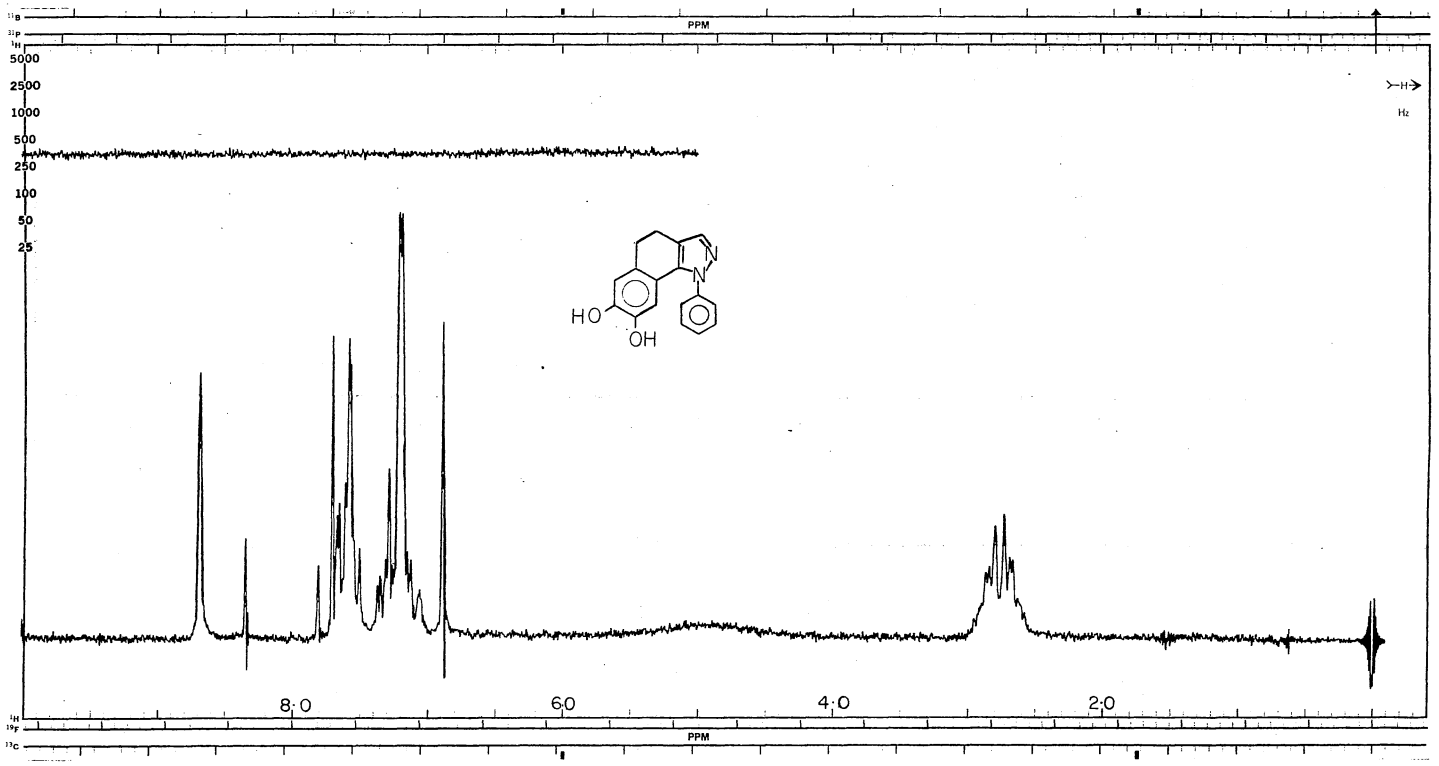
PLATE LXIII



4,5-Dihydro-7,8-dimethoxy-1-phenyl-1H-benz[g]indazole (195)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 64 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.5

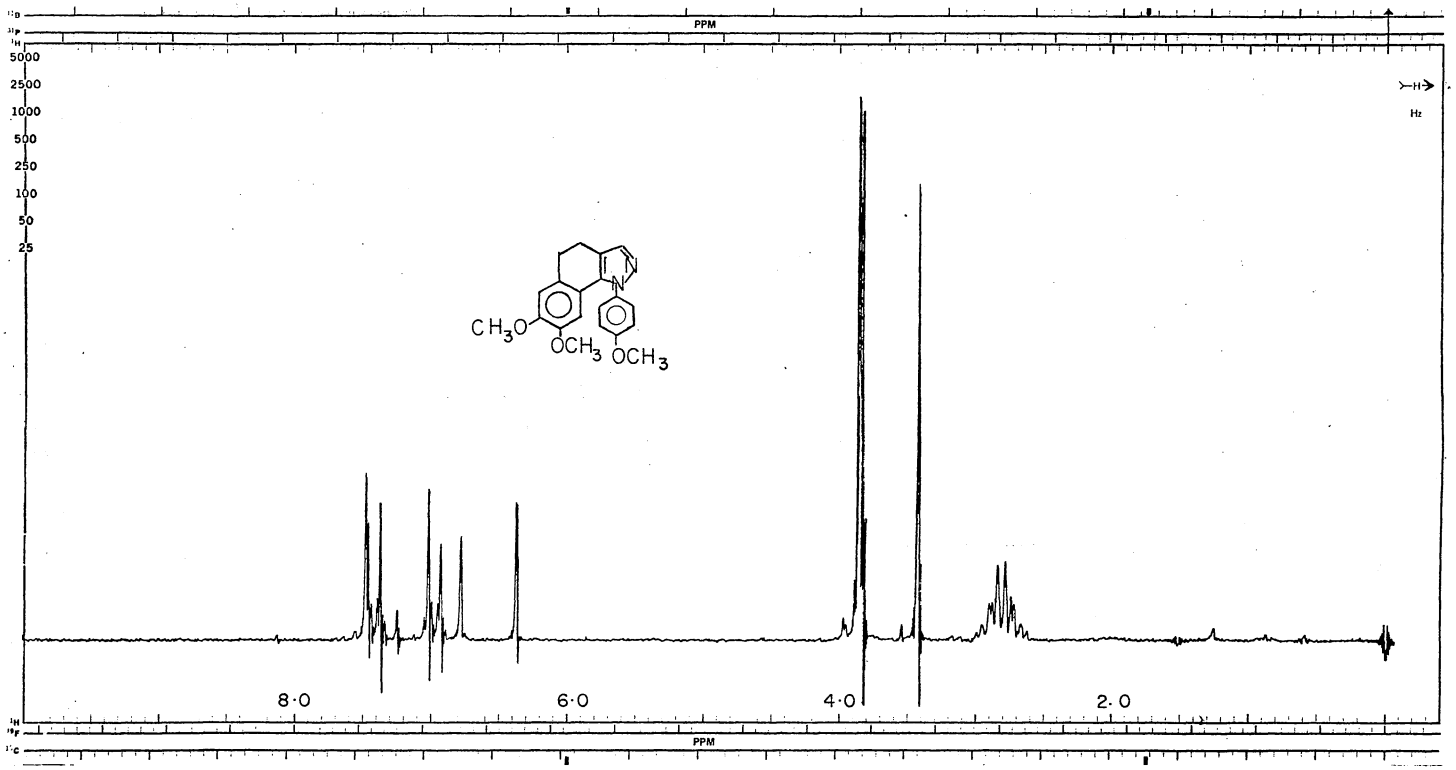
PLATE LXIV



4,5-Dihydro-1-phenyl-1H-benz[g]indazole-7,8-diol (196)

Solvent. . . C_5D_5N	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 6.3

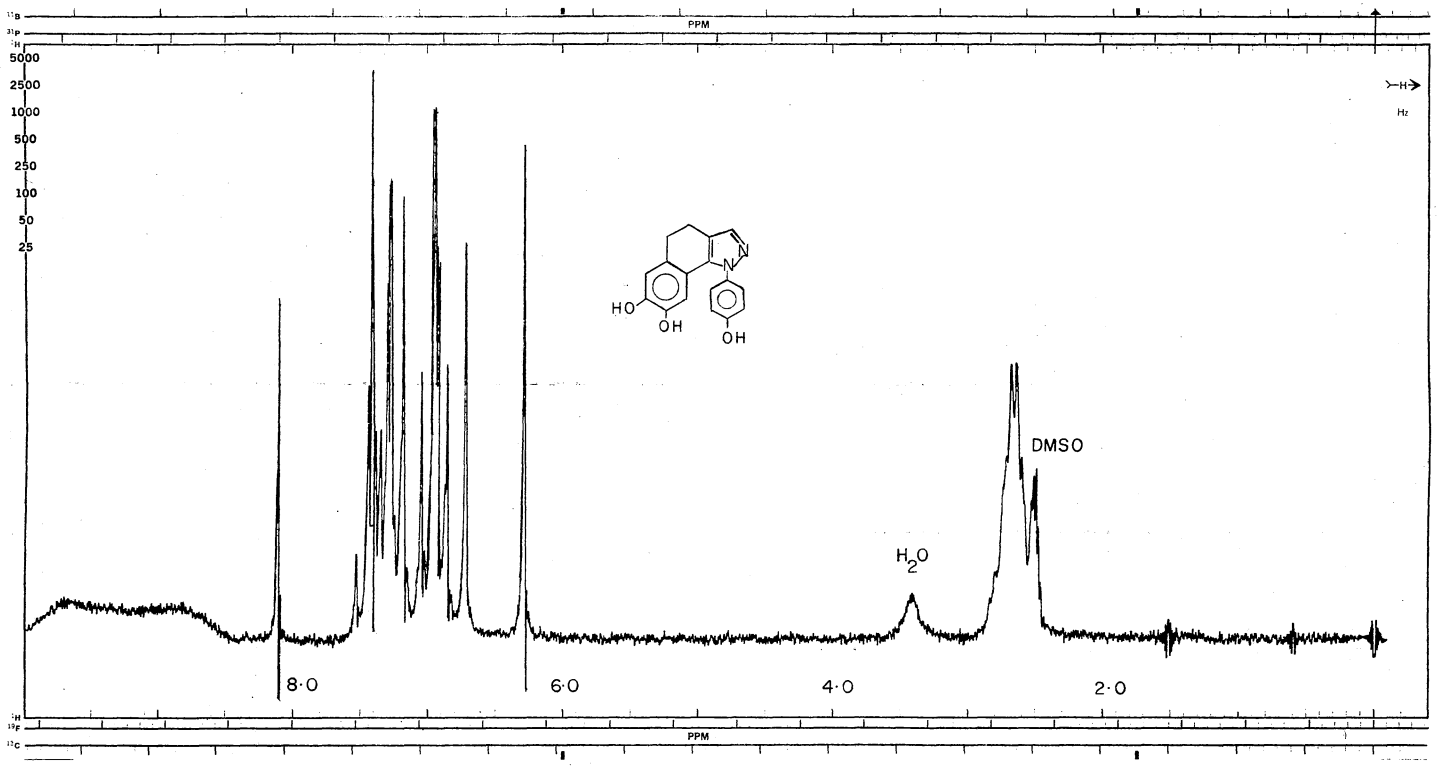
PLATE LXV



4,5-Dihydro-7,8-dimethoxy-1-(p-methoxyphenyl)-1H-benz[g]indazole (197)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.0

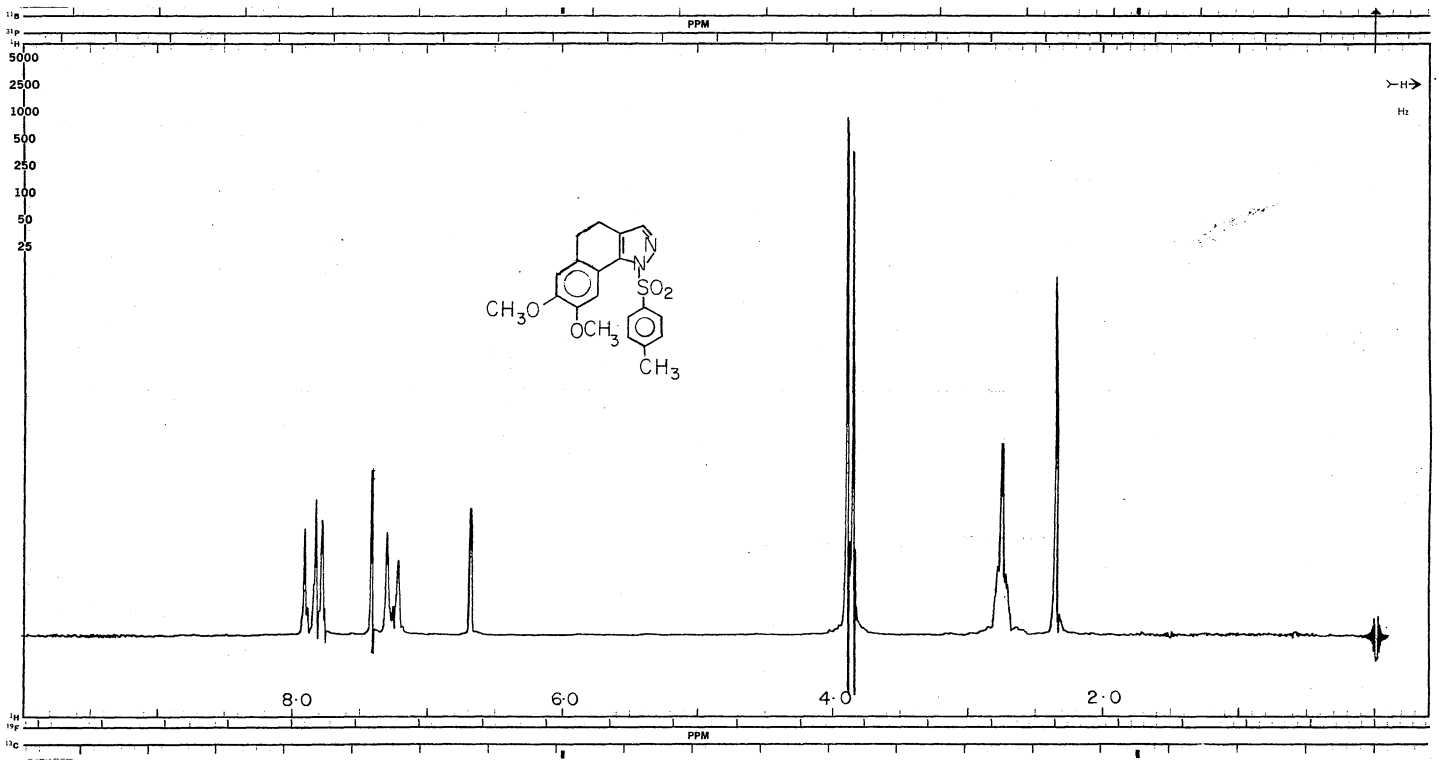
PLATE LXVI



4,5-Dihydro-1-(p-hydroxyphenyl)-1H-benz[g]indazole-7,8-diol (198)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 67 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 8

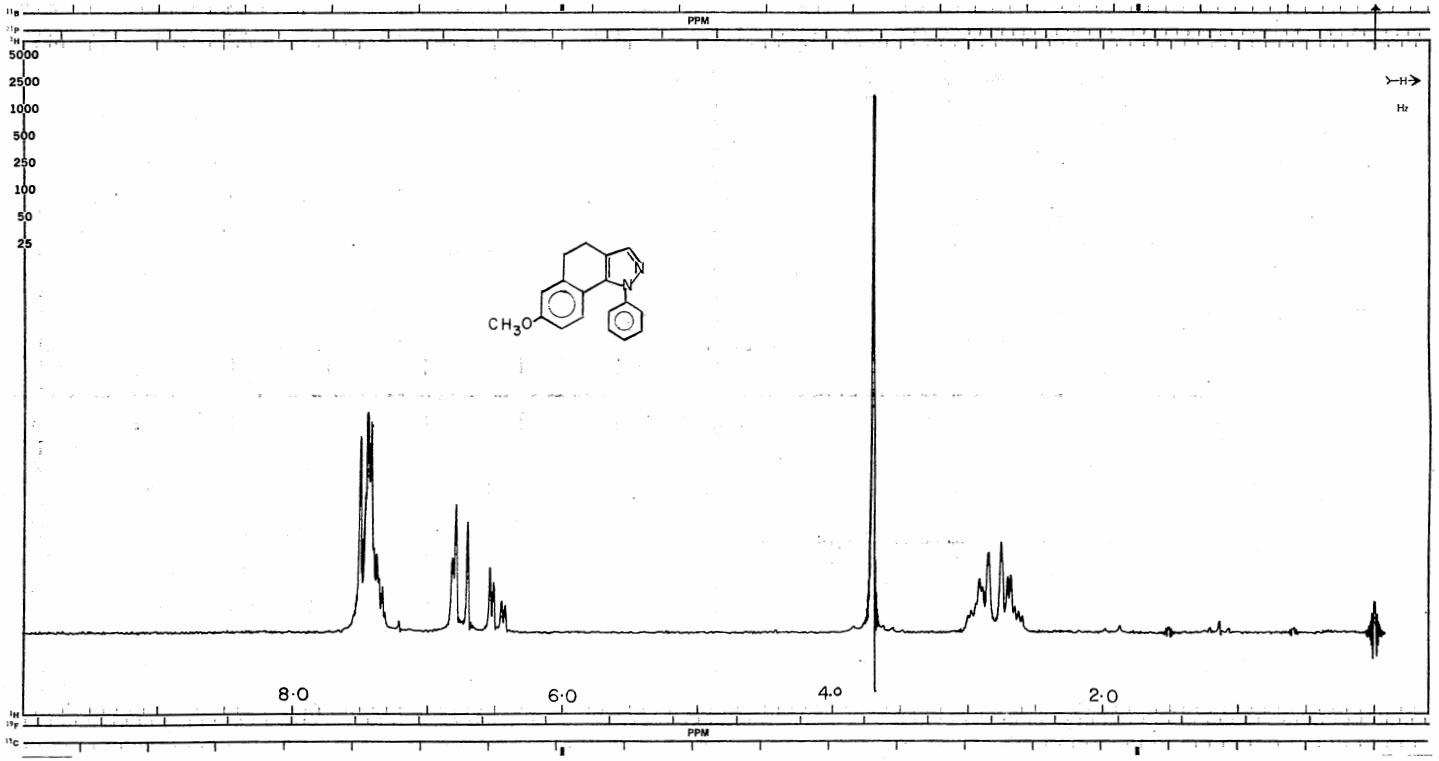
PLATE LXVII



4,5-Dihydro-7,8-dimethoxy-1-(p-tolylsulfonyl)-1H-benz[g]indazole (199)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 64 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.0

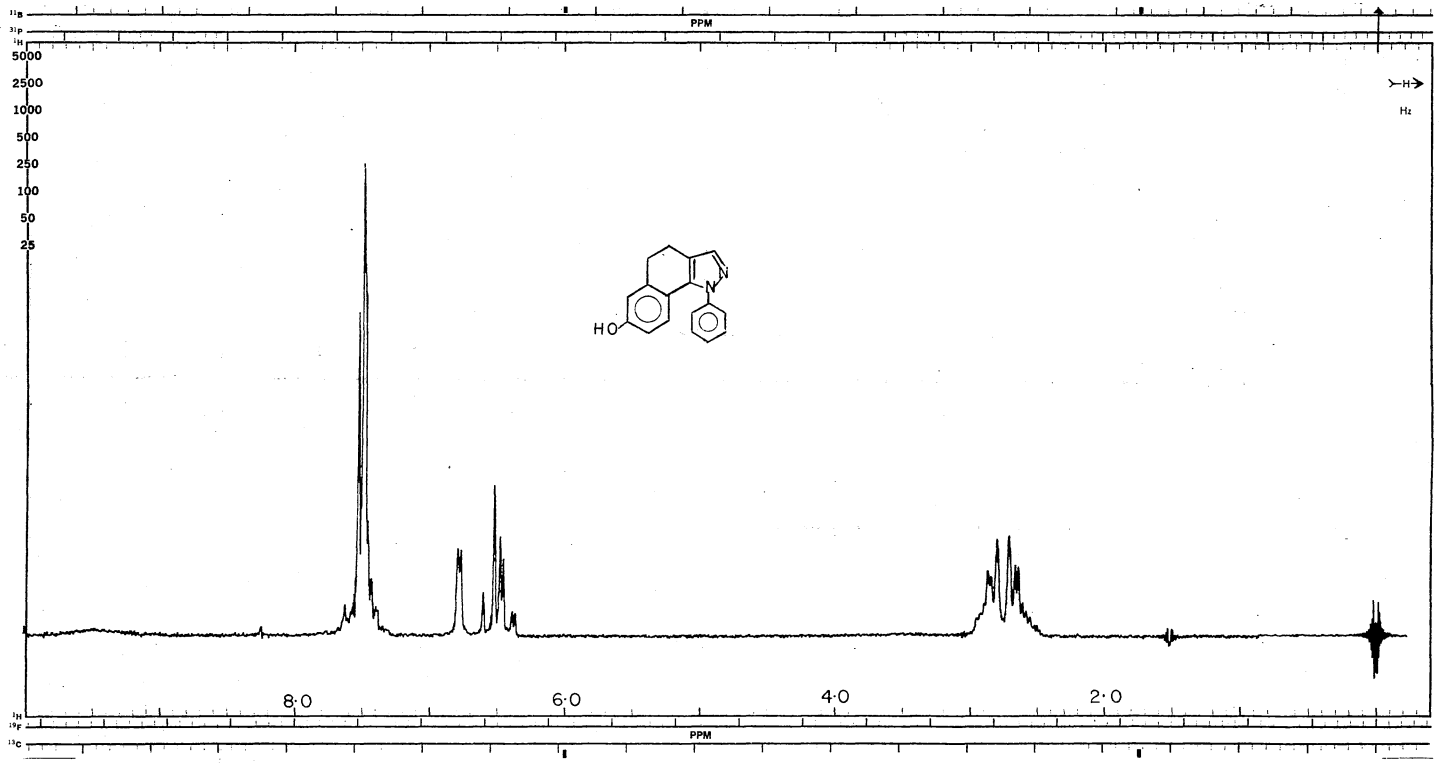
PLATE LXVIII



4,5-Dihydro-7-methoxy-1-phenyl-1H-benz[g]indazole (203)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 67 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.5

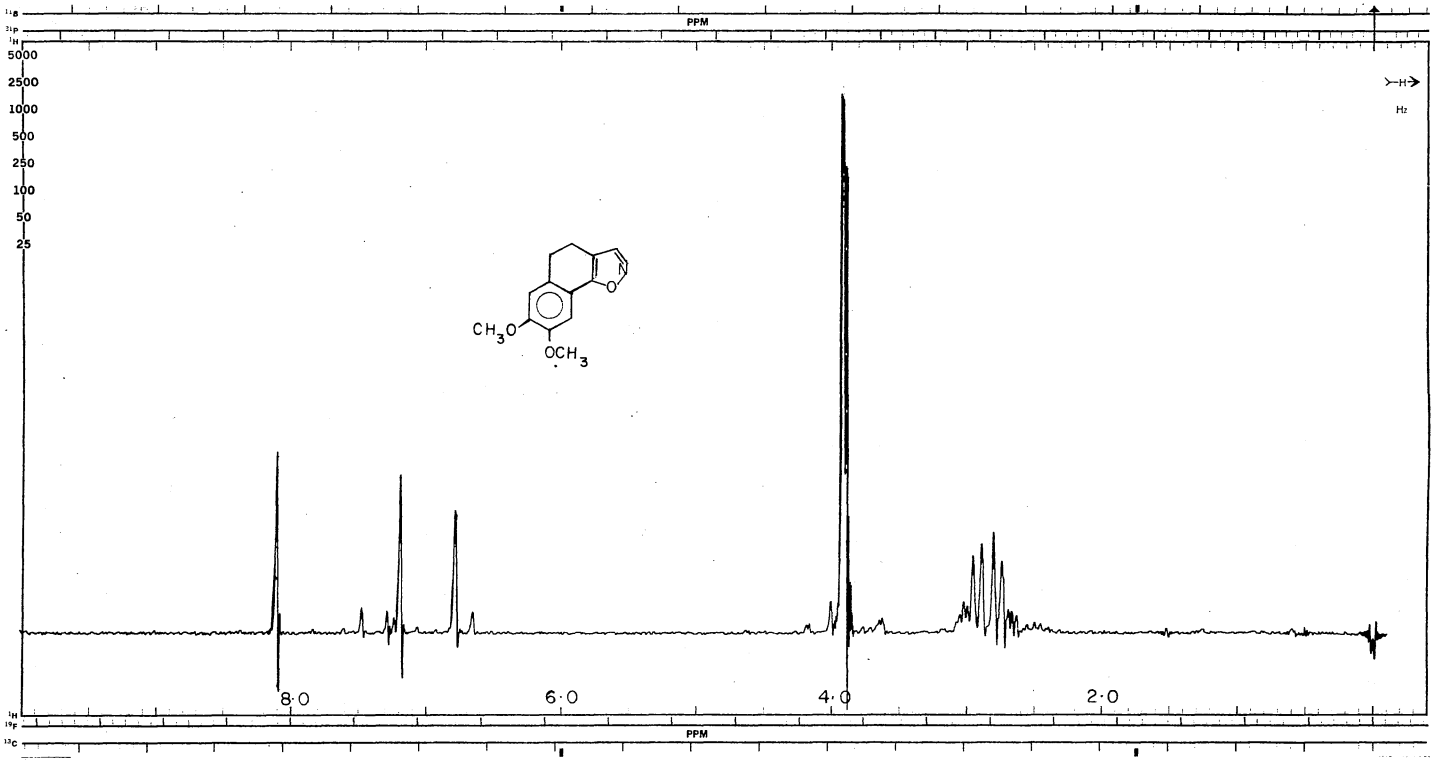
PLATE LXIX



4,5-Dihydro-1-phenyl-1H-benz[g]indazol-7-ol (204)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 61 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 1.6

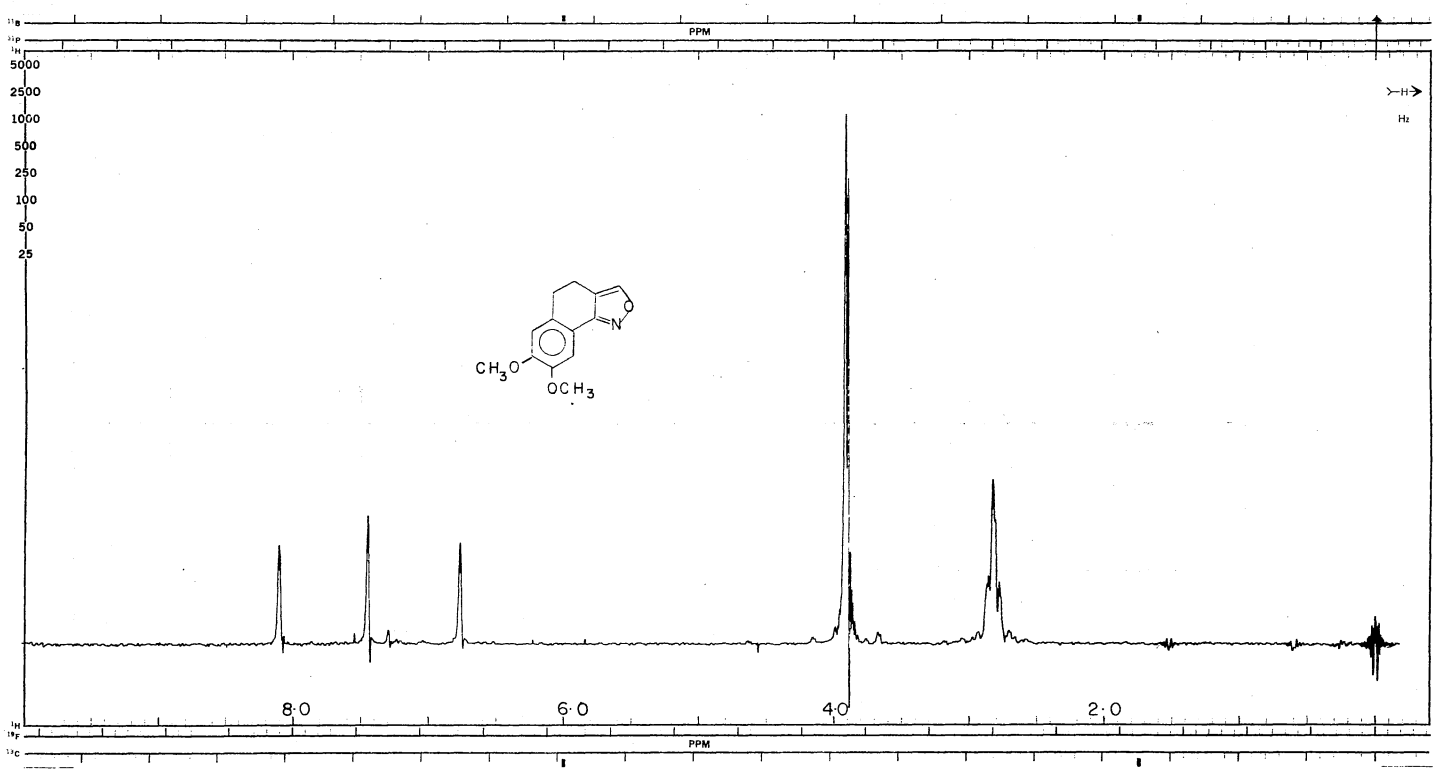
PLATE LXX



4,5-Dihydro-7,8-dimethoxynaphth[2,1-d]isoxazole (185)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 62 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 1.6

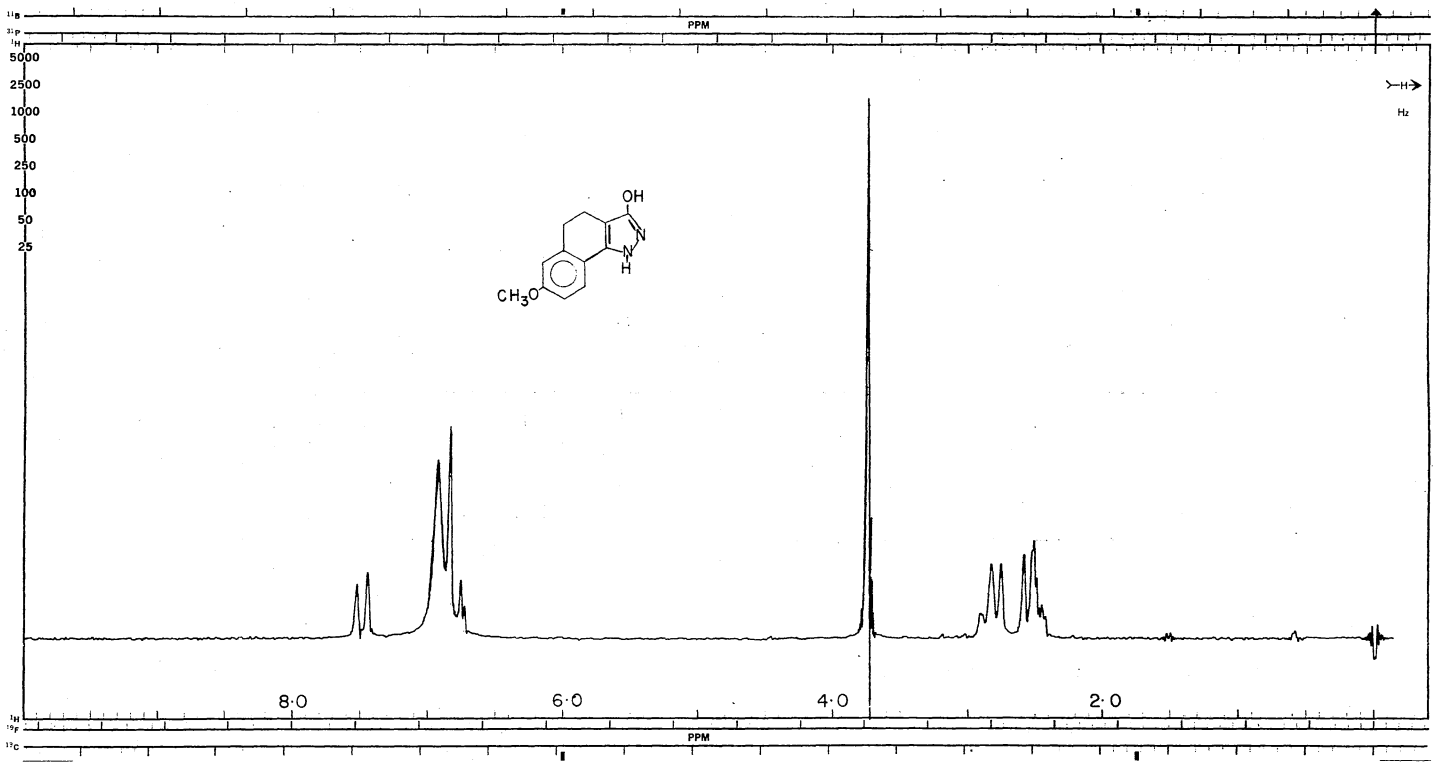
PLATE LXXI



4,5-Dihydro-7,8-dimethoxynaphth[1,2-c]isoxazole (186)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 62 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 2.0

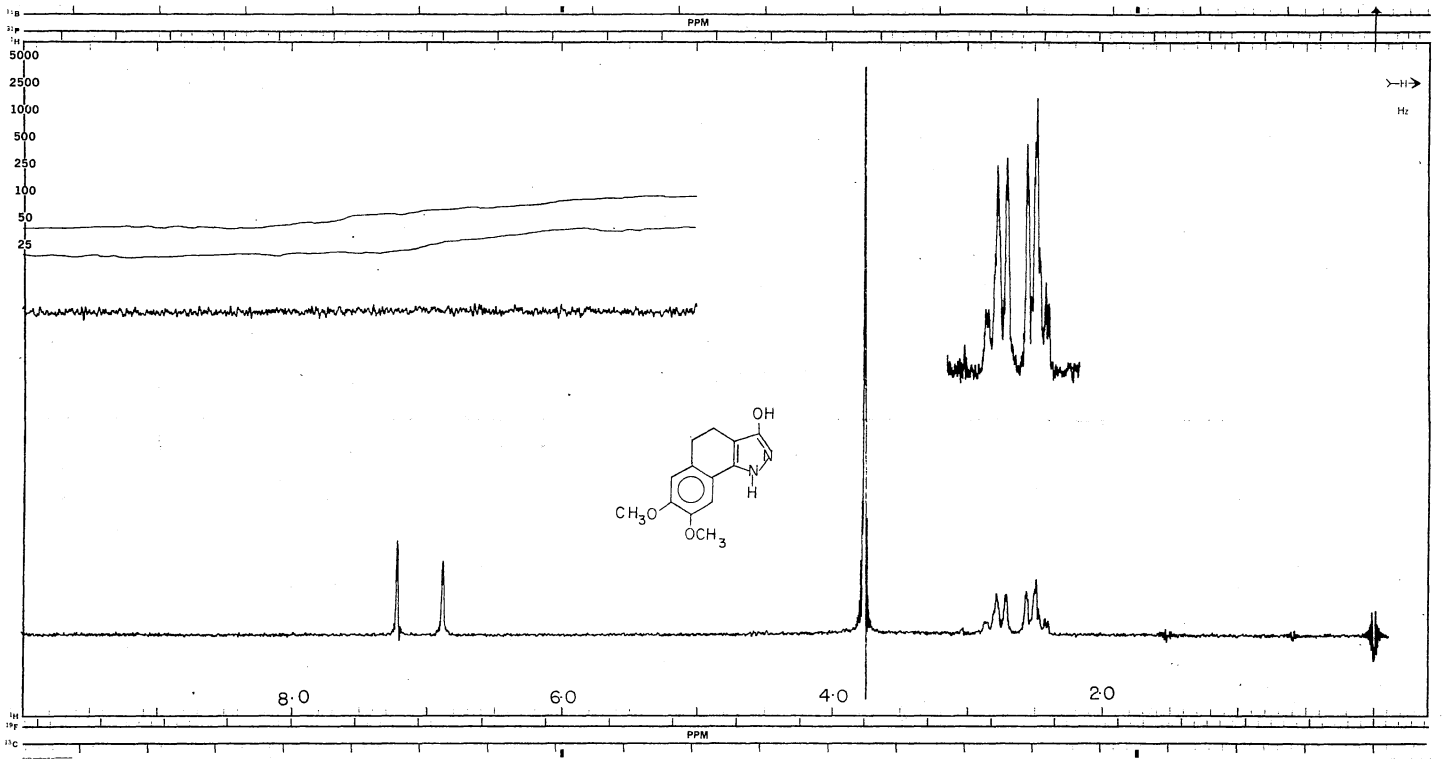
PLATE LXXII



2,3a,4,5-Tetrahydro-7-methoxy-3H-benz[g]indazol-3-one (233)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 66 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 1.6

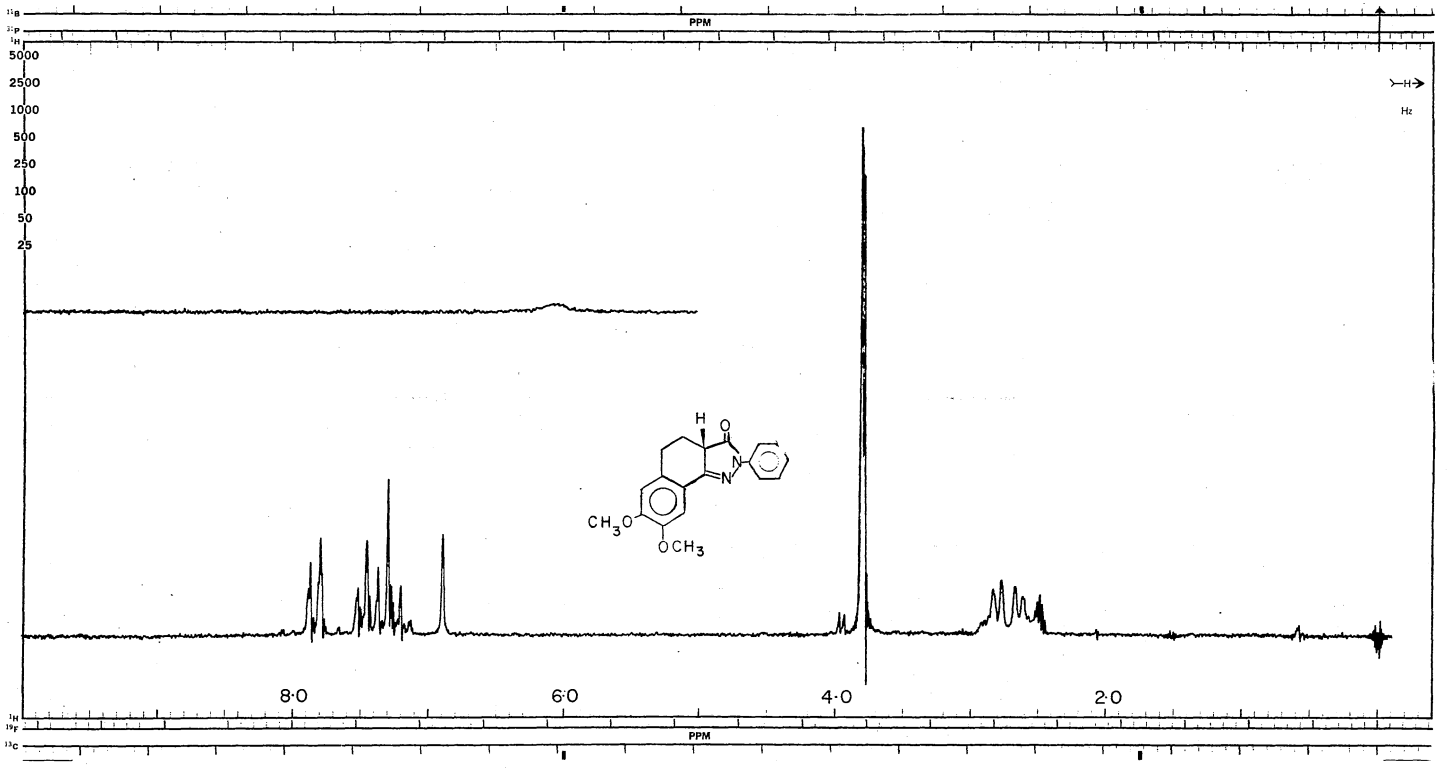
PLATE LXXIII



2,3a,4,5-Tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one (207)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 69 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.5

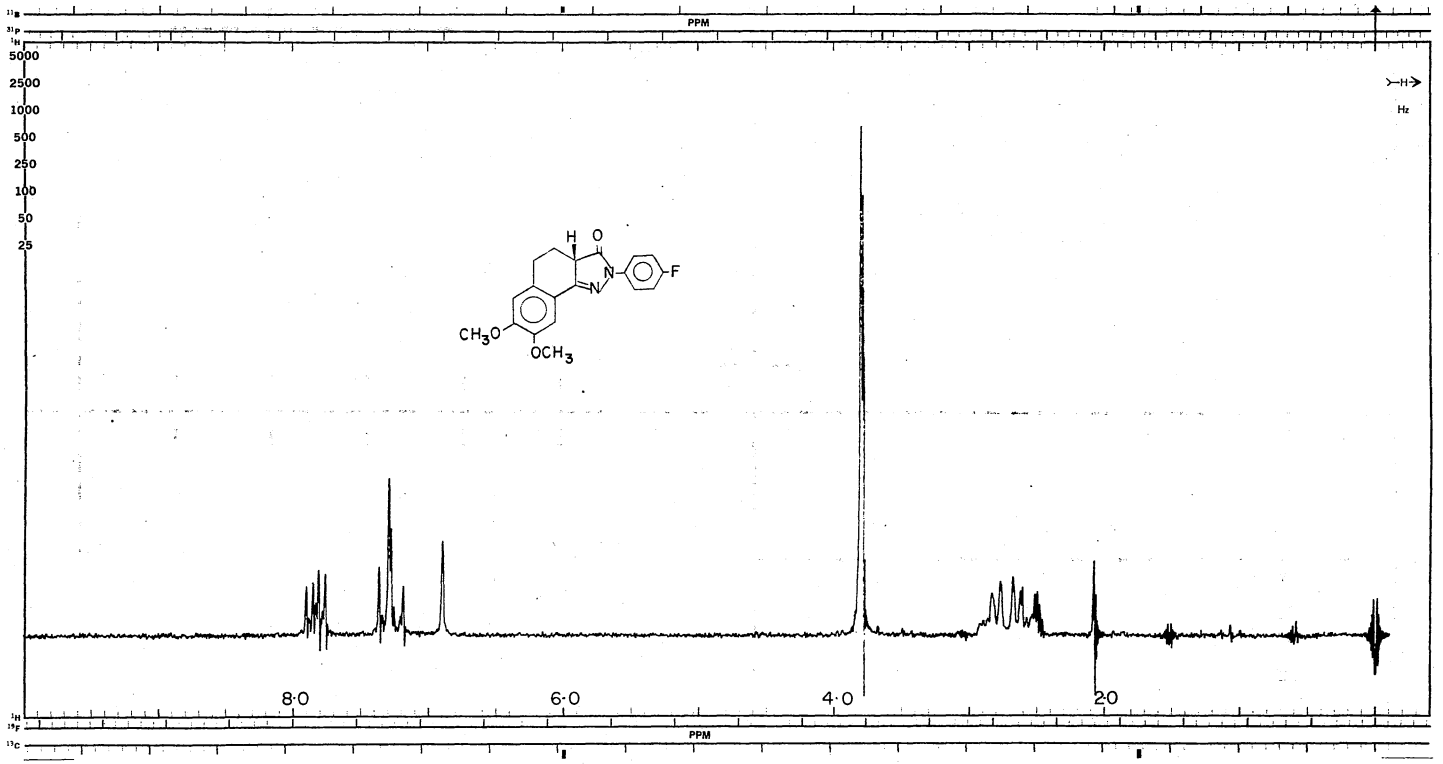
PLATE LXXIV



2,3a,4,5-Tetrahydro-7,8-dimethoxy-2-phenyl-3H-benz[g]indazol-3-one (208)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 60 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 3.2

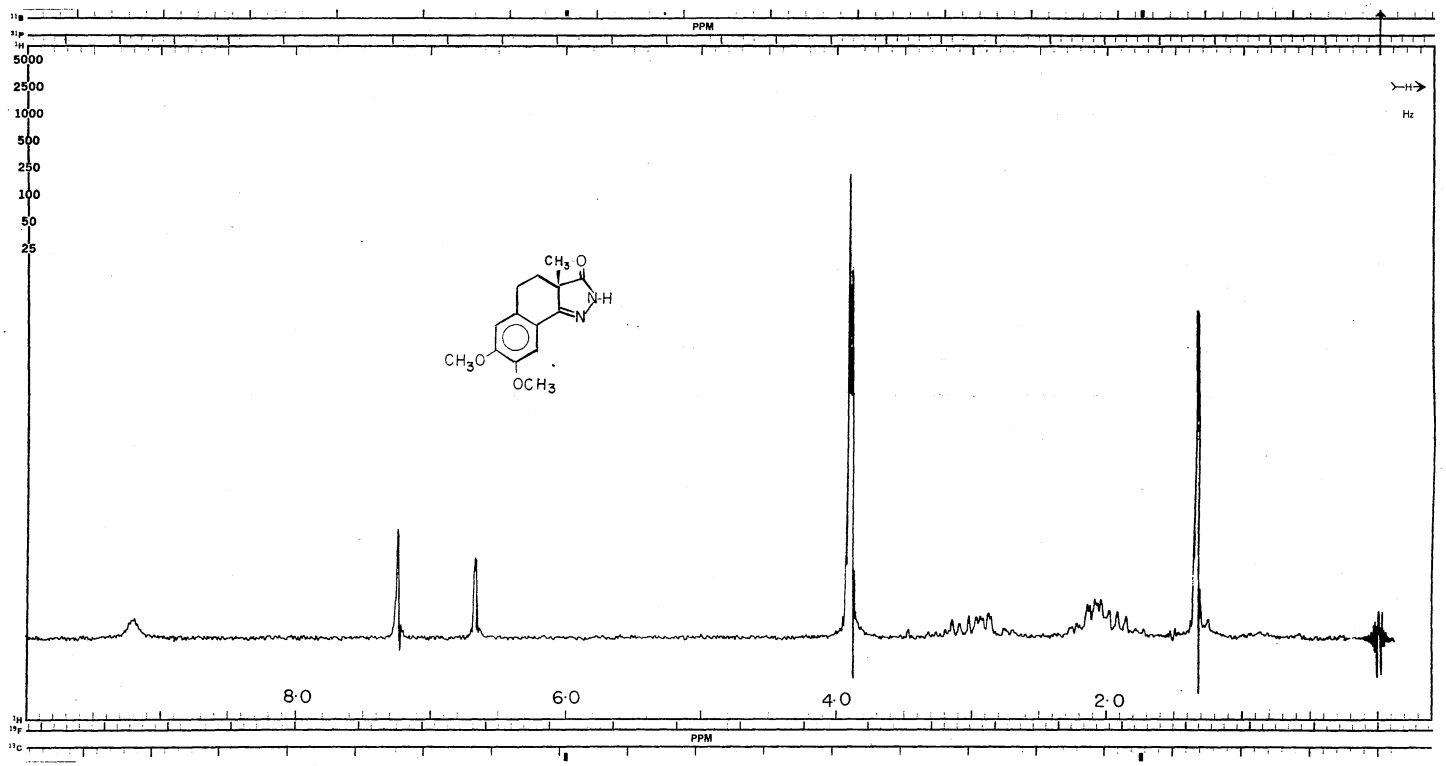
PLATE LXXV



2-(p-Fluorophenyl)-2,3a,4,5-tetrahydro-7,8-dimethoxy-3H-benz[g]indazol-3-one (209)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 61 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 3.2

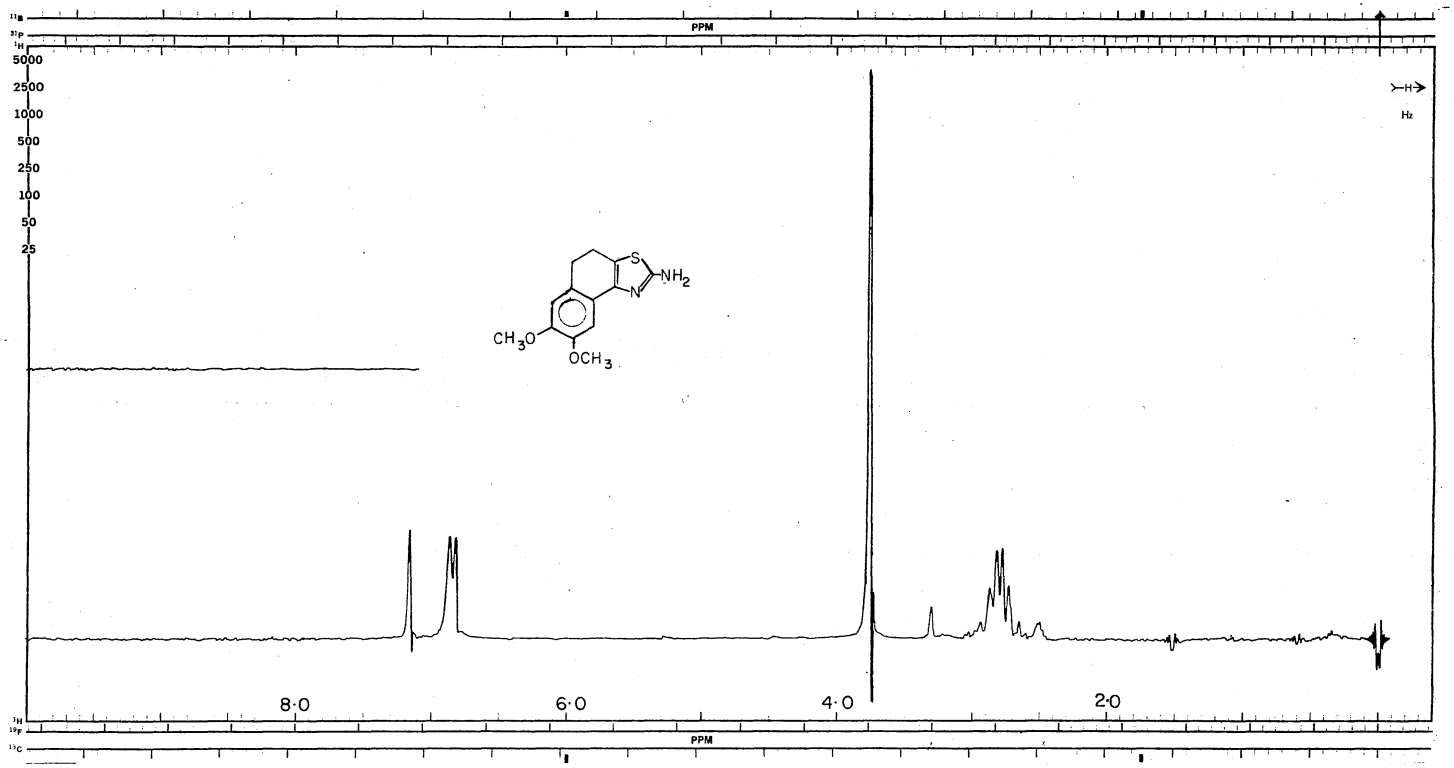
PLATE LXXVI



2,3a,4,5-Tetrahydro-7,8-dimethoxy-3a-methyl-3H-benz[g]indazol-3-one (210)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 3.2

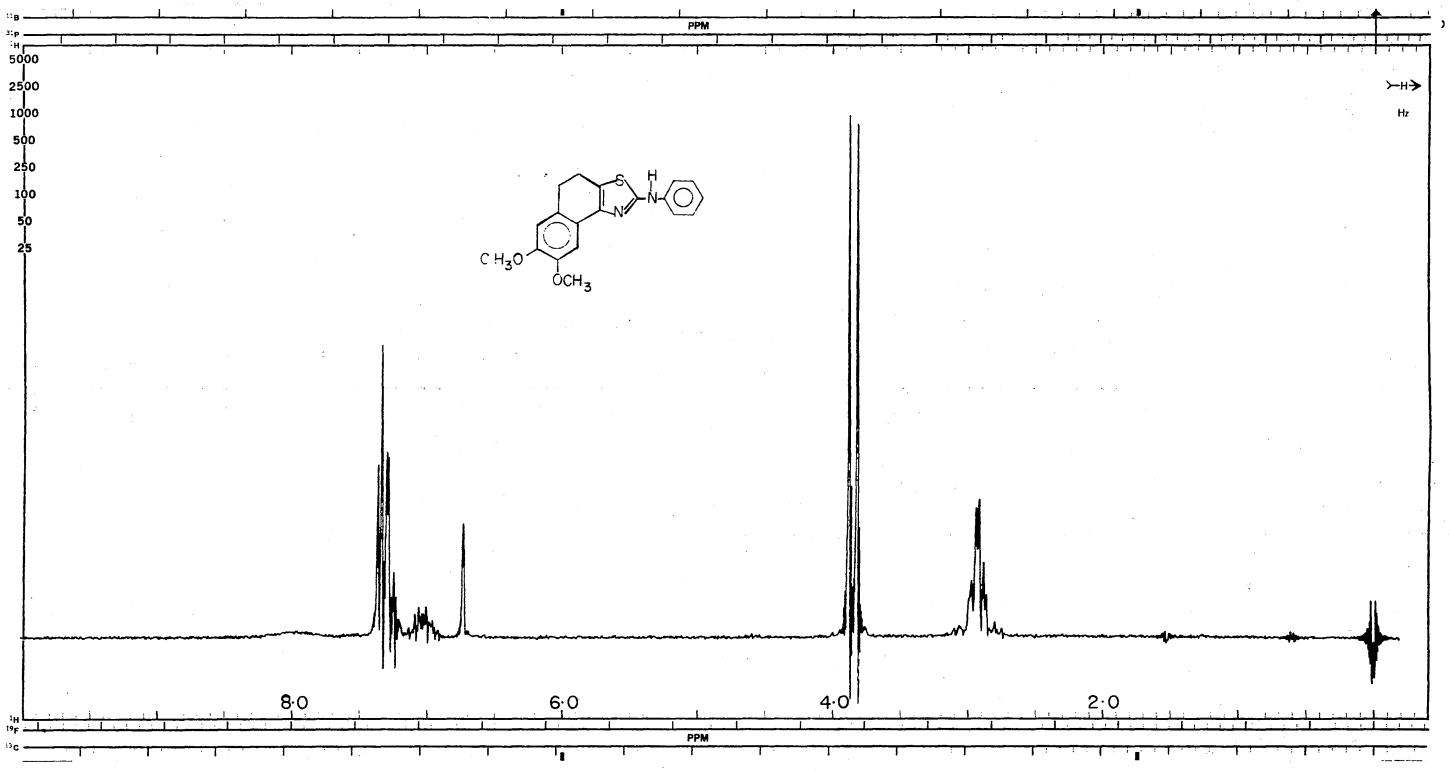
PLATE LXXVII



2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (211)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 61 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 2.5

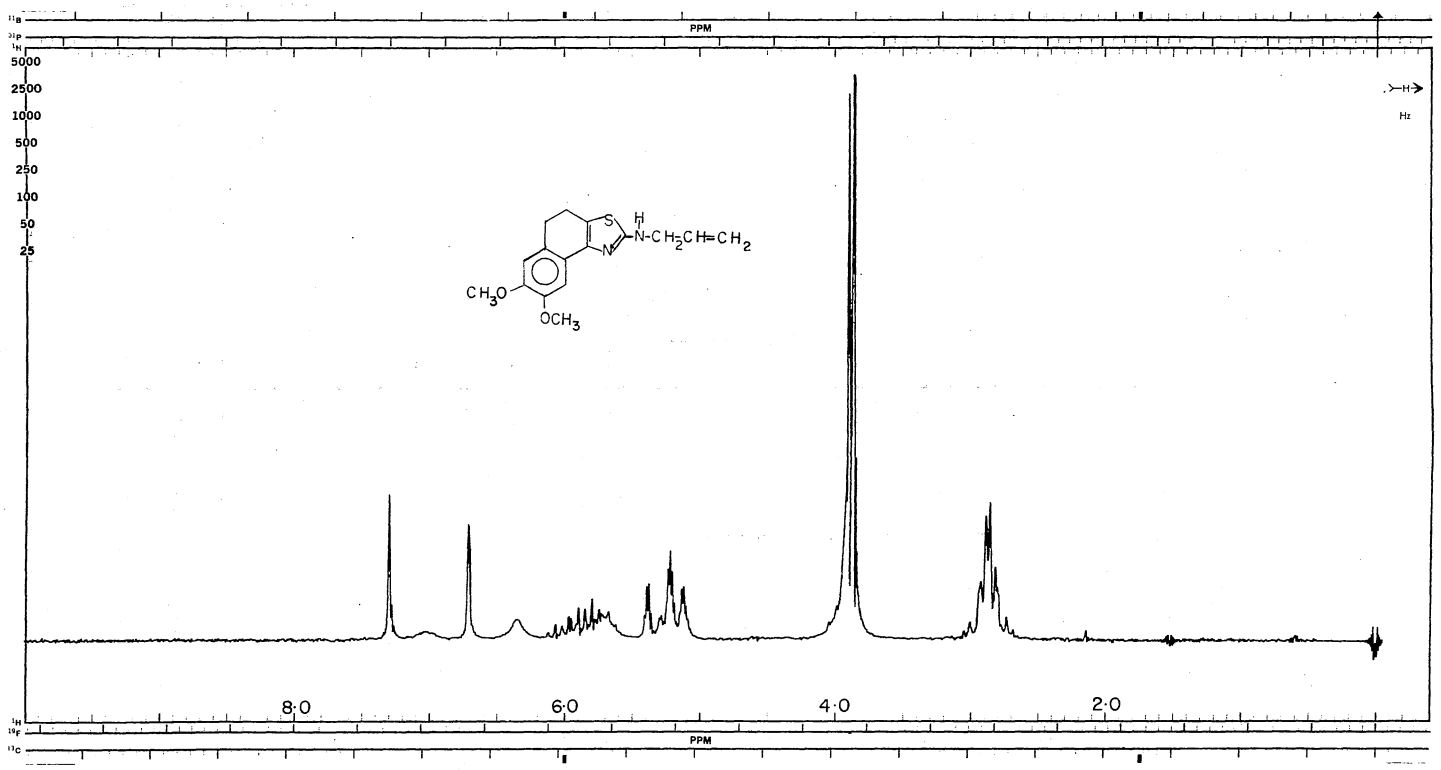
PLATE LXXVIII



2-Anilino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (212)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 61 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.0

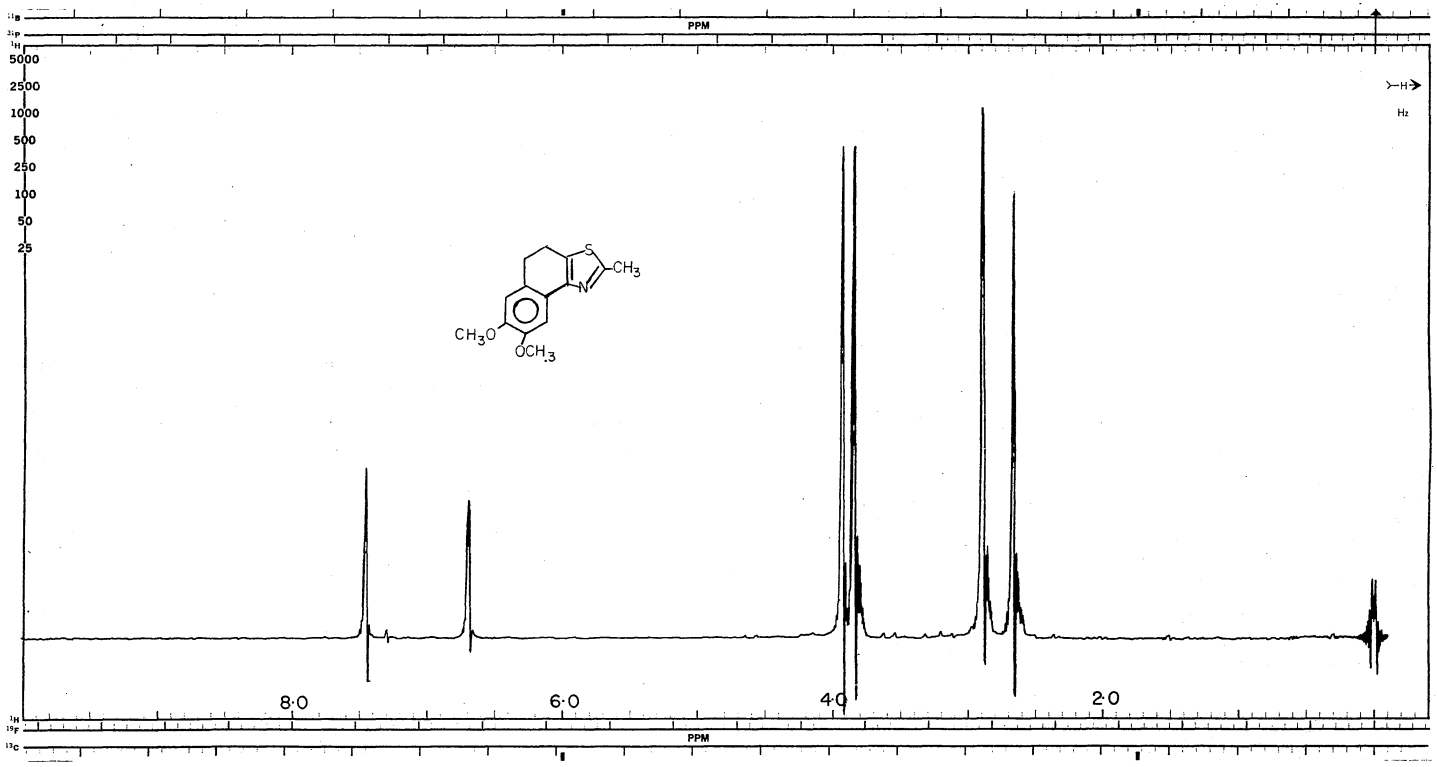
PLATE LXXIX



2-(Allylamino)-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (213)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.0

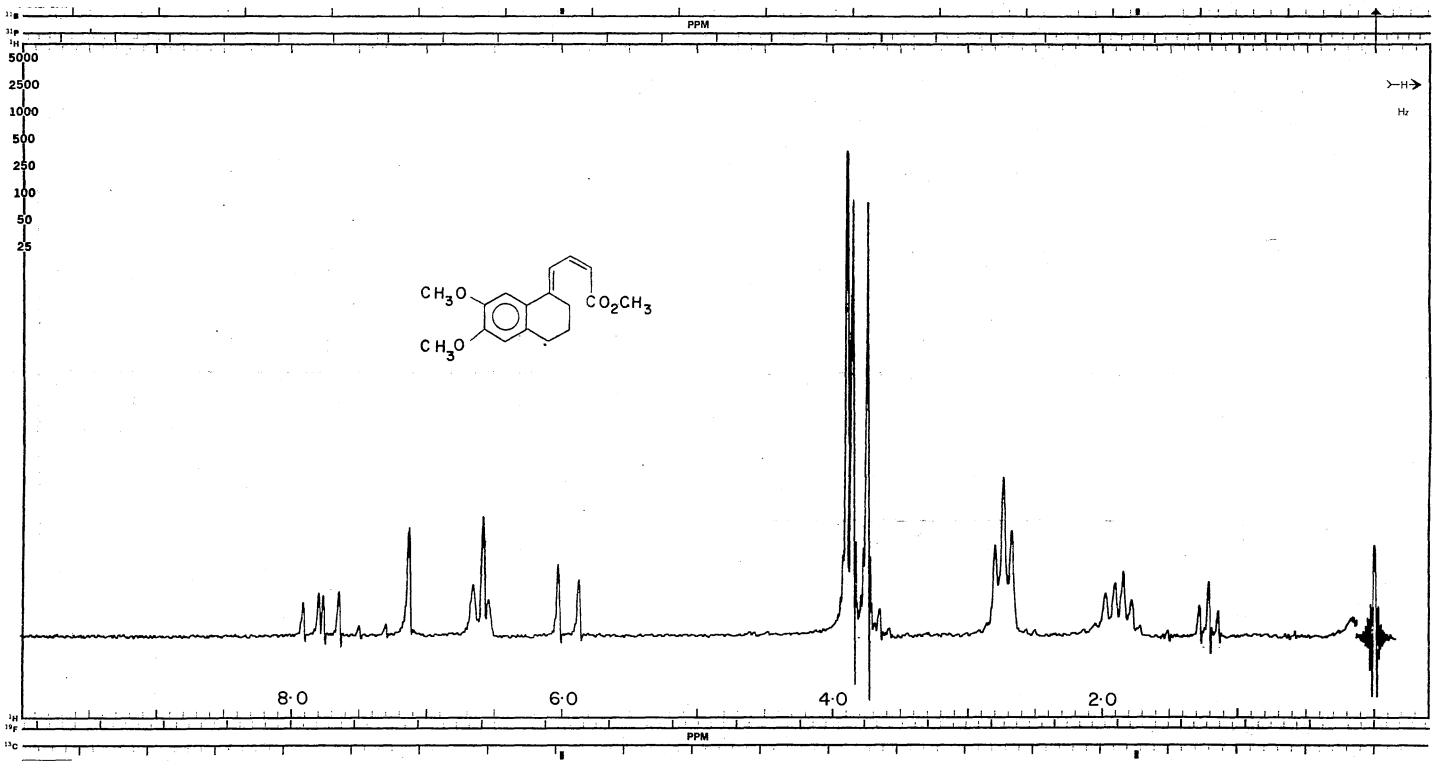
PLATE LXXX



4,5-Dihydro-7,8-dimethoxy-2-methylnaphtho[1,2-d]thiazole (214)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 1.0

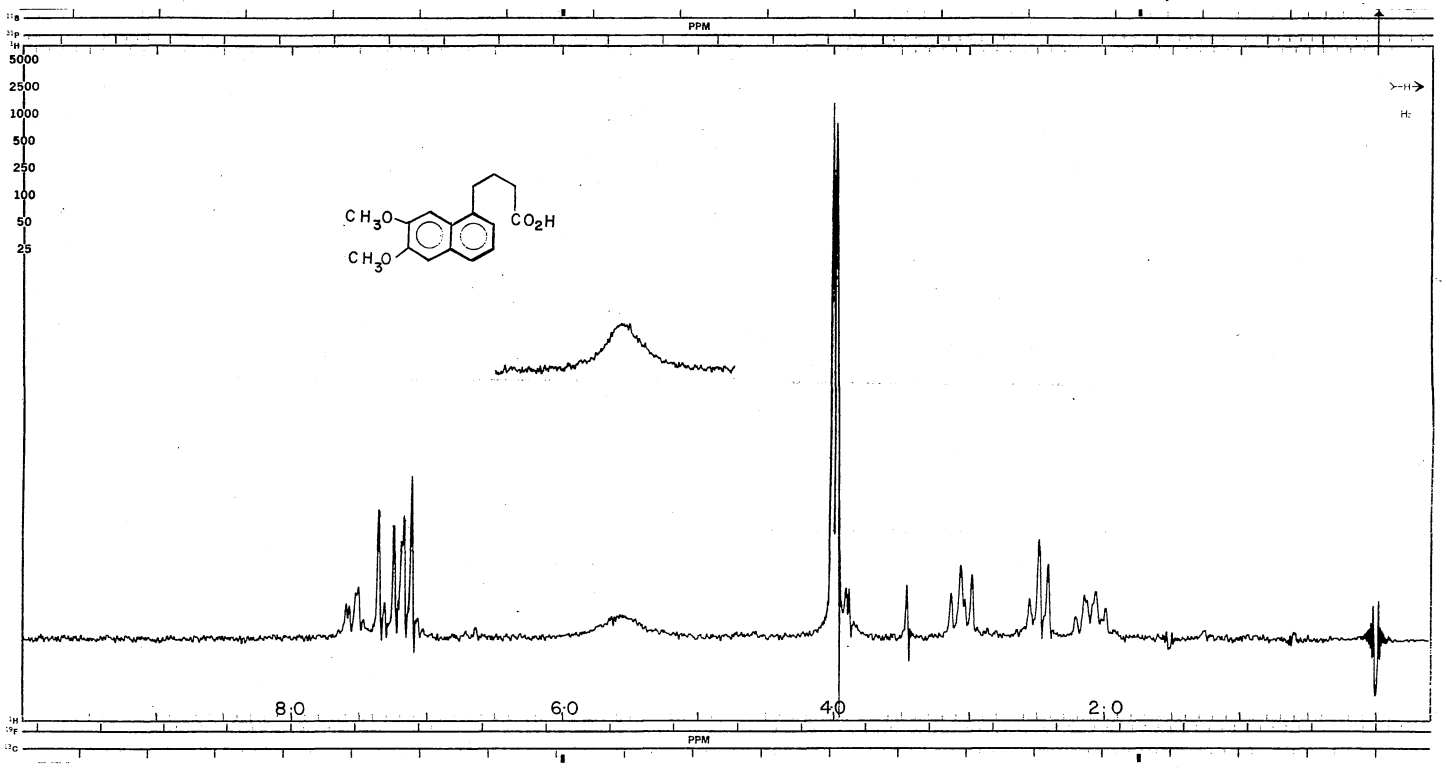
PLATE LXXXI



Methyl 3,4-dihydro-6,7-dimethoxy-$\Delta^{1(2H),\gamma}$-naphthalenecrotonate (235)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 62 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 2.0

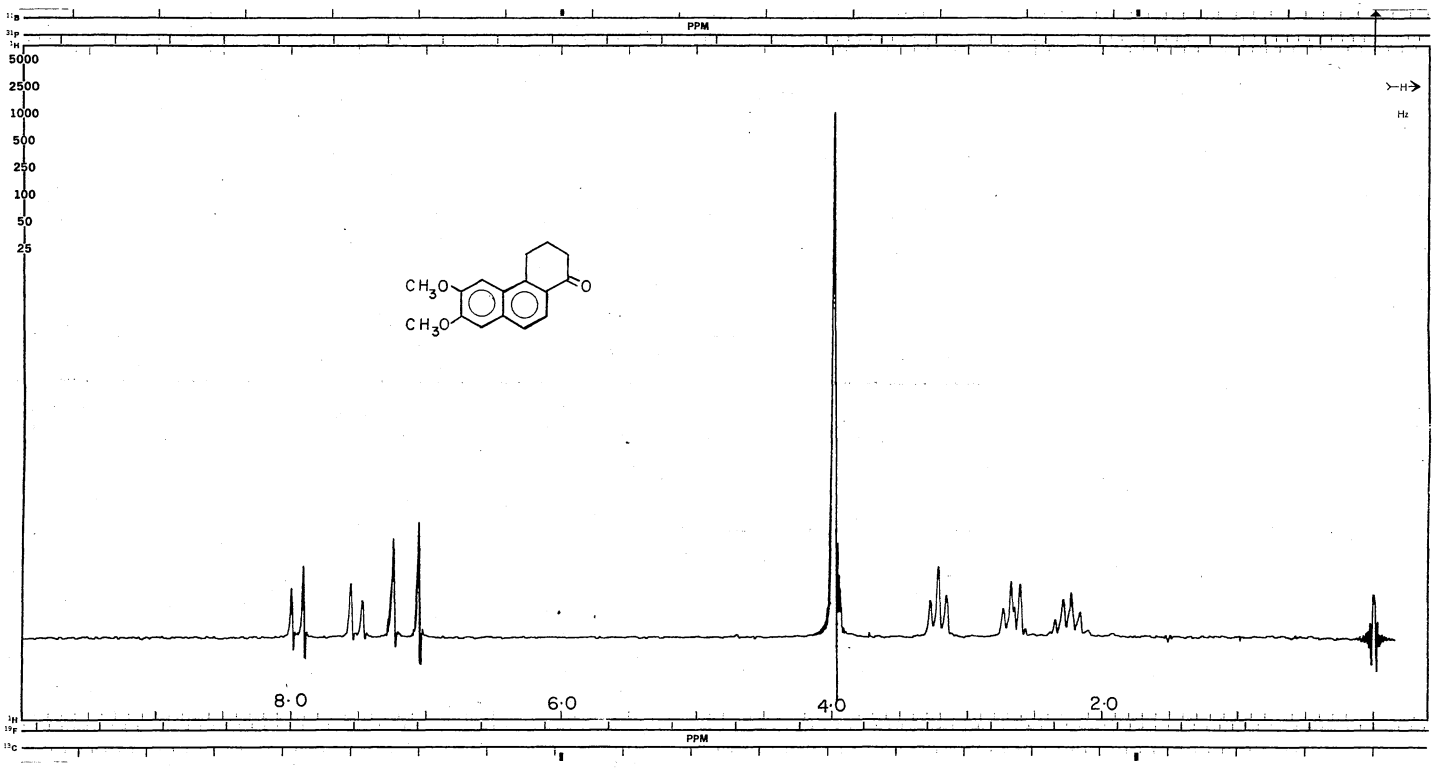
PLATE LXXXII



6,7-Dimethoxy-1-naphthalenebutyric Acid (236)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 69 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 2.0

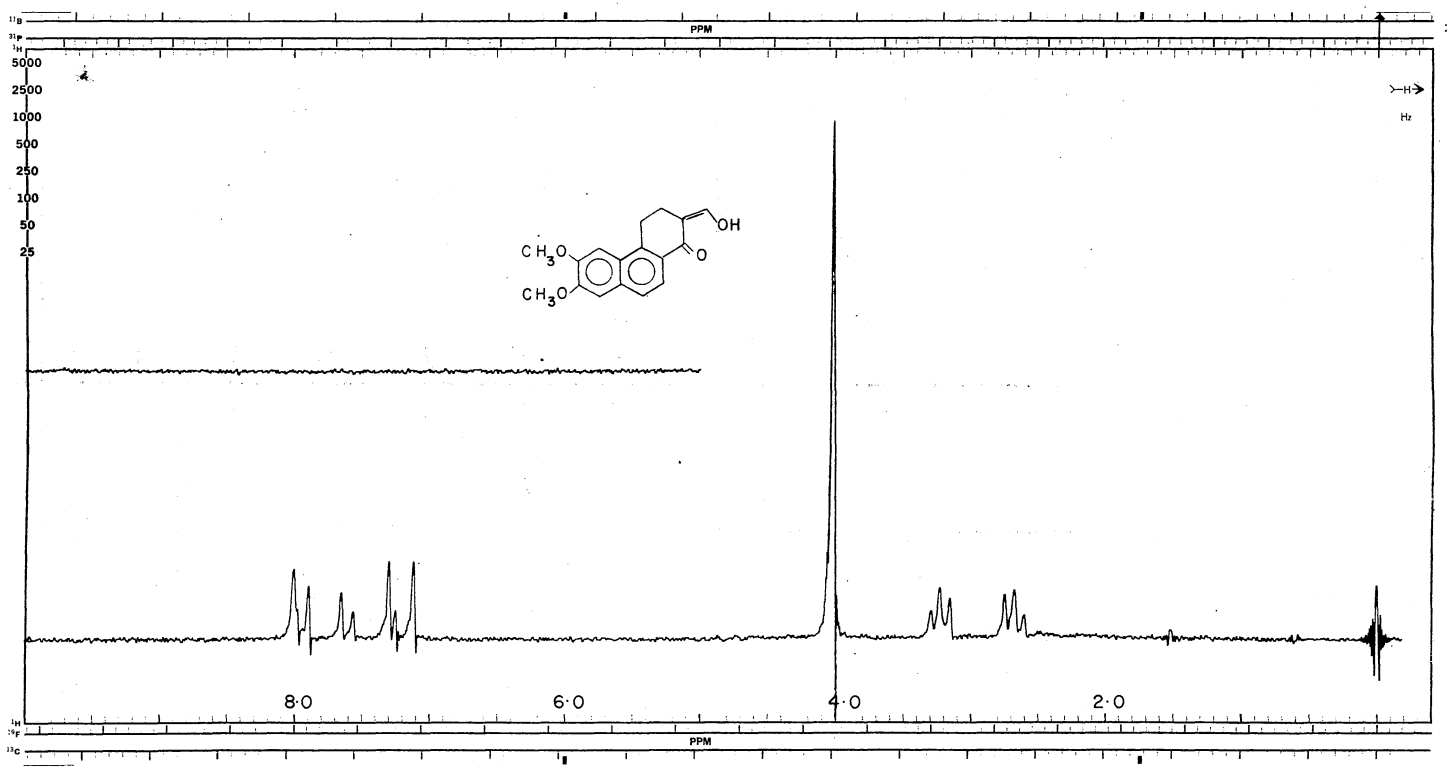
PLATE LXXXIII



3,4-Dihydro-6,7-dimethoxy-1(2H)-phenanthrone (188)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 67 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 1.0

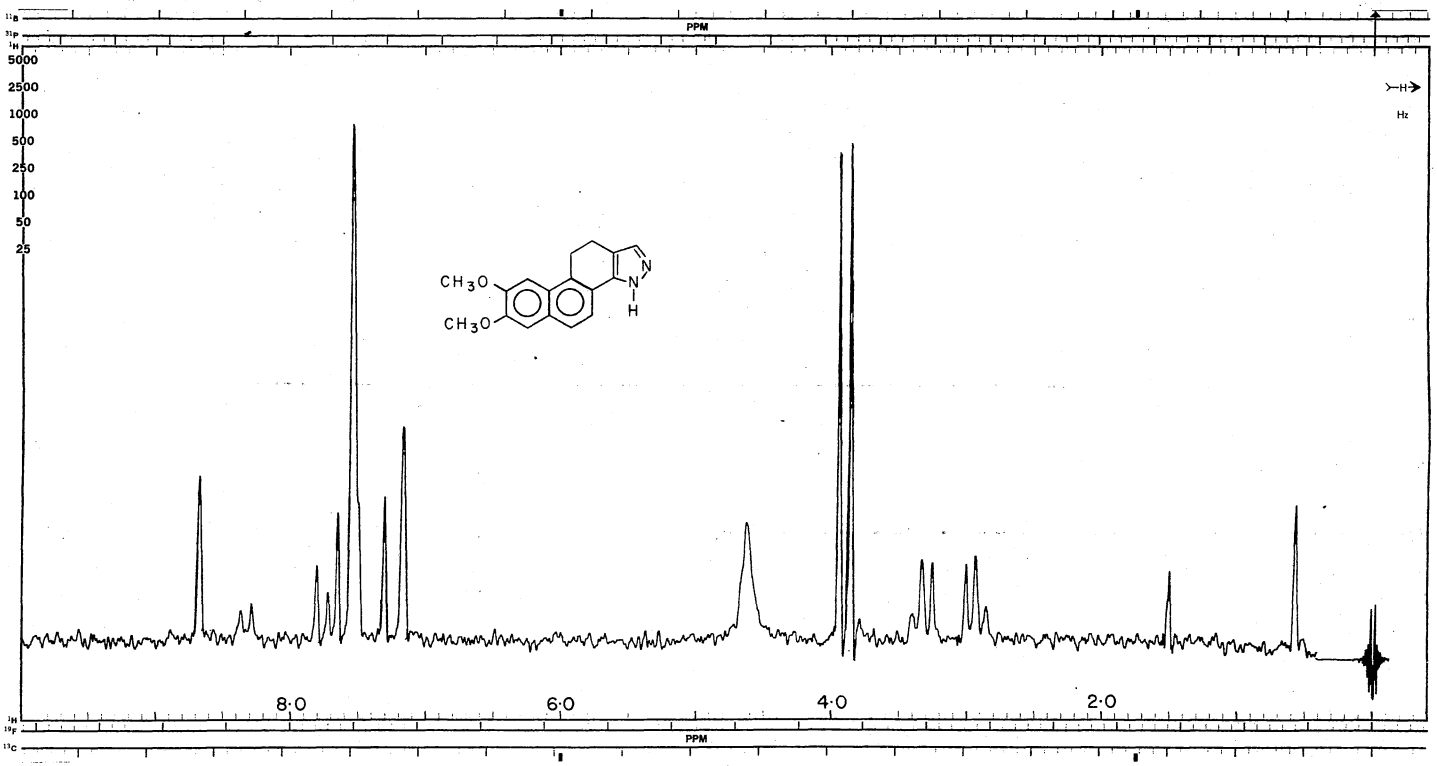
PLATE LXXXIV



3,4-Dihydro-2-(hydroxymethylene)-6,7-dimethoxy-1(2H)-phenanthrone (237)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 67 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 3.2

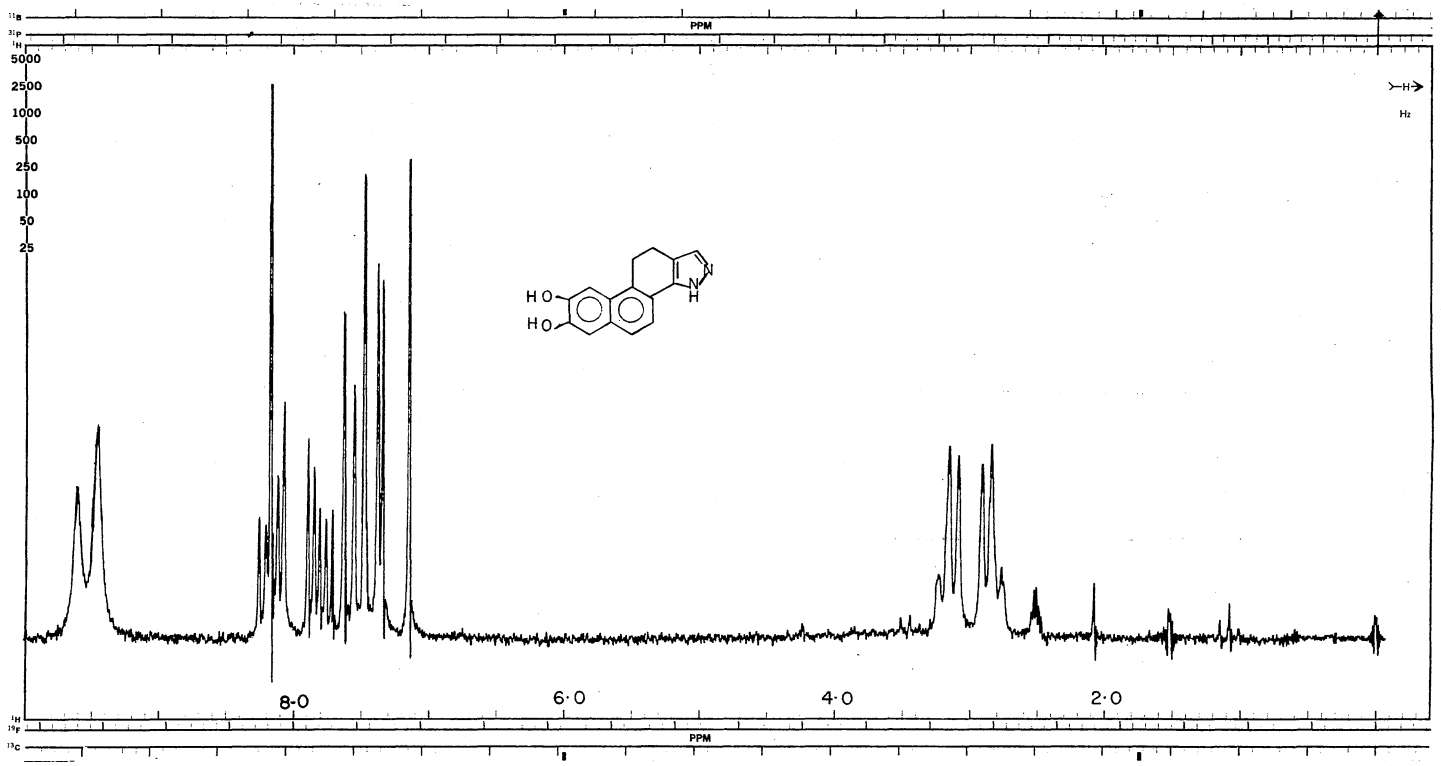
PLATE LXXXV



10,11-Dihydro-7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (215)

Solvent. . . C_5D_5N	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 71 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . 20.0

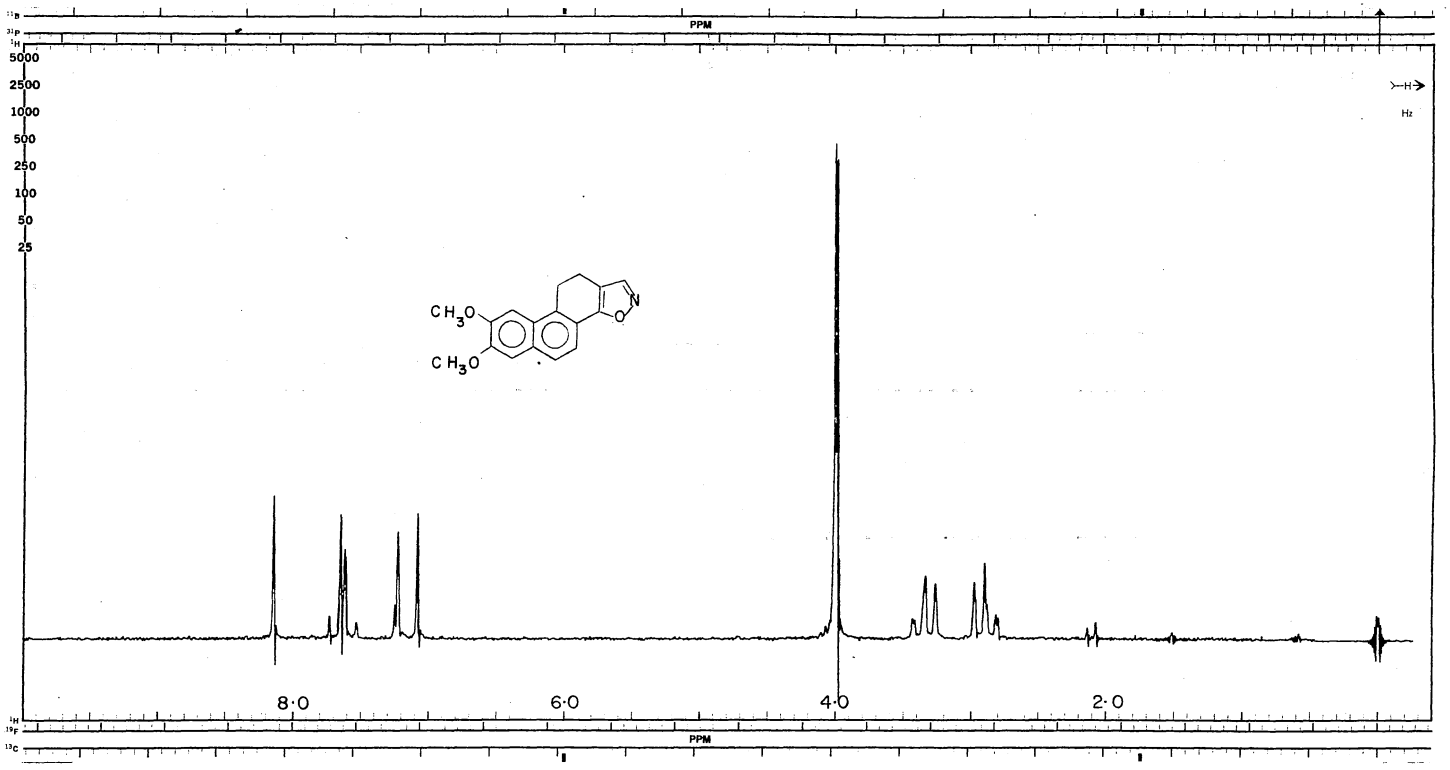
PLATE LXXXVI



10-11-Dihydro-3H-phenanthro[1,2-c]pyrazole-7,8-diol (216)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 70 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 8.0

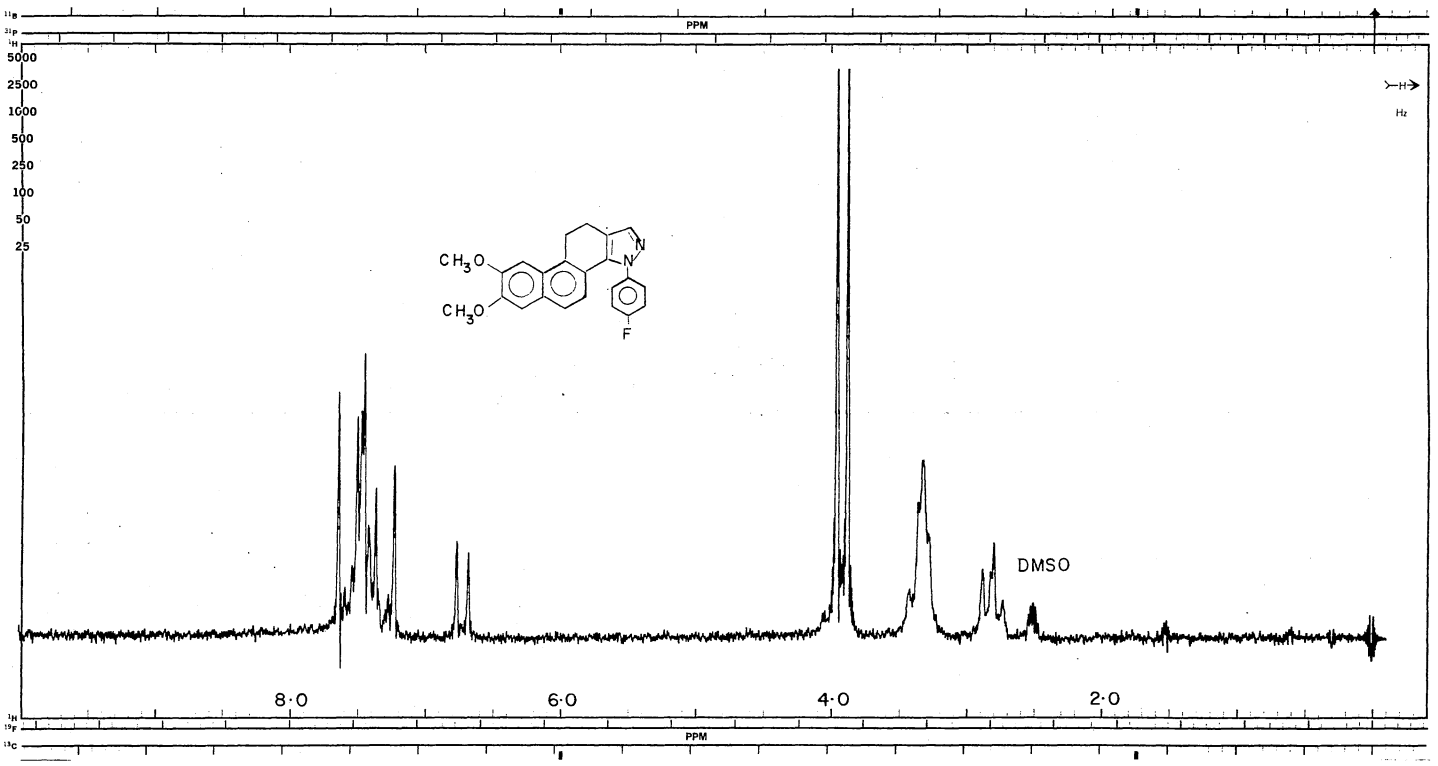
PLATE LXXXVII



10,11-Dihydro-7,8-dimethoxyphenanthro[2,1-d]isoxazole (190)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 2.0

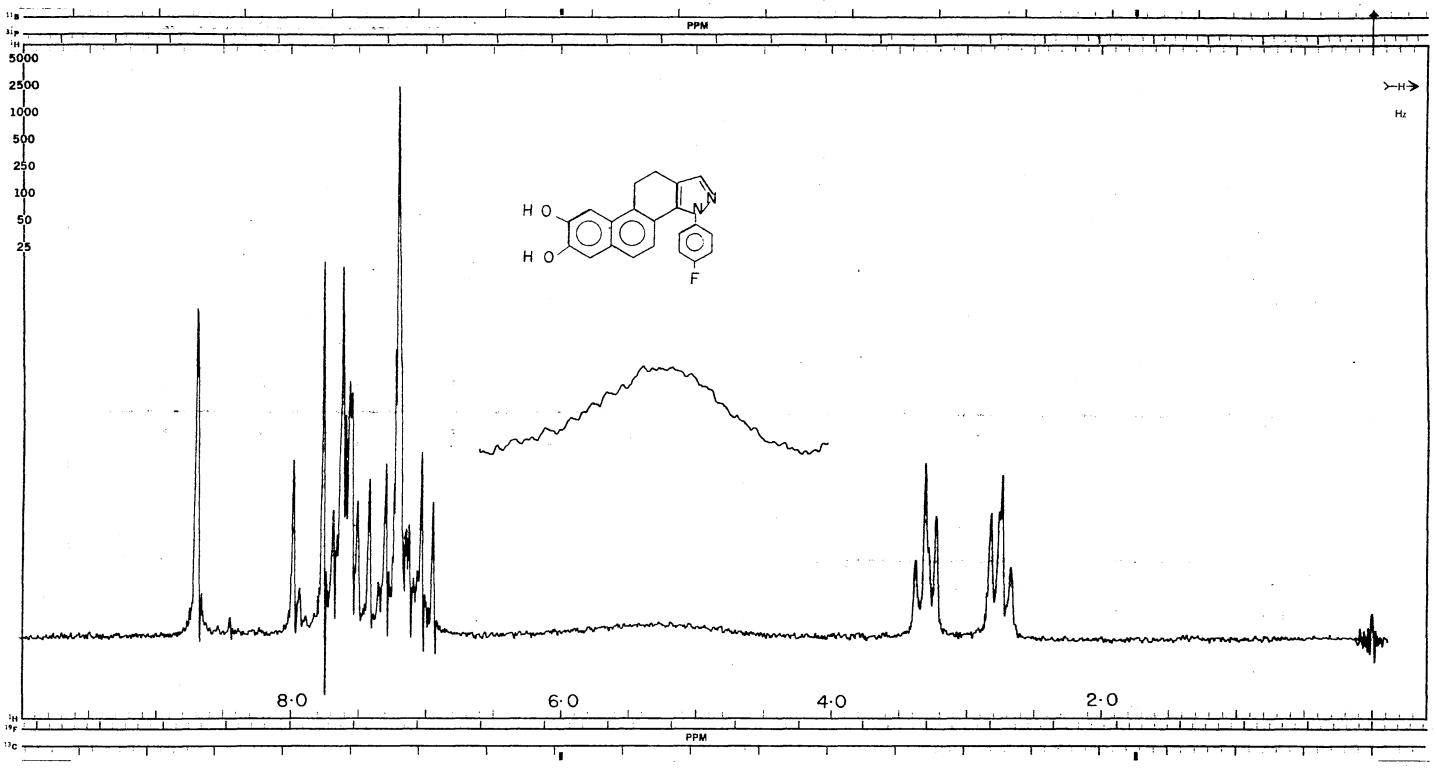
PLATE LXXXVIII



10,11-Dihydro-1-(p-fluorophenyl)-7,8-dimethoxy-3H-phenanthro[1,2-c]pyrazole (217)

Solvent. . DMSO-d_6	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 69 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 8.0

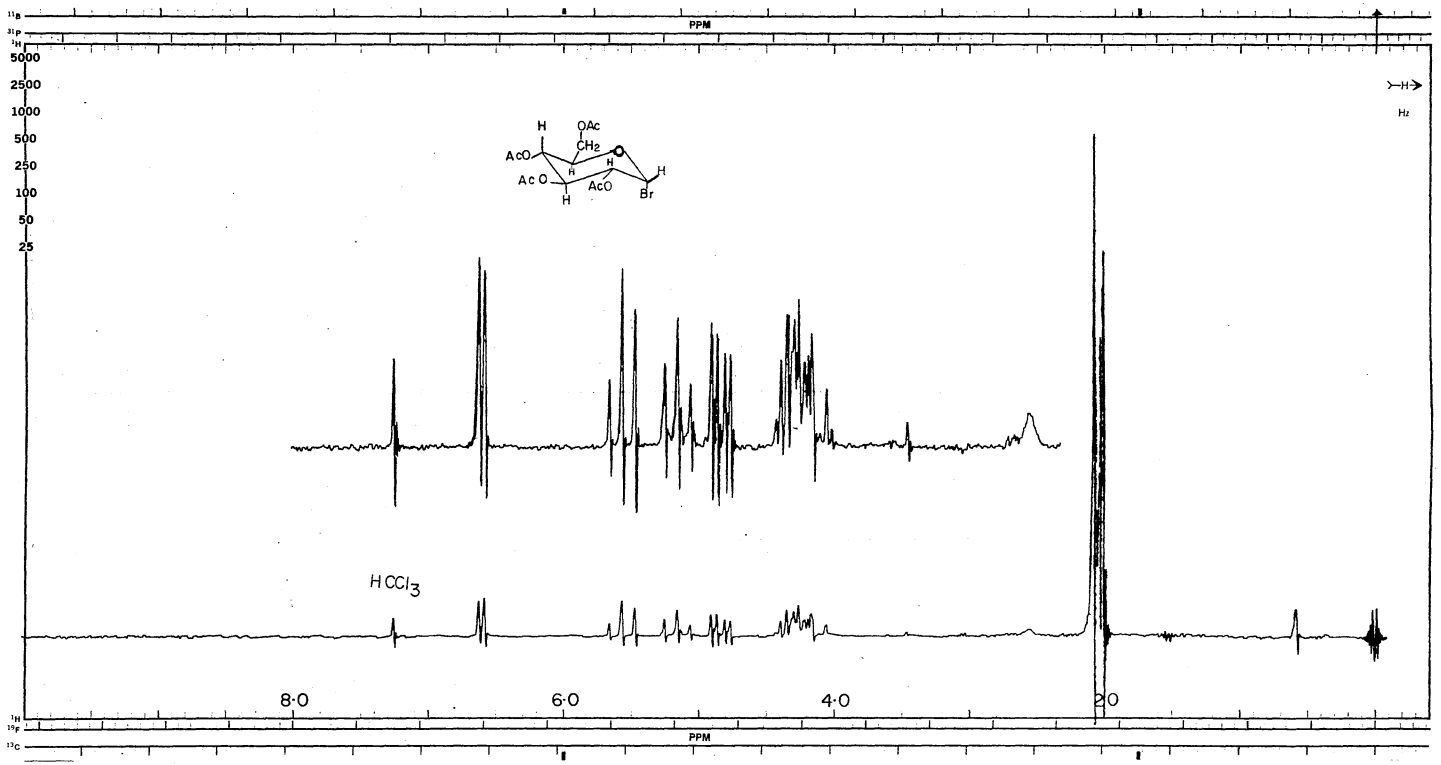
PLATE LXXXIX



10,11-Dihydro-1-(p-fluorophenyl)-3H-phenanthro[1,2-c]pyrazole-7,8-diol (218)

Solvent. . . C_5D_5N	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 70 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 5.0

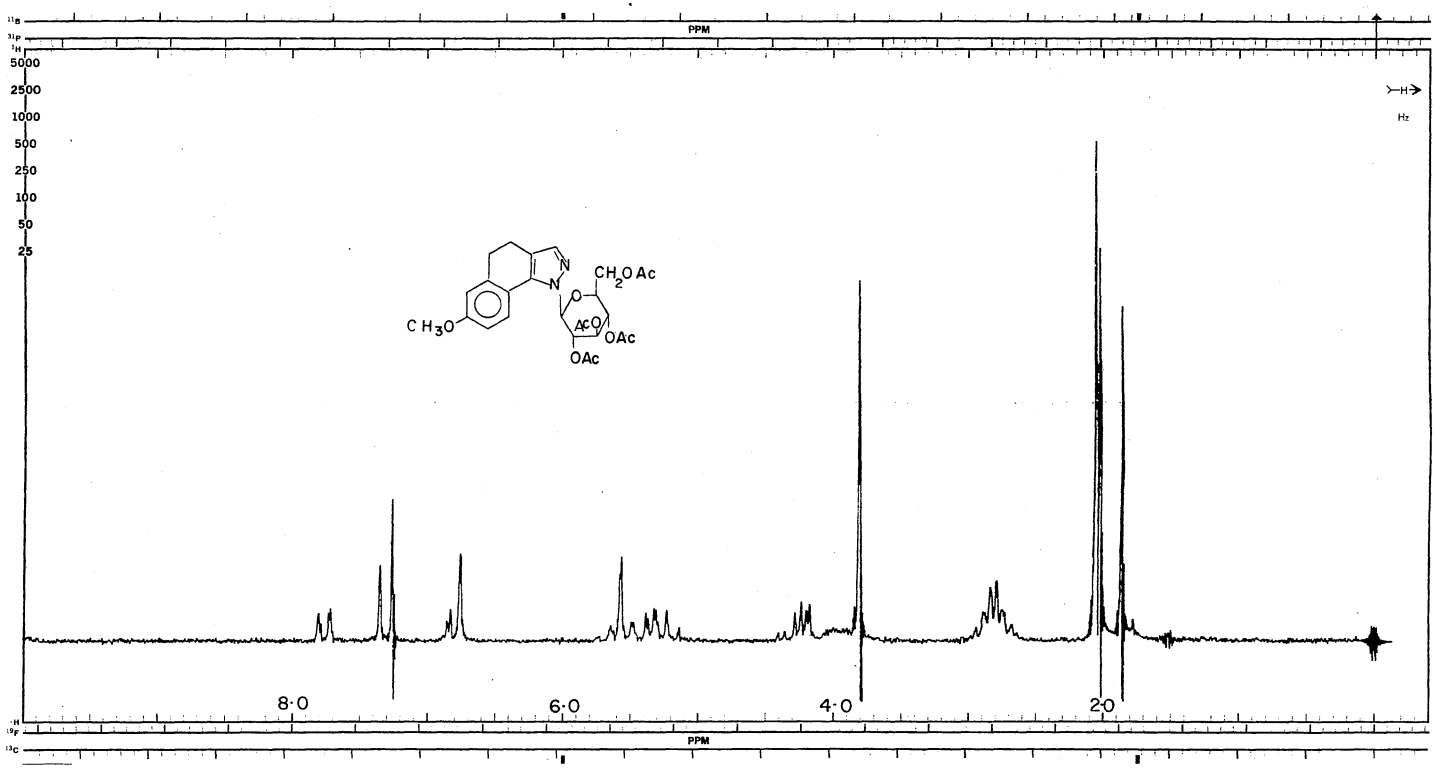
PLATE XC



2,3,4,6-Tetra-O-acetyl-α-D-glucosyl bromide (238)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 63 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 82701 Hz	S.A. . . 2.5

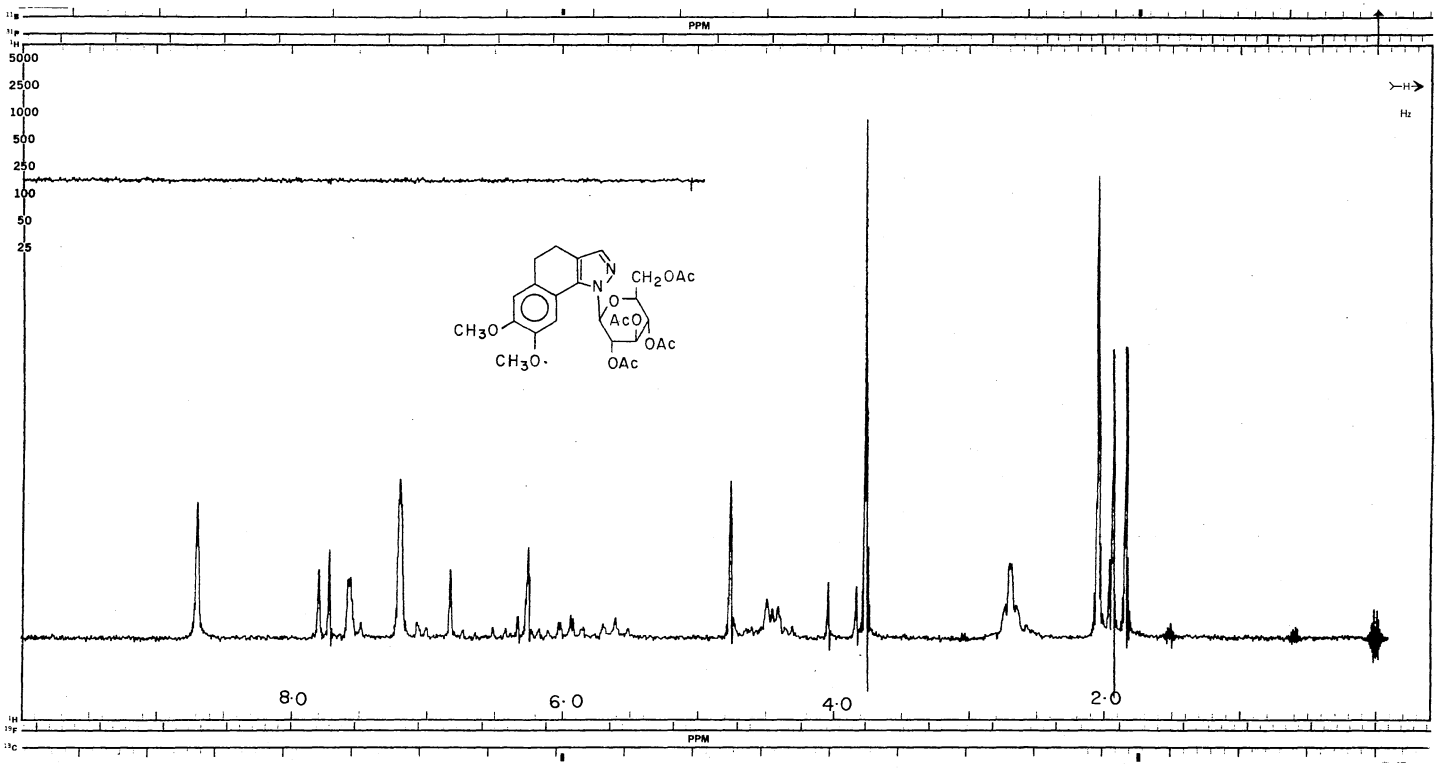
PLATE XCI



1-β-D-Glucopyranosyl-4,5-dihydro-7-methoxy-1H-benz[g]indazole Tetraacetate (ester) (206)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 65 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 3.2

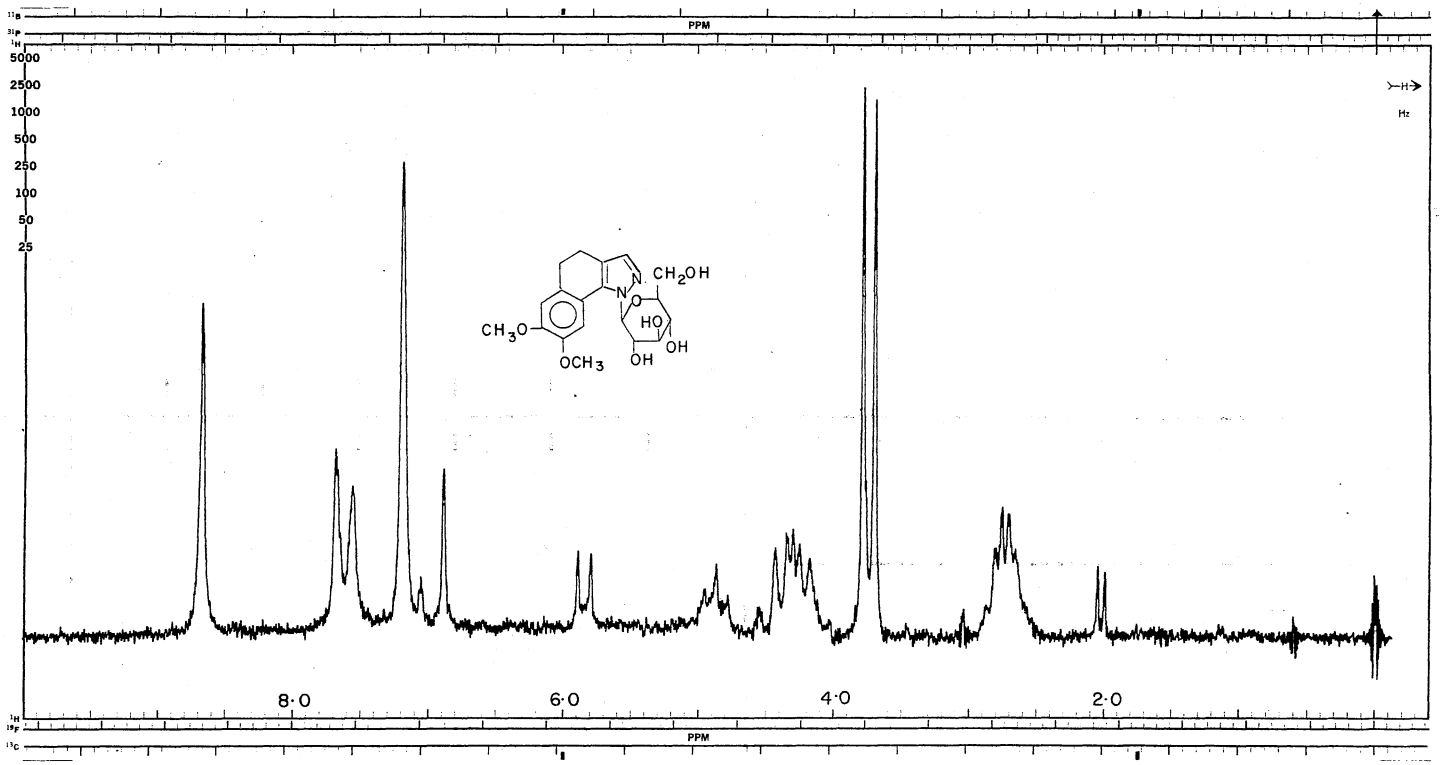
PLATE XCII



1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole Tetraacetate (ester) (201)

Solvent. . . C_5D_5N	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 63 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 4.0

PLATE XCIII

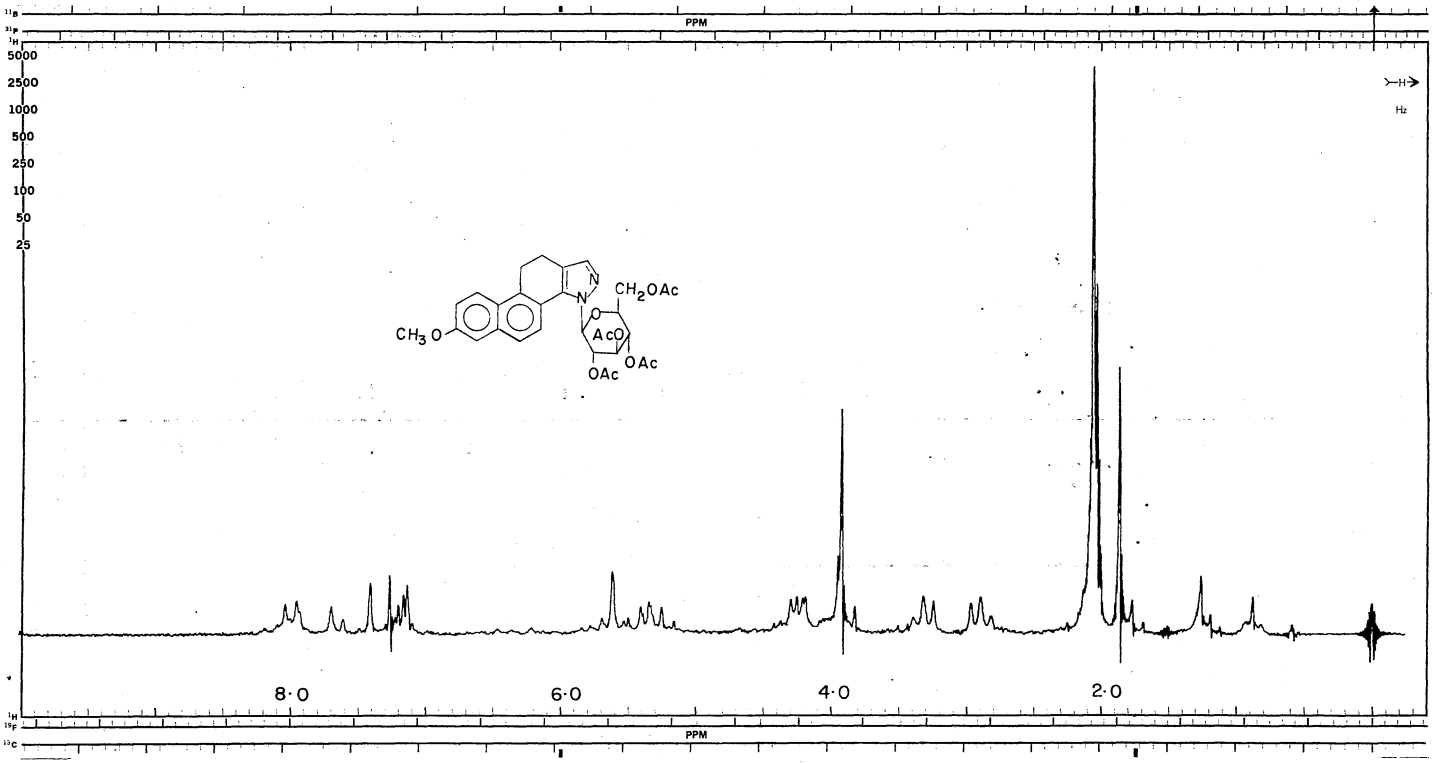


1-β-D-Glucopyranosyl-4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole (202)

Solvent. . . C_5D_5N O.F. . . .100.1 MHz F.B. . . . . 2 Hz R.F. . 70 db

S.W. . . . 1000 Hz S.T. . . . 500 sec S.O. . . 83701 Hz S.A. . 10.0

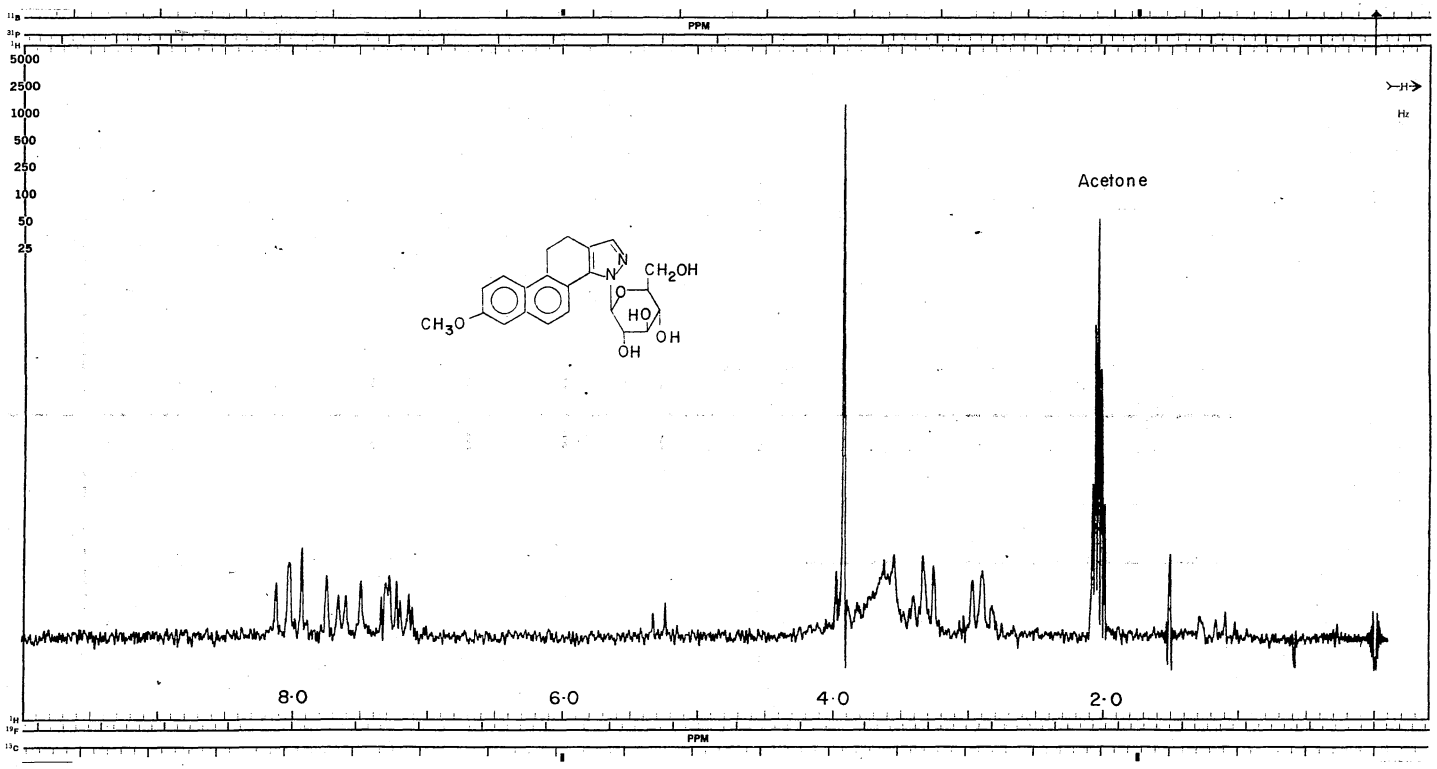
PLATE XCIV



3-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole Tetraacetate (ester) (220)

Solvent. . . $DCCl_3$	O.F. . . .100.1 MHz	F.B. . . . . 2 Hz	R.F. . 70 db
S.W. . . . 1000 Hz	S.T. . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 2

PLATE XCV



3-β-D-Glucopyranosyl-10,11-dihydro-7-methoxy-3H-phenanthro[1,2-c]pyrazole (221)

Solvent. . Acetone-d_6	O.F. . . .100.1 MHz	F.B. . . . . 1 Hz	R.F. . 73 db
S.W. . . . 1000 Hz	S.T. . . . 500 sec	S.O. . . 83701 Hz	S.A. . . 16

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VITA

Mohamed Mohamed Hashem

Candidate for the Degree of

Doctor of Philosophy

Thesis: SYNTHESIS OF HETEROCYCLIC STEROIDS CONTAINING VICINAL METHOXYL (AND HYDROXYL) GROUPS IN THE A RING AND RELATED MODEL SYSTEMS—POSSIBLE POTENTIATORS OF DRUG ACTIVITY IN CANCER CHEMOTHERAPY

Major Field: Chemistry

Biographical:

Personal Data: The author was born in Alexandria, Egypt, on April 5, 1942, the son of Mohamed and Fatehia Hashem. On February 13, 1969 he was married to Samia A. Abou-Taleb.

Education: The author graduated from Abbassia secondary school, Alexandria, Egypt in 1959. He received the Bachelor of Science degree (Special in Chemistry) from Alexandria University, Egypt, in July, 1963 and a Master of Science degree (Organic Chemistry) from Alexandria University in May, 1967. In January, 1973, he was admitted to the Graduate College of Oklahoma State University, Stillwater, Oklahoma, where he completed the requirements for the Doctor of Philosophy in May, 1975.

Professional Experience: The author was a teaching assistant and research assistant, 1973-75, at Oklahoma State University. He was a Post-Master's Teaching Assistant at University of Missouri-Kansas City, 1969-1972. From 1967-1969, the author held a position of Lecturer (Assistant) of Organic Chemistry at Alexandria University, Egypt. During the years 1963-1967, the author participated as a Demonstrator of Chemistry in the Chemistry Departments of Ain-Shams University, Cairo, and Alexandria University, Alexandria, Egypt. He received the "Undergraduate Distinction Awards for Excellent Achievement" from 1960-1963. The author was recipient of a summer research fellowship (1971), University of Missouri-Kansas City and an U.S.P.H.S. (N.I.H., Cancer Institute, CA 14343) research assistantship (1974), Oklahoma State University. During summers of 1961 and 1962, the author participated in the industrial summer student training programs of the National Paper

Industries and Caustic Soda from Sea Water Company, both in Alexandria, Egypt.

Membership in Professional Societies: The author is a member of American Chemical Society, American Association for the Advancement of Science, American Association for University Professors, Phi Lambda Upsilon, and Sigma Xi.