SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF SUBSTITUTED PYRAZOLES, ISOXAZOLES, PYRAZOLONES, AND PYRIMIDINES CONTAINING A TRIMETHOXYARENE FUNCTION

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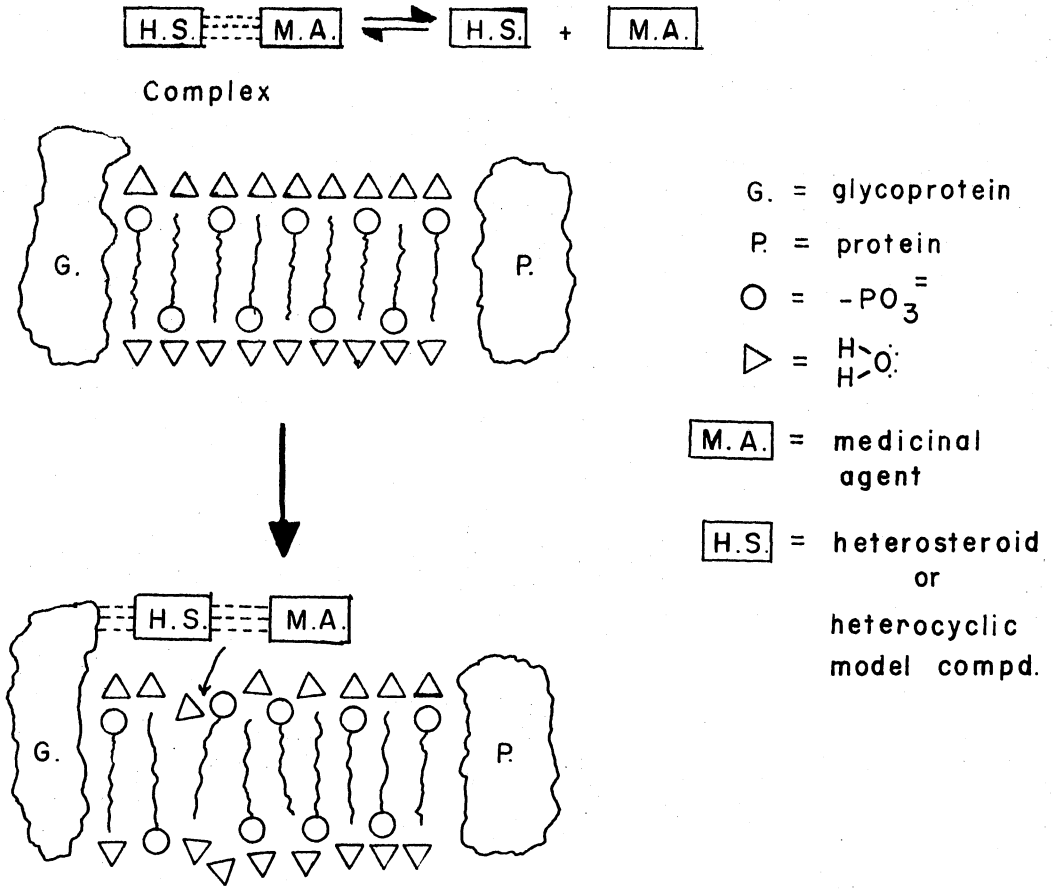
CHAPTER I

HISTORICAL

One currently active area in cancer chemotherapy involves the study of drug transport across membranes.[20,57,82] Conceptually, the phenomenon of membrane penetration by a medicinal agent could be potentiated by complex formation with another molecule which in turn could alter the membrane's structure, at least temporarily, to permit a more rapid movement of the medicinal agent or the complex into a cell. One theory for the structure of membranes includes a monolayer (a lipid bilayer could behave similarly) of phospholipids held together by a highly ordered water layer.[20,57,82] Also present in the membrane structure are usually protein and glycoprotein molecules among others. A hypothetical membrane surface (a monolipid layer is illustrated but the theory could be applied to a bilayer system for which there is also considerable evidence) is provided (Scheme 1) to illustrate a possible mechanism by which potentiation of activity of a medicinal agent might occur via complex binding to a protein on the membrane surface.

A molecular complex is depicted between a medicinal agent and a heterosteroid (or related model heterocyclic compound) which we shall discuss shortly. "Ordered water" near the membrane surface is a generally accepted postulate based on much physical evidence resulting, however, from <u>in vitro</u> studies. Some recent dielectric measurements of



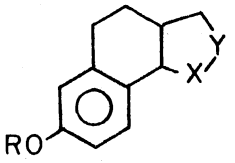
Penetration of membrane by complex (or by the medicinal agent).

Note increased fluidity in lipid layer.

Scheme 1.

membranes suggest an apparent thickness of water layers adjacent to membranes of up to 40,000 Å (4 μ thick).[37] The value may be too high but the data support also a "rigidity and orderliness" of water near the membrane. If the heterosteroid possessed a highly polar group, which we shall call a "hydropolar head", it is not unreasonable that this group, if properly positioned on the membrane surface (e.g., bound to a protein

or glycoprotein) alone or in the complex, could through perhaps dipole-dipole repulsive interactions disrupt the "ordered water" to permit a temporary "increased fluidity" in the lipid layer.[42] Thus the medicinal agent or the complex could penetrate the cell more rapidly and efficiently. Consequently, a possible ramification of complexation studies would be to determine the parameters in a heterocycle which could ultimately promote easy complexation with a medicinal agent and/or induce more efficient penetration of a cell by a medicinal agent. The complexation could greatly prolong effective use of a drug before an organism developed resistance to it so that massive amounts were required. Obviously, the latter is less than desirable since large doses of a medicinal agent can often have pronounced and adverse side effects. Finally, it is also conceivable that a "lipophilic head" and "hydrophilic head" in a molecule could improve cell penetration. This is currently being evaluated in our laboratory for systems as shown.

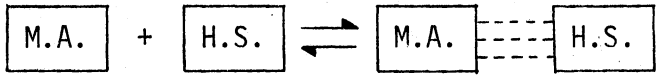


X,Y = heteroatoms [hydrophilic head]

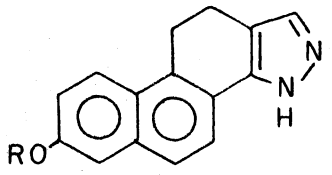
R = long chain [lipophilic head]

The role of steroids in chemotherapy is well documented but the structure-activity relationship of heterosteroids is a relatively new area.[41,143] Assuming that a heterocycle (such as a heterosteroid) could form a molecular complex with a medicinal agent and this complex could bind to the surface of a membrane (perhaps through complexation with a protein[23,80] via hydrogen bonding, a charge-transfer mechanism, or π-π overlap or a combination thereof), one can envision the initial structure of complex-membrane as shown in Scheme 1. Of course, the

stability of such a complex would likely be of paramount importance since the medicinal agent must presumably exist at least partially free to be effective inside the cell. A study of the equilibrium process forming a complex between an anticancer agent and a heterosteroid is needed but selection of examples is likely to be critical if a correlation is to be investigated between K_{eq} and biological activity.



The use of heterosteroids offers the novel opportunity to form charge-transfer complexes with medicinals, a situation not commonly possible with many naturally occurring steroids since most do not possess heteroatoms such as N or S which permit ready electron transfer. Interactions of this type between compounds and biologically important substances, such as proteins, are rare but known in the literature. Similarly π-π overlap and hydrogen bonding between substrate and certain molecules at a reactive site are also documented although, to be sure, the data are based primarily upon analogies to *in vitro* systems rather than *in vivo* results. On the assumption that heterosteroids and structurally related systems could provide drug potentiation (possibly through the mechanisms described above) or separate and unique activity, considerable effort has been initiated within the past 6 to 8 years for developing syntheses for such molecules. A molecular complex between actinomycin D and 10,11-dihydro-3*H*-naphth[1,2-*g*]indazol-7-ol (1a) has been studied via PMR, UV, and fluorescence spectroscopy.[43,44] Although the molecular complex was eight times as effective as actinomycin D alone against *Bacillus subtilis*, the potentiation factor fell to about 1.04 in mice. The field of chemotherapy using heterosteroids is only



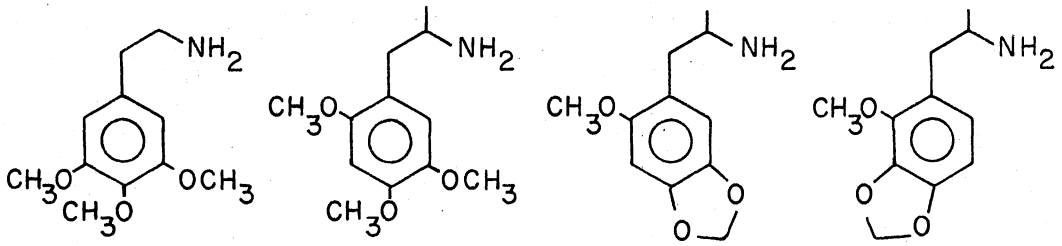
1 a R = H
b R = CH_3

in its infancy, and it will require considerable synthetic finesse to design and prepare structures capable of improving drug efficiency with minimum toxicity. This theory of potentiation can obviously be related to the "synergism theory", and the role of synergism in chemotherapy has been recognized for many years but not completely understood. Moreover, primary screening processes of mixtures of two drugs in B. subtilis or even in animals may not give positive results, and yet the activity of such a mixture could be considerable in man.

A molecular complex of actinomycin D and 5'-deoxyguanylic acid is known[8] as is also the case with valinomycin and K^+.[96] Both of the medicinals are important clinically. A synergistic effect was recently recorded for the increased life span of mice inoculated with L-1210 ascitic tumor cells.[10] The magnitude of this synergism increased as the dosage of either cytosine arabinoside and methotrexate or both was increased. At maximum dosage (12 mg. methotrexate/kg. plus 1200 mg. cytosine arabinoside/kg.) the drug combination completely eradicated tumor cells of 11 of 40 mice and extended the mean survival of the remaining 29 animals by 23-64 days (up to 332%) beyond control survival (7 ± 1 days).[10]

An exciting related area involves complexes of medicinal agents with antibodies in cancer chemotherapy.[51] It seems quite reasonable that some of the molecular forces maintaining the integrity of such

complexes must be those discussed above for heterosteroids or simpler heterocycles. For example, the ease with which many hallucinogens and tranquilizers affect higher organisms make related heterocyclic systems worthy of cautious examination. Mescaline (2) and related compounds 3-5

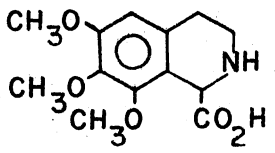


2 3 4 5

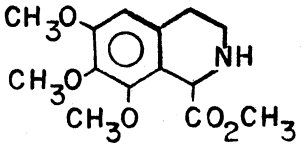
conceivably cross membrane barriers in certain cellular systems[35] and yet closely related heterocyclic model systems have not been systematically investigated for possible complexation with or potentiation of activity of clinically used anticancer agents. The area appears ripe for study but will need synthetic organic chemists and biochemists collaborating to be fruitful.

Polymethoxy-substituted compounds are widely distributed in the field of natural products. A few representative alkaloids recently isolated containing three or more methoxy groups are shown in Figure 1; some other recently isolated natural products containing polymethoxy groups are shown in Figure 2.

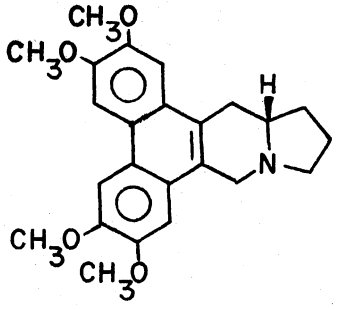
Many polyalkoxy compounds synthesized display biological activity. There has been a considerable amount of work on 3,4,5-trimethoxyphenyl-substituted compounds of possible psychotropic activity.[122] At first appearance, these compounds have little chemical relationship except the possession of 3,4,5-trimethoxyphenyl groups. Recently synthesized compounds containing such a group are the benzoyloxazolidine 6, 4-(3,4,5-



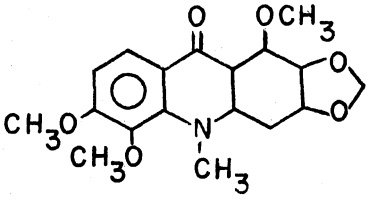
O-methylpeyoxylic acid[77]
(Trace constituent of peyote)



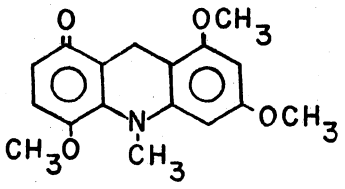
Methyl O-methylpeyoxylate[77]
(Trace constituent of peyote)



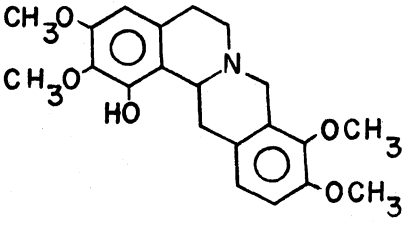
Tylophorine[58] (Major alkaloid from Tylophora asthmatica)



1,5,6-Trimethoxy-2,3-methylenedioxy-10-methylacridone[145] (Isolated from the bark of Teclea boiviniana)

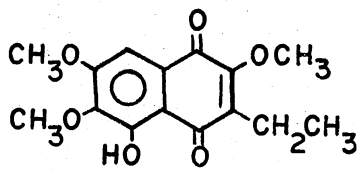


1,3,5-Trimethoxy-10-methylacridone[145] (From Teclea boiviniana)

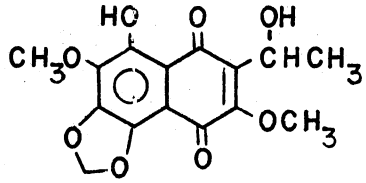


Capaurine[89] (Constituent of four plants)

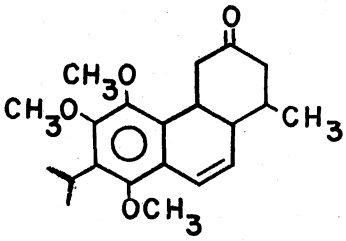
Figure 1. A Few Representative Alkaloids Containing Polymethoxy Functions



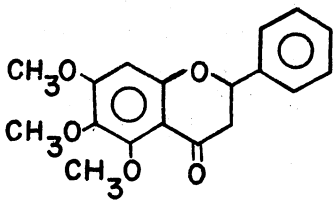
Lomandrone[36] (A pigment in Lomandra hastilis)



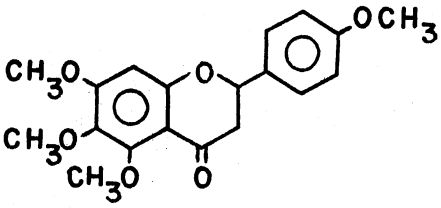
Lomastilone[36] (A pigment in Lomandra hastilis)



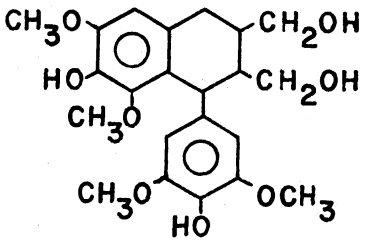
Coleon β[116] (A yellow dye of Coleus igniarius leaf glands)



5,6,7-Trimethoxyflavone[90] (Isolated from Kichxia lanigera)



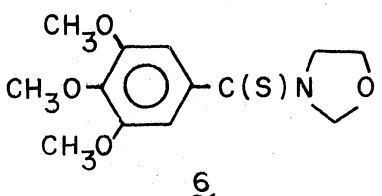
5,6,7,4'-Tetramethoxyflavone[90] (Isolated from Kichxia lanigera)



Lyoniresionol[124] (Isolated from heartwood of Ulmus thomasii)

Figure 2. Some Natural Products Containing Polymethoxy Functions

trimethoxythiobenzoyl)morpholine (7), and five other 3,4,5-trimethoxybenzamides, which were screened for central nervous system depressant activity in mice.[111] Compounds 6 and 7 depressed conditioned avoidance



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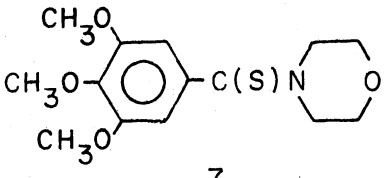
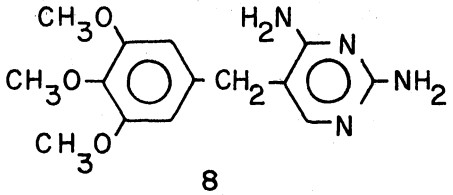


7

behavior and exploratory hypermotility. Antibiograms confirmed the sensitivity of group A streptococci towards a new chemotherapeutic agent Eusaprim (drug trade name) containing trimethoprim (8) and sulfamethoxazole.[139] Papaverine (9) given to anesthetized cats decreased arterial



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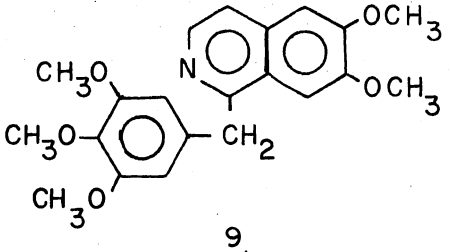
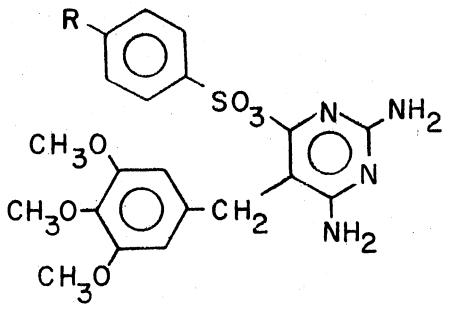
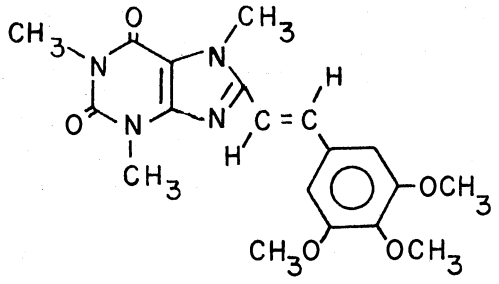


9

pressure and blood flow in the renal and superior mesenteric veins, increased blood flow in the coronary sinus and sagittal sinus of the brain, and had a biphasic effect on femoral vein flow.[1] Six 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-6-(arylsulfonyloxy)pyrimidines (10) showed bacteriostatic activity on Streptococcus hemolyticus, E. coli, Pseudomonas pyocyanae and Staphylococcus pyogenes aureus.[47] trans-8-(3,4,5-Trimethoxystyryl)caffeine (11) is now being evaluated for use as a cerebral stimulant.[110]

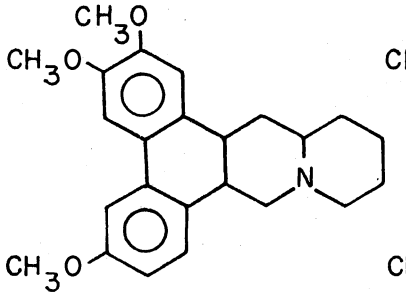


10 R = H, CH_3, Cl, Br, $CH_3C(O)NH$, $C_2H_5C(O)NH$



11

The alkaloid cryptopleurine (12), a natural product from Boehmeria cylindrica, has a significant cytotoxic effect against Eagle's 9KB carcinoma of the nasopharynx in cell culture and is responsible for part of the antiviral activity observed in tests with crude extracts of B. cylindrica.[85] In screens to determine the inhibitory mechanism of



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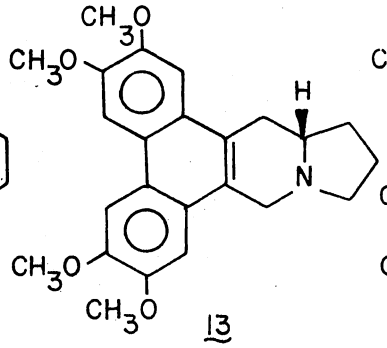

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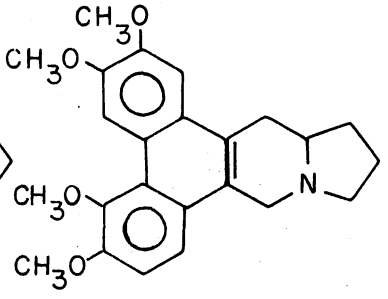

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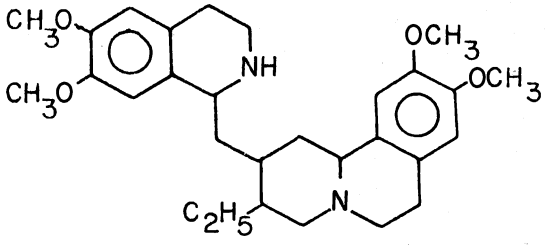

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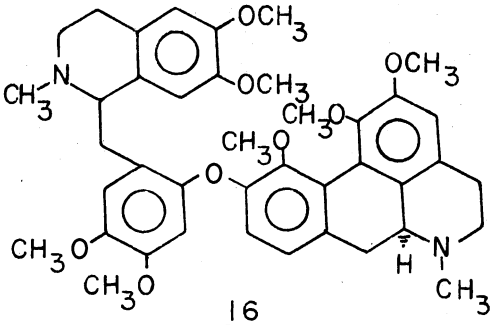
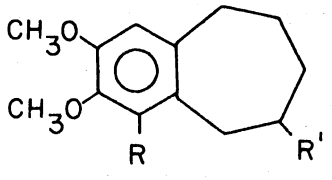


16

tylophorine (13) and tylocerbrine (14), inhibitors of 80s-type ribosomes, it was shown that there was possible binding to the 80s ribosome and the 60s subunit;[15] emetine (15) showed no antibiotic binding in the same tests.[15] Thalicarpine (16), a tumor-inhibitory aporphine benzylisoquinoline alkaloid, has recently been synthesized.[87]

Parkhurst and co-workers[105] have reported the synthesis of some benzocycloheptane derivatives and the results of preliminary screening for pharmacological activity in mice. All these compounds are benzocycloheptane derivatives with methoxy and/or hydroxy substitution on the benzene ring. Substitution of OH for OCH_3 at R in most of the compounds had little effect on activity. Also noted was a lack of enhancement of depressant activity. In one case, a stimulant response in mice was noted (17bd) while the hydroxy derivative 17ad produced a depressant behavior.

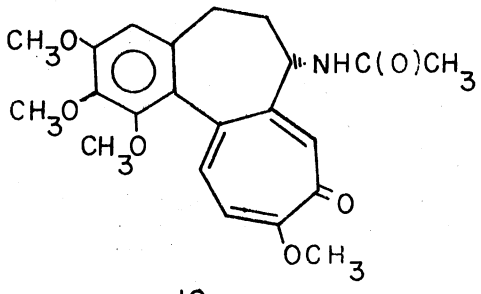


17

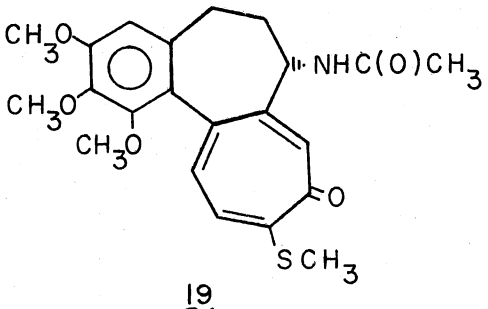
R = a -OH
b $-OCH_3$

R' = c =O
d $=NNHC(O)NH_2$
e $=NNHC(S)NH_2$
f =NOH
g $-NH_2$, H
h $-NHCO_2CH_3$, H

The alkaloid colchicine (18) has long been known to be a mitotic poison.[56] It recently has been reported that a 1% solution of colchicine caused chromosome doubling in the green alga Oedogonium acmandrium.[120] Preliminary results indicate that the methyl ether of thiocolchicine (19) shows greater cytotoxicity against L-1210 leukemia than colchicine;[61] other alkyl ethers of thiocolchicines showed lower activity in the same tests.[61]



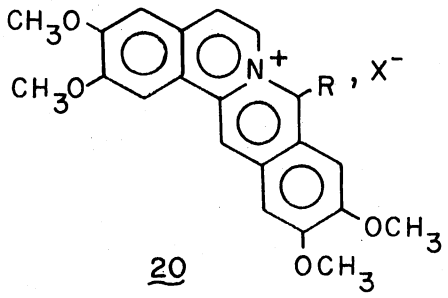
18



19

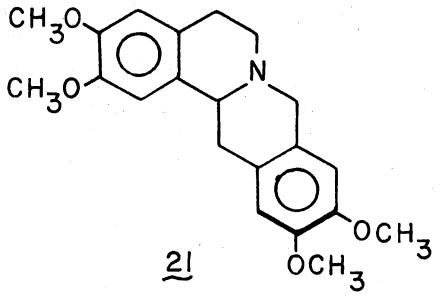
Zee-Cheng and co-workers[155] reported the preparation and activity against leukemias L-1210 and P-388 of several alkoxybenzophenanthridinuim salts. It was found that 20a and 20c showed greater antileukemic activity than Coralyne (20b); 20d was virtually inactive.

Protoberberine derivatives 21a-c were prepared by Kametani[76] by reaction of 20d with the corresponding acid. These derivatives were useful as analgesic, vasodilating, and hypotensive agents.

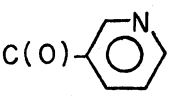


20

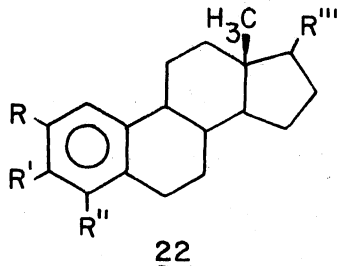
R = a -H
b $-CH_3$
c $-C_2H_5$
d $-(CH_2)_2CH_3$



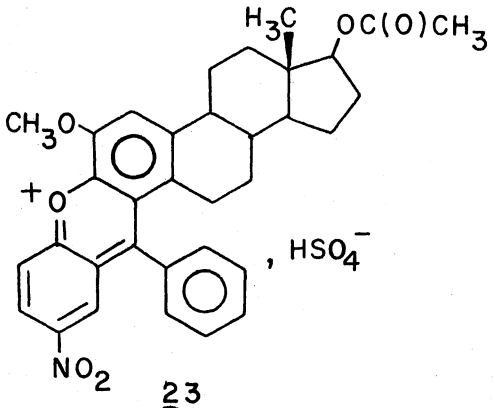
21

R = a $-OC(O)CH_3$
b 
c $-p-CH_3C_6H_4SO_2O$
d -H

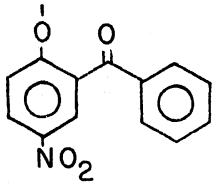
The synthesis of compounds having poly(lower alkoxy)estrane structures was first reported by Axelrod, Rao, and Baeder.[12] Compound 22e was obtained by two different methods. In the first approach 17β-acetoxy-2-methoxyestra-1,3,5(10)-triene 3-(2'-benzoyl-4'-nitrophenyl) ether 22a was allowed to react with concentrated sulfuric acid to give the xanthylium acid sulfate salt 23. Oxidation of 23 was effected



22



23

22a R = OCH_3, R' =  , R'' = H, R''' = O_2CCH_3

b R = OCH_3, R' = " , R'' = OCH_3, R''' = O_2CCH_3

c R = OCH_3, R' = OH, R'' = OCH_3, R''' = O_2CCH_3

d R = R' = R'' = OCH_3, R''' = O_2CCH_3

e R = R' = R'' = OCH_3, R''' = OH

f R = OCH_3, R' = OH, R'' = H, R''' = O_2CCH_3

g R = OCH_3, R' = OH, R'' = NO_2, R''' = O_2CCH_3

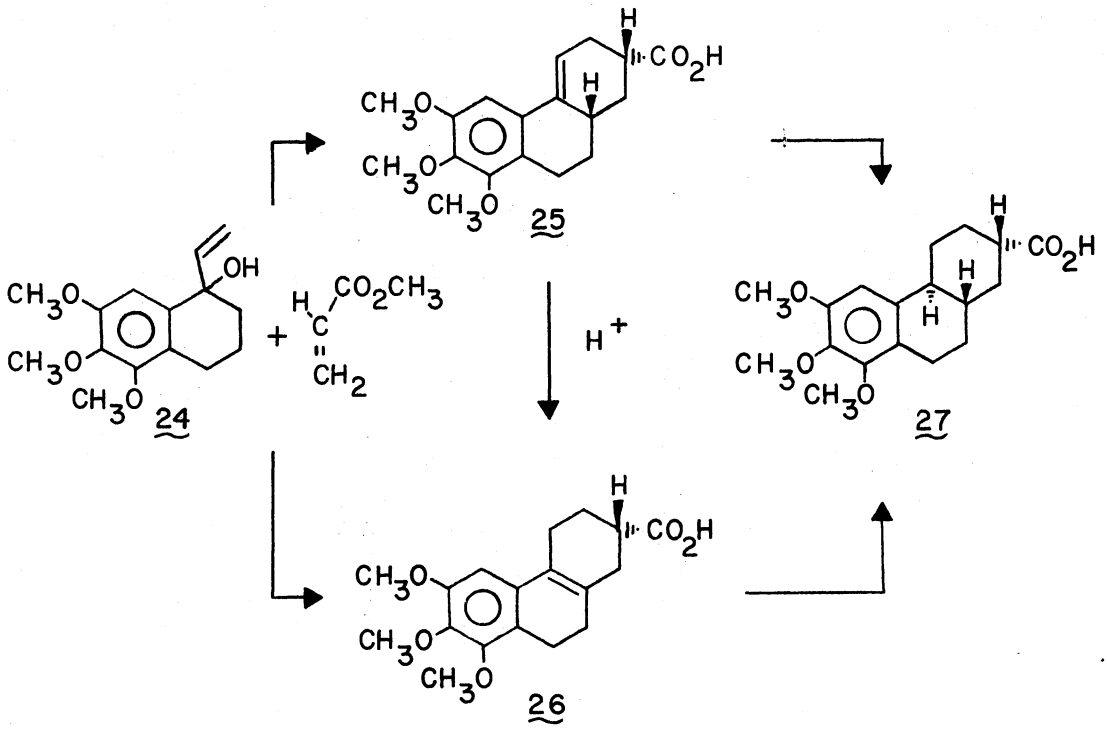
h R = R' = OCH_3, R'' = NO_2, R''' = O_2CCH_3

i R = R' = OCH_3, R'' = NH_2, R''' = O_2CCH_3

with 30% H_2O_2, and the crude product was treated with diazomethane to give 22b. The aryl group in 22b was removed by boiling with piperidine to give 22c, which, when allowed to react with methyl sulfate and anhydrous potassium carbonate in acetone, gave 22d. Alkaline hydrolysis of 22d with 1N methanolic KOH gave 2,3,4-trimethoxyestra-1,3,5(10)-trien-17β-ol (22e). The second method to obtain 22e involved the reaction of 22f with 1 equiv. of concentrated nitric acid in acetic acid to give 22g. Diazomethane and nitro compound 22g reacted to give 22h. Catalytic hydrogenation of 22h using Raney nickel catalyst gave

22i. The amino compound 22i was diazotized with sodium nitrite in 1:1 acetic acid / dioxane. A resulting crude phenol was methylated with dimethyl sulfate and anhydrous potassium carbonate in acetone to give 22e. Initial biological testing[11] of 22e indicated some analgesic activity when compared to some clinically active standard analgesics, but further laboratory testing[146] indicated the compound was devoid of pharmacologic activity.

Roa and co-workers[114] reported the preparation of two isomeric hexahydro-6,7,8-trimethoxyphenanthrene-2α-carboxylic acids 25 and 26 from the Diels-Alder condensation of 3,4-dihydro-5,6,7-trimethoxy-1-vinylnaphthalene (24) with methyl acrylate (Scheme 2). Acid 25 isomerized to 26 in the presence of acid. Both 25 and 26 gave the same octahydrophenanthrenecarboxylic acid 27 on reduction with a limited



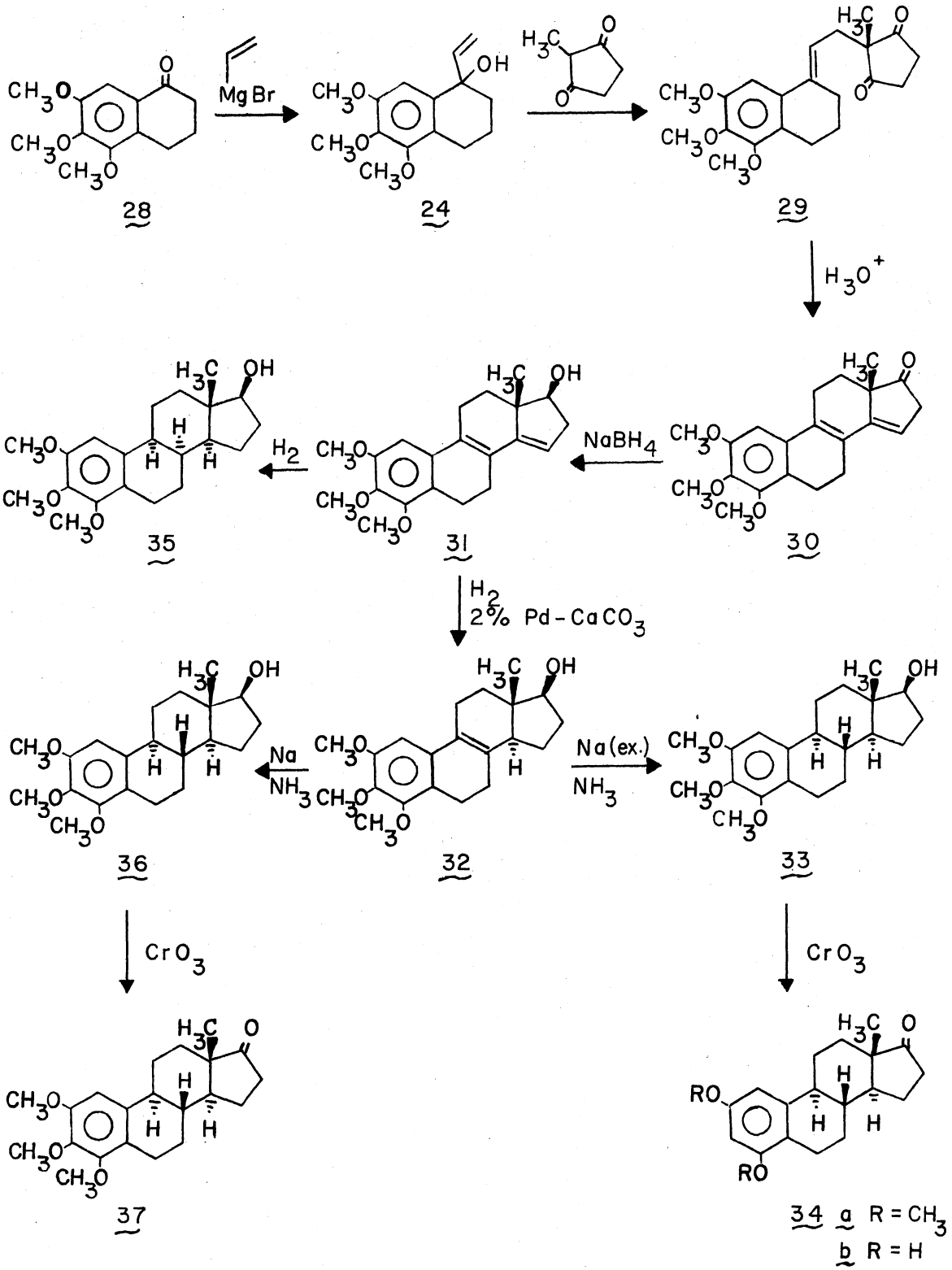
Scheme 2

quantity of Na and liquid NH_3. No biological screening data was reported for these compounds.

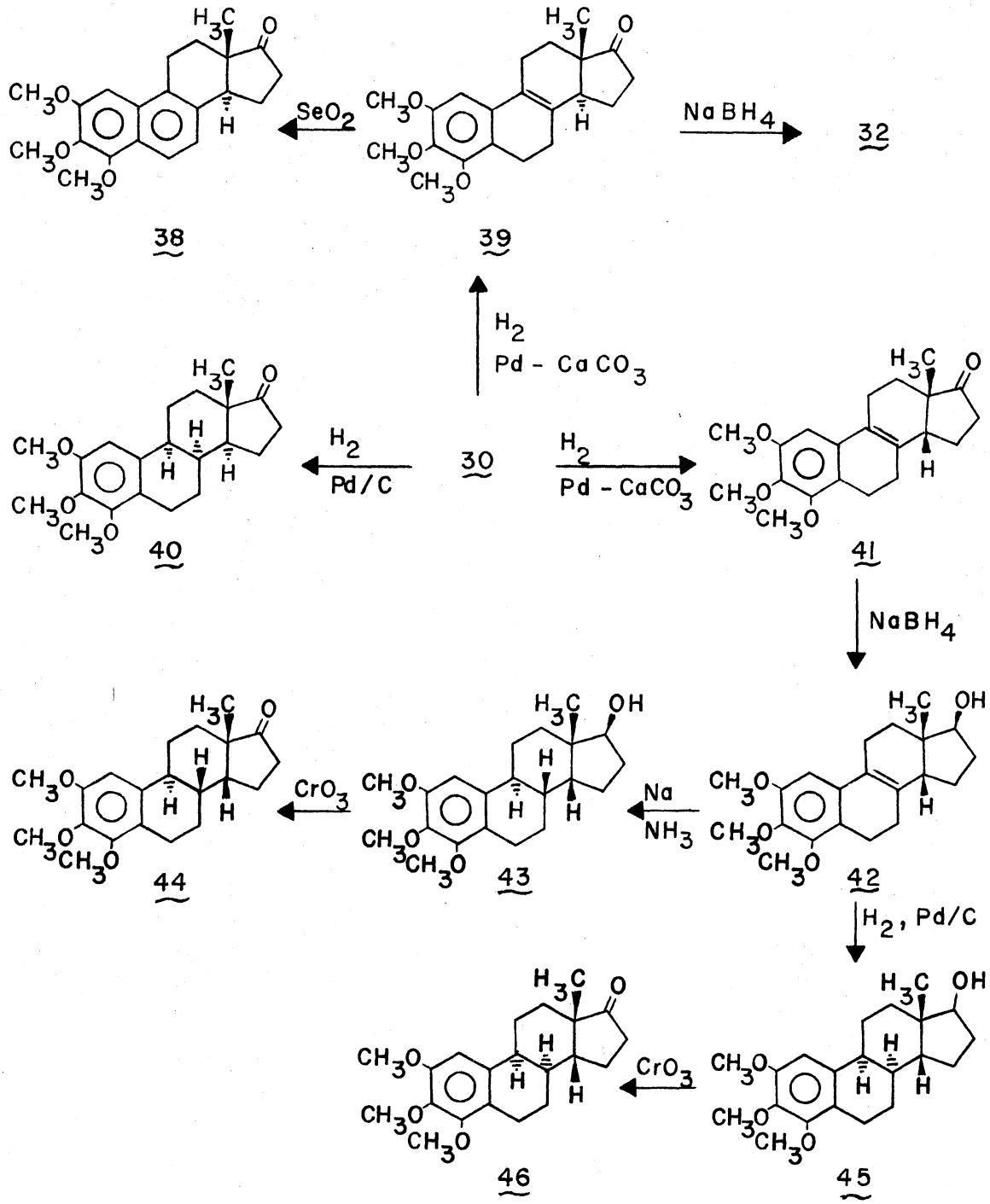
Rao, Jacob, and Axelrod[113] reported the total synthesis of steroids containing a trimethoxybenzene ring. They initially described[12] the synthesis of (+)-2,3,4-trimethoxyestra-1,3,5(10)-trien-17β-ol (37) by two different methods from an (+)-estradiol, but the overall yield by these routes was low. Scheme 3 shows an improved route to 37[113] and similar compounds. 3,4-Dihydro-5,6,7-trimethoxynaphthalen-1(2H)-one (28) was treated with vinylmagnesium bromide to give 24. Condensation of this alcohol 24 with 2-methylcyclopentane-1,3-dione in the presence of Triton B afforded 29 which, on boiling with p-toluenesulfonic acid in benzene, cyclized to yield 2,3,4-trimethoxyestra-1,3,5(10)-8,14-pentaen-17-one (30). Compound 30 was then reduced with sodium borohydride in methanol to give 31. Selective hydrogenation of the 14,15-double bond over 2% palladium on calcium carbonate gave the tetraenol 32. Completion of the synthesis of 36 involved stereoselective reduction of the styrenoid bond in 32 by metal-ammonia. Excess metal-ammonia gave the dimethoxy derivative 33.

For the preparation of stereoisomers of (±)-2,3,4-trimethoxyestranes the pentaenone 30 served as an ideal intermediate (Scheme 4). These compounds are presently undergoing examination for biological activity. Initial pharmacological tests indicated that 36 possessed strong analgesic activity; however, further testing revealed that the analgesic activity originally claimed was not reproducible.[113]

A number of physiologically active azasteroids have been reported and several reviews on this subject have been written.[4,84,92,128,129,137] Recently the total synthesis of heterocyclic steroidal systems has been


28
MgBr
24
29
H_3O^+
30
$NaBH_4$
31
H_2
35
H_2
2% Pd-$CaCO_3$
36
Na
NH_3
32
Na(ex.)
NH_3
33
CrO_3
CrO_3
37
34 a R = CH_3
b R = H

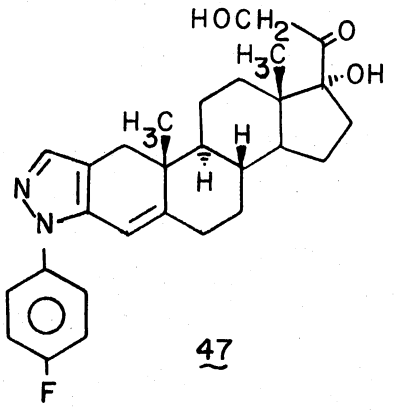
Scheme 3


SeO2
NaBH4
32
38
39
H2
Pd - CaCO3
H2
Pd/C
30
H2
Pd - CaCO3
40
41
NaBH4
CrO3
Na
NH3
44
43
42
H2, Pd/C
CrO3
46
45

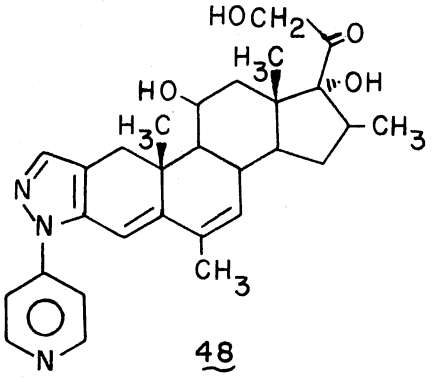
Scheme 4

reviewed by Huisman.[71,72] Since this field has been reviewed through 1970,[99] only pertinent azasteroids reported in the 1971-1974 journals will be discussed here.

Pyrazoles containing 2'-aryl substituents impart enhanced anti-inflammatory activity when fused to the corticoid nucleus at the 2,3 positions.[60] 17α,21-Dihydroxy-20-oxopregn-4-eno[3,2-c]-2'-(4-fluorophenyl)pyrazole (47) was 30 times as potent in local granuloma tests as hydrocortisone. 11β,17α,21-Trihydroxy-6,11-dimethyl-4,6-pregnadieno[3,2-c]-2'-(4-pyridyl)pyrazole (48) exhibits high vasocon-



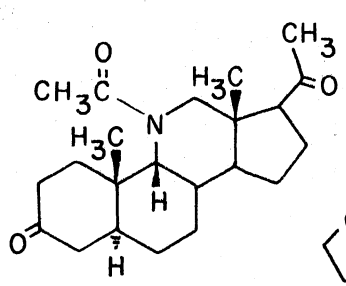
47



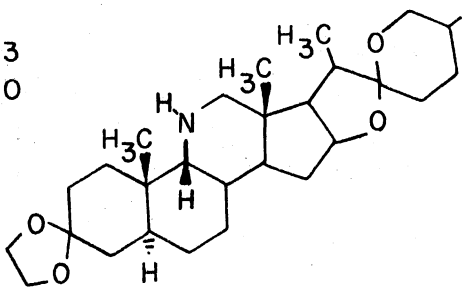
48

striction activity in human volunteers and is clinically effective in the treatment of psoriasis.

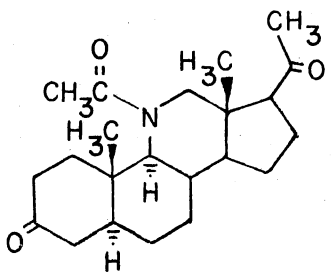
Rastogi, Chowdhury, and Engel[115] recorded the first synthesis of 11-aza-9β-steroids, both in the spirostane and 3,20-dioxygenated pregnane series. They reported the synthesis of N-acetyl-11-aza-5α,9β-pregnane-3,20-dione (49) and the 11-aza-9β-spirostane 50. The synthesis of the 3,20-dioxygenated-11-azapregnane with "normal" (α) configuration in position 9 has also been completed.[34] No biological activity has been reported for the 11-aza-9β-steroids.



49

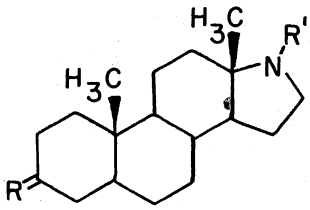


50



51

Several biologically active 17-azasteroids have appeared recently. The 17-azasteroids 52 and 53 were prepared[141] by reducing their 16-oxo

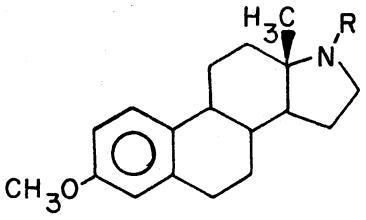


52

a R = OCH_2CH_2O, R' = H, CH_3, C_2H_5

b R = O, R' = CH_3

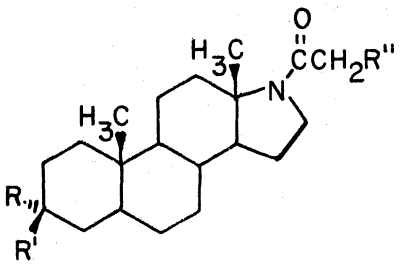
c R = H, OH, R' = H



53

R = H, C_2H_5, CH_2CH_2OH

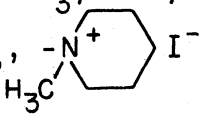
or 20-oxo derivatives with $LiAlH_4$. Both 52 and 53 were intermediates for bactericidal and hypocholesteremic steroids. Tuba and Bor[142] reported the preparation of the 17-azandrostanes 54 and the 17-azaestratrienes 55 from the treatment of the free 17-azasteroid with $ClCH_2COCl$ and then substitution of the other R". Members of 55 were catatonic, particularly against Icterus gravis neonatorum. The quaternary salts 55 have curare-like activity and the piperazinyl derivatives are antibacterial.

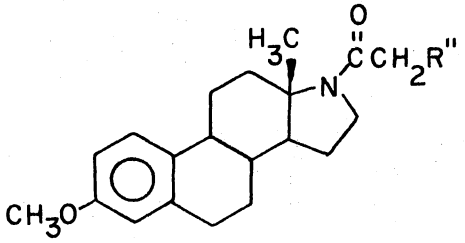


54

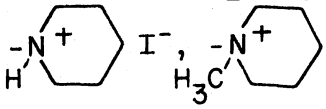
RR' = OCH_2CH_2O, =O

R = H, R' = OH

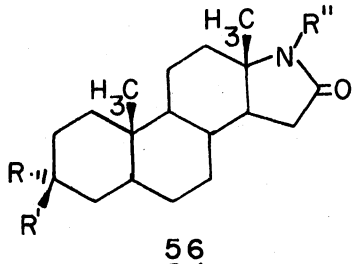
R" = -Cl, $-O_2CCH_3$, -OH, $-O_3SCH_3$, 



55

R" = -Cl, -I, $-O_2CCH_3$,  , , $-N^+(C_2H_5)_3\ I^-$

The androstane derivatives 56 were obtained[140] by the Hofmann degradation of 16,17-seco-16,17-imides and optional alkylation with R" of the 17-unsubstituted compounds. These androstane derivatives 56 are useful as bactericides.



56

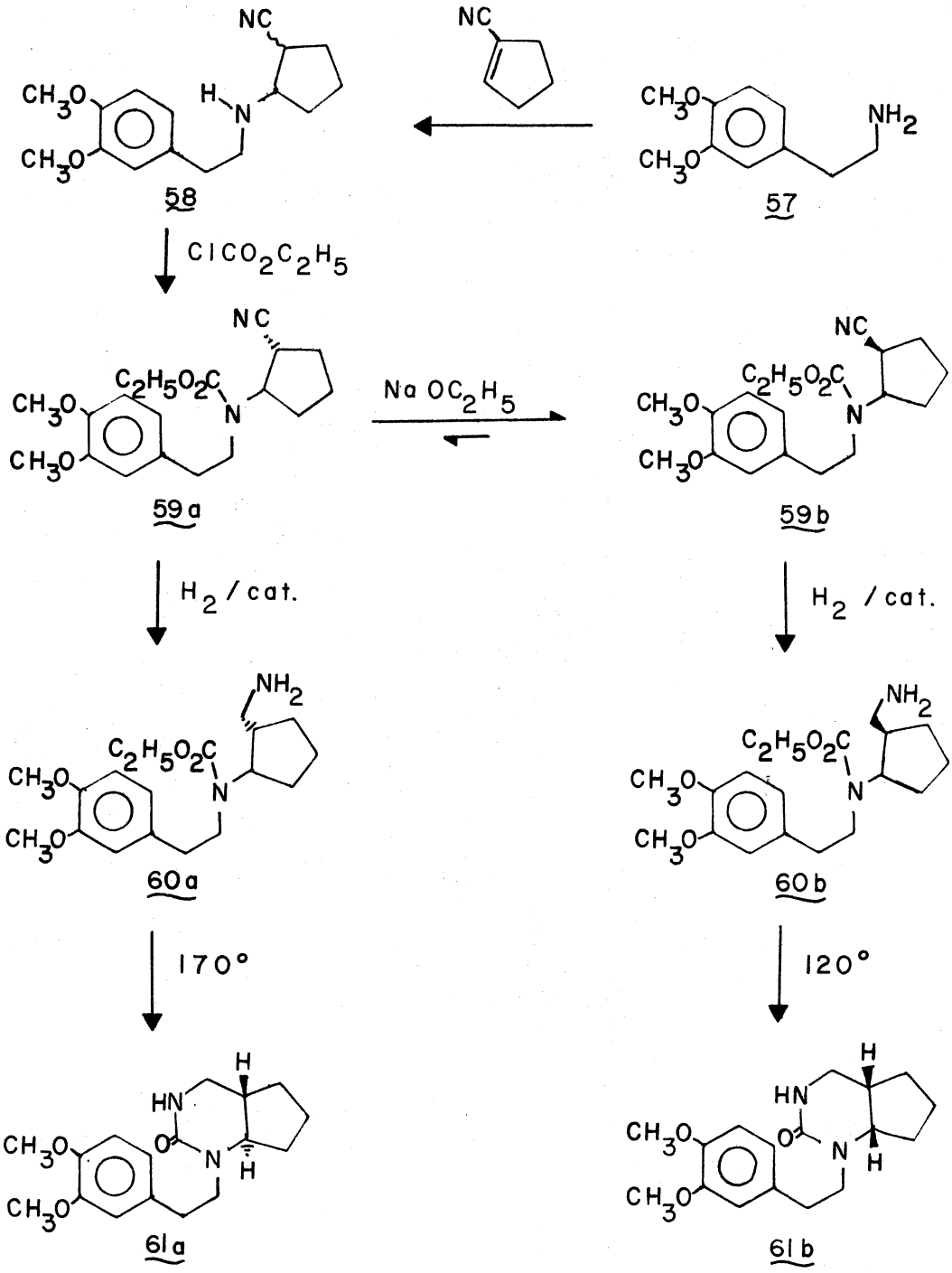
RR' = OCH_2CH_2O, R" = H

R = OH, R' = H, R" = H

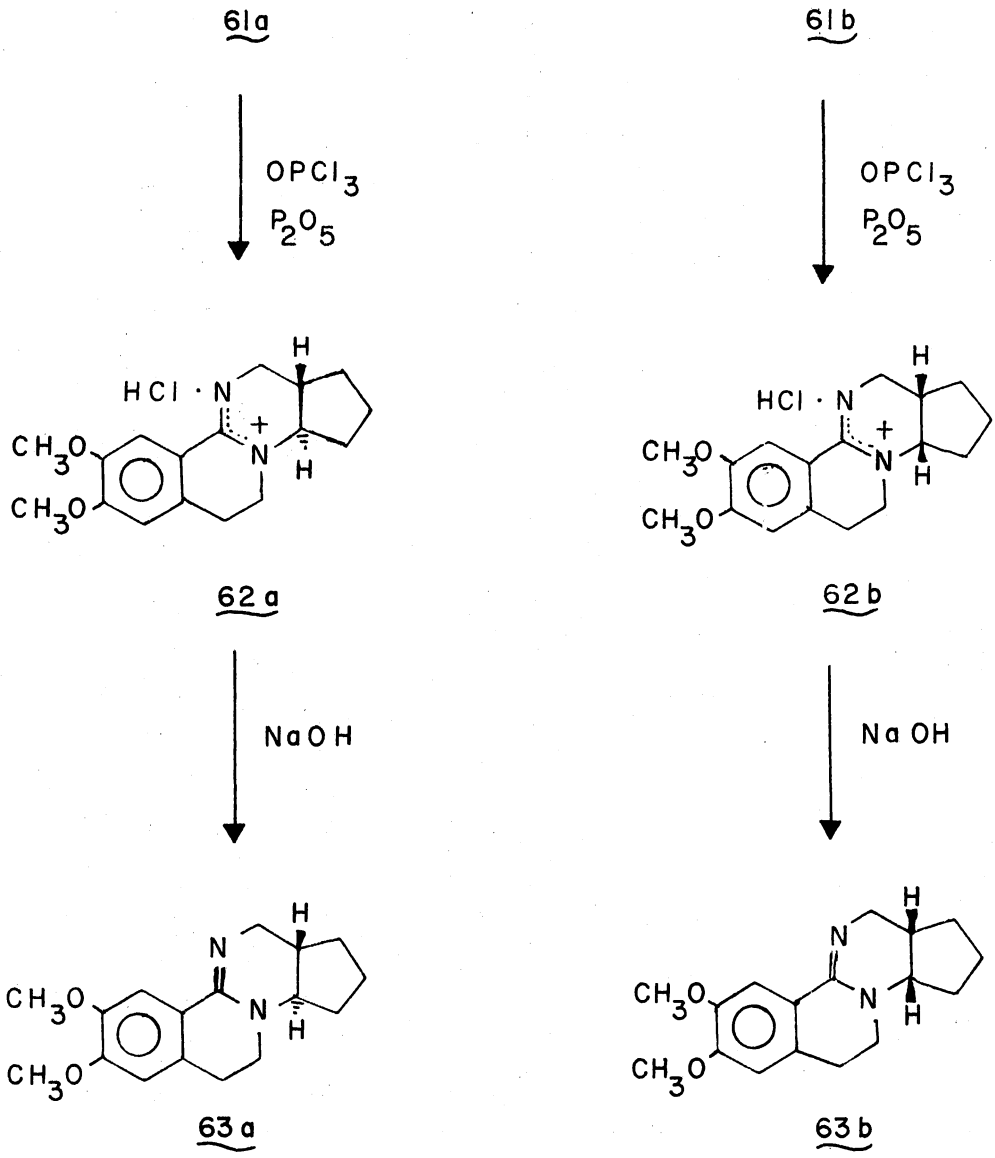
RR' = OCH_2CH_2O, R" = CH_3

RR' = OCH_2CH_2O, R" = C_2H_5

The synthesis[103] of the 8,11-diazasteroid skeleton is summarized in Scheme 5. Surprisingly, no biological data were recorded for these compounds.


NC
CH3O
CH3O
H
N
58
NC
CH3O
CH3O
NH2
57
ClCO2C2H5
NC
C2H5O2C
N
CH3O
CH3O
59a
Na OC2H5
NC
C2H5O2C
N
CH3O
CH3O
59b
H2 / cat.
H2 / cat.
NH2
C2H5O2C
N
CH3O
CH3O
60a
NH2
C2H5O2C
N
CH3O
CH3O
60b
170°
120°
H
HN
O
N
H
CH3O
CH3O
61a
H
HN
O
N
H
CH3O
CH3O
61b

Scheme 5

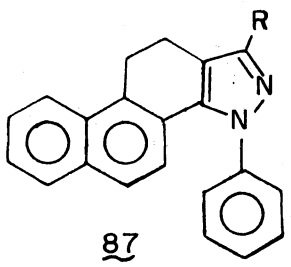


Scheme 5 (Continued)

Isoxazole and pyrazole derivatives can easily be made from the corresponding α-hydroxymethylene ketones. Hence from 64 the following compounds were prepared[52] (Scheme 6): benzo[h]thiochromano[3,4-d]-isoxazole (65), benzo[h]thiochromano[4,3-c]isoxazole (66), and 1-hydroxy-3H-benzo[h]thiochromano[4,3-c]pyrazole (69). Currently, biological screening data are unavailable. Likewise, the following compounds were synthesized from the α-hydroxymethylene ketone 72 (Scheme 7): 3a-hydroxy-4-methyl-7-methoxy-10,11-dihydro-Δ^1-isoxazolino|5,4-i|-phenanthridine (73), 4-methyl-7-methoxy-10,11-dihydroisoxazolo[5,4-i]-phenanthridine (74), and 4-methyl-7-methoxy-10,11-dihydro-2H-pyrazolo-[3,4-i]phenanthridine (75).[91]

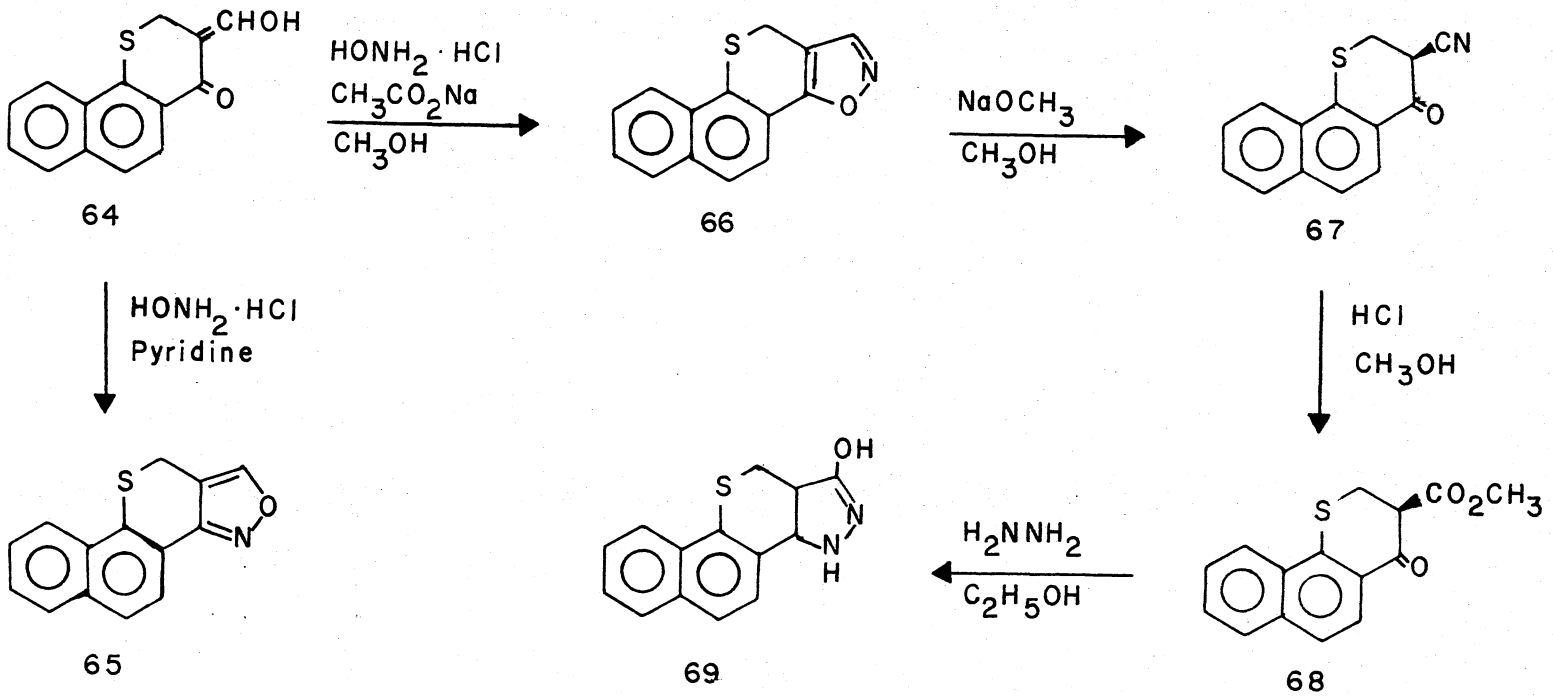
Several 11-oxa-15,16-diaza analogues of equilenin have been synthesized and screened by Kasturi and Arunachalam[78] (Scheme 8), including the pyrazoles 81a, 81b, 83a, and 83b, the isoxazoles 80a, 80b, 82a, and 82b, and the pyrazolinones 86a and 86b. Surprisingly, none of these showed any significant biological activity except the isoxazole 80b, which exhibited weak antidepressant activity at an oral dose of 300 mg/kg in mice.

Bonnardeaux and Lematre[19] studied the physiological properties of 15,16-diazagonaheptene derivatives 87a-d in rats, rabbits, cats, and

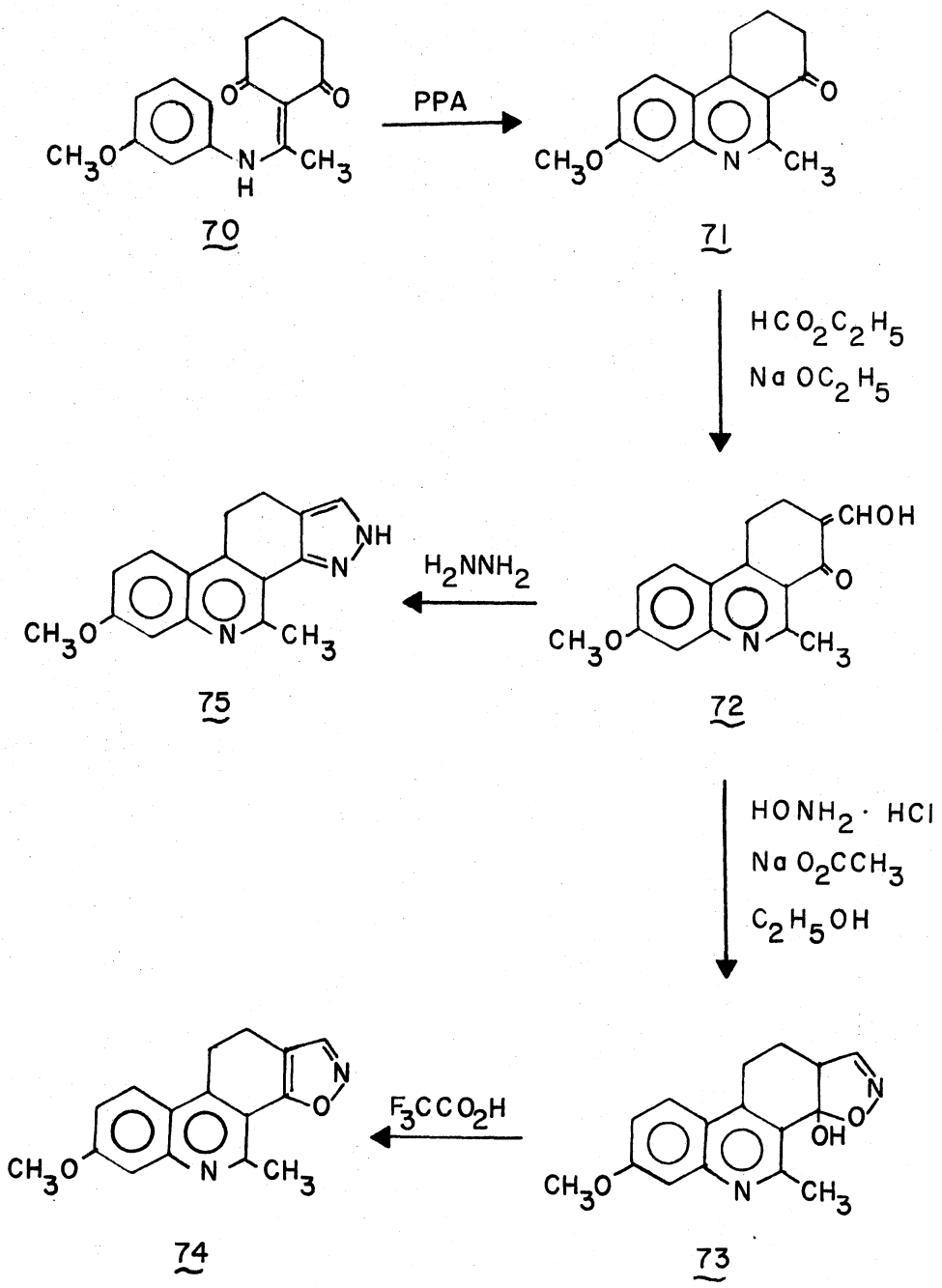


87

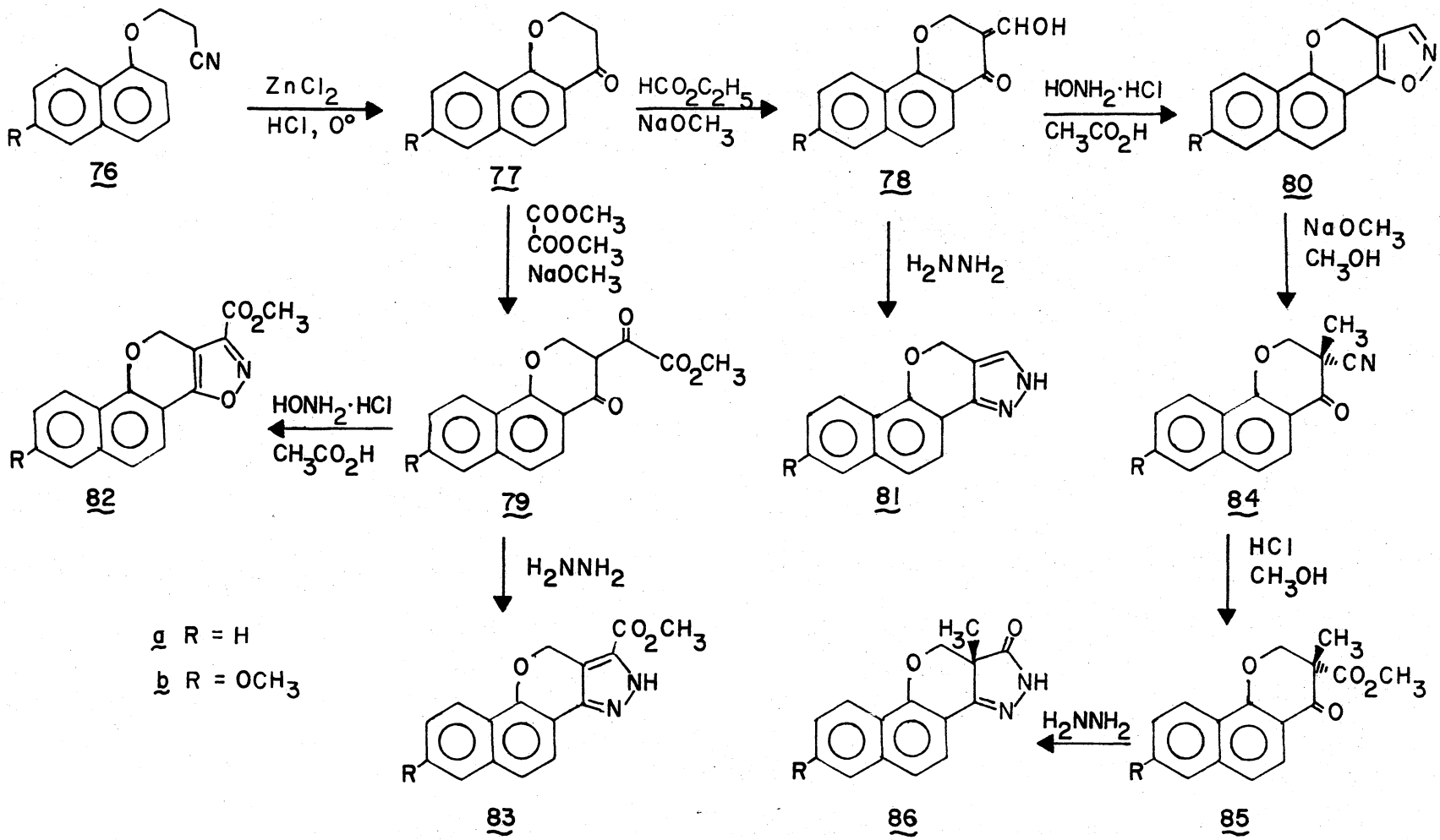
a R = H
b R = CO_2H
c R = $CO_2C_2H_5$
d R = $C(O)CH_3$


CHOH
S
O
64
HONH2 · HCl
CH3CO2Na
CH3OH
N
O
66
NaOCH3
CH3OH
CN
67
HONH2·HCl
Pyridine
65
HCl
CH3OH
CO2CH3
68
OH
N
H
69
H2NNH2
C2H5OH

Scheme 6


PPA
$HCO_2C_2H_5$
$NaOC_2H_5$
H_2NNH_2
$HONH_2 \cdot HCl$
NaO_2CCH_3
C_2H_5OH
F_3CCO_2H
70
71
72
73
74
75

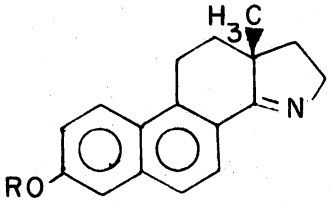
Scheme 7


ZnCl2
HCl, 0°
HCO2C2H5
NaOCH3
HONH2·HCl
CH3CO2H
COOCH3
COOCH3
NaOCH3
H2NNH2
NaOCH3
CH3OH
HONH2·HCl
CH3CO2H
H2NNH2
HCl
CH3OH
H2NNH2
a R = H
b R = OCH3
76
77
78
80
82
79
81
84
83
86
85

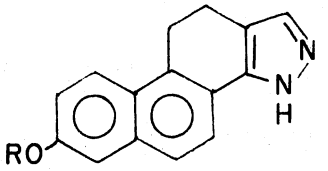
Scheme 8

dogs. It was found that only those compounds which had a free carbonyl group in a position directly opposite to their phenyl function were active. The main observed action was water retention concomitant with hypertension.

Morgan, Berlin, Durham, and Chesnut reported the synthesis of the equilenin 15-azasteroid analogues[101] 88a and 88b and the 15,16-diaza-equilenin derivatives[100] 1a and 1b. 1,10,11,11a-Tetrahydro-11a-methyl-



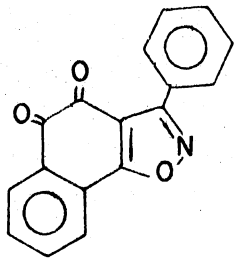
88 a R = H
b R = CH_3



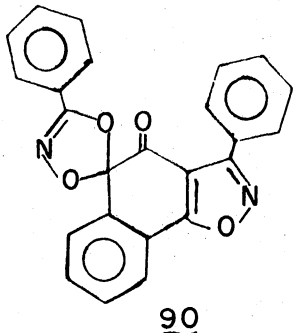
1 a R = H
b R = CH_3

2H-naphth[1,2-g]indol-7-ol (88a) and 1,10,11,11a-tetrahydro-7-methoxy-11a-methyl-2H-naphth[1,2-g]indole (88b) inhibited growth of KB and L-M cells in the culture.[67] The indazole 1a exhibited *in vitro* activity against a variety of microorganisms.[100]

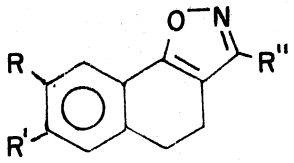
A few "model" azasteroids with the A, C, and D rings only have recently shown biological activity. Watanabe and Ogata[149] developed the synthesis of substituted naphth[2,1-d]isoxazoles such as 3-phenyl-naphth[1,2-d]isoxazole-4,5-dione (89), which was found to be an effective fungicide against *Colletotrichum lagenarium* at 100 ppm, and substituted naphth[2,1-d]isoxazol-4-ones such as 3,3'-diphenylspiro[1,4,2-dioxazole]-5,5'-(4'H)naphth[2,1-d]isoxazol-4-one (90), which proved to be fungicidal against *Sphaerotheca fuliginea* at 500 ppm. Suzuki, Staya, and Minami[136] synthesized 3-substituted naphthisoxazoles 91a-d and 92



89



90

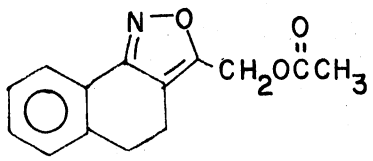


91 a R = OCH_3, R' = H, R'' = CH_2CO_2H

b R = R' = H, R'' = $CH_2C(O)NH_2$

c R = R' = H, R'' = CO_2H

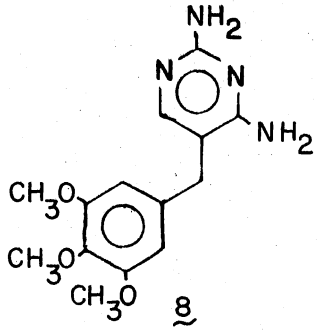
d R = Cl, R' = OCH_3, R'' = CO_2H



92

which were found to be antiinflammatory, analgesic, antipyretic, and antirheumatic.

There are many pyrimidines of biological and medicinal interest. Cheng has recently reviewed this topic extensively.[28,29,30] Of several 5-benzyl-2,4-diaminopyrimidines that were synthesized and tested for antibacterial activity,[119] 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine (8), also known as trimethoprim, was the most effective against both Gram-positive microorganisms and Gram-negative bacteria. Compound 8 was later reported[28] to produce a rapid clinical remission in all cases of infection with both "normal" and a chloroquine-pyrimethamine-resistant strain of Plasmodium falciparum in human beings.



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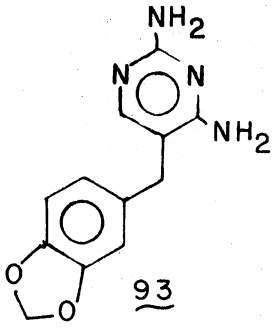

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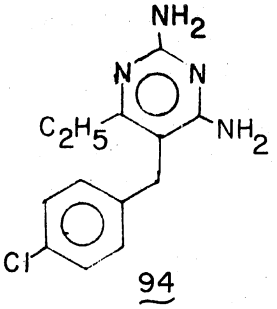


94

It is the only compound so far reported that produces positive responses in human malarias but not in P. berghei infections in rodents.[112]

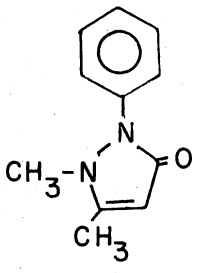
5-Piperonyl-2,4-diaminopyrimidine (93), which is closely related in structure to trimethoprim (8) and the antimalarial compound pyrimethamine (94), combines the therapeutic effect of the former against chloroquine-resistant strains of P. falciparium with the prophylactic and therapeutic effects of the latter. Compound 94 is effective against P. berghei at dose levels where 93 is void of activity, and it does not depress cardiac function as do the two parent compounds.[112]

The nature of structure-activity relationships of compounds is an enormously complicated problem although Hansch has developed a working semiquantitative theory.[62] The binding of the drug to the receptor is of critical importance.[82] In general, bonds formed between a drug and a receptor are relatively weak so that the reaction produced is reversible; that is, the drug-receptor bond is cleaved and the drug ceases to act as soon as its concentration in the extracellular fluids decreases sufficiently. This is exactly what is sought when pharmacodynamic agents are involved so that the response caused by the drug will last for only a limited time. Types of binding which have generally been

considered important to drug-receptor interactions are: ionic attraction (5 to 10 kcal/mole), ion-dipole or dipole-dipole interactions (1 to 7 kcal/mole), hydrogen binding (1 to 7 kcal/mole), charge transfer (1 to 7 kcal/mole), hydrophobic interactions (∿ 1 kcal/mole), and van der Waals forces (0.5 to 1 kcal/mole) between electrons of one atom and the nucleus of another.[82]

An example of the drug-receptor complexation through ionic and secondary bonds has been suggested in local anesthetics and their respective receptor sites. Anesthetics have been tentatively linked to the receptor site by weak bonds,[117] which could explain why the effect produced was reversible and of only short duration.

The presence or absence of biological action in certain compounds is ascribed, in some cases, to the capacity for forming or not forming hydrogen bonds. This fact influences their physiochemical properties and hence their pharmacodynamic activity. 1-Phenyl-2,3-dimethyl-5-pyrazolone (antipyrine) (95), which is soluble in water and moderately soluble in ether, has analgetic properties; its partly demethylated analog, 1-phenyl-3-methyl-5-pyrazolone (96), being insoluble in water



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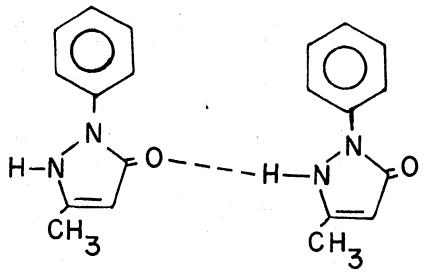


96

and only slightly soluble in ether, has no analgetic activity. This discrepancy may be attributed to the fact that the former compound does not form intermolecular hydrogen bonds, whereas the latter compound

does.[40]

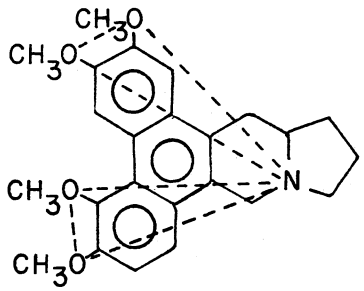
Baker postulates that there are two classes of donors and two classes of acceptors involved in charge-transfer complexes. Donors involved would be: a) those rich in π-electrons (alkenes, alkynes, and aromatic compounds, especially those with electron-donating substituents) or b) those that have an unshared electron pair such as R-$\ddot{O}$:, R-$\ddot{S}$:, R-$\ddot{X}$:, R_3N:, etc. (the same groups that act as proton acceptors in hydrogen bonds). Acceptors would be: a) those compounds deficient in π-electrons by containing groups that withdraw electrons very strongly and b) compounds with weakly acidic hydrogens, such as alkyl-O-H, Ar-O-H, R-S-H, etc. (the same kinds of molecules that act as proton donors in hydrogen bonding).

Certain enzymes that interact with drugs have many nonpolar chains on their surfaces. Several drugs, likewise, possess nonpolar regions in their structures. These chains can be either aryl or alkyl. It is expected that hydrophobic forces intervene in the formation of macromolecule-drug complexes and that they can be of quite appreciable magnitude.[82] Van der Waals forces, although weaker than others that act in biological systems, are of utmost importance in the stabilization of protein structures, because their interactions are much more numerous than the interactions of hydrogen bonds and ionic bonds.[94]

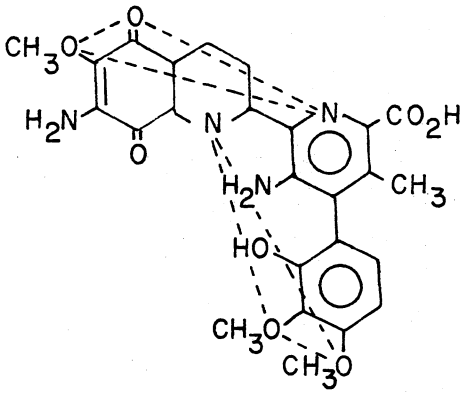
Orientation of the drug to the receptor could be of importance when multiple types of bonding are involved. A striking number of drugs contain certain atoms strategically positioned at a distance of about 55 Å from each other,[109] which is the distance between two turns of the

α helix in proteins. The fact that the effective functional groups (hydroxyl and amino) are capable of hydrogen bonding suggests that the molecules of such drugs could attach themselves to proteins via hydrogen bonds. Consequently, a change could result in the native hydrogen bonding arrangement and the shape of the protein molecules. Obviously, a great change in an enzyme's conformation at its active site could markedly alter its specificity. Drug action could be the consequence of such alteration in an enzyme.

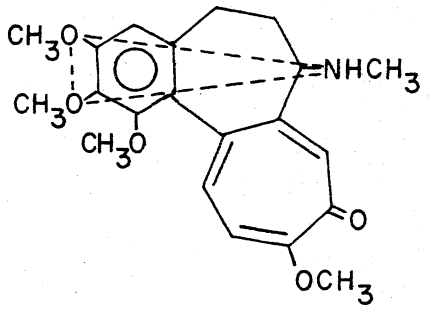
Cheng and Zee-Cheng[154] have noted a common structural feature among a number of antileukemic agents. The empirical treatment of data consists of a triangulation process involving distance between one nitrogen and two oxygen atoms. A few of the examples they cite are given in Figure 3. The triangular relationship process for several compounds has revealed distances for a $N\text{-}O^1$ bond of 7.80 ± 0.56 Å, a $N\text{-}O^2$ bond of 8.62 ± 0.58 Å, and an $O^1\text{-}O^2$ bond of 3.35 ± 0.65 Å (Figure 3). Conceivably these distances are absolutely critical in the binding to one of the pertinent receptor sites in certain biopolymers (proteins, polysaccharides, nucleic acids, etc.) involved in leukemia geneses. The position of the three atoms could result in inhibition of the active sites of the enzymes, in alteration of the specificity of enzyme systems, in disturbance of the template molecules in the transcription process, in changing the permeability of certain biological membranes, or in causing other interruptions of biological functions. Of the 36 compounds Zee-Cheng and Cheng mentioned, 29 were found to have antileukemic activity and 7 did not. Twenty-seven (27) of the active chemicals showed a common triangular relationship. The seven compounds which were not active



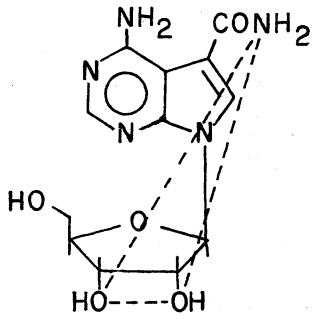
Tylocrebrine



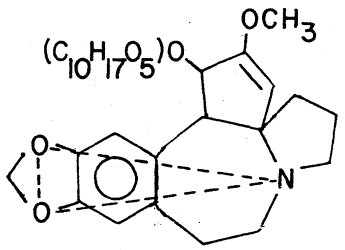
Streptonigrin



Demecolcine



Sangivamycin



Harringtonine

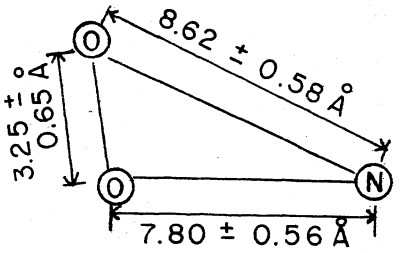
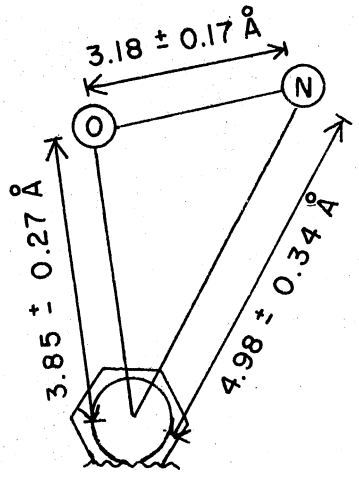
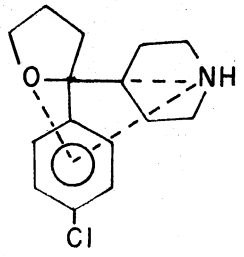


Figure 3. Common Triangulation of Heteroatom Distances in Some Antileukemic Compounds

had other common features, but did not appear to have a similar triangular relationship involving the heteroatoms. The triangular pattern cannot be used to explain the antileukemic activity of hydroxyurea, ellipticine, and biological alkylating agents.

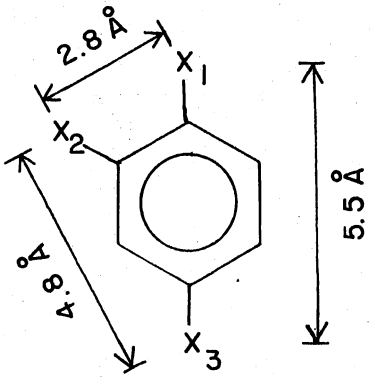
Cheng[25] reported another common triangular feature among certain antimalarial cinchona alkaloids [amino alcohols and 2-(p-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran]. Here each series of compounds is composed of three parts: a planar (aromatic or heteroaromatic) ring, an oxygen-containing portion, and a nonplanar nitrogen-containing portion (Figure 4). Later he proposed[26] a common structural feature among several classes of antimalarial agents involving three electronegative atoms (X_1, X_2, and X_3) each possessing at least one lone pair of electrons, such as nitrogen, oxygen, or sulfur (Figure 5). Additional work, perhaps molecular orbital calculations of preferred conformations of molecules and electron-density distribution on atoms, could be instructive to determine the significance of this preliminary work.[79] As an example of this approach for diagnostic utility, Kier was able to propose a working hypothetical model, with representative muscarinic receptor sites, after determining the preferred conformations of acetylcholine, L-(+)-muscarine, and D-(-)-muscarone using extended Hückel theory molecular orbital calculations.[80] This structural relationship of heteroatoms may be useful in the design of improved drugs.

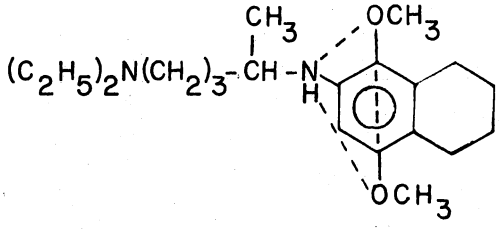




2-(p-Chlorophenyl)-2-(4-piperidyl)-tetrahydrofuran

Figure 4. Common Triangulation in Antimalarial Alkaloids





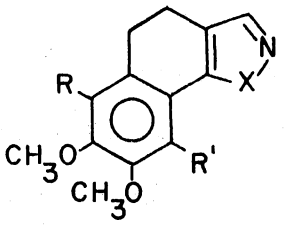
2-[4-Diethylamino-(1-methylbutyl)-amino]-1,4-dimethoxynaphthalene

Figure 5. Common Triangulation in Several Classes of Antimalarial Agents

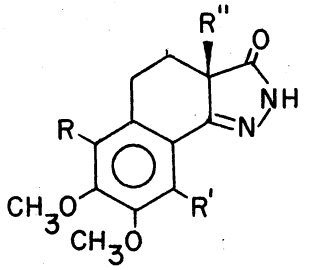
CHAPTER II

RESULTS AND DISCUSSION

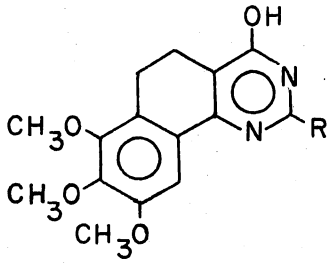
Objectives of this research have been many-faceted with regard to: the synthesis of compounds combining heterocyclic ring functions and a trimethoxyphenyl group, the type of and distance between heteroatoms in the compounds prepared, and the structure-activity relationships in these sytems as determined with microbial and tissue culture screens. We have been able to develop preparative methods for the following heterosteroids and model compounds.



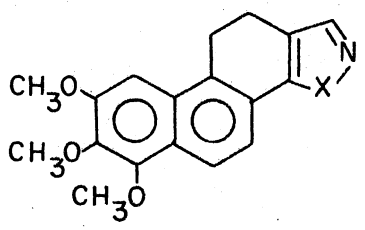
97 R = OCH_3, R' = H, X = NH
98 R = H, R' = OCH_3, X = NH
99 R = OCH_3, R' = H, X = O
100 R = H, R' = OCH_3, X = O



101 R = OCH_3, R' = H, R'' = H
102 R = OCH_3, R' = H, R'' = CH_3
103 R = H, R' = OCH_3, R'' = CH_3

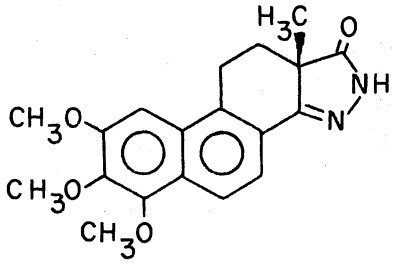


104 R = NH_2
105 R = SH



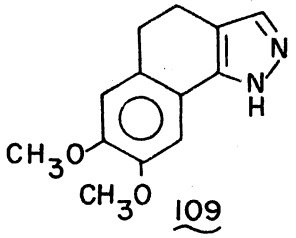
106 X = NH

107 X = O

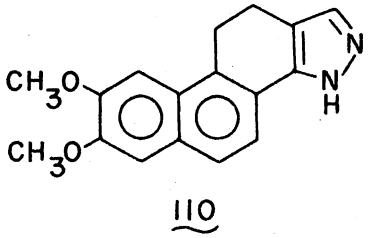


108

Distances and angles between heteroatoms were calculated for the pyrazoles 97, 98, and 106 and the isoxazoles 99, 100, and 107 using x-ray diffraction data of similar types of compounds. The dimethoxy analogs (109 and 110) of the "model" pyrazole 97 and pyrazolosteroid 106 were available in our Laboratory[64] and were included in the calculations, biological screening, and structure-activity correlation studies. Also included was the thiazole 111 because of its pronounced effect in



109



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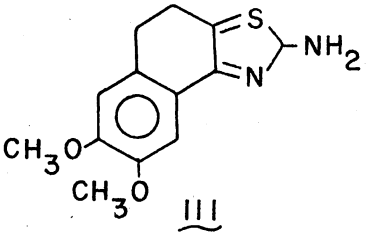


111

the tissue culture screens. Results of these calculations are shown in Tables XII, XIII, XIV, and XV.

Primary screens of all products were initiated with growth studies of Bacillus subtilis W23 and Pseudomonas fluorescens NND. These data were obtained in part in this joint project by members of Dr. Durham's research group in the Department of Microbiology. Table X contains the results of these activity screens. It is interesting that the most

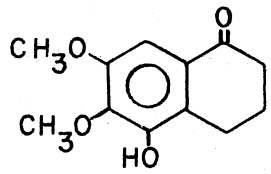
consistent inhibition of growth was observed with the pyrazoles. Because of this activity, the pyrazoles were evaluated for their ability to inhibit cell plating efficiency of the human tumor cell line - KB. Results of the tissue culture screens are given in Table XI.

A comparison of the distances and angles between heteroatoms and the percent plating efficiency of KB cells in the presence of the compound was made. Figure 10 suggests that, at least in the compounds which have been tested to date, the closer the value of the ratio $\frac{O^1\text{-}N}{O^2\text{-}N}$ is to unity, the less inhibition is observed. The greater the deviation from one of this ratio, the greater the inhibition. One can certainly speculate that the distance between two or more active sites on the biological substrate could be related to distances between the heteroatoms in our compounds as has been suggested in other drug-receptor systems.[82] In the cases examined (which to be sure are fewer than desirable from a statistical basis) no obvious correlation is apparent between the $O^1\text{-}N\text{-}O^2$ angle (as calculated from the triangulation process) and percent plating efficiency (see Figure 11).

Synthetic Techniques

The method of synthesis for 5,6,7-trimethoxy-3,4-dihydro-1(2H)-naphthalenone (28) (one of the key starting tetralones) was recently optimized.[132] Classical methods of Haworth,[65] i.e., Friedel-Crafts succinoylation and Clemmensen reduction followed by cyclization, involved several difficulties. However, the general approach has been applied successfully by many workers to the preparation of 28 but in less yield.[65,89,98] Methoxy group cleavage (the group was usually in the ortho position)[65,70,89,98] was a common side reaction in Friedel-Crafts

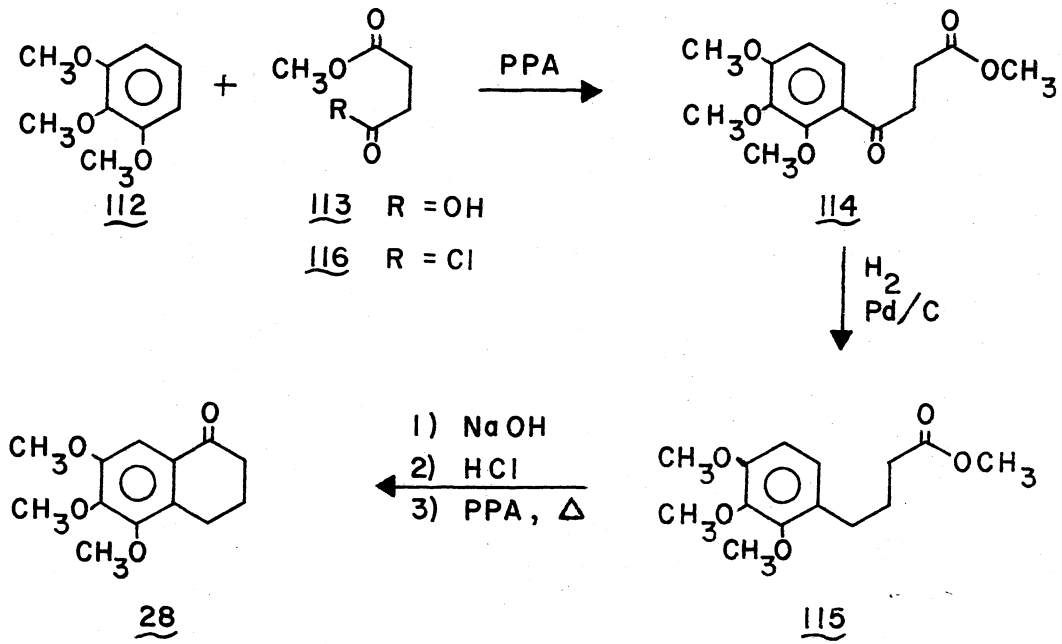
reactions involving these types of compounds making isolation of products and purification difficult. Moreover, the major product from the reaction was the 5-hydroxy derivative of 28 which had to be remethylated.



In our hands the use of 3-carbomethoxypropanoic acid and 115% PPA under "succinoylation conditions" with 1,2,3-trimethoxybenzene (Scheme 9) circumvented this problem and provided the necessary intermediate 114 in good yield without the production of a mixture of methylated and partially methylated products. Hydrogenolysis of aryl-substituted ketones over Pd/C has been an efficient method for reduction to the corresponding hydrocarbons.[23] By utilizing lower reaction temperatures and longer reaction times in the cyclization of 115 with PPA, Snider and co-workers[132] minimized the problem of methoxyl cleavage which had been reported in this type of reaction.[75]

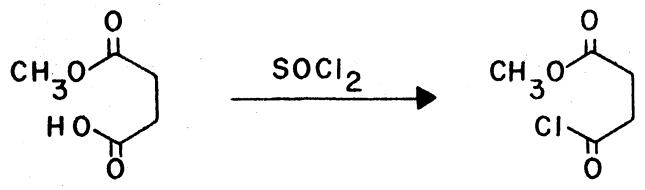
Owing to the efficiency of each step, the reduction, saponification and cyclization process to yield the final product was realized in an overall yield of > 80% for 28 (based on 114) without isolation and purification of any intermediates. This compares to a yield of 60-70% of demethylated 28 from the keto ester 115 via the more classical methods of Haworth previously alluded to.

It was found that when 3-carbomethoxypropanoic acid 113 was converted to the acid chloride 116 which was allowed to react with 112 in the presence of PPA (Scheme 9), the reaction time was shortened considerably (45 min. vs. 2.5 hr. when the acid itself was used). However, the heavy evolution of HCl gas must be handled with care.



112 + 113 R = OH / 116 R = Cl → 114 → 115 → 28

Scheme 9

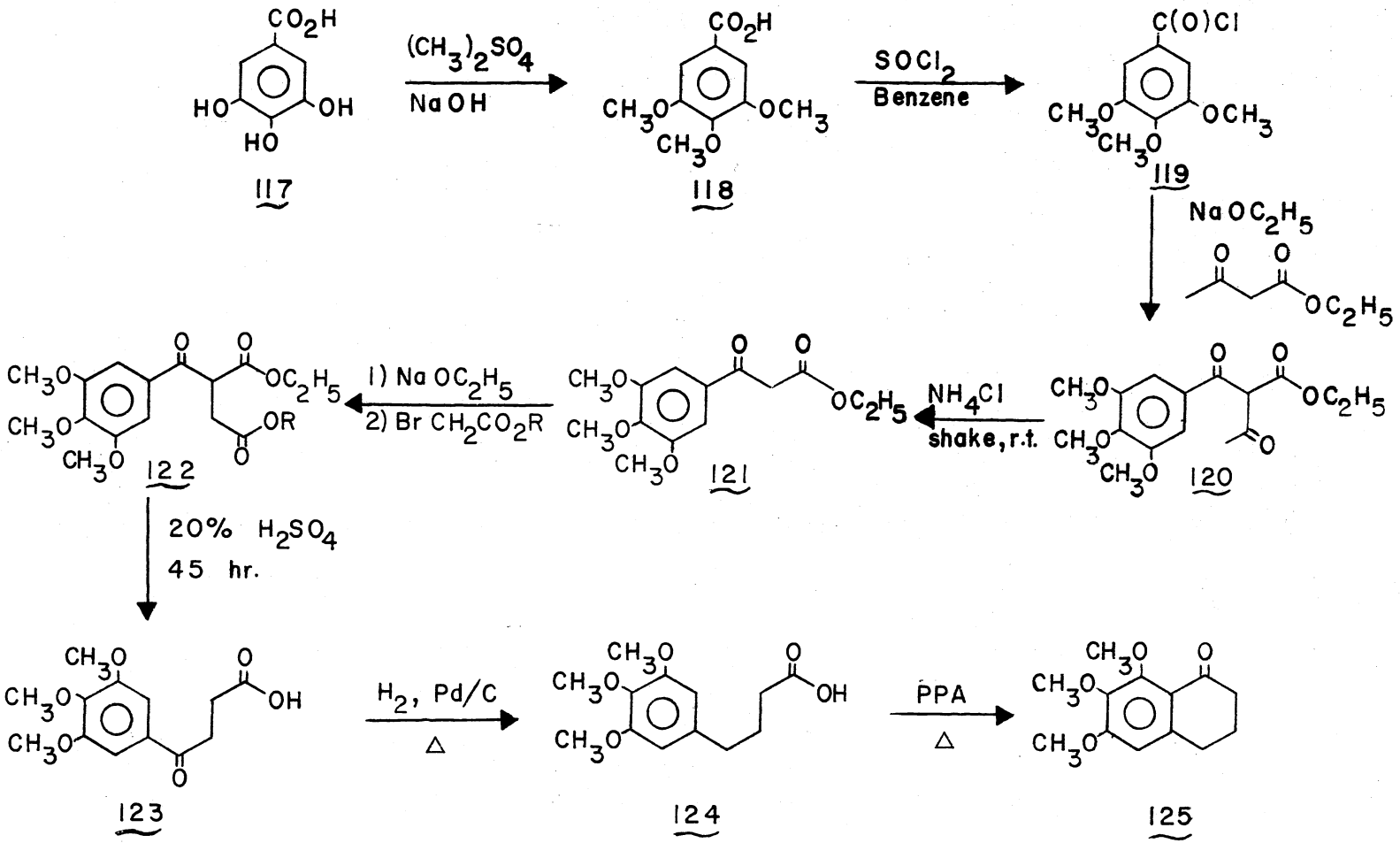


113 116

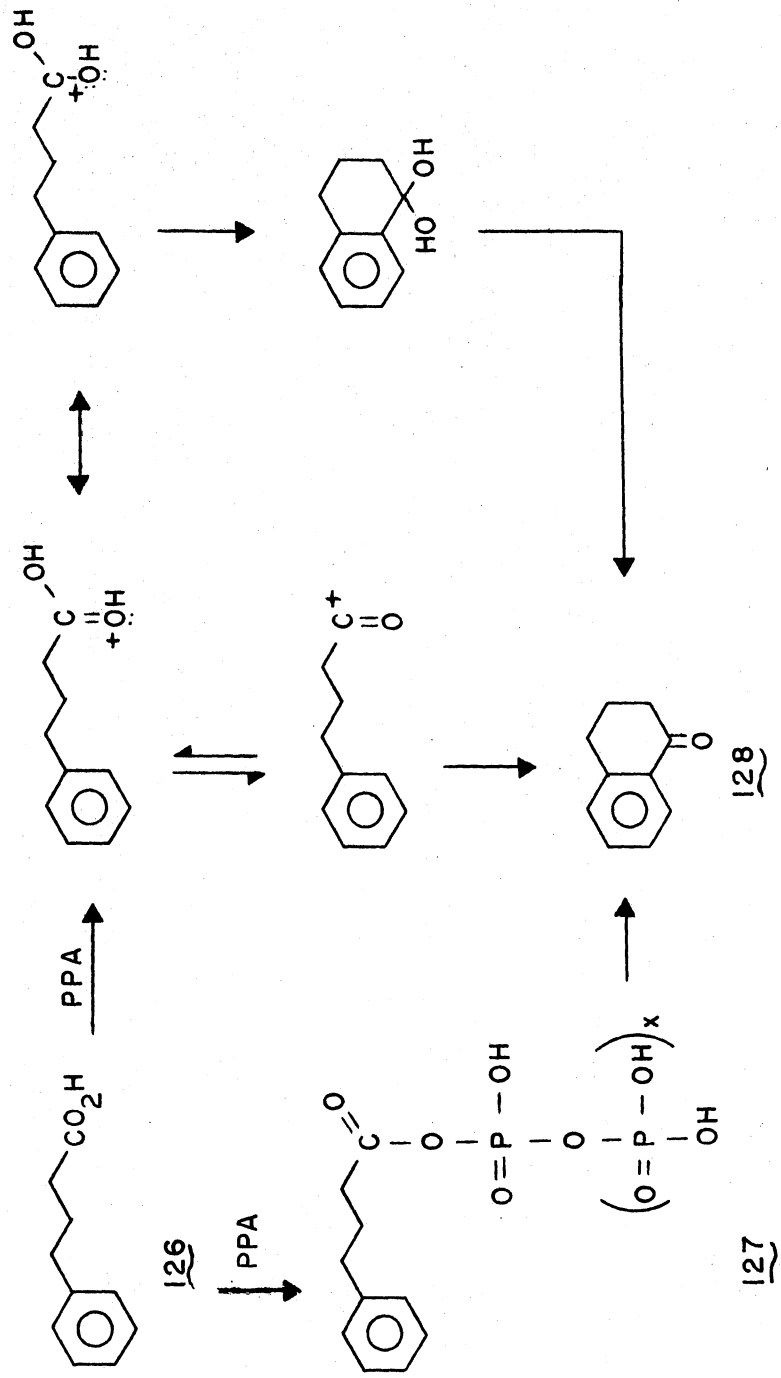
The other key tetralone 125 was prepared by a multistep sequence starting from gallic acid (117) as showed in Scheme 10. Trimethylgallic acid (118) was obtained by treatment of 117 with dimethyl sulfate in the presence of base.[93] The acid chloride 119 was treated in a classic base-catalyzed acetoacetic ester synthesis[81] to form ethyl 3,4,5-trimethoxybenzoylacetoacetate (120). Following deacylation of 120 by ammonium chloride, the β-keto ester 121 condensed with ethyl bromoacetate (sodium ethoxide) to form the diester 122 which, upon boiling with 20% sulfuric acid for 45 hr,[66] gave the γ-keto acid 123. Reduction of the keto function with hydrogen in the presence of 10% Pd/C and cyclization of 124 in PPA produced the key tetralone 125.

According to the literature, polyphosphoric acid (PPA) may function simultaneously as a protic acid, a Lewis acid, and a phosphorylating agent.[6] Thus in the cyclization of γ-phenylbutyric acid (126), protonation or the formation of a mixed anhydride 127 is postulated as the initial stage (as shown in Scheme 11) in the formation of 1-tetralone (128).[86]

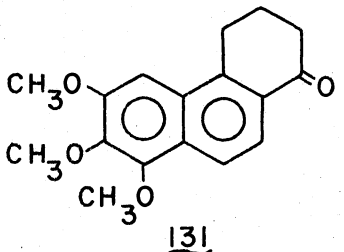
Phenanthrone 131 (the key starting material for the synthesis of the heterosteroid systems 106, 107, and 108) was synthesized from tetralone 28 by initial condensation with methyl γ-bromocrotonate in a Reformatsky reaction. This was followed by dehydration and isomerization (heating with Pd/C in an CO_2 atmosphere) to form the naphthalene-


CO2H
HO
OH
HO
117
(CH3)2SO4
NaOH
CO2H
CH3O
OCH3
CH3O
118
SOCl2
Benzene
C(O)Cl
CH3O
OCH3
CH3O
119
NaOC2H5
O
O
OC2H5
CH3O
CH3O
CH3O
OC2H5
O
O
120
NH4Cl
shake, r.t.
CH3O
CH3O
CH3O
OC2H5
O
O
121
1) NaOC2H5
2) Br CH2CO2R
CH3O
CH3O
CH3O
OC2H5
O
O
OR
O
122
20% H2SO4
45 hr.
CH3O
CH3O
CH3O
O
OH
O
123
H2, Pd/C
△
CH3O
CH3O
CH3O
O
OH
124
PPA
△
CH3O
CH3O
CH3O
O
125

Scheme 10

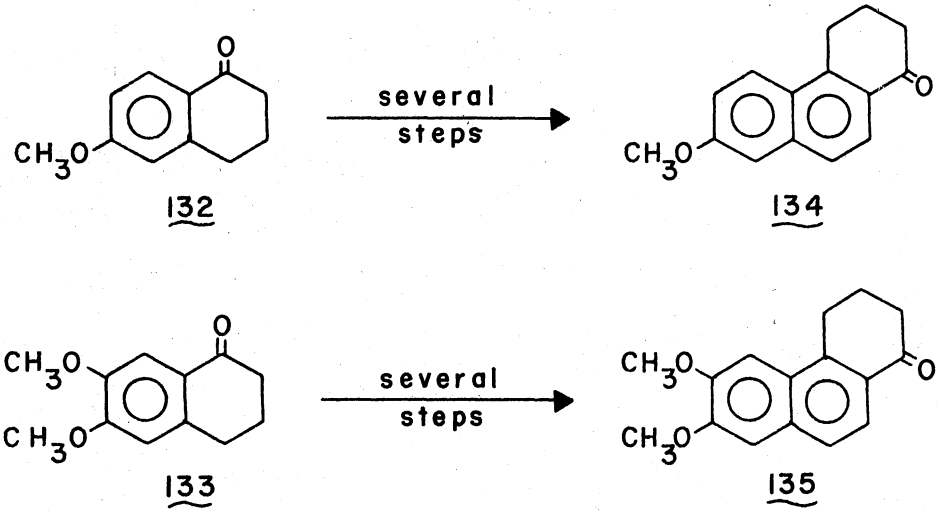


Scheme II



131

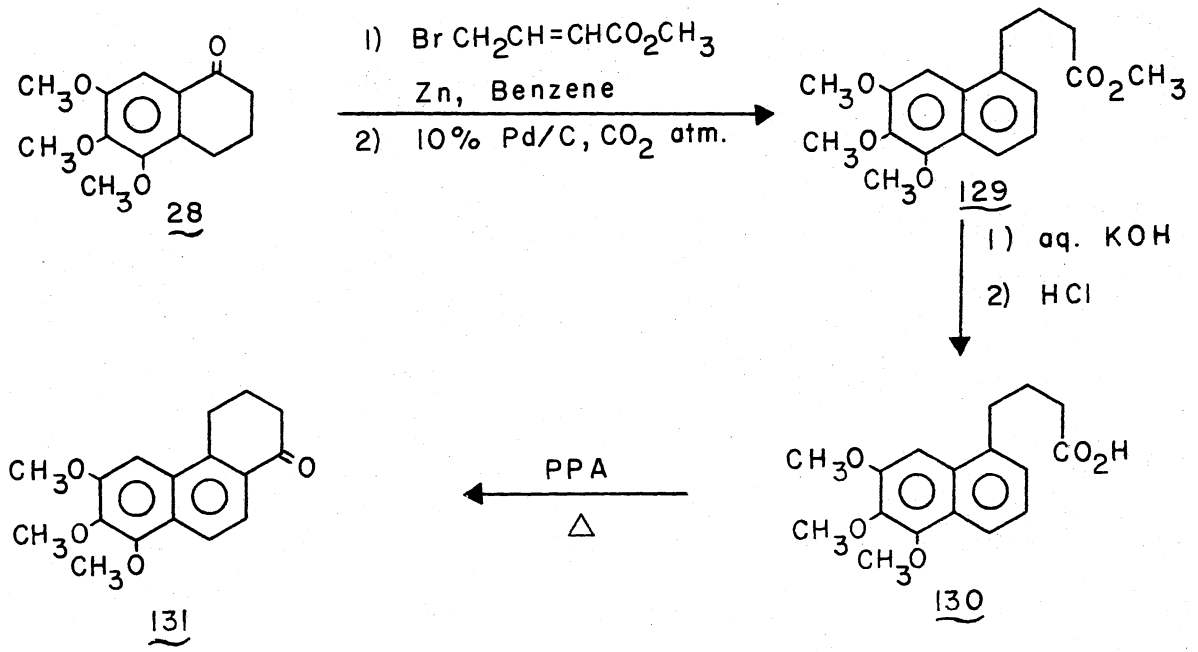
butyric ester 129 which was saponified in aqueous potassium hydroxide. The resulting acid 130 cyclized in the presence of PPA to form 131 (Scheme 12). This identical procedure has been used for the formation of 3,4-dihydro-7-methoxy-1(2H)-phenanthrone (134)[100] from 6-methoxy-1-tetralone (132) and 3,4-dihydro-6,7-dimethoxy-1(2H)phenanthrone (135)[64] from 6,7-dimethoxy-1-tetralone (133).



132 134

133 135

One unexpected aspect of this synthesis in the case of trimethoxy-substituted phenanthrone 131 was the difficulty in purification of the final product. Cyclization with PPA yielded a black tar. Passing this material through a column of neutral alumina (C_6H_6) followed by sublimation of the product gave only a low yield (7.9% based on 28) of 131. In contrast, in the case of 134, simple chromatography of the reaction mixture on an alumina column provided pure 134 (18.6% based on 132).[99]

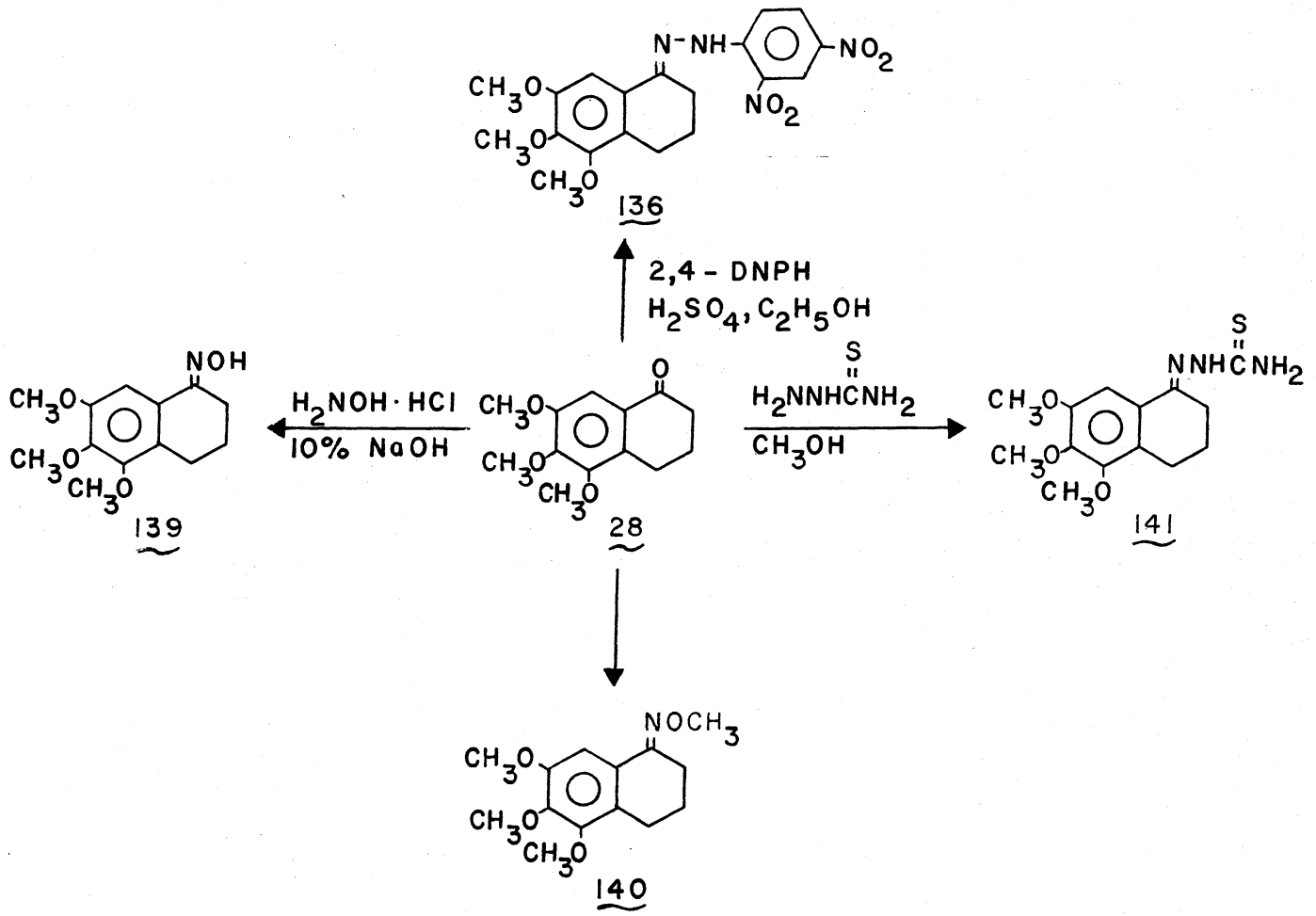

1) Br CH2CH=CHCO2CH3
Zn, Benzene
2) 10% Pd/C, CO2 atm.
28
129
1) aq. KOH
2) HCl
130
PPA
△
131

Scheme 12

Phenanthrone 135 was purified by Soxhlet extraction with n-heptane in fair yield (30.8%).[64]

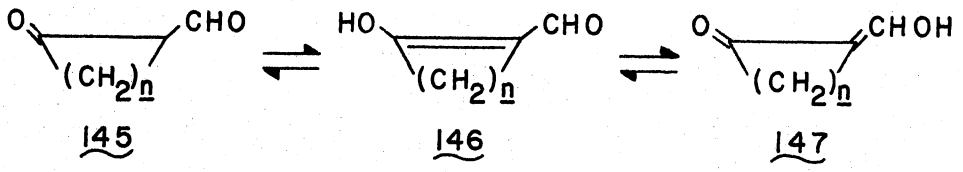
A comparison of melting points of the various phenanthrones reveals a very interesting phenomenon. The monomethoxy phenanthrone 134 is reported to melt at 98-100°;[99] the dimethoxy phenanthrone 135 melts at 210-211°.[64] Interestingly, the trimethoxy phenanthrone 131 melts at 137-138°. Possibly a higher order of symmetry in phenanthrone 135 could cause such deviation from the expected increase of melting point as the molecular weight increased. A different trend may exist in the case of the tetralones: 6-methoxy-1-tetralone (132) melts at 78.4-79°;[134] 6,7-dimethoxy-1-tetralone (133) melts at 99-100°;[64] 5,6,7-trimethoxy-1-tetralone (28) melts at 74.5-76°;[132] and 6,7,8-trimethoxy-1-tetralone (125) melts at 124-125°.[65] No intuitively obvious explanation is available to explain this trend since tetralones 132, 133 and 125 show an increase in melting point with an increase in molecular weight. Tetralone 28 seems to be the exception to the rule in this case; yet, it would seem to be more symmetrical than its isomer 125.

2,4-Dinitrophenylhydrazone derivatives 136, 137, and 138 were made for each tetralone and the phenanthrone 131. Several other derivatives were prepared from 3,4-dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (28) by classic techniques[50,126,127] (Scheme 13), including the oxime 139, methoxime 140, and thiosemicarbazone 141. Each compound was characterized by IR, NMR, and either elemental data obtained or the value for the molecular ion (peak-matched), on the mass spectrometer (Tables V, VI, and IX). Microbial screening was also obtained (Table X). None of the derivatives showed appreciable activity, unfortunately.


N-NH
NO2
NO2
CH3O
CH3O
CH3O
136
2,4 - DNPH
H2SO4, C2H5OH
NOH
H2NOH · HCl
10% NaOH
O
H2NNHCNH2
CH3OH
S
NNHCNH2
139
28
141
NOCH3
140

Scheme 13

Treatment of the tetralone 28 or 125 or the phenanthrone 131 with ethyl formate in the presence of sodium methoxide gave the corresponding hydroxymethylene derivative 142, 143 or 144. It is recognized that many tautomeric forms of this type of compound could exist. Terinski and Kozluk[138] studied the direction of enolization in several α-formylcyclanones (Scheme 14, n = 3 - 7). When forms 146 and 147 were examined

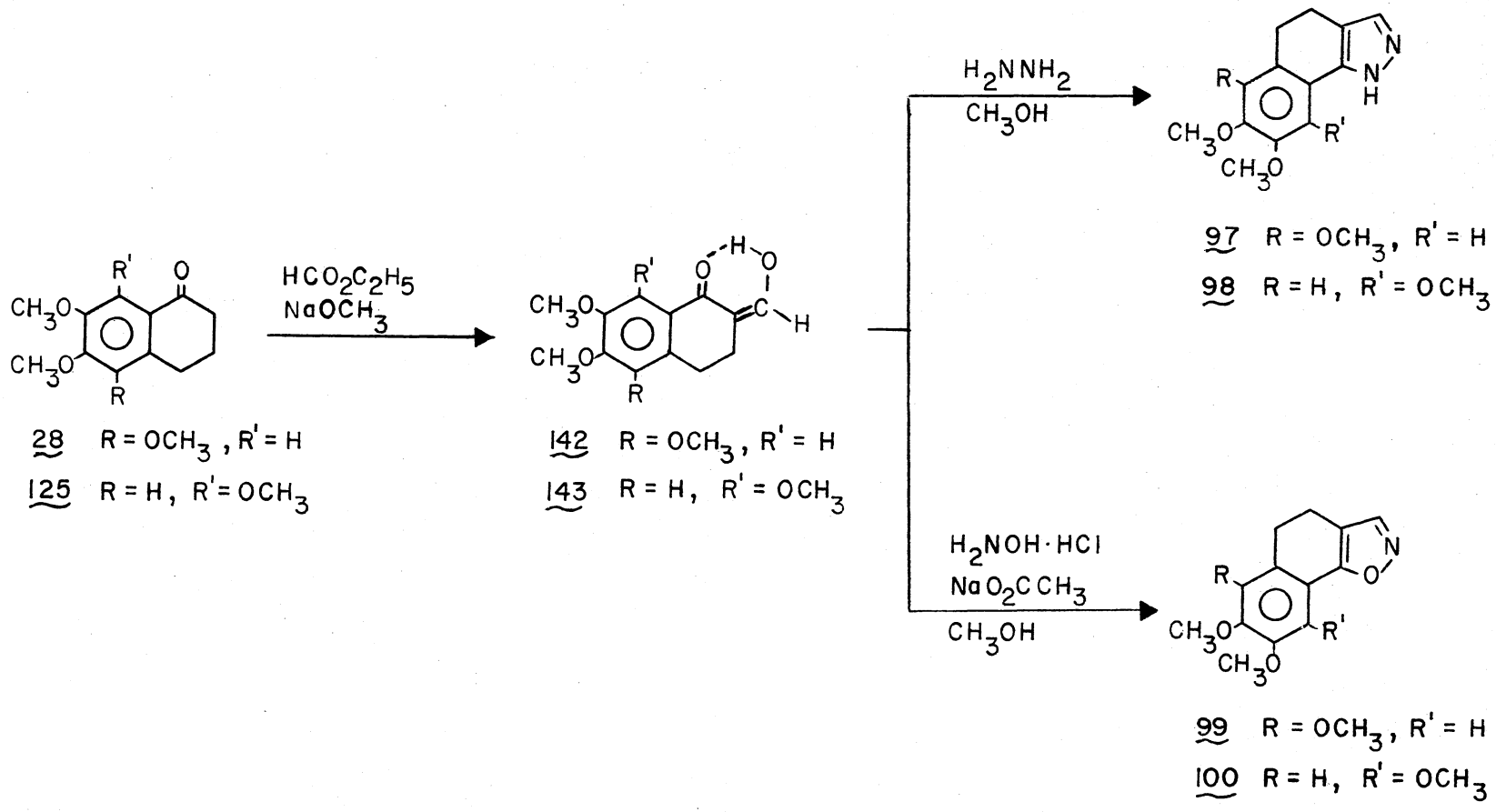


145 146 147

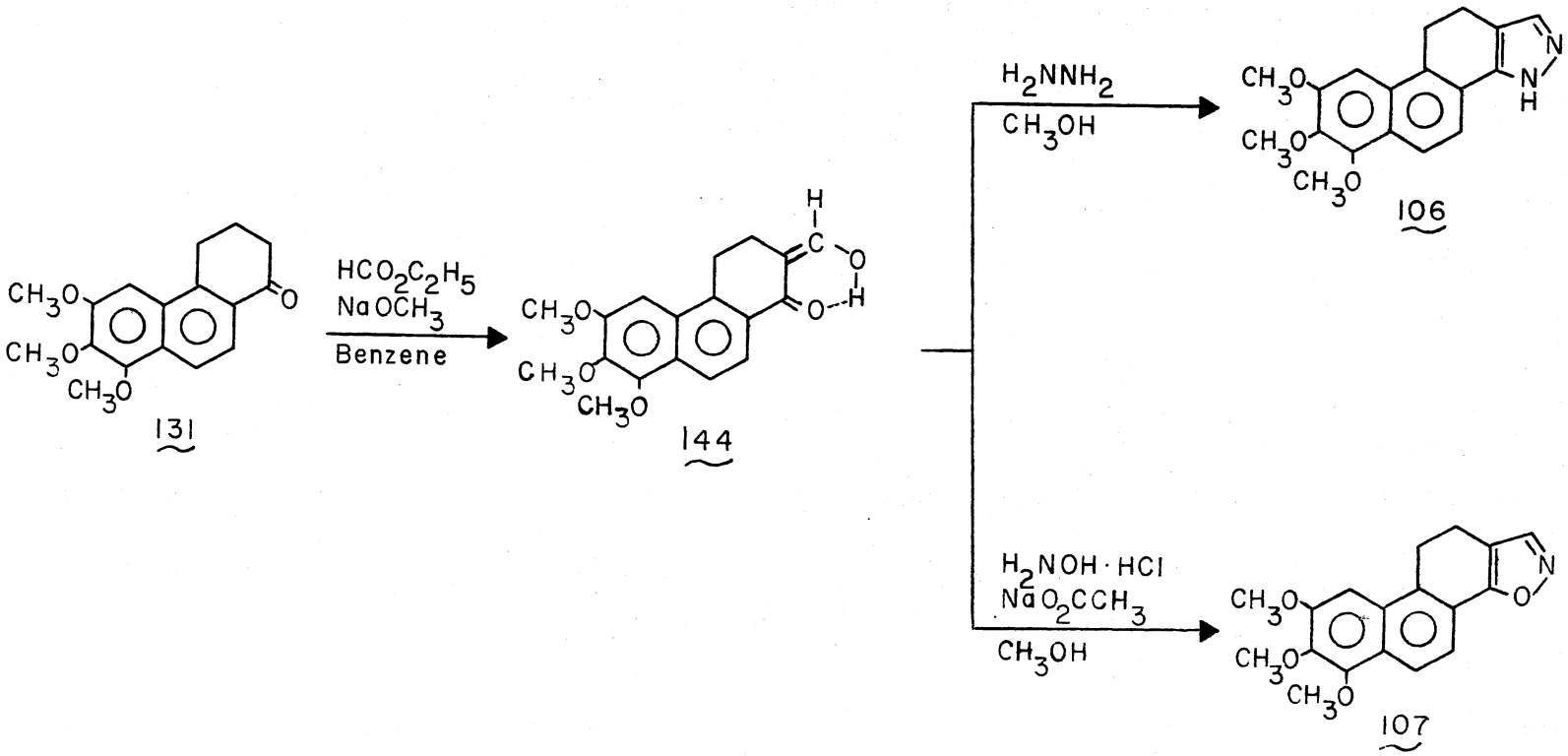
Scheme 14

by NMR, IR, and UV analysis, it was found that the amount of the keto-hydroxymethylene compound 147 decreased in the order $C_5 > C_7$, $C_8 > C_6 > C_9$. This suggested initially that the hydroxymethylene derivatives in our work exist primarily in the enol-aldehyde form 146 since the ring size involved contains six carbons. However, it is interesting to note that there is only one carbonyl absorption in the IR spectra of the hydroxymethylene compounds (which corresponds to the keto function) and a definite hydroxyl absorption (Table V). This seems to indicate that the keto-hydroxymethylene compound form may predominate in our structures in the solid state. This might be the result of conjugation with the adjacent aromatic ring. Although it is recognized that both tautomeric forms are conjugated, only one form contains an OH group.

Treatment of the hydroxymethylene derivatives with > 95% hydrazine in methanol produced the pyrazoles in good yield (Schemes 15 and 16). Since two isomeric forms were possible, the NMR spectra were carefully inspected. Pyrazole 75 was reported to have the structure given because

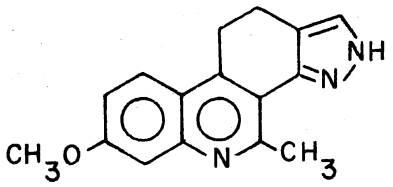

HCO2C2H5
NaOCH3
H2NNH2
CH3OH
H2NOH·HCl
NaO2CCH3
CH3OH
28 R = OCH3, R' = H
125 R = H, R' = OCH3
142 R = OCH3, R' = H
143 R = H, R' = OCH3
97 R = OCH3, R' = H
98 R = H, R' = OCH3
99 R = OCH3, R' = H
100 R = H, R' = OCH3

Scheme 15

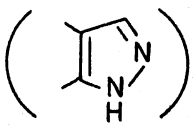
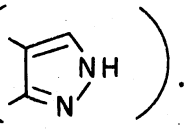

CH3O
CH3O
CH3O
O
131
HCO2C2H5
NaOCH3
Benzene
H
C
O
O
H
144
H2NNH2
CH3OH
N
N
H
106
H2NOH·HCl
NaO2CCH3
CH3OH
N
O
107

Scheme 16

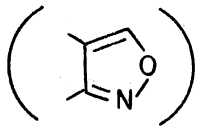
the NMR spectrum (DMSO-d_6 solvent) showed a triplet (J_{HH} = 0.7 Hz) at



75

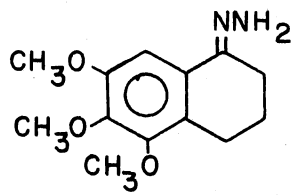
δ 7.52 (1H) which was assigned to the lone =CH proton.[91] A broad singlet at δ 12.70 was assigned to the -NH proton. In all three cases the pyrazoles prepared showed a singlet for =CH (97, δ 7.33; 98, δ 7.41; 106, δ 7.43, see Table VI) and a higher field signal for the -NH proton [97, δ 7.40-7.76 (bs); 98, δ 8.78-9.02 (bs); 106, δ 7.47 (s)]. Pyrazole 98 showed a slightly lower field shift, probably because of the methoxy influence at C(9). In view of these data, we tentatively concluded that the correct form for our pyrazoles was consistent for the 1H form  rather than the 2H form  . An x-ray analysis would be helpful here. Both types of tautomers are reported in the literature[3,22,78,88] but often little or no conclusive evidence has been given for the form reported.[78,88]

The isoxazole derivatives 99, 100 and 107 were prepared from the corresponding hydroxymethylene compounds (Schemes 15 and 16) by the procedure of Guthrie and co-workers[59] for the formation of the [2,3-d]-isomer. This process involved heating (100°) the hydroxymethylene intermediate with hydroxylamine hydrochloride and sodium acetate in glacial acetic acid for 30 min. No attempt was made to obtain the

[3,2-c]-isomer  using hydroxylamine hydrochloride in pyridine.[59] There is no reason to doubt that we indeed obtained the [2,3-d]-isomer as evidenced by the IR (Table V) and NMR (Table VI) data.

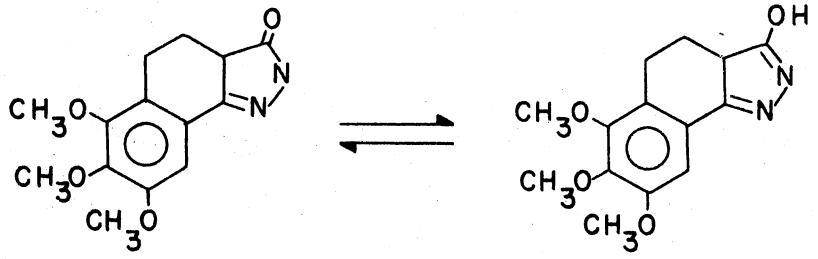
Formation of the α-keto ester 148 from the tetralone 28 was successfully achieved by heating 28 in anhydrous dimethyl carbonate in the presence of slightly less than two equivalents of sodium methoxide. When only one equivalent of sodium methoxide was used, primarily starting material was obtained. Slight deactivation of the sodium methoxide due to long storage might be a critical factor in the amount of material needed for a successful reaction. Because no absorption for O-H appeared in either the IR or NMR spectra (Tables V and VI) and a very definite doublet of doublets (1H) occurred in the NMR spectrum (δ 3.47-3.67, J_{HH} = 6 Hz, J_{HH} = 9 Hz), it would appear that little enolization occurred. This is somewhat surprising since, through enolization, the molecule would be completely conjugated.

Treatment of the α-keto ester 148 with > 95% hydrazine in absolute methanol yielded pyrazolone 101 (4,5-dihydro-6,7,8-trimethoxy-1H-benz[g]indazole) (34%). Because of the presence of tetralone 28 in the crude α-keto ester 143 used in the reaction, the hydrazone derivative 149 was formed. Characterization by IR, NMR and mass spectral analyses



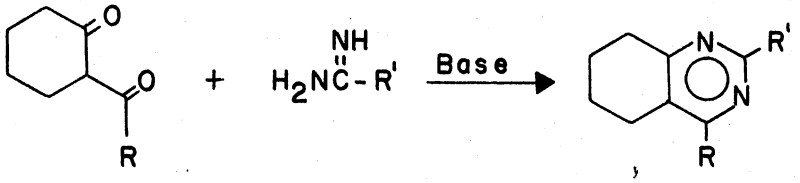
149

(Plates XI, XII and Table VIII) quickly identified 149 and the expected pyrazolone was then isolated from the original filtrate. An intense absorbance at 2.95-4.70 μ in the infrared spectrum (Table V) and a broad singlet at δ 9.00-11.20 in the NMR spectrum (Table VI) indicated that some enolization occurs, as might be anticipated since a longer conjugated system is available in tautomer 101a.[64]



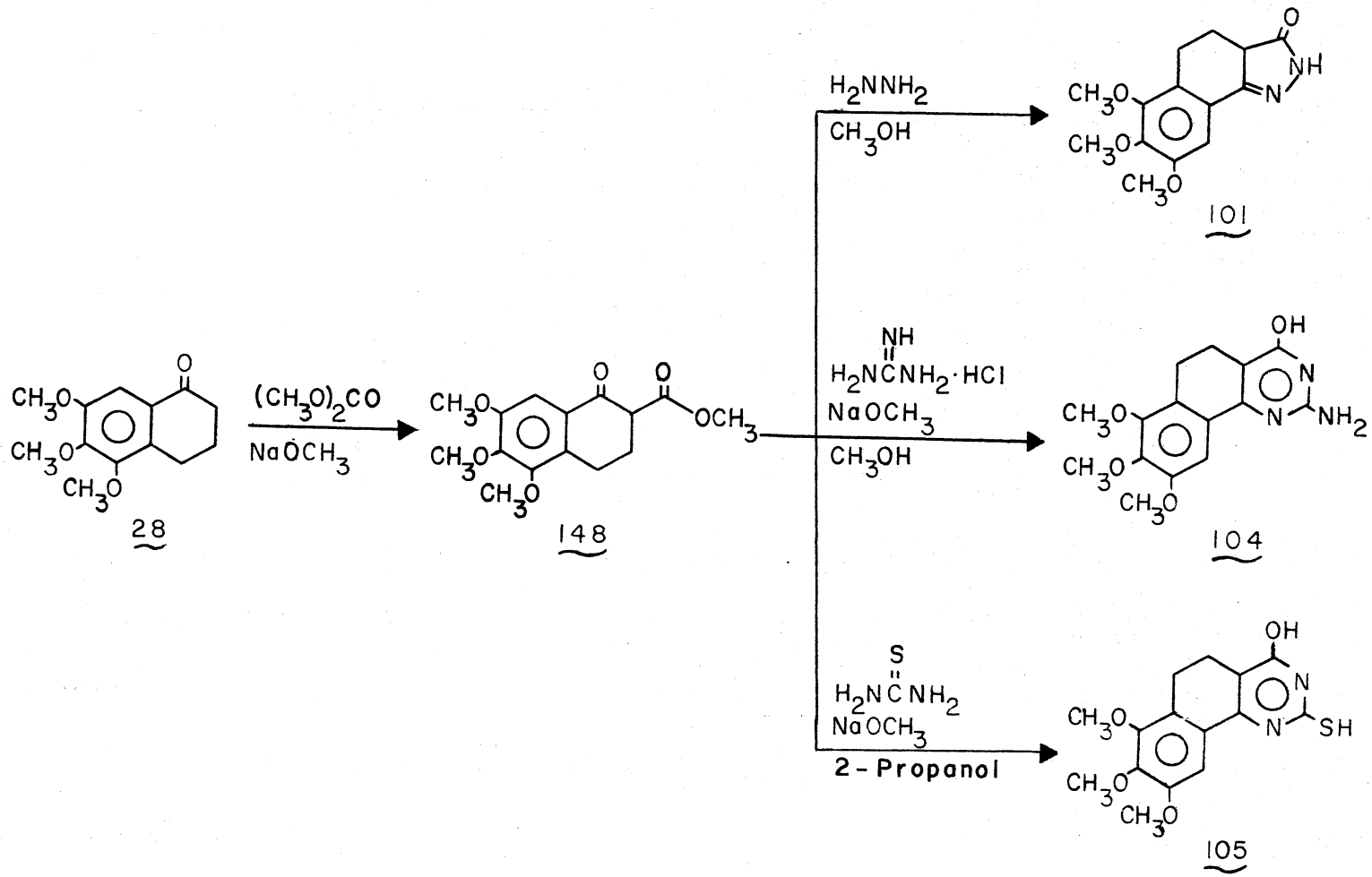
101 101a

Synthetic methods for 5,6,7,8-tetrahydroquinazolines have recently been discussed.[131] A widely employed method involves a base-catalyzed condensation of amidine or amidine analogs with β-dicarbonyl compounds.[9] Condensation of guanidine hydrochloride and methyl 1,2,3,4-tetrahydro-

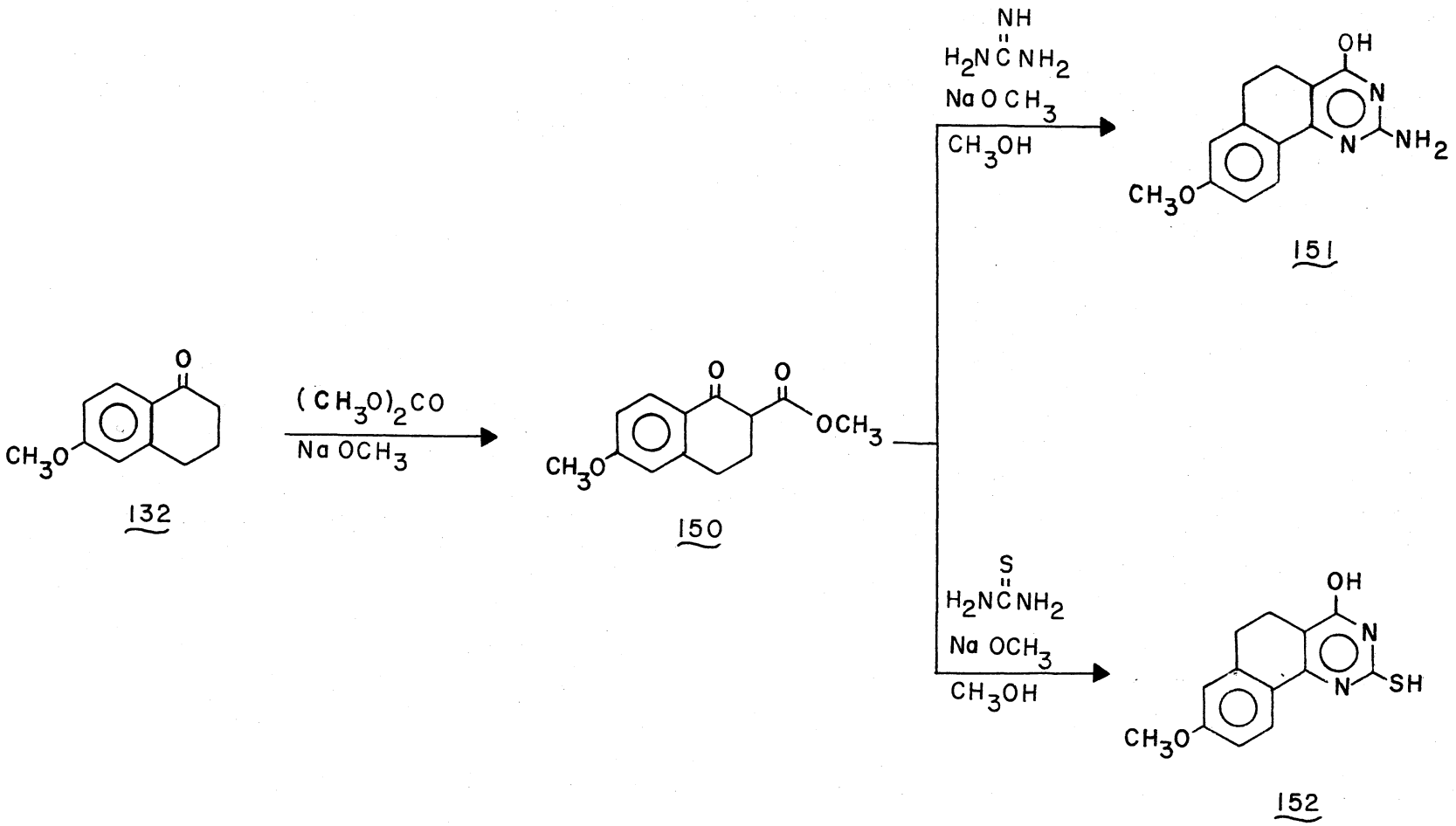


5,6,7-trimethoxy-1-oxo-2-naphthoate (148) in the presence of slight excess (more than two equivalents) of sodium methoxide produced 2-aminopyrimidine 104 after boiling (9 hr) in methanol (Scheme 17).

Application of the same reaction conditions to 148 in the presence of thiourea did not provide the thiol analog. However, by changing the solvent to a higher-boiling alcohol (2-propanol) and increasing the reaction time (24 hr.), 5,6-dihydro-2-mercapto-7,8,9-trimethoxybenzo-


CH3O
CH3O
CH3O
O
28
(CH3O)2CO
NaOCH3
148
OCH3
H2NNH2
CH3OH
101
NH
H2NCNH2·HCl
NaOCH3
CH3OH
OH
N
NH2
104
S
H2NCNH2
NaOCH3
2-Propanol
SH
105

Scheme 17


O
CH3O
132
(CH3O)2CO
NaOCH3
O
O
OCH3
CH3O
150
NH
H2NCNH2
NaOCH3
CH3OH
OH
N
N
NH2
CH3O
151
S
H2NCNH2
NaOCH3
CH3OH
OH
N
N
SH
CH3O
152

Scheme 18

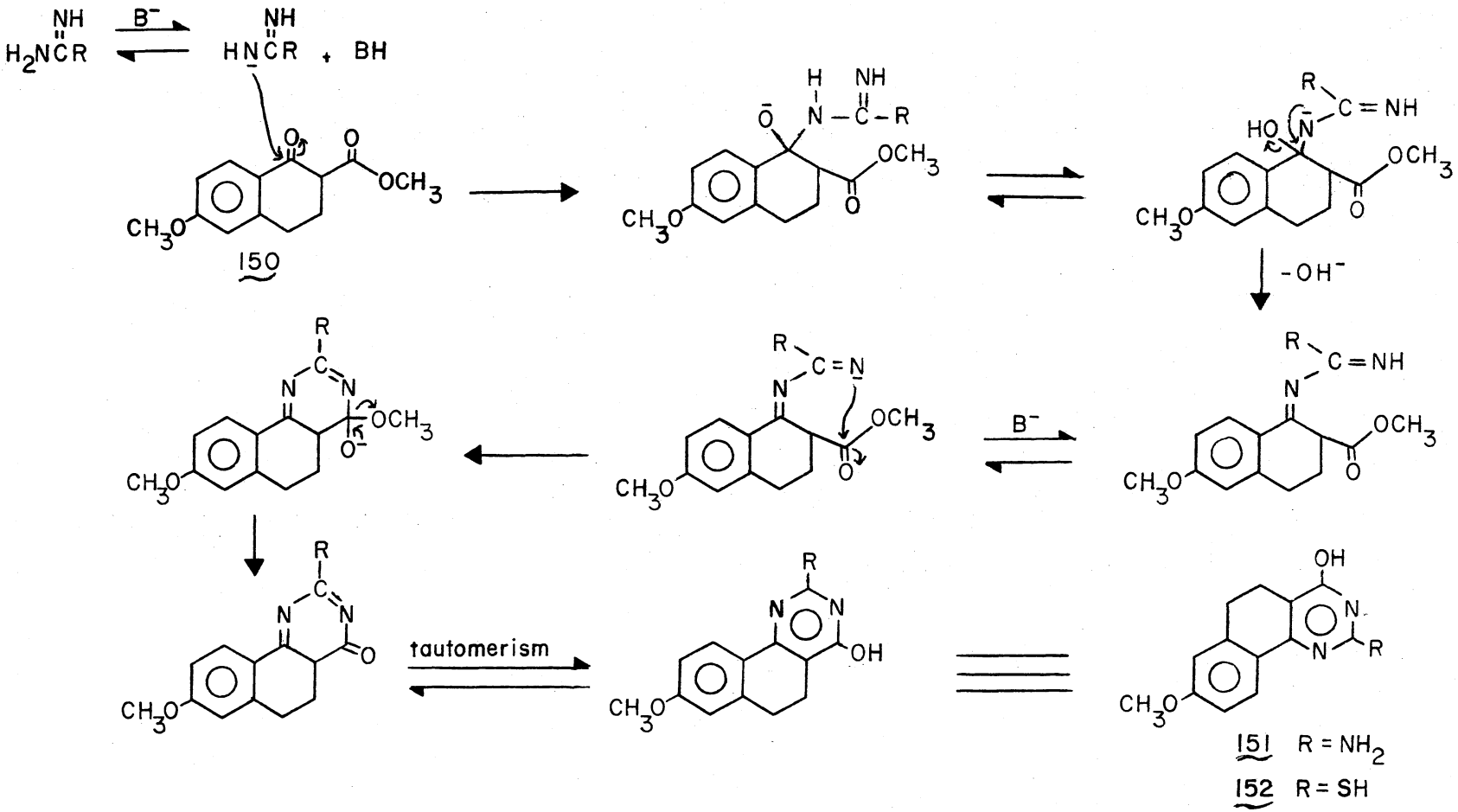
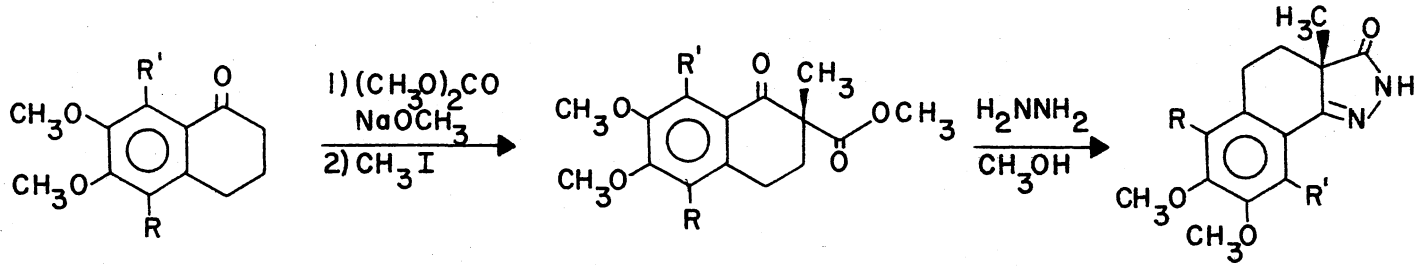


Figure 6. Proposed Mechanism for Base-Catalyzed Condensation of Amidines with α-Keto Ester 150



28 R = OCH_3, R' = H

125 R = H, R' = OCH_3

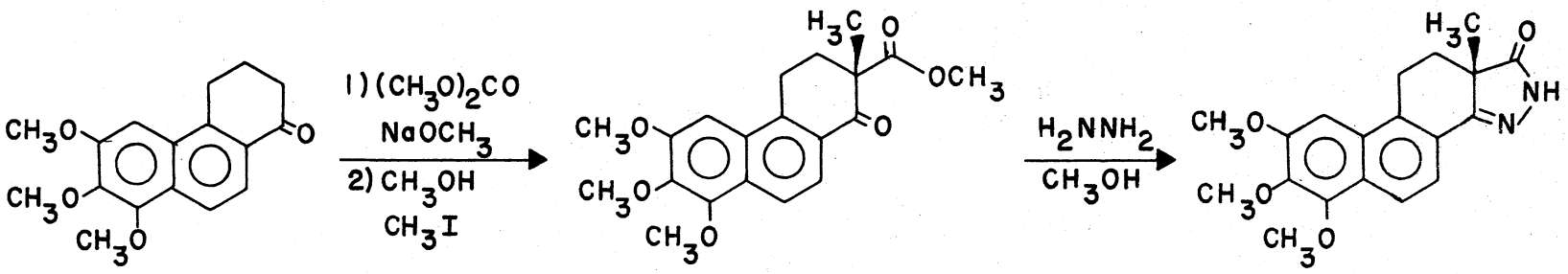
153 R = OCH_3, R' = H

154 R = H, R' = OCH_3

102 R = OCH_3, R' = H

103 R = H, R' = OCH_3

Scheme 19



131 155 108

Scheme 20

[h]quinazolin-4-ol (105) (11.2%) was isolated. As is typical of pyrimidine derivatives, neither 104 nor 105 was appreciably soluble in many organic solvents, e.g., ether, benzene, and chloroform. However, partial water solubility hindered product isolation. Only after very slow neutralization of the reaction mixture with acetic acid (while cooling in an ice/H_2O bath) could a solid product be obtained.

From methyl 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthoate (150) (prepared from tetralone 132 and dimethyl carbonate) the corresponding 2-aminopyridimine 151 and 2-thiopyrimidine 152 were prepared (Scheme 18). In both cases, methanol was used, and the reaction mixture was boiled (4 hr.). The difference in reactivity of the methyl ester 150 might be attributed to the slight inductive effect of the added methoxy groups in ester 148. A proposed mechanism is presented in Figure 6.

In one case the α-keto ester 148 was not isolated, but, in the presence of an additional equivalent of base, methyl iodide in methanol was added to form 153.[118] Likewise, 154 was prepared from the tetralone 125. Treatment of either 153 or 154 with > 95% hydrazine in methanol yielded the corresponding pyrazolones 102 and 103 (Scheme 19).

The pyrazolosteroid 108 was obtained in analogous steps (Scheme 20). The phenanthrone 131 was converted to the α-keto ester 155 via initial heating (15 min.) with dimethyl carbonate in the presence of four equivalents of sodium methoxide. Methanol was added and the reaction mixture cooled before methyl iodide was added. Heating (60°) 155 with hydrazine in anhydrous methanol produced the pyrazolone 108. It is interesting that the yield of the steroid pyrazolone 108 was so much lower (32.2%) than the yield of either 102 (84.5%) or 103 (90%). This might be partially due to a mass action effect (starting materials

for 102 being 10 times the molar quantities for 108), and perhaps to the solubility of the molecules (155 being less soluble in methanol than 153).

A listing of products, their melting points, and yields from 3,4-dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (28) is given in Table I. An analogous listing of data is given in Tables II and III for 3,4-dihydro-6,7,8-trimethoxy-1(2H)-phenanthrone (131) and 3,4-dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (125) respectively. Products and pertinent data for products from 6-methoxy-1-tetralone (132) are given in Table IV. As is typical in pyrimidines (104, 105, 151, and 152), all have very high melting points with decomposition.

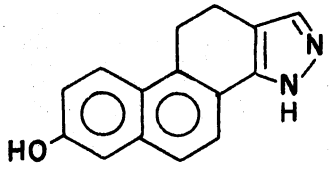
Characteristic IR peaks for each product are given in Table V. There is a distinct C-H (Ar-H) peak for each product at 3.40-3.45 μ. There is always a strong absorbance for the aromatic methoxy ($Ar-OCH_3$) groups somewhere between 8.84 and 9.20 μ. The monomethoxy compounds show a weaker absorbance in this region as would be expected.

The NMR chemical shifts and coupling constants of products are given in Table VI. A comparison of chemical shifts for the protons in the methoxy function(s) in 6-methoxy-1-tetralone (132), 6,7-dimethoxy-1-tetralone (133), 5,6,7-trimethoxy-1-tetralone (28), 6,7,8-trimethoxy-1-tetralone (125), and specific derivatives is shown in Table VII. At the moment, unequivocal proton assignments cannot be made in the NMR spectra of any of the trimethoxy products. It is worthy of note that there appears to be no general pattern in the chemical shifts of the hydrogen atoms in supposedly related methoxy groups. In fact, in the pyrazolone 102 the protons of all three methoxy groups appear as one singlet. Expanding the sweep width to 250 Hz rather than 1000 Hz still

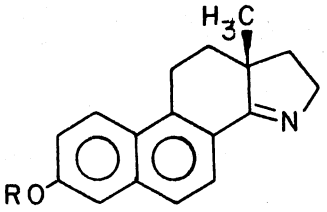
resulted in only one singlet. Other proton assignments were in agreement with the proposed structure.[64]

Mass spectral data for most compounds appear in Table VIII. All compounds analyzed exhibited a molecular ion corresponding to their respective molecular weights. Several compounds were characterized by peak matching selected m/e values. These results are given in Table IX.

Owing to the biological activity displayed by compounds 88a, 88b,[67] and 1a,[100] attempts were initiated to prepare similar compounds with

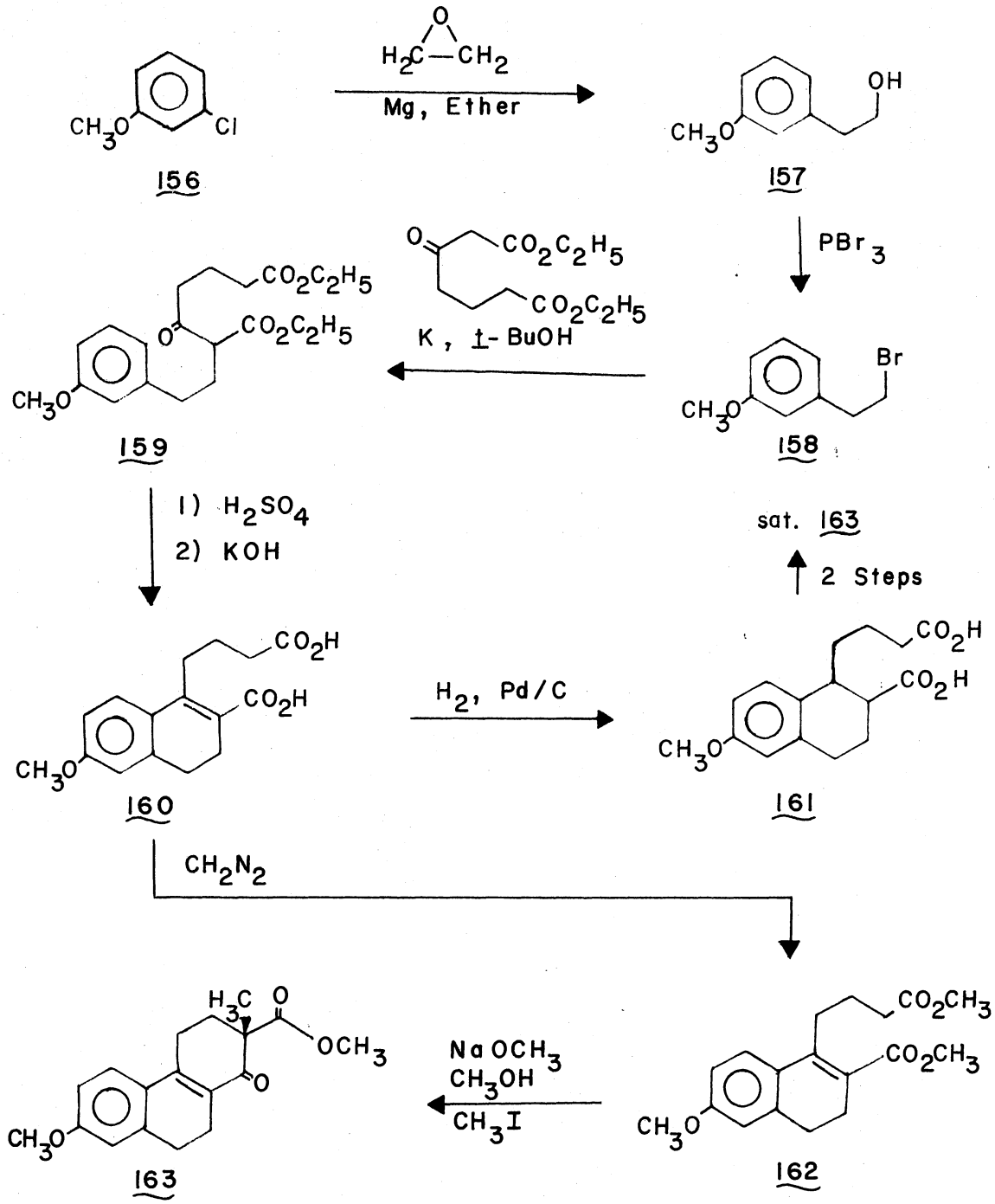


1a



88 a R = H
b R = CH_3

a saturated and partially saturated B ring. Several procedures have been recorded for making intermediate 163 from β-(6-methoxy-1-naphthyl)-ethyl bromide (158).[13,73,151,152] Scheme 21 was proposed to involve the fewest steps of highest efficiency for the preparation of 163.[73] Since m-methoxyphenethyl bromide (158) was not available commercially, it was synthesized. Employment of the entrainment method[106] for making Grignard reagents and condensation of the Grignard from m-chloroanisole (156) with ethylene oxide led to crude m-methoxyphenethyl alcohol (157). Purification processes (column chromatography or spinning band distillation) were unsuccessful in separating the alcohol 157 from 156. Slightly crude alcohol 157 was treated with PBr_3 via the method of Hooz and Gilani.[69] Gas-liquid chromatography indicated that the reaction was not complete. Attempts to distill the final product under


Mg, Ether
156
157
PBr3
158
K, t-BuOH
159
1) H2SO4
2) KOH
sat. 163
2 Steps
160
H2, Pd/C
161
CH2N2
162
NaOCH3
CH3OH
CH3I
163

Scheme 21

TABLE I

3,4-DIHYDRO-5,6,7-TRIMETHOXY-1(2H)-NAPHTHALENONE (28) AND DERIVATIVES

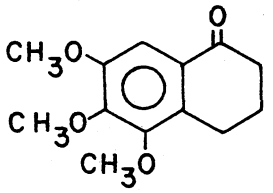
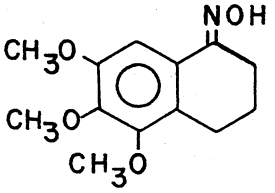
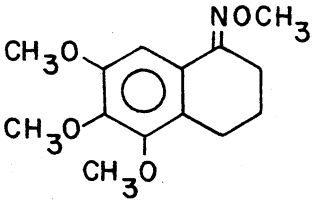
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone		28	74.5-76	
Oxime of 28		139	102-103	51
Methoxime of 28		140	55-56.5	35

TABLE I (Continued)

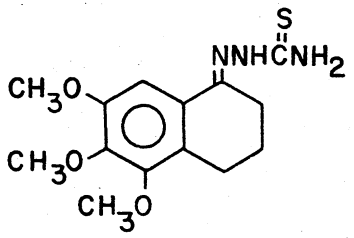
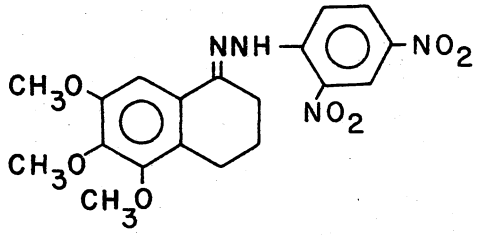
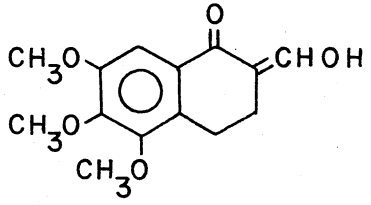
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
Thiosemicarbazone of 28		141	185-186 (dec.)	61
2,4-Dinitrophenylhydrazone of 28		136	244-245	66
3,4-Dihydro-2-(hydroxymethylene)-5,6,7-trimethoxy-1(2H)-naphthalenone		142	74-76	69

TABLE I (Continued)

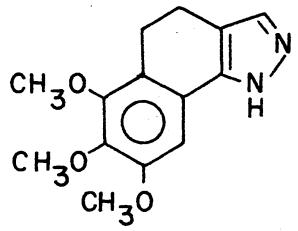
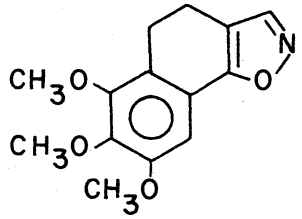
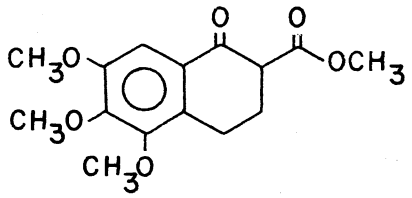
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole		97	94-95	68
4,5-Dihydro-6,7,8-trimethoxynaphth-[1,2-d]isoxazole		99	92-93	67
Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-oxo-2-naphthoate		148	71-74	65

TABLE I (Continued)

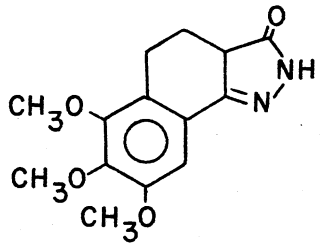
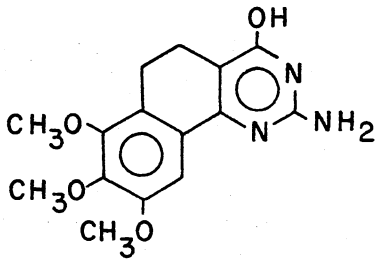
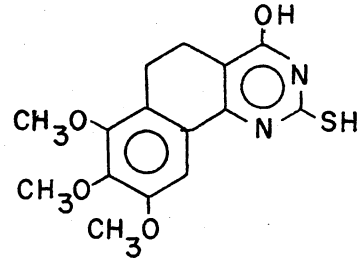
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole		101	235-237	34
5,6-Dihydro-2-amino-7,8,9-trimethoxybenzo[h]quinazolin-4-ol		104	255-257 (dec.)	26
5,6-Dihydro-2-mercapto-7,8,9-trimethoxybenzo[h]quinazolin-4-ol		105	206-207 (dec.)	11.2

TABLE I (Continued)

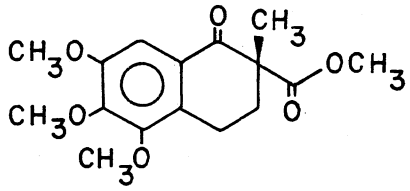
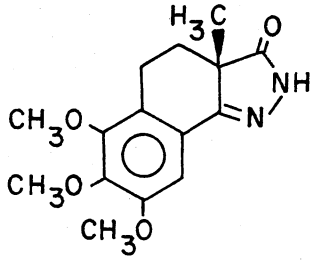
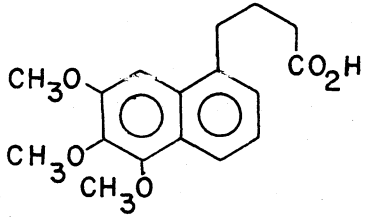
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methyl-1-oxo-2-naphthoate		153	166-168/ .3-.5 mm. (b.p.)	71.5
2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one		102	186-188	84.5
5,6,7-Trimethoxy-1-naphthalene-butyric Acid		130	127-128	36

TABLE II

3,4-DIHYDRO-6,7,8-TRIMETHOXY-1(2H)-PHENANTHRONE (131) AND DERIVATIVES

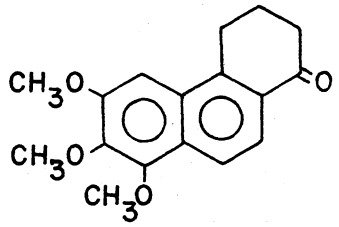
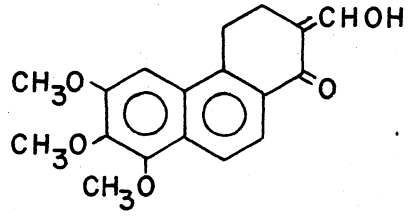
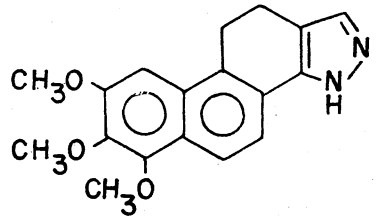
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
3,4-Dihydro-6,7,8-trimethoxy-1(2H)-phenanthrone		131	137-138	7.9
3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-phenanthrone		144	144.5-146.5	91
10,11-Dihydro-6,7,8-trimethoxy-3H-phenanthro[1,2-c] pyrazole		106	169-171	72

TABLE II (Continued)

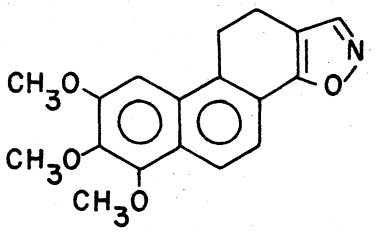
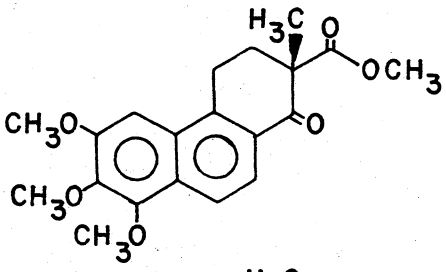
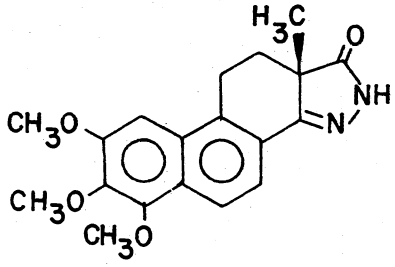
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
10,11-Dihydro-7,8,9-trimethoxy-phenanthro[1,2-d]isoxazole		107	142-143	86
Methyl 1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-phenanthrenecarboxylate		155	138-139	84.5
2,10,11,11a-Tetrahydro-6,7,8-trimethoxy-11a-methyl-1H-phenanthro[1,2-c]pyrazol-1-one		108	205-206	32.2

TABLE III

3,4-DIHYDRO-6,7,8-TRIMETHOXY-1(2H)-NAPHTHALENONE (125) AND DERIVATIVES

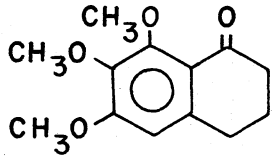
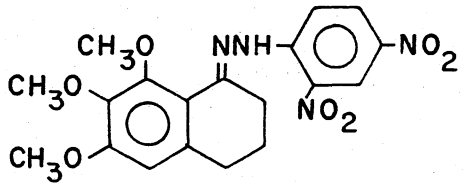
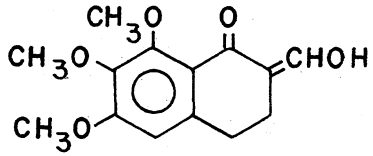
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone		125	118-121	
2,4-Dinitrophenylhydrazone of 125		137	204-205	31
3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-naphthalenone		143	69-71	38.5

TABLE III (Continued)

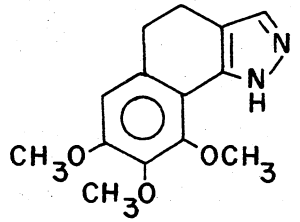
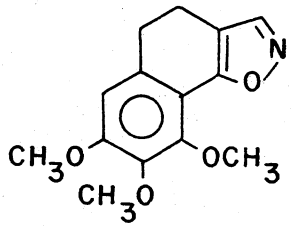
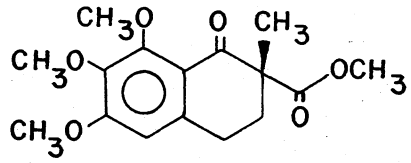
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole		98	159-161	26
4,5-Dihydro-7,8,9-trimethoxy-naphth[1,2-d]isoxazole		100	128-130	55
Methyl 1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-naphthoate		154	82-84	48

TABLE III (Continued)

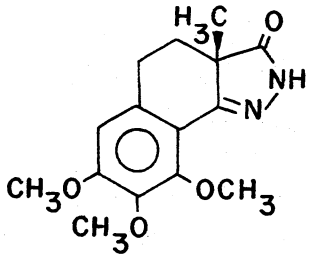
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
2,3a,4,5-Tetrahydro-7,8,9-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one		103	224.5-225	90

TABLE IV

PYRIMIDINES FROM 3,4-DIHYDRO-6-METHOXY-1(2H)-NAPHTHALENONE (132) AND ESTER INTERMEDIATE

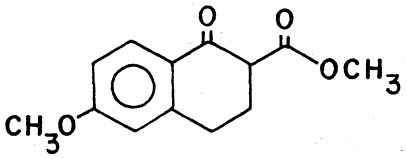
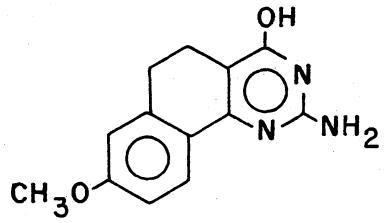
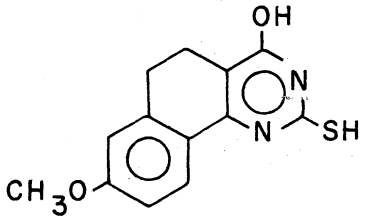
Compound Name	Structure	Cpd.	m.p., °C	Yield, %
Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthoate		150	77-79	76
5,6-Dihydro-2-amino-8-methoxy-benzo[h]quinazolin-4-ol		151	325-327 (dec.)	27
5,6-Dihydro-2-mercapto-8-methoxy-benzo[h]quinazolin-4-ol		152	290-294 (dec.)	12

TABLE V

INFRARED SPECTRA OF PRODUCTS[a]

Cpd.	ArC-H	Characteristic Bands	$Ar-OCH_3$	Miscellaneous Bands
28	3.42 (s)	keto C=O, 6.00 (vs)	9.08 (s)	6.31 (s), 6.88 (vs), 7.52 (vs), 9.90 (s), 12.38 (m)
139	3.43 (vs)	N-OH, 3.10-3.25 (m)	9.00 (vs)	6.80 (s), 7.38 (vs), 9.72 (s), 12.50 (m)
140	3.45 (s)	$N-OCH_3$, 2.90-3.10 (w)	9.00 (vs)	6.88 (w), 9.55 (vs), 9.80 (s), 12.50 (w)
141	3.43 (w)	N-C(N)=S, 6.85 (vs)	9.01 (vs)	3.00 (m), 3.12 (m), 3.22 (m), 8.00 (s), 11.80 (s)
136	3.45 (w)	NH, 3.10 (w) $Ar-NO_2$, 6.22 (vs)	9.00 (s)	7.51 (vs), 8.03 (m), 9.84 (vs), 11.96 (m)
142	3.41 (s)	OH, 2.75-3.10 (m) keto C=O, 6.08 (vs)	9.15 (vs)	7.40 (w), 7.53 (w), 8.83 (vs), 11.43 (s)
97	3.45 (vs)	N-H, 3.25 (s)	9.10 (vs)	6.80 (s), 7.12 (s), 9.65 (s), 12.68 (w)
99	3.42 (w)	C=N, 6.45 (w)	9.12 (vs)	6.90 (vs), 7.14 (vs), 8.01 (s), 11.69 (s), 12.59 (w), 12.80 (w)

TABLE V (Continued)

Cpd.	ArC-H	Characteristic Bands	$Ar-OCH_3$	Miscellaneous Bands
148	3.43 (vs)	ester C=O, 5.78 (vs) keto C=O, 5.99 (vs)	9.01 (vs)	6.30 (vs), 7.41 (vs), 8.01 (s), 9.78 (s), 11.70 (m)
101	3.43 (s)	OH, NH, 2.95-4.70 (vs)	8.98 (vs)	6.28 (s), 7.61 (s), 9.63 (s), 13.10 (w)
104	3.41 (s)	NH, 2.85-3.15 (m) OH, 3.35-3.70 (m) C=N, 6.00-6.25 (vs)	8.97 (s)	7.11 (s), 8.03 (w), 10.05 (w), 13.00 (s)
105	3.43 (s)	OH, SH, 3.10-3.60 (w) C=N, 6.00-6.25 (vs)	8.97 (vs)	6.45 (vs), 8.38 (vs), 10.15 (m), 12.04 (s)
153	3.43 (s)	ester C=O, 5.79 (vs) keto C=O, 5.96 (vs)	8.95 (vs)	6.85 (s), 7.41 (s), 8.01 (s), 9.28 (w), 11.60 (w)
102	3.45 (s)	OH, NH, 3.05-3.65 (s) C=O, 5.94 (vs)	8.95 (s)	6.85 (s), 7.81 (s), 9.60 (w), 11.96 (w), 13.98 (w)
130	3.43 (s)	OH, 3.10-4.00 (w) acid C=O, 5.83 (vs)	8.97 (vs)	7.60 (s), 7.82 (s), 12.17 (s)
131	3.44 (w)	keto C=O, 5.98 (vs)	9.06 (vs)	6.79 (vs), 8.00 (vs), 9.68 (s), 11.96 (s)

TABLE V (Continued)

Cpd.	ArC-H	Characteristic Bands	$Ar-OCH_3$	Miscellaneous Bands
144	3.43 (s)	OH, 2.80-3.10 (w) keto C=O, 6.10 (vs)	8.93 (vs)	6.75 (vs), 8.18 (vs), 9.60 (s), 12.05 (s), 12.40 (s)
106	3.44 (s)	NH, 3.04 (s)	8.99 (vs)	7.10 (w), 7.93 (m), 9.68 (w), 12.18 (s), 12.45 (s)
107	3.42 (w)	C=N, 6.25 (s)	8.96 (vs)	6.72 (vs), 7.92 (vs), 9.60 (w), 12.08 (s)
155	3.45 (s)	ester C=O, 5.80 (vs) keto C=O, 5.95 (vs)	8.93 (vs)	6.78 (s), 7.95 (s), 9.65 (w), 12.07 (w)
108	3.43 (w)	NH, 3.18 (w) keto C=O, 5.90 (vs)	8.94 (vs)	7.11 (s), 9.55 (s), 12.55 (w)
125	3.44 (s)	keto C=O, 6.01 (vs)	9.06 (s)	6.30 (vs), 7.99 (s), 11.85 (s), 12.45 (w)
137	3.43 (w)	NH, 2.80-3.10 (w) $Ar-NO_2$, 6.20 (vs)	9.02 (vs)	6.30 (vs), 7.48 (s), 9.90 (w), 13.50 (w)
143	3.40 (s)	OH, 2.80-3.10 (w) keto C=O, 6.07 (vs)	9.15 (s)	6.28 (vs), 7.55 (s), 10.10 (s), 12.35 (s)
98	3.41 (vs)	NH, 3.09 (vs)	9.18 (vs)	6.75 (vs), 7.80 (s), 8.74 (s), 11.74 (s), 12.40 (s)

TABLE V (Continued)

Cpd.	ArC-H	Characteristic Bands	Ar-OCH_3	Miscellaneous Bands
100	3.44 (w)	C=N, 6.30 (w)	9.20 (vs)	6.80 (s), 6.92 (s), 7.60 (w), 9.99 (s), 12.40 (w)
154	3.43 (s)	ester C=O, 5.79 (vs) keto C=O, 5.98 (vs)	8.84 (vs)	6.30 (vs), 7.85 (s), 8.00 (s), 10.10 (w)
103	3.44 (s)	NH, 2.80-3.70 (s) C=O, 5.80 (vs)	8.86 (vs)	6.32 (s), 9.20 (s), 12.04 (w), 13.64 (w)
150	3.42 (w)	ester C=O, 5.78 (vs) keto C=O, 6.01 (vs)	9.01 (w)	6.97 (s), 8.22 (vs), 8.69 (s), 11.86 (s)
151	3.50 (s)	NH_2, 3.15 (s) OH, 3.60-3.90 (s) C=N, 6.10-6.50 (vs)	9.01 (w)	7.25 (s), 7.98 (s), 12.78 (w), 13.18 (w)
152	3.45 (w)	OH, 2.85-3.05 (w) SH, 3.90 (w) C=N, 6.05-6.20 (s)	9.00 (w)	6.50 (s), 8.28 (w), 12.20 (s)

[a]Values given in wavelength (microns). The intensity of each peak is indicated as follows: (s) - strong, (vs) - very strong, (m)-medium, (w) - weak, (vw) - very weak. The spectra were all taken on KBr pellets, except 130, which was taken as a film.

TABLE VI

NMR CHEMICAL SHIFTS AND COUPLING CONSTANTS OF PRODUCTS

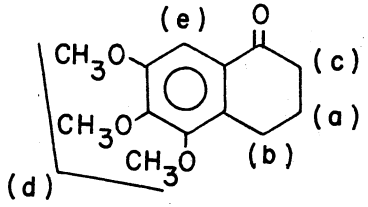
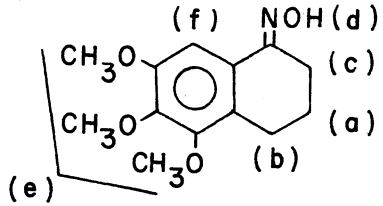
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	28	II	$DCCl_3$	1.92-2.24 (p)	2	CH_2 (a)
				J_{HH} = 6.2 c.p.s.		
				2.50-2.68 (t)	2	CH_2 (b)
				J_{HH} = 6.2 c.p.s.		
				2.80-2.98 (t)	2	CH_2 (c)
				J_{HH} = 6.2 c.p.s.		
				3.89, 3.87, 3.95 (3s)	9	OCH_3 (d)
				7.39 (s)	1	Ar-H (e)
	139	IV	$DCCl_3$	1.92-2.26 (p)	2	CH_2 (a)
				J_{HH} = 6.2 c.p.s.		
				2.86-3.06 (t)	2	CH_2 (b)
				J_{HH} = 6.2 c.p.s.		

TABLE VI (Continued)

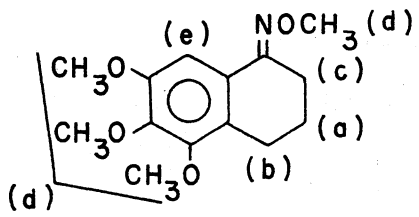
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	139			3.12-3.32 (t)	2	CH_2 (c)
				J_{HH} = 6.2 c.p.s.		
				3.40-3.80 (s)	1	OH (d)
				4.00, 4.14 (2s)	9	OCH_3 (e)
				7.36 (s)	1	Ar-H (f)
	140	VI	$DCCl_3$	1.96-2.30 (p)	2	CH_2 (a)
				J_{HH} = 6 c.p.s.		
				2.92-3.10 (t)	2	CH_2 (b)
				J_{HH} = 6 c.p.s.		
				3.17-3.36 (t)	2	CH_2 (c)
				J_{HH} = 6 c.p.s.		

TABLE VI (Continued)

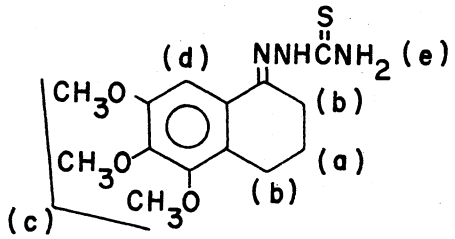
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	140			3.98, 4.01	12	OCH_3 (d)
				4.19, 4.27 (4s)		
				7.35 (s)	1	Ar-H (e)
	141	VIII	CF_3CO_2H	1.96-2.24 (m)	2	CH_2 (a)
				2.72-3.02 (m)	4	CH_2 (b)
				3.98, 4.00, 4.11 (3s)	9	OCH_3 (c)
				7.62 (s)	1	Ar-H (d)
				11.28 (s) under CF_3CO_2H		NH (e)

TABLE VI (Continued)

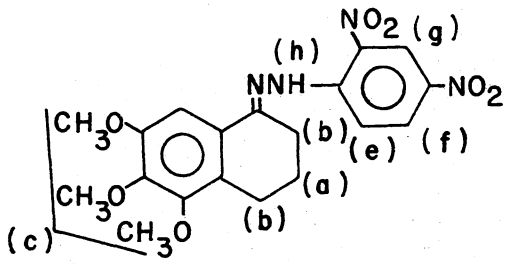
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	136	X	$DCCl_3$	1.88-2.18 (m)	2	CH_2 (a)
				2.62-2.92 (m)	4	CH_2 (b)
				3.88, 3.94, 3.97 (3s)	9	OCH_3 (c)
				7.54 (s)	1	Ar-H (d)
				7.98-8.15 (d)	1	Ar-H (e)
				J ortho = 10 c.p.s.		
				8.28-8.48 (d of d)	1	Ar-H (f)
				J ortho = 10 c.p.s.		
				J meta = 3 c.p.s.		
				9.10-9.17 (d)	1	Ar-H (g)
				J meta = 2 c.p.s.		
				11.30-11.42 (s)	1	NH (h)

TABLE VI (Continued)

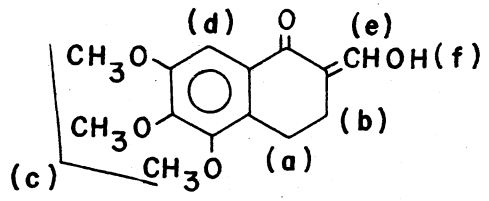
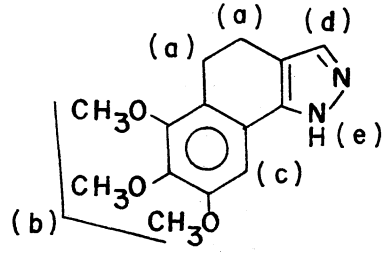
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	142	XIV	$DCCl_3$	2.32-3.54 (m)	2	CH_2 (a)
				2.66-2.89 (m)	2	CH_2 (b)
				3.85, 3.90, 3.95 (3s)	9	OCH_3 (c)
				6.54 (s)	1	Ar-H (d)
				8.00-8.20 (s)	1	CH (e)
				14.3-14.7 (s)	1	OH (f)
	97	XVI	$DCCl_3$	2.60-3.02 (m)	4	CH_2CH_2 (a)
				3.74, 3.86, 3.88 (3s)	9	OCH_3 (b)
				7.17 (s)	1	Ar-H (c)
				7.33 (s)	1	CH (d)
				7.40-7.76 (6s)	1	NH (e)

TABLE VI (Continued)

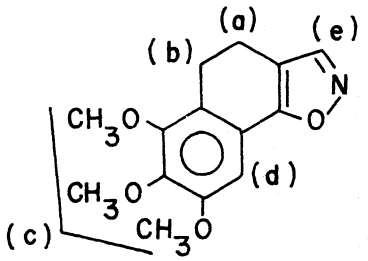
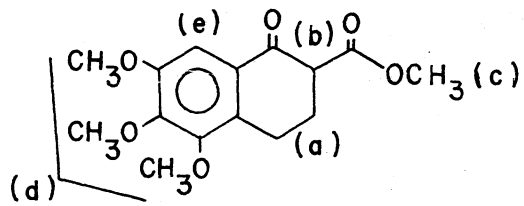
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	99	XVIII	$DCCl_3$	2.58-2.83 (m)	2	CH_2 (a)
				2.86-3.10 (m)	2	CH_2 (b)
				3.86 (s)	3	OCH_3 (c)
				3.90 (s)	6	
				7.05 (s)	1	Ar-H (d)
				8.11 (s)	1	CH (e)
	148	XX	$DCCl_3$	2.14-3.08 (m)	3	CH_2CH_2 (a)
				3.47-3.67 (d of d)	1	CH (b)
				J_{HH} = 6 c.p.s.		
				J_{HH} = 9 c.p.s.		
				3.77 (s)	3	OCH_3 (c)
				3.87, 3.89, 3.94 (3s)	9	OCH_3 (d)

TABLE VI (Continued)

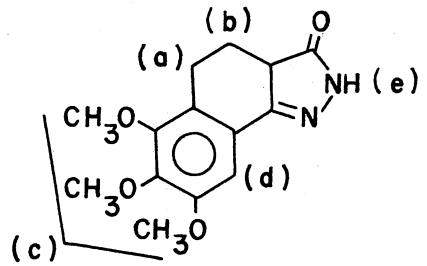
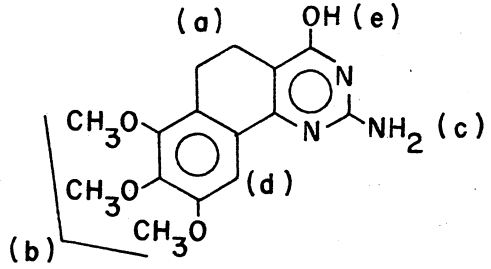
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	148			7.38 (s)	1	Ar-H (e)
	101	XXII	$DCCl_3$	2.38-2.58 (m)	2	CH_2 (a)
				2.66-2.90 (m)	2	CH_2 (b)
				3.75 (s)	6	OCH_3 (c)
				3.81 (s)	3	
				7.10 (s)	1	Ar-H (d)
				9.00-11.20 (bs)	1	NH, OH (e)
	104	XXIV	DMSO-d_6	2.38-2.82 (m)	2	CH_2CH_2 (a)
				3.75, 3.79, 4.03 (3s)	9	OCH_3 (b)
				6.25-6.48 (s)	2	NH_2 (c)
				7.49 (s)	1	Ar-H (d)

TABLE VI (Continued)

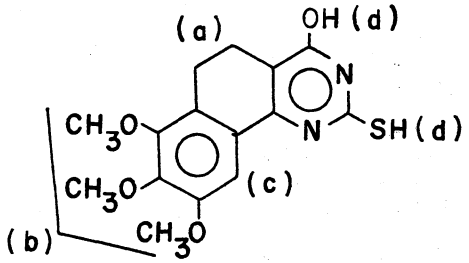
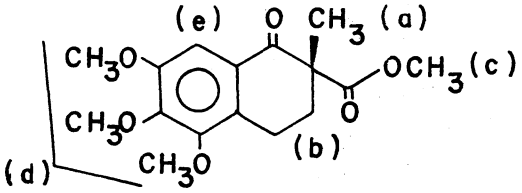
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	104	XXVI		10.60-10.94	1	OH (e)
	105		DMSO-d_6	2.32-2.84 (m)	2	CH_2CH_2 (a)
				3.76, 3.82, 3.91 (3s)	9	OCH_3 (b)
				7.53 (s)	1	Ar-H (c)
				12.10-12.52 (d)	2	SH, OH (d)
	153	XXVIII	$DCCl_3$	1.46 (s)	3	CH_3 (a)
				1.80-3.10 (m)	4	CH_2CH_2 (b)
				3.66 (s)	3	OCH_3 (c)
				3.85 (s)	3	OCH_3 (d)
				3.89 (s)	6	
				6.45 (s)	1	Ar-H (e)

TABLE VI (Continued)

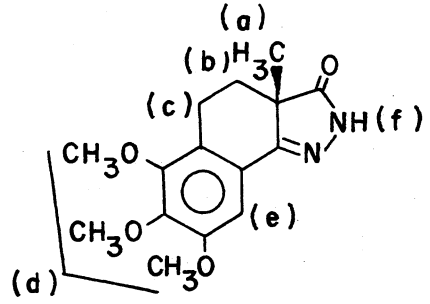
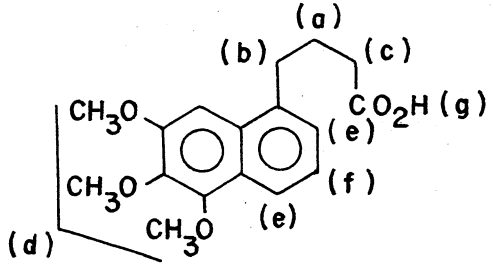
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	102	XXX	$DCCl_3$	1.34 (s)	3	CH_3 (a)
				1.58-2.34 (m)	2	CH_2 (b)
				2.80-3.04 (m)	2	CH_2 (c)
				3.90 (s)	9	OCH_3 (d)
				7.11 (s)	1	Ar-H (e)
				9.26 (s)	1	NH (f)
	130	XXXII	$DCCl_3$	1.88-2.25 (p)	2	CH_2 (a)
				J_{HH} = 6.5 c.p.s.		
				2.39-2.60 (t)	2	CH_2 (b)
				J_{HH} = 6.5 c.p.s.		
				2.94-3.16 (t)	2	CH_2 (c)
				J_{HH} = 6.5 c.p.s.		

TABLE VI (Continued)

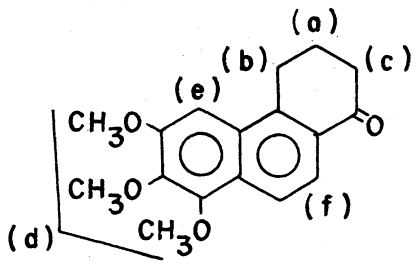
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	130			3.97 (s)	6	OCH_3 (d)
				4.02 (s)	3	
				7.14-7.38 (m)	3	Ar-H (e)
				7.84-8.05 (m)	1	Ar-H (f)
				8.30-9.30 (bs)	1	OH (g)
	131	XXXIV	$DCCl_3$	2.10-2.40 (p)	2	CH_2 (a)
				J_{HH} = 6 c.p.s.		
				2.60-2.79 (t)	2	CH_2 (b)
				J_{HH} = 6 c.p.s.		
				3.17-3.35 (t)	2	CH_2 (c)
				J_{HH} = 6 c.p.s.		

TABLE VI (Continued)

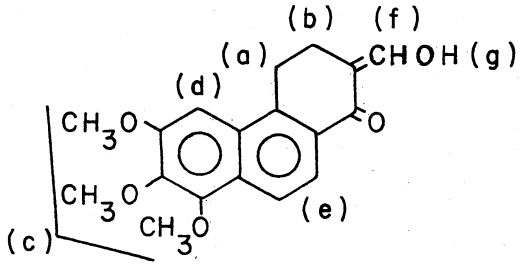
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	131			3.99 (s)	6	OCH_3 (d)
				4.01 (s)	3	
				7.14	1	Ar-H (e)
				7.98	2	Ar-H (f)
	144	XXXVI	$DCCl_3$	2.58-2.79 (t)	2	CH_2 (a)
				J_{HH} = 8 c.p.s.		
				3.14-3.34 (t)	2	CH_2 (b)
				J_{HH} = 8 c.p.s.		
				4.01 (s)	6	OCH_3 (c)
				4.04 (s)	3	
				7.16 (s)	1	Ar-H (d)
				7.88-8.01 (m)	2	Ar-H (e)

TABLE VI (Continued)

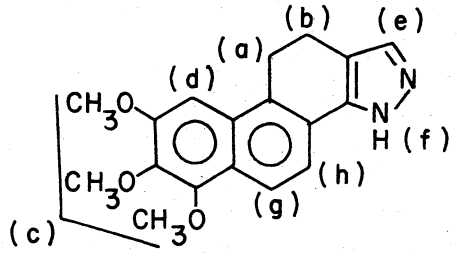
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	144			7.88-8.00 (s)	1	CH (f)
				14.38-14.70 (bs)	1	OH (g)
	106	XXXVIII	$DCCl_3$	2.82-3.04 (t)	2	CH_2 (a)
				J_{HH} = 7 c.p.s.		
				3.18-3.40 (t)	2	CH_2 (b)
				J_{HH} = 7 c.p.s.		
				3.98, 4.00, 4.03 (3s)	9	OCH_3 (c)
				7.16 (s)	1	Ar-H (d)
				7.43 (s)	1	CH (e)
				7.47 (s)	1	NH (f)
				7.81-7.95 (d)	1	Ar-H (g)
				J ortho = 9 c.p.s.		

TABLE VI (Continued)

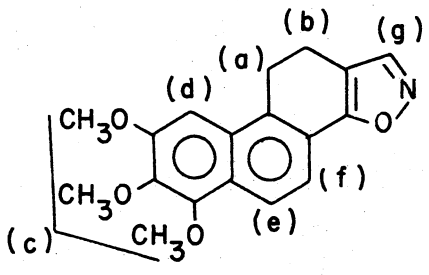
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	106			7.95-8.09 (d)	1	Ar-H (h)
				J ortho = 9 c.p.s.		
	107	XL	$DCCl_3$	2.82-3.06 (t)	2	CH_2 (a)
				J_{HH} = 8 c.p.s.		
				3.25-3.55 (t)	2	CH_2 (b)
				J_{HH} = 8 c.p.s.		
				3.89, 4.00, 4.03 (3s)	9	OCH_3 (c)
				7.11 (s)	1	Ar-H (d)
				7.69-7.80 (d)	1	Ar-H (e)
				J ortho = 9 c.p.s.		
				8.00-8.14 (d)	1	Ar-H (f)
				J ortho = 9 c.p.s.		

TABLE VI (Continued)

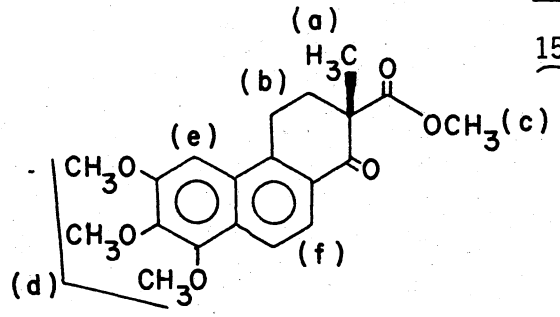
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	107			8.17 (s)	1	CH (g)
	155	XLII	$DCCl_3$	1.55 (s)	3	CH_3 (a)
				1.98-3.40 (m)	4	CH_2CH_2 (b)
				3.63 (s)	3	OCH_3 (c)
				4.00 (s)	6	OCH_3 (d)
				4.03 (s)	3	
				7.11 (s)	1	Ar-H (e)
				8.00 (s)	2	Ar-H (f)

TABLE VI (Continued)

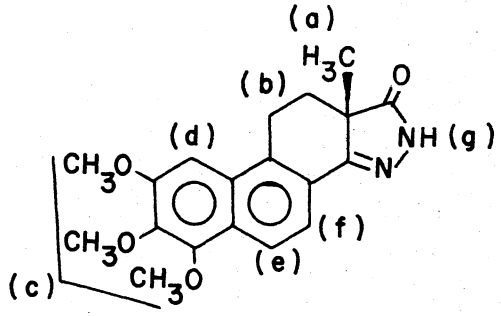
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	108	XLIV	$DCCl_3$	1.38 (s)	3	CH_3 (a)
				1.66-3.42 (m)	4	CH_2CH_2 (b)
				4.01 (s)	6	OCH_3 (c)
				4.05 (s)	3	
				7.06 (s)	1	Ar-H (d)
				7.68-7.84 (d)	1	Ar-H (e)
				J ortho = 9 c.p.s.		
				7.97-8.14 (d)	1	Ar-H (f)
				J ortho = 9 c.p.s.		
				8.84-8.99 (bs)	1	NH (g)

TABLE VI (Continued)

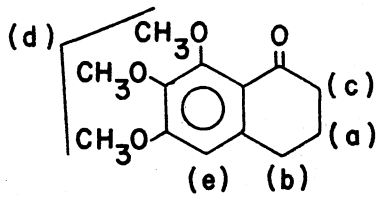
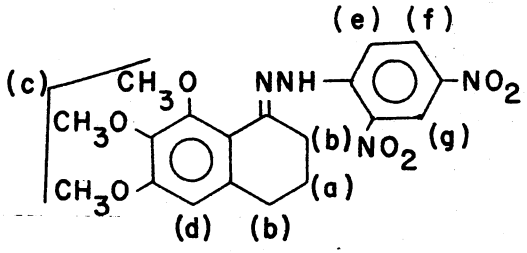
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	125	XLVI	$DCCl_3$	1.84-2.20 (p)	2	CH_2 (a)
				J_{HH} = 6 c.p.s.		
				2.49-2.68 (t)	2	CH_2 (b)
				J_{HH} = 6 c.p.s.		
				2.78-2.97 (t)	2	CH_2 (c)
				J_{HH} = 6 c.p.s.		
				3.85, 3.90 (2s)	9	OCH_3 (d)
				6.52 (s)	1	Ar-H (e)
	137	XLVIII	$DCCl_3$	I.83-2.13 (m)	2	CH_2 (a)
				2.62-2.90 (m)	4	CH_2 (b)
				3.93-3.99 (2s)	9	OCH_3 (c)
				6.55 (s)	1	Ar-H (d)

TABLE VI (Continued)

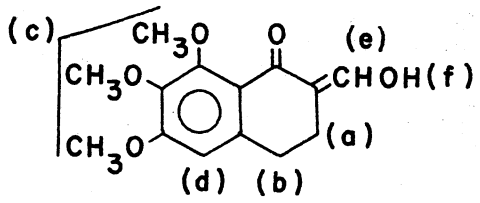
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	137			8.07-8.23 (d) J ortho = 9 c.p.s.	1	Ar-H (e)
				8.27-8.44 (d of d) J ortho = 9 c.p.s. J meta = 3 c.p.s.	1	Ar-H (f)
				9.12-9.19 (d) J meta = 3 c.p.s.	1	Ar-H (g)
				11.35 (s)	1	NH (h)
	143	L	$DCCl_3$	2.33-2.55 (m)	2	CH_2 (a)
				2.67-2.90 (m)	2	CH_2 (b)
				3.87, 3.91, 3.96 (3s)	9	OCH_3 (c)
				6.54 (s)	1	Ar-H (d)

TABLE VI (Continued)

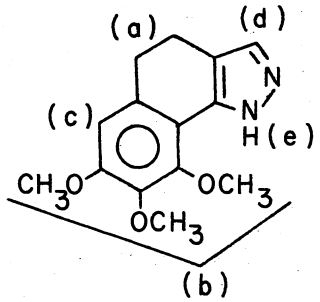
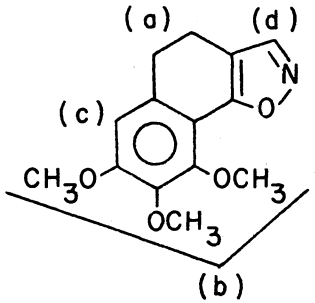
Structure	Cpd.	Plate	Solvent	(values) (p.p.m.)[a]	Integr.	Assignments
	143			8.02-8.19 (d)	1	CH (e)
				14.3-14.7 (bs)	1	OH (f)
	98	LII	$DCCl_3$	2.60-2.98 (m)	4	CH_2CH_2 (a)
				3.86, 4.01 (2s)	9	OCH_3 (b)
				6.60 (s)	1	Ar-H (c)
				7.41 (s)	1	CH (d)
				8.78-9.02 (bs)	1	NH (e)
	100	LIV	$DCCl_3$	2.59-3.06 (m)	4	CH_2CH_2 (a)
				3.89, 4.00 (2s)	9	OCH_3 (b)
				6.63 (s)	1	Ar-H (c)
				8.11 (s)	1	CH (d)

TABLE VI (Continued)

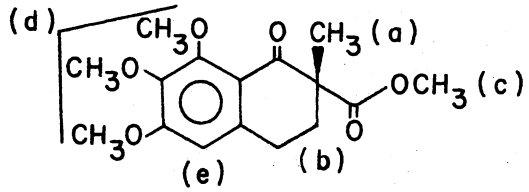
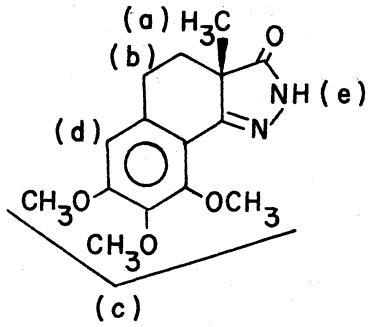
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	154	LVI	$DCCl_3$	1.47 (s)	3	CH_3 (a)
				1.80-3.10 (m)	4	CH_2CH_2 (b)
				3.67 (s)	3	OCH_3 (c)
				3.83, 3.88, 3.89 (3s)	9	OCH_3 (d)
				6.45 (s)	1	Ar-H (e)
	103	LVIII	$DCCl_3$	1.31 (s)	3	CH_3 (a)
				1.62-3.22 (m)	4	CH_2CH_2 (b)
				3.88, 3.94 (2s)	9	OCH_3 (c)
				6.52 (s)	1	Ar-H (d)
				8.85 (s)	1	NH (e)

TABLE VI (Continued)

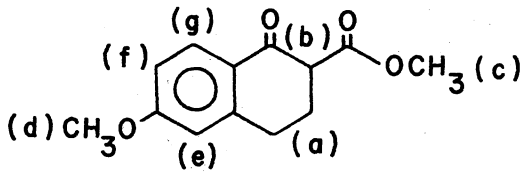
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	150	LX	$DCCl_3$	2.24-3.10 (m)	4	CH_2CH_2 (a)
				3.48-3.68 (d of d) J_{HH} = 9 c.p.s. J_{HH} = 6 c.p.s.	1	CH (b)
				3.78 (s)	3	OCH_3 (c)
				3.86 (s)	3	OCH_3 (d)
				6.66-6.74 (d) J meta = 3 c.p.s.	1	Ar-H (e)
				6.76-6.92 (d of d) J ortho = 9 c.p.s. J meta = 3 c.p.s.	1	Ar-H (f)
				7.96-8.10 (d) J ortho = 9 c.p.s.	1	Ar-H (g)

TABLE VI (Continued)

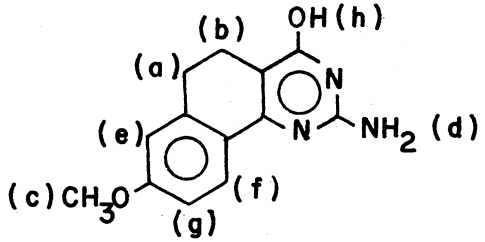
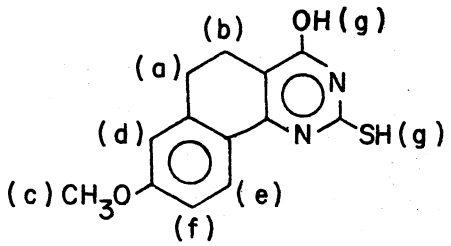
Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	151	LXII	DMSO-d_6	2.38-2.63 (m)	2	CH_2 (a)
				2.65-2.88 (m)	2	CH_2 (b)
				3.98 (s)	3	OCH_3 (c)
				6.29 (s)	2	NH_2 (d)
				6.81 (s)	1	Ar-H (e)
				6.80-6.94 (m)	1	Ar-H (f)
				7.85-8.00 (d of d)	1	Ar-H (g)
				J ortho = 9 c.p.s.		
				J meta = 3 c.p.s.		
				10.68 (s)	1	OH (h)

TABLE VI (Continued)

Structure	Cpd.	Plate	Solvent	δ (values) (p.p.m.)[a]	Integr.	Assignments
	152	LXIV	DMSO-d_6	2.32-2.59 (t)	2	CH_2 (a)
				J_{HH} = 8 c.p.s.		
				2.64-2.90 (t)	2	CH_2 (b)
				J_{HH} = 8 c.p.s.		
				4.00 (s)	3	OCH_3 (c)
				6.91 (s)	1	Ar-H (d)
				6.79-6.96 (d)	1	Ar-H (e)
				J ortho = 10 c.p.s.		
				7.90-8.06 (d)	1	Ar-H (f)
				J ortho = 10 c.p.s.		
				11.98-12.40 (bs)	2	OH, SH (g)

[a]The multiplicity of each peak is indicated as follows: singlet, s; broad singlet, bs; doublet, d; triplet, t; pentet, p; multiplet, m.

TABLE VII

COMPARISON OF NMR CHEMICAL SHIFTS FOR PROTONS OF SPECIFIC METHOXY COMPOUNDS[a]

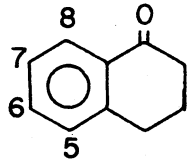
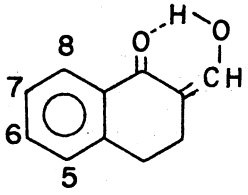
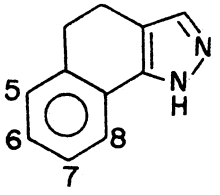
Cpd. Reference	6-OCH_3	6,7-di-OCH_3	5,6,7-tri-OCH_3	6,7,8-tri-OCH_3
	3.81	3.90 3.95	3.87 3.89 3.95	3.85(1)[b] 3.90(2)
	3.79	3.90(2)	3.85 3.90 3.95	3.87 3.91 3.96
	3.72	3.75 3.90	3.88(2) 3.90(1)	3.86(2) 4.01(1)

TABLE VII (Continued)

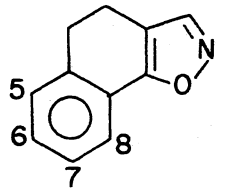
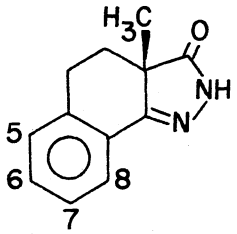
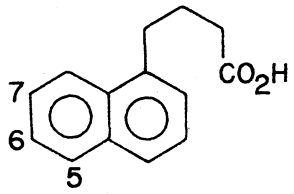
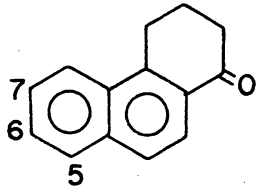
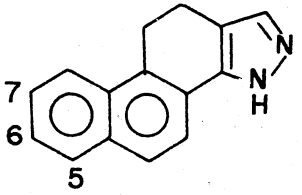
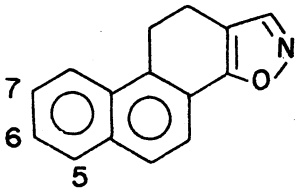
Cpd. Reference	6-OCH_3	6,7-di-OCH_3	5,6,7-tri-OCH_3	6,7,8-tri-OCH_3
		3.88 3.90	3.86(1) 3.90(2)	3.89(2) 4.00(1)
		3.80 4.01	3.91(3)	3.88 3.89 3.95
	3.91	3.98 4.00	3.97(2) 4.02(1)	

TABLE VII (Continued)

Cpd. Reference	6-OCH_3	6,7-di-OCH_3	5,6,7-tri-OCH_3	6,7,8-tri-OCH_3
	3.83		4.02(2) 4.03(1)	
	3.81	3.88 3.92	3.98 4.00 4.03	
		3.99 4.00	3.89 4.01 4.03	

[a]Values given in δ units; in $DCCl_3$.
[b]Figures in parentheses denote number of methoxy groups via peak integration. Where not noted, the peak integration corresponds to only one methoxy group.

TABLE VIII

INTENSE IONS IN THE MASS SPECTRA OF PRODUCTS[a]

Cpd.	Pressure (mm.)	Probe Temp. (°C)	Source Temp. (°C)	M^+(% RI)[b]	m/e(% RI)
28	2.4×10^{-6}	40	210	236(100)	51(9), 77(18), 79(11), 91(11), 107(10), 135(10), 151(10), 165(23), 180(12), 193(21), 194(11), 195(11), 221(26), 237(18)
139	3.5×10^{-6}	70	160	251(100)	15(8), 33(17), 35(9), 36(20), 38(10), 51(8), 77(12), 115(8), 116(8), 191(8), 236(28), 252(16)
140	1×10^{-5}	25	160	265(57)	41(24), 43(23), 55(16), 57(27), 70(16), 71(16), 77(19), 113(15), 149(100), 159(16), 167(47), 250(15)
141	8×10^{-6}	105	160	309(35)	28(49), 29(37), 31(33), 32(51), 51(75), 77(71), 91(38), 151(55), 193(32), 221(55), 236(100), 237(63), 292(43)

TABLE VIII (Continued)

Cpd.	Pressure (mm.)	Probe Temp. (°C)	Source Temp. (°C)	M^+(% RI)[b]	m/e(% RI)
142	3.8×10^{-6}	60	210	264(100)	77(9), 161(16), 189(18), 190(10), 204(33), 205(18), 220(11), 221(19), 233(18), 235(20), 236(19), 249(20), 265(17)
97	4×10^{-6}	50	180	260(100)	15(8), 28(19), 31(12), 51(5), 77(4), 131(10), 159(7), 185(13), 202(7), 217(6), 245(61), 246(10), 261(18)
99	4×10^{-6}	50	220	261(100)	75(7), 130(5), 163(9), 178(6), 184(8), 189(7), 206(7), 218(8), 236(8), 246(35), 247(5), 262(18)
148	2.5×10^{-5}	60	250	294(27)	165(9), 180(5), 193(6), 204(5), 219(5), 221(14), 235(9), 236(100), 237(11), 262(11), 263(5), 295(5)
101	3.4×10^{-6}	150	210	276(100)	115(3), 147(3), 175(4), 192(3), 201(6), 205(5), 218(3), 233(4), 261(57), 274(3), 275(5), 277(8), 278(4)

TABLE VIII (Continued)

Cpd.	Pressure (mm.)	Probe Temp. (°C)	Source Temp. (°C)	M^+(% RI)[b]	m/e(% RI)
102	1.2×10^{-5}	90	150	290(41)	14(38), 18(21), 28(100), 32(23), 40(23), 44(9), 77(7), 115(8), 116(6), 131(7), 181(6), 247(7), 275(10), 291(8)
104	2.8×10^{-6}	155	240	303(100)	43(5), 152(6), 186(7), 202(5), 228(4), 230(4), 244(4), 272(8), 288(19), 289(4), 302(23), 304(19)
131	4.6×10^{-6}	90	190	286(100)	63(19), 75(17), 101(16), 115(23), 126(16), 127(27), 128(37), 129(25), 139(20), 157(44), 172(20), 228(23), 243(28), 271(24), 287(22)
144	4×10^{-6}	65	205	314(100)	64(5), 138(5), 151(5), 164(5), 225(5), 254(10), 271(14), 284(12), 285(7), 286(11), 299(18), 315(22)
106	3×10^{-6}	85	210	310(74)	77(13), 89(19), 126(17), 152(17), 155(36), 181(25), 223(23), 224(13), 251(38), 267(61), 295(90), 296(20), 308(14), 309(100), 311(11)

TABLE VIII (Continued)

Cpd.	Pressure (mm.)	Probe Temp. (°C)	Source Temp. (°C)	M^+(% RI)[b]	m/e(% RI)
107	3×10^{-6}	110	250	311(100)	127(4), 129(4), 182(6), 215(4), 230(7), 253(4), 258(5), 268(9), 296(14), 297(4), 312(18)
155	5.3×10^{-6}	75	200	358(100)	15(60), 28(34), 59(18), 115(24), 127(17), 141(21), 149(18), 172(19), 215(20), 230(27), 258(17), 298(49), 299(27), 359(24)
108	2.8×10^{-6}	150	260	340(100)	139(6), 152(7), 153(7), 165(6), 211(5), 282(8), 297(15), 325(18), 326(5), 341(20)
125	7.4×10^{-6}	50	160	236(96)	43(21), 77(18), 79(24), 91(17), 150(25), 151(22), 165(52), 193(28), 203(29), 207(20), 208(18), 221(100), 222(25), 237(17)
143	5×10^{-6}	50	210	264(100)	43(35), 51(13), 77(14), 149(15), 161(15), 203(13), 204(16), 221(15), 235(27), 236(21), 249(17), 263(33), 265(23)

TABLE VIII (Continued)

Cpd.	Pressure (mm.)	Probe Temp. (°C)	Source Temp. (°C)	M^+(% RI)[b]	m/e(% RI)
98	3×10^{-6}	70	200	260(100)	51(29), 63(31), 65(18), 75(22), 76(21), 77(43), 78(18), 87(18), 115(20), 130(26), 131(54), 159(31), 185(28), 202(42), 245(20), 261(19)
100	6×10^{-6}	80	200	261(100)	15(15), 51(20), 63(15), 77(21), 115(14), 131(13), 191(13), 203(17), 208(15), 218(22), 246(26), 262(52)
154	3×10^{-6}	60	260	308(25)	90(6), 121(5), 165(27), 193(53), 194(8), 208(100), 209(12), 221(19), 233(10), 234(7), 248(34), 249(24), 250(9), 261(7)
103	2.2×10^{-6}	100	200	290(100)	69(13), 115(6), 131(5), 230(15), 231(42), 232(26), 246(8), 247(9), 261(5), 275(12), 291(20)
150	5.8×10^{-6}	60	210	234(70)	43(9), 77(10), 91(10), 103(10), 120(21), 148(100), 149(10), 174(39), 175(18), 176(36), 200(10), 201(12), 202(45), 203(19), 235(12)

TABLE VIII (Continued)

Cpd.	Pressure (mm.)	Probe Temp. (°C)	Source Temp. (°C)	M^+(% RI)	m/e(% RI)
151	2.4×10^{-6}	150	260	260(100)	18(34), 28(40), 31(19), 43(29), 45(21), 115(17), 227(25), 228(20), 242(57), 243(64), 259(78), 261(17)
152	2.8×10^{-6}	165	260	243(85)	43(10), 115(10), 130(8), 199(12), 200(12), 214(18), 225(15), 242(100), 244(16)

[a]All spectra were recorded at 70 eV (ionization potential).

[b]M^+ symbolizes the molecular cation.

TABLE IX

RESULTS OF PEAK MATCHING ON SELECTED INTERMEDIATES AND PRODUCTS

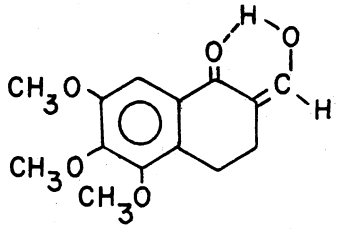
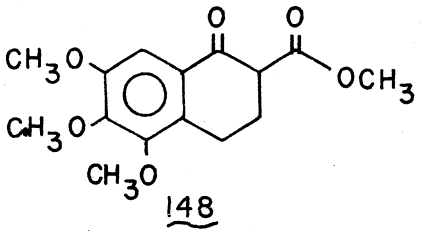
Cpd.	Formula	Fragment[a]	m/e	Possible Formula[b]	Calc'd	Found
 142	$C_{14}H_{16}O_5$	M^+	264	~~$C_{12}H_{14}N_3O_4$~~	264.0984	264.0989
				$\boxed{C_{14}H_{16}O_5}$	264.0998	
		M^+-15	249	~~$C_{11}H_{11}N_3O_4$~~	249.0749	249.0762
				$\boxed{C_{13}H_{13}O_5}$	249.0762	
		M^+-31	233	~~$C_{11}H_{11}N_3O_3$~~	233.0800	233.0813
				$\boxed{C_{13}H_{13}O_4}$	233.0814	
 148	$C_{15}H_{18}O_6$	M^+	294	~~$C_{18}H_{16}NO_3$~~	294.1130	294.1104
				$\boxed{C_{15}H_{18}O_6}$	294.1103	

TABLE IX (Continued)

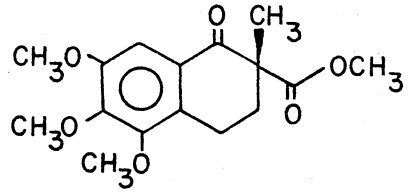
Cpd.	Formula	Fragment[a]	m/e	Possible Formula[a]	Calc'd	Found
148		M^+-58	236	~~$C_9H_{12}N_6O_2$~~	236.1022	
				~~$C_{11}H_{14}N_3O_3$~~	236.1035	236.1014
				$\boxed{C_{13}H_{16}O_4}$	236.1048	
		M^+-73	221	~~$C_8H_9N_6O_2$~~	221.0787	
				~~$C_{10}H_{11}N_3O_3$~~	221.0800	221.0780
				$\boxed{C_{12}H_{13}O_4}$	221.0814	
 153	$C_{16}H_{20}O_6$	M^+	308	~~$C_{12}H_{16}N_6O_4$~~	308.1233	
				~~$C_{14}H_{18}N_3O_5$~~	308.1246	308.1258
				$\boxed{C_{16}H_{20}O_6}$	308.1260	

TABLE IX (Continued)

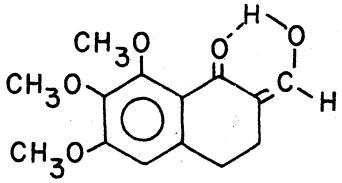
Cpd.	Formula	Fragment[a]	m/e	Possible Formula[b]	Calc'd	Found
153		M^+-15	293	$C_{15}H_{17}O_6$	293.1025	
				~~$C_{16}H_{13}N_4O_2$~~	293.1038	293.1034
				~~$C_{18}H_{15}NO_3$~~	293.1052	
	$C_{14}H_{16}O_5$	M^+	264	~~$C_{12}H_{14}N_3O_4$~~	264.0984	264.0989
				$C_{14}H_{16}O_5$	264.0998	
		M^+-18	236	~~$C_9H_{12}N_6O_2$~~	236.1022	236.1019
				$C_{13}H_{16}O_4$	236.1048	
		M^+-43	221	$C_{12}H_{13}O_4$	221.0814	221.0819
				~~$C_{13}H_9N_4$~~	221.0827	

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TABLE IX (Continued)

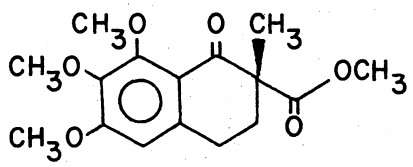
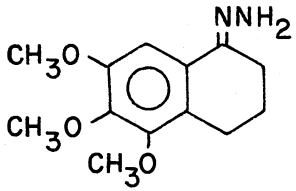
Cpd.	Formula	Fragment[a]	m/e	Possible Formula[b]	Calc'd	Found
 154	$C_{16}H_{20}O_6$	M^+	308	~~$C_{12}H_{16}N_6O_4$~~	308.1233	
				~~$C_{14}H_{18}N_3O_5$~~	308.1246	308.1252
				$C_{16}H_{20}O_6$	308.1260	
		M^+-15	293	$C_{15}H_{17}O_6$	293.1025	
				~~$C_{16}H_{13}N_4O_2$~~	293.1038	293.1031
				~~$C_{18}H_{15}NO_3$~~	293.1052	
 149	$C_{13}H_{18}N_2O_3$	M^+	250	~~$C_{11}H_{16}N_5O_2$~~	250.1304	250.1311
				$C_{13}H_{18}N_2O_3$	250.1317	
		M^+-15	235	~~$C_{10}H_{13}N_5O_2$~~	235.1069	235.1075
				$C_{12}H_{15}N_2O_3$	235.1083	

TABLE IX (Continued)

Cpd.	Formula	Fragment[a]	m/e	Possible Formula[b]	Calc'd	Found
149		M^+-31	219	$C_{11}H_{11}N_2O_3$	219.0770	219.0806
				~~$C_{14}H_9N_3$~~	219.0797	
	$C_{13}H_{14}O_4$	M^+	234	$C_{13}H_{14}O_4$	234.0892	234.0896
				~~$C_{14}H_{10}N_4$~~	234.0905	
		M^+-32	202	~~$C_{10}H_{18}N_3O_2$~~	202.0616	202.0618
				$C_{12}H_{10}O_3$	202.0630	
		M^+-60	174	~~$C_9H_8N_3O$~~	174.0667	174.0684
				$C_{11}H_{10}O_2$	174.0681	

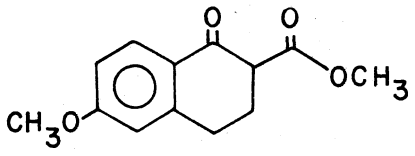


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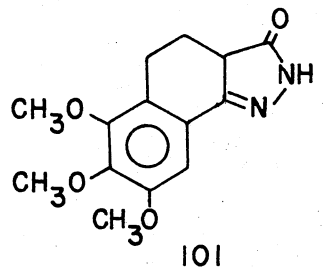
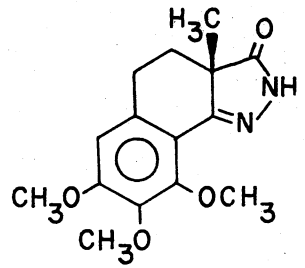
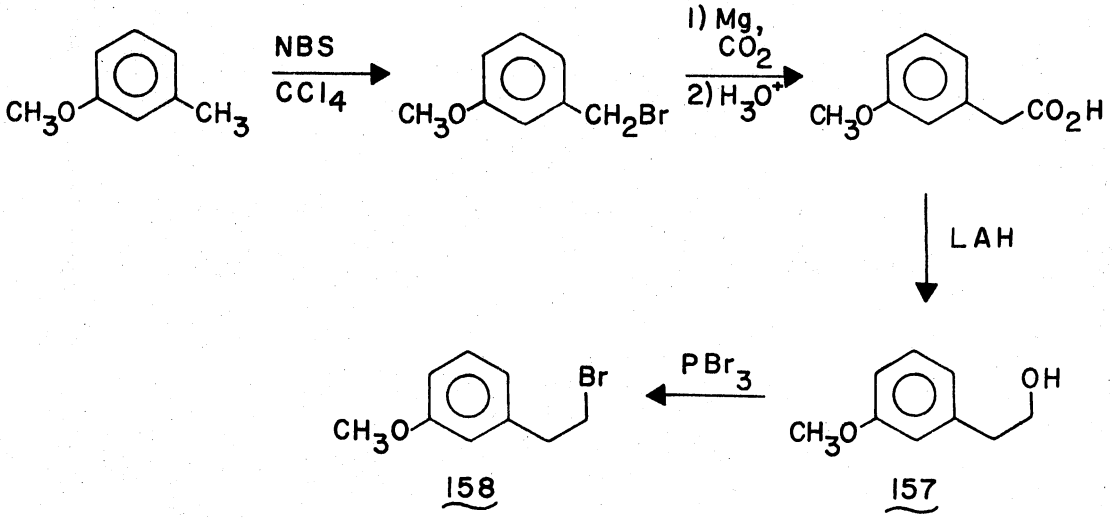
TABLE IX (Continued)

Cpd.	Formula	Fragment[a]	m/e	Possible Formula[b]	Calc'd	Found
 101	$C_{14}H_{16}N_2O_4$	M^+	276	~~$C_{12}H_{14}N_5O_3$~~	276.1097	276.1099
				$\boxed{C_{14}H_{16}N_2O_4}$	276.1110	
		M^+-15	261	$\boxed{C_{13}H_{13}N_2O_4}$	261.0875	261.0891
				~~$C_{14}H_9N_6$~~	261.0889	
 103	$C_{15}H_{18}N_2O_4$	M^+	290	~~$C_{13}H_{16}N_5O_3$~~	290.1253	290.1253
				$\boxed{C_{15}H_{18}N_2O_4}$	290.1266	
		M^+-15	275	$\boxed{C_{14}H_{15}N_2O_4}$	275.1032	275.1036
				~~$C_{15}H_{11}N_6$~~	275.1045	
		M^+-59	231	~~$C_{12}H_{13}N_3O_2$~~	231.1008	231.1025
				$\boxed{C_{14}H_{15}O_3}$	231.1021	

[a] M^+ symbolizes the molecular action.

[b] Confirmed fragment $\boxed{}$, unobserved fragment ~~~~.

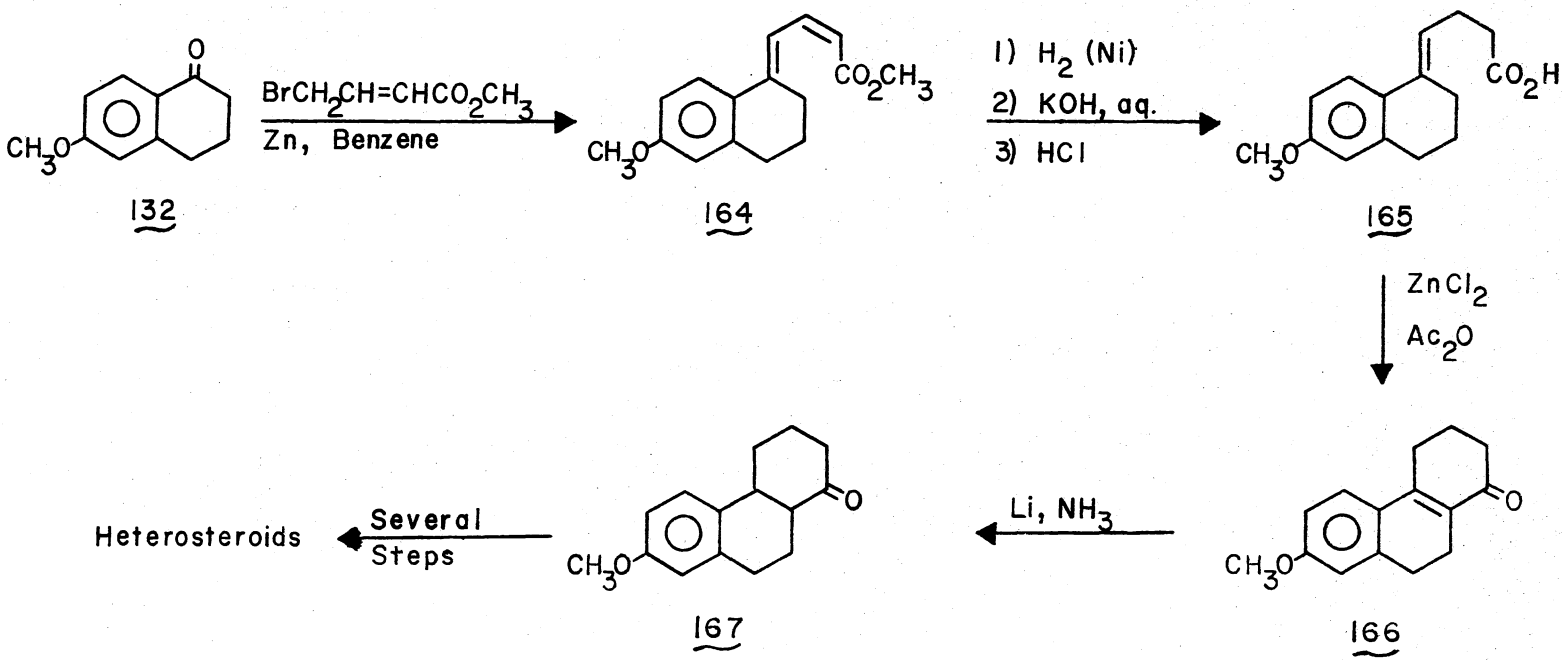
vacuum via a spinning band distillation apparatus led to alkene formation to yield m-methoxystyrene and subsequent polymerization. None of the bromide 158 was isolated in a pure form. After repeating this general procedure several times without success, an alternate method was tried (Scheme 22). It had been reported that the purity of the N-



Scheme 22

bromosuccinimide (NBS) was critical to the preparation of bromomethylarenes.[33] However, even after purification of NBS, only the bromoarene derivative (4-bromo-3-methylanisole) could be obtained from treatment of m-methylanisole with NBS.[95] Thus an alternate scheme was proposed (Scheme 23).

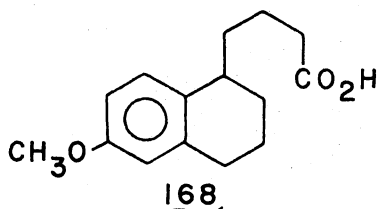
Stork had recorded[134] the preparation of 164 from the Reformatsky reaction of 6-methoxy-1-tetralone (132) and methyl γ-bromocrotonate. Reduction of expected ester 164 with hydrogen in the presence of Raney nickel at room temperature (followed by hydrolysis) gave the partially reduced acid 165 which he successfully cyclized to the phenanthrone 166 in a zinc chloride-acetic anhydride mixture. Phenanthrone 166 could



132 164 165 166 167

Scheme 23

then easily be converted to 167 with lithium metal in liquid ammonia.[32] Villani and co-workers[148] studied the hydrogenation step in this sequence and found that only in the presence of a small amount of acetic acid and freshly prepared Raney nickel (W-2) could a good yield of 165 be achieved. Following strict adherence to the described quantity of reagents and reaction conditions, attempts to prepare 165 from pure 164 were initiated. In three separate trials only the completely saturated acid 168 was isolated. The Raney nickel was freshly prepared each time



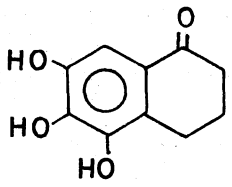
168

following the method of Mozingo.[102] One explanation of the failure to obtain 165 could be the difference in activity of the nickel catalyst. Thus, attempts to prepare 166 or 167 were abandoned.

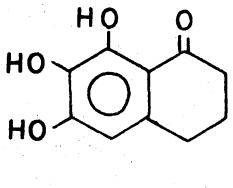
In view of the importance of water solubility in biological activity of many compounds, efforts were made to cleave the methoxy groups to give hydroxy functions. Many methods are known for complete or partial demethylation of polymethyl aryl ethers. A few representative examples are: the use of 20% HCl for partial demethylation,[133] hydrogen bromide-acetic acid cleavage of methoxytetralones,[70] demethylation of khellin by magnesium iodide,[123] demethylation of the tetramethyl ether with aluminum chloride-sodium chloride to yield spinochrome N,[130] cleavage of alkyl ethers with lithium iodide,[63] demethylation of aryl methyl ethers by boron tribromide,[41,97] use of 48% hydrogen bromide in the cleavage of

dimethoxyhetero compounds,[64] and the use of pyridine hydrochloride in methoxy cleavage of several naturally occurring compounds.[39,54]

When 48% hydrogen bromide was used in the trial preparation of 3,4-dihydro-1(2H)-naphthalenone-5,6,7-triol (169), only a tar formed. Heating 5,6,7-trimethoxy-1-tetralone (28) with freshly fused pyridine hydrochloride for two hours gave a slightly impure 3,4-dihydro-1(2H)-naphthalenone-5,6,7-triol (169). Treatment of the 6,7,8-trimethoxy-1-tetralone (125) under the same conditions did give pure 170 as indicated



169



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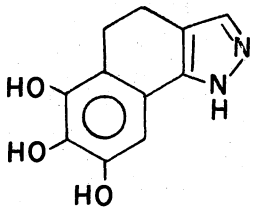

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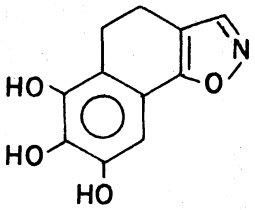

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by elemental and spectral analyses. However, treatment of pyrazole 97 with freshly fused pyridine hydrochloride resulted in a partially demethylated product, as evidenced by the NMR data, which showed a singlet (δ 3.78) in the methoxy region. Possibly a longer reaction time was needed in this system for cleavage of all the methoxy groups but this was not attempted. Attempts to obtain the trihydroxy derivative of isoxazole 99 gave only a tar residue from which no product could be isolated.

Microbial and Tissue Culture Screening Techniques

The initial screens chosen, while limited in scope, were to determine activity of a compound against growth of bacterial or tumor cells. Bacillus subtilis W23 (a prototrophic strain) and Pseudomonas

fluorescens NND were chosen for the microbial screening. Bacillus subtilis is an aerobic, gram-positive rod which grows in a minimal medium, using glucose as the sole source of carbon and energy. Pseudomonas fluorescens is a gram-negative rod. It also grows in a minimal medium. The Pseudomonads are resistant to many drugs, including actinomycin D, and are the cause of many deaths in cancer patients.[18,121] The inhibition of growth of bacteria is a general screen and could show inhibitory effects of the compound but without providing evidence for the mechanism of inhibition. These tests have the advantage of ease of performance and can be run utilizing a suspension of the test compound. Use of the suspension permits the screening of water-insoluble compounds but obscures possible advantages of good aqueous solubility which could reduce the dosage needed. Bacillus subtilis and P. fluorescens were maintained on 0.5% glucose salts minimal medium.[16] A weighed sample ($\sim$ 1 mg.) of compound to be tested was suspended in 0.5 ml. of dimethyl sulfoxide (DMSO) and diluted with sterile water (4.5 ml.). Growth experiments were performed in tubes (12 mm x 150 mm) containing 5.0 ml. of glucose salts medium, 0.5 ml. of DMSO solution and 0.2 ml. of cell inoculum to give a final volume of 5.7 ml., which turned out to be 91 µg/ml (final compound concentration). The cultures were incubated for 12 to 14 hr. at 37° with constant shaking and cell growth was measured by following the change in absorbance at 540 mm in a Coleman Junior II Spectrophotometer (18-mm light path).[31,68] Optical density generally started at 0.04 and was read at 1 hr. intervals. Inhibition was shown by little or no change in optical density over a period of 12 to 14 hr. All samples were run in either duplicate or triplicate with the same number of controls so either inhibition or activation of growth could be

observed. The results of the microbial screens are given in Table X.

Those compounds showing some activity in the microbial screens were evaluated on their ability to inhibit the plating efficiency of the human tumor cell line - KB. The latter is an established cell line derived from human tumors of the nasopharynx. Plating efficiency encompasses the ability of the cells to attach to a surface and complete all cell cycle functions responsible for colony formation. This procedure requires small volumes of test compound and it is very repeatable and relatively simple to run. All tissue culture procedures suffer from the necessity of requiring test compounds in solution, and the lack of the presence of such variables as excretion processes, filtration processes, hormone interaction, etc., that might be confronted by a compound in the whole animal.

The KB cells, originally obtained from Dr. Vernon Scott (University of Oklahoma Medical School), were grown at 37° using medium 199 supplemented with 10% calf serum. A known weight of the test compound was dissolved in 0.05 ml. DMSO and 2.0 ml. of water was added. To 10 mm x 35 mm Falcon plastic tissue culture dishes was added 1.5 ml. of the aqueous solution containing the test compound (of known conc.) and 1.5 ml. of 2x medium containing the KB cells for a total of 3.0 ml. of 1x medium (growth medium of 1x is the ideal nutrient level for these cells) containing approximately 10^3 cells/plate. The cultures were incubated in a CO_2 gas phase incubator (5% CO_2) at 37° for 7 days. After removal of the medium, the plates were washed with Hank's salt solution and the cells stained with 0.5% aqueous crystal violet, rinsed, and dried. The colonies were counted microscopically and the relative plating efficiency calculated using the control value of 100%. Samples

TABLE X

ACTIVITY OF PRODUCTS IN MICROBIAL TESTS

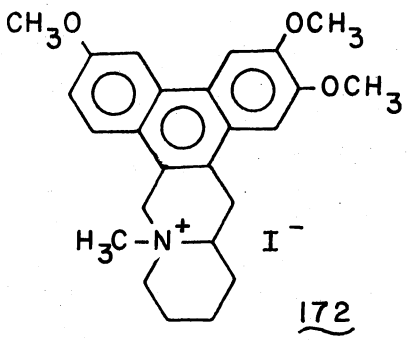
Compound Name	Cpd.	B. subtilis[a]	P. fluorescens
Oxime of 28	139	+	-
Methoxime of 28	140	+	-
Thiosemicarbazone of 28	141	+	-
2,4-Dinitrophenylhydrazone of 28	136	+	-
4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole	97	± (4 hr. lag)	-
4,5-Dihydro-6,7,8-trimethoxy-naphth[2,1-d]isoxazole	99	-	-
2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one	102	-	-
4,5-Dihydro-7,8,9-trimethoxy-1H-benz[g]indazole	98	+	-
4,5-Dihydro-7,8,9-trimethoxy-naphth[2,1-d]isoxazole	100	not tested	not tested
2,3a,4,5-Tetrahydro-7,8,9-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one	103	not tested	not tested
10,11-Dihydro-6,7,8-trimethoxy-3H-phenanthro[1,2-c]pyrazole	106	+	-
10,11-Dihydro-6,7,8-trimethoxy-phenanthro[2,1-d]isoxazole	107	-	-
2,10,11,11a-Tetrahydro-6,7,8-trimethoxy-11a-methyl-1H-phenanthro[1,2-c]pyrazol-1-one	108	-	-

[a]Inhibition shown by +; no inhibition, -; slight inhibition or delayed inhibition by ±.

were always run in either duplicate or triplicate. Results of the tissue culture screen are given in Table XI. Plots showing the effect of concentration of the test compound and percent plating efficiency are shown in Figure 7. It must be recalled that as the percent plating efficiency decreases, the inhibition for the formation of colonies, and hence for growth, increases.

Calculations of Distances Between Heteroatoms of Selected Products

Since models were not used in determining the distance between heteroatoms, several assumptions had to be made to obtain reasonable bond lengths and angles which could be used in the calculations of O-N-O distances. First, each molecule was considered planar with respect to the aromatic region and conjugated double bonds. Also, the internal bond angles of the aromatic rings were considered to be 120°.[135] Simple C-C bond lengths were assumed to be 1.54 Å; simple C=C bond lengths were considered to be 1.34 Å; and the single bond between two double bonds, C=C-C=C, was taken to be 1.49 Å.[135] The crystal data obtained from DL-iso-crystopleurine methiodide (172) reported by Fridrichsons and Mathieson[53] gave approximate distances between the aromatic C and the



172

C-O 1.36 ± 0.02 Å

ArC=C 1.39 ± 0.02 Å

TABLE XI

PERCENT PLATING EFFICIENCY OF KB CELLS VERSUS CONCENTRATION OF PYRAZOLES AND 111

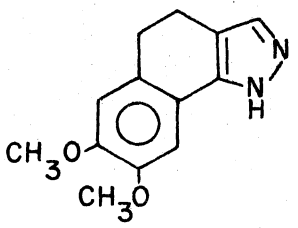
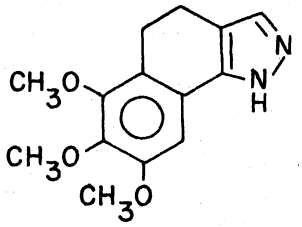
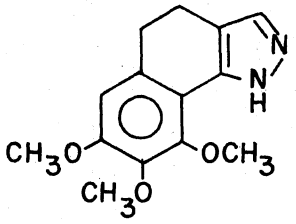
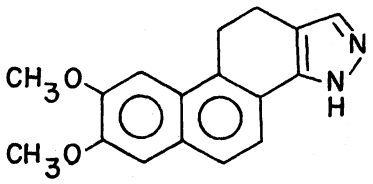
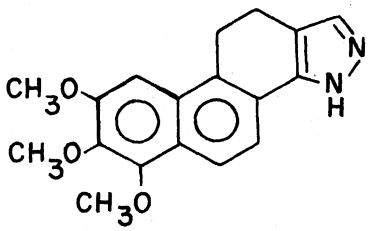
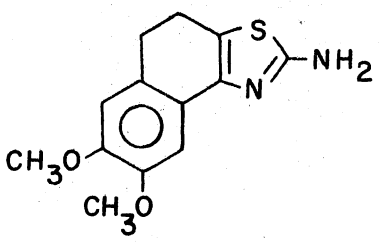
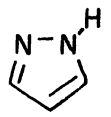
Cpd. Structure	Cpd.	Conc. (μg/ml.)	% Pl. Eff.
	109	0-3 6 12.5 25 50 150-250	100 93 81 65 31 0
	97	0-25 50 150-250	100 91 0
	98	0-12.5 25 50 150 250	100 75 14 3 0
	110	0-250	100
	106	0-25 50 150 250	100 70 15 0

TABLE XI (Continued)

Cpd. Structure	Cpd.	Conc. (μg/ml.)	% Pl. Eff.
	111	50 150	56 0

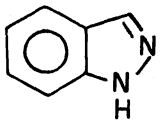
methoxy O (C-O) was taken to be 1.36 Å; the C=C bond distances in the aromatic portion of the molecule were averaged to be 1.39 Å.

In the pyrazole systems, pertinent data were obtained from x-ray diffraction data reported by Cour and Rasmussen[38] on pyrazole (173). Assumptions made using this model were: C-NH bond distance, 1.34 Å; N-N bond distance, 1.34 Å; ∠ N-N(H)-C, 112.4°; ∠ C-C-N(H), 106.5°. Later the bond lengths and angles for indazole (174) were evaluated by Escande



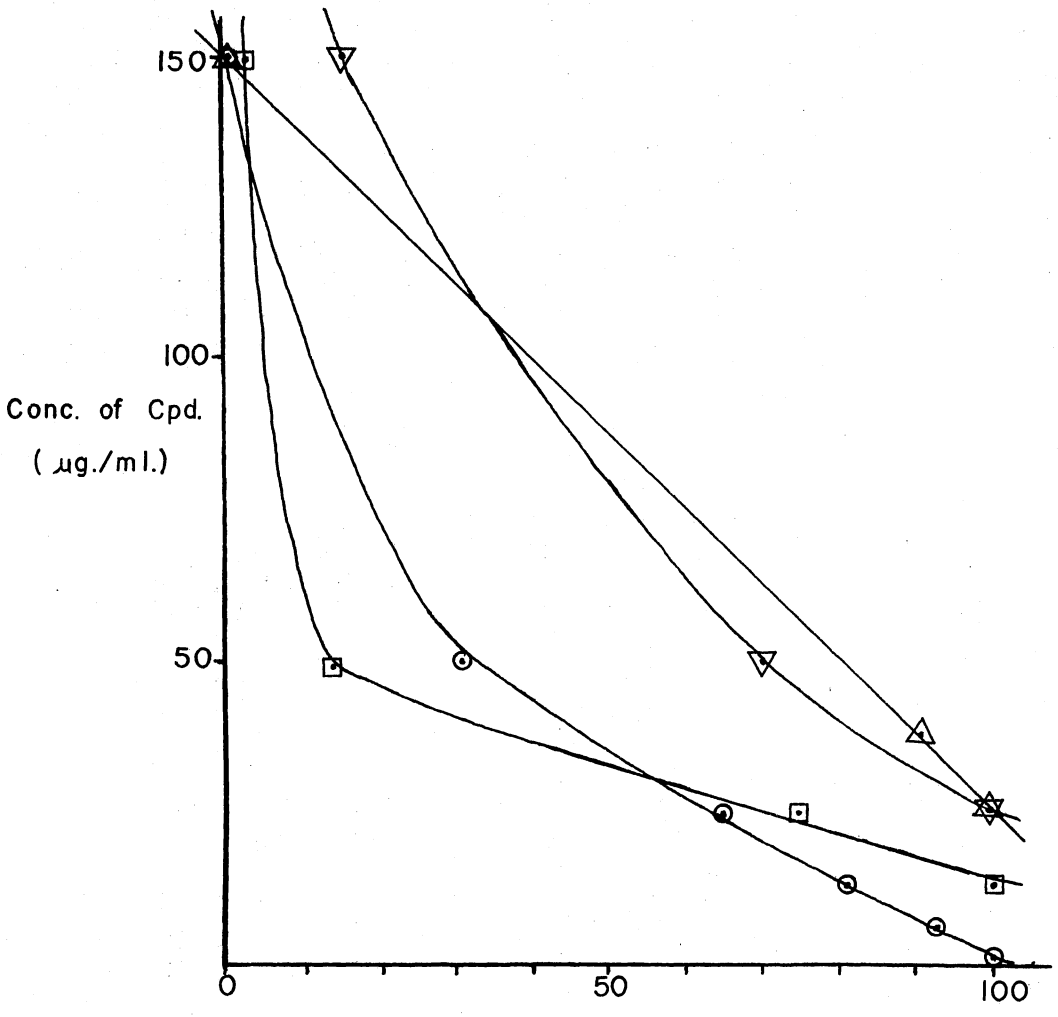
173

C-NH	1.34 ± 0.02 Å
N-N	1.34 ± 0.02 Å
∠ N-N(H)-C	112.4 ± 0.06°
∠ C-C-N(H)	106.5 ± 0.06°



174

C-NH	1.35 ± 0.01 Å
N-N	1.38 ± 0.01 Å
∠ N-N(H)-C	110 ± 1.0°
∠ C-C-N(H)	107.4 ± 1.0°



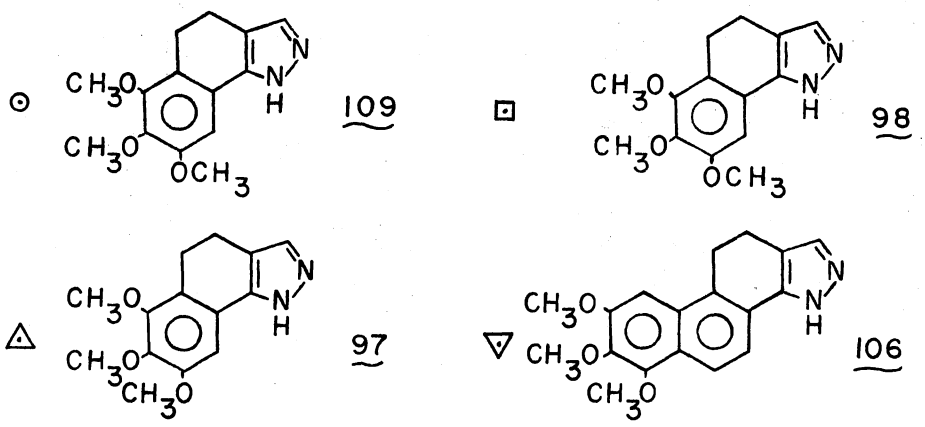
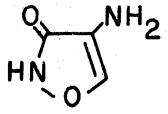


Figure 7. Concentration of Compound vs. Percent Plating Efficiency on KB Cells

and Lapasset,[46] but recalculation using the values for indazole made little difference in the systems reported here.

4-Amino-3-isoxazolidine (175)[143] was used as a model for obtaining data for the isoxazole systems. It was recognized that this was not a



175

N-O	1.37 ± 0.02 Å
C-O	1.36 ± 0.02 Å
∠ C-O-N	109 ± 1°

perfect model, yet due the scarcity of related models this seemed to be the most efficient. From 175, the N-O distance is approximated to be 1.37 Å, C-O distance ∿ 1.36 Å, and the ∠ C-O-N ∿ 109°.

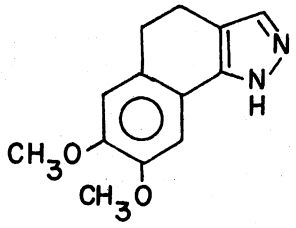
Thiophene (176)[2] was used as a model in estimating the C-S bond

176

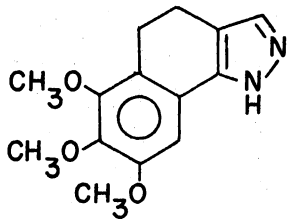
C-S	1.72 ± 0.02 Å
∠ C-S-C	91.3 ± 0.2°

length to be 1.72 Å and the C-S-C angle to be 91.3° in the thiazole 111.

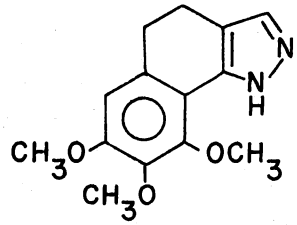
Computations were done by a triangulation between points of estimated distances and making use of simple trigonometric functions. A representative example of the computations is shown in Figure 8 for 3,4-dihydro-6,7-dimethoxy-1H-benz[g]indazole (109). Similar calculations



109

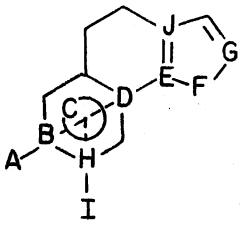


97



98

were made on pyrazoles 97 and 98. In the case of 97, triangles ΔKCE in 177 (C denotes the center of the aromatic ring), ΔKEF in 178, and ΔKFG in 179 were used to determine heteroatom distances of KF = 6.17 Å and



Assume that ΔBCH and ΔACI are equilateral triangles with internal angles of 60°:

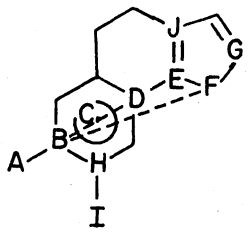
BC = BH = HC = 1.39 Å

AB = HI = 1.36 Å

AC = IC = AI = AB + BC = 1.36 + 1.39 = 2.75 Å

Assume A and E are colinear

AE = AC + CD + DE = 2.75 + 1.39 + 1.49 = 5.63 Å



Consider ΔAEF

$\angle$ JEF = 106.5°, $\angle$ AEJ = 120°

EF = 1.34 Å

$\angle$ AEF = 360° − $\angle$ AEJ − $\angle$ JEF

$\angle$ AEF = 360° − 120° − 106.5° = 133.5°

$AF^2 = AE^2 + EF^2 - (\cos \angle AEF)(2)(AE)(EF)$

$AF^2 = (5.63)^2 + (1.34)^2 - (\cos 133.5^\circ)(2)(5.63)(1.34)$

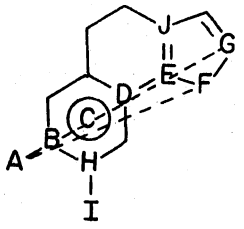
AF = 6.63 Å

$$\cos \angle AFE = \frac{(EF)^2 + (AF)^2 - (AE)^2}{2(EF)(AF)}$$

Figure 8. Calculation of Heteroatom Distances in 3,4-Dihydro-6,7-dimethoxy-1H-benz[g]-indazole (109)

$$\cos \angle AFE = \frac{(1.34)^2 + (6.63)^2 - (5.63)^2}{2(1.34)(6.63)}$$

$$\angle AFE = 38.0^{\circ}$$



Consider ΔAFG

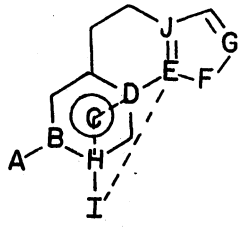
$\angle EFG = 112.8^{\circ}$, $FG = 1.34$ Å

$\angle AFG = \angle AFE + \angle EFG = 38^{\circ} + 112.8^{\circ} = 150.8^{\circ}$

$AG^2 = AF^2 + FG^2 - (\cos \angle AFG)(2)(AF)(FG)$

$AG^2 = (6.63)^2 + (1.34)^2 - (\cos 150.8^{\circ})(2)(6.63)(1.34)$

$AG = 7.81$ Å



Consider ΔCEI

$CE = CD + DE = 1.39 + 1.49 = 2.88$ Å

$\angle ECI = 120^{\circ}$

$EI^2 = (CI)^2 + (CE)^2 - (\cos \angle ECI)(2)(CI)(CE)$

$EI^2 = (2.75)^2 + (2.88)^2 - (\cos 120^{\circ})(2)(2.75)(2.88)$

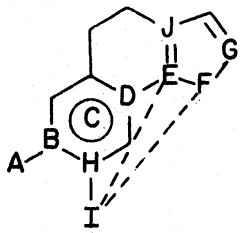
$EI = 4.88$ Å

$$\cos \angle CEI = \frac{(CE)^2 + (CI)^2 - (EI)^2}{2(CE)(CI)}$$

Figure 8 (Continued)

$$\cos \angle CEI \frac{(2.88)^2 + (2.75)^2 - (4.88)^2}{2(2.88)(2.75)}$$

$\angle CEI = 29.2^{\circ}$



Consider ΔEFI

$\angle FEI = \angle AEF - \angle CEI = 133.5^{\circ} - 29.2^{\circ} = 104.3^{\circ}$

$FI^2 = (EF)^2 + (EI)^2 - (\cos \angle FEI)(2)(EF)(EI)$

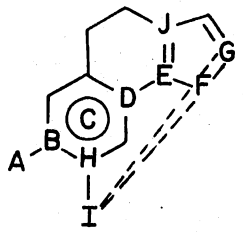
$FI^2 = (1.34)^2 + (4.88)^2 - (\cos 104.3^{\circ})(2)(1.34)(4.88)$

$FI = 5.37$ Å

$$\cos \angle EFI = \frac{(EF)^2 + (FI)^2 - (EI)^2}{2(EF)(FI)}$$

$$\cos \angle EFI = \frac{(1.34)^2 + (5.37)^2 - (4.88)^2}{2(1.34)(5.37)}$$

$\angle EFI = 61.6^{\circ}$



Consider ΔFGI

$\angle GFI = \angle EFG + \angle EFI = 112.8^{\circ} + 61.6^{\circ} = 174.0^{\circ}$

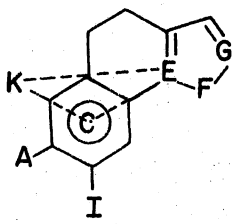
$IG^2 = (GF)^2 + (FI)^2 - (\cos \angle GFI)(2)(GF)(FI)$

$IG^2 = (1.34)^2 + (5.37)^2 - (\cos 174.4^{\circ})(2)(1.34)(5.37)$

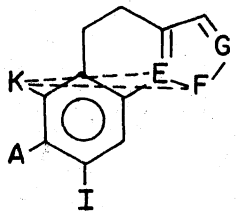
$IG = 6.71$ Å

Figure 8 (Continued)

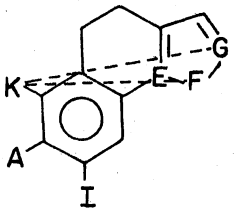
KG = 7.05 Å. Previous calculations on 169 were used for heteroatom distances of AF = 6.63 Å, AG = 7.81 Å, IF = 5.37 Å, and IG = 6.71 Å.



177

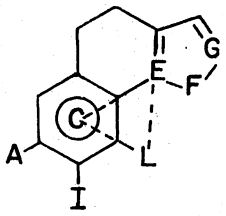


178

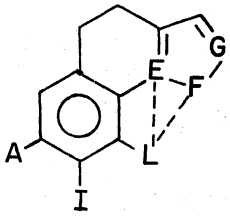


179

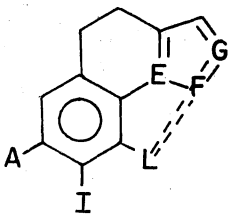
Triangles ΔLEC in 180, ΔLEF in 181, and ΔLFG in 182 were used for



180

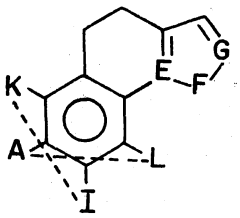


181

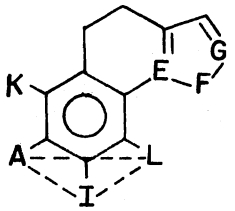


182

the heteroatom distances LF and LG in pyrazole 98. The values found were: LF = 2.80 Å and LG = 4.13 Å. Values for AF, AG, FI, and GI were assumed to be identical to those calculated for 109. Distances KI and AL as shown in (183) are considered identical; AL was calculated using triangle ΔAIL in 184 by assuming angle AIL to be 120°. Thus the



183



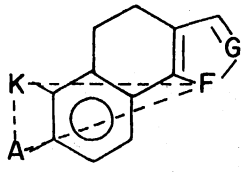
184

$$AL^2 = (AI)^2 + (LI)^2 - (\cos \angle AIL)(2)(AI)(LI)$$

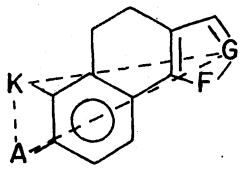
$$AL^2 = (2.75)^2 + (2.75)^2 - (\cos 120^\circ)(2)(2.75)(2.75)$$

$$AL = 4.76 \text{ Å}$$

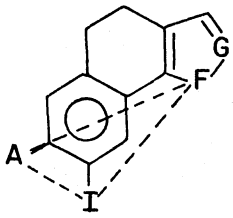
distance between the most distant methoxy groups in all of the trimethoxy systems prepared was calculated to be 4.76 Å. Identical types of computations were made for the isoxazoles 99 and 100, using bond lengths EF = 1.36 Å and FG = 1.37 Å and bond angle ∠ EFG = 109°.[143] Tabulations of the resulting distances are given in Table XII, with the distances calculated on the "model" pyrazoles 109, 97, and 98. Table XIV contains the O-N-O angle values calculated using triangles ΔKAF in 185, ΔKAG in 186, ΔAFI in 187, ΔAGI in 188, ΔFIL in 189, and ΔGIL in 190 in the simple trigonometric function cos ABC = $\frac{AB^2 + BC^2 - AC^2}{2(AB)(BC)}$.



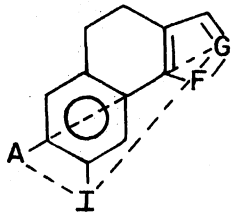
185



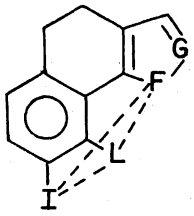
186



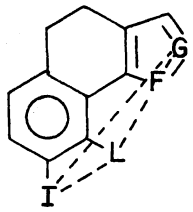
187



188



189

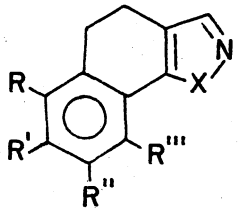


190

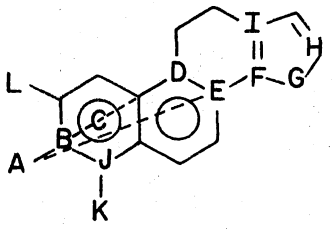
Steps used in calculating heteroatom distances in the heterosteroids 106 and 107 are shown in Figure 9 for the pyrazole 106. The identical sequence was used for the isoxazole 107, the only difference being the insertion of appropriate bond lengths and angles for O-N and C-O bonds (see discussion of 175 on page 126). Tabulation of the final results is shown in Table XIII. Calculation of O-N-O angles was

TABLE XII

CALCULATED HETEROATOM DISTANCES (Å) IN "MODEL" PYRAZOLES



Cpd.	R	R'	R"	R'"	X	R'-R"	R-R" or R'-R"'	R-X	R'-X	R"-X	R'"-X	R-N	R'-N	R"-N	R'"-N
109	H	CH_3O	CH_3O	H	N	2.75	-	6.17	6.63	-	-	7.05	7.81	-	-
97	CH_3O	CH_3O	CH_3O	H	N	2.75	4.76	6.17	6.63	5.37	-	7.05	7.81	6.71	-
98	H	CH_3O	CH_3O	CH_3O	N	2.75	4.76	-	6.63	5.37	2.80	-	7.81	6.71	4.13
203	H	CH_3O	CH_3O	H	O	2.75	-	6.18	6.64	-	-	7.00	7.81	-	-
99	CH_3O	CH_3O	CH_3O	H	O	2.75	4.76	6.18	6.64	5.39	-	7.00	7.81	6.74	-
100	H	CH_3O	CH_3O	CH_3O	O	2.75	4.76	-	6.64	5.39	2.81	-	7.81	6.74	4.18



Assume planarity of all atoms signified.

Consider ΔADE.

$AD = AC + CD = 2.75 + 2(1.39) = 5.53$ Å

$DE = 1.39$ Å (C=C)

$\angle ADE = 120^{\circ}$

$AE^2 = (AD)^2 + (DE)^2 - (\cos \angle ADE)(2)(AD)(DE)$

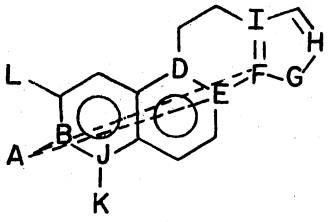
$AE^2 = (5.53)^2 + (1.39)^2 - (\cos 120^{\circ})(2)(5.53)(1.39)$

$AE = 6.37$ Å

$$\cos \angle AED = \frac{(DE)^2 + (AE)^2 - (AD)^2}{2(DE)(AE)}$$

$$\cos \angle AED = \frac{(1.39)^2 + (6.37)^2 - (5.53)^2}{2(1.39)(6.37)}$$

$\angle AED = 49.1^{\circ}$



Consider ΔAEF

$\angle AEF = \angle AED + \angle DEF = 49.1^{\circ} + 120^{\circ} = 169^{\circ}$

$AF^2 = (AE)^2 + (EF)^2 - (\cos \angle AEF)(2)(AE)(EF)$

$AF^2 = (6.37)^2 + (1.39)^2 - (\cos 169^{\circ})(2)(6.37)(1.39)$

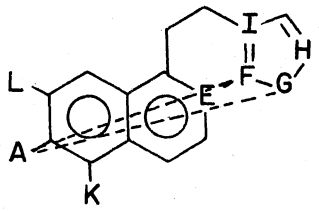
Figure 9. Calculation of Heteroatom Distances in 10,11-Dihydro-6,7,8-trimethoxy-3H-phenanthro[1,2-c]pyrazole (106)

$AF = 7.84\ \mathring{A}$

$$\cos \angle AFE = \frac{(AF)^2 + (EF)^2 - (AE)^2}{2(AF)(EF)}$$

$$\cos \angle AFE = \frac{(7.84)^2 + (1.39)^2 - (6.37)^2}{2(7.84)(1.39)}$$

$\angle AFE = 8.5^\circ$



Consider ΔAFG

$\angle EFG = 133.5^\circ$, $FG = 1.34\ \mathring{A}$

$\angle AFG = \angle AFE + \angle EFG = 8.5^\circ + 133.5^\circ = 142^\circ$

$AG^2 = (AF)^2 + (FG)^2 - (\cos \angle AFG)(2)(AF)(FG)$

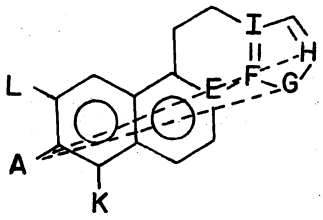
$AG^2 = (7.84)^2 + (1.34)^2 - (\cos 142^\circ)(2)(7.84)(1.34)$

$AG = 8.62\ \mathring{A}$

$$\cos \angle AGF = \frac{(AG)^2 + (FG)^2 - (AF)^2}{2(AG)(FG)}$$

$$\cos \angle AGF = \frac{(8.62)^2 + (1.34)^2 - (7.84)^2}{2(8.62)(1.34)}$$

$\angle AGF = 50.7^\circ$



Consider ΔAGH

$\angle FGH = 112.8^\circ$, $GH = 1.34\ \mathring{A}$

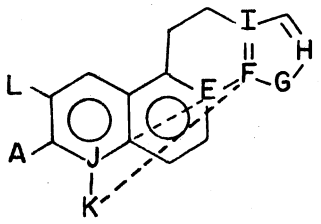
Figure 9 (Continued)

$\angle AGH = \angle AGF + \angle FGH = 50.7^{\circ} + 112.8^{\circ} = 163.5^{\circ}$

$AH^2 = (AG)^2 + (GH)^2 - (\cos \angle AGH)(2)(AG)(GH)$

$AH^2 = (8.62)^2 + (1.34)^2 - (\cos 163.5^{\circ})(2)(8.62)(1.34)$

$AH = 9.91 \text{ Å}$



Consider ΔKJF

$KJ = 1.36 \text{ Å}$, $KJF = 120^{\circ}$

$JF = JE + EF = 3(1.39) + 1.49 = 5.66 \text{ Å}$

$KF^2 = (KJ)^2 + (JF)^2 - (\cos \angle KJF)(2)(KJ)(JF)$

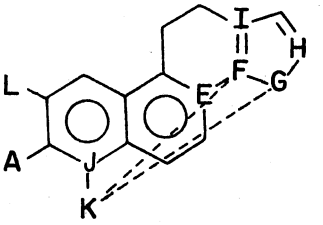
$KF^2 = (1.36)^2 + (5.66)^2 - (\cos 120^{\circ})(2)(1.36)(5.66)$

$KF = 6.45 \text{ Å}$

$$\cos \angle KFJ = \frac{(JF)^2 + (KF)^2 - (KJ)^2}{2(JF)(KF)}$$

$$\cos \angle KFJ = \frac{(5.66)^2 + (6.45)^2 - (1.36)^2}{2(5.66)(6.45)}$$

$\angle KFJ = 10.5^{\circ}$



Consider ΔKFG

$\angle KFG = \angle EFG - \angle JFK = 133.5^{\circ} - 10.5^{\circ} = 123^{\circ}$

$FG = 1.34 \text{ Å}$

Figure 9 (Continued)

$KG^2 = (KF)^2 + (FG)^2 - (\cos \angle KFG)(2)(KF)(FG)$

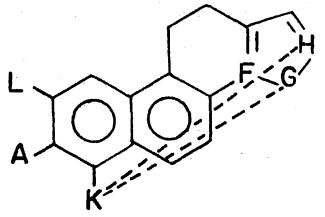
$KG^2 = (6.45)^2 + (1.34)^2 - (\cos 123^\circ)(2)(6.45)(1.34)$

$KG = 7.27$ Å

$$\cos \angle KGF = \frac{(KG)^2 + (FG)^2 - (KF)^2}{2(KG)(FG)}$$

$$\cos \angle KGF = \frac{(7.27)^2 + (1.34)^2 - (6.45)^2}{2(7.27)(1.34)}$$

$\angle KGF = 48.0^\circ$



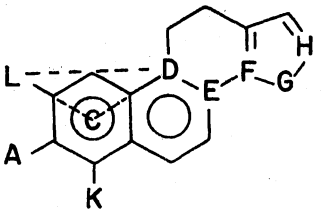
Consider ΔKGH

$\angle KGH = \angle FGH = \angle KGF = 112.8^\circ + 48^\circ = 160.8^\circ$

$KH^2 = (KG)^2 + (GH)^2 - (\cos \angle KGH)(2)(KG)(GH)$

$KH^2 = (7.27)^2 + (1.34)^2 - (\cos 160.8^\circ)(2)(7.27)(1.34)$

$KH = 8.55$ Å



Consider ΔLCD

$\angle LCD = 120^\circ$, $LC = 2.75$ Å, $CD = 2(1.39) = 2.88$ Å

$LD^2 = (LC)^2 + (CD)^2 - (\cos \angle LCD)(2)(LC)(CD)$

$LD^2 = (2.75)^2 + (2.88)^2 - (\cos 120^\circ)(2)(2.75)(2.88)$

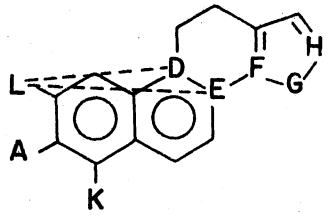
$LD = 4.82$ Å

Figure 9 (Continued)

$$\cos \angle LDC = \frac{(LD)^2 + (CD)^2 - (LC)^2}{2(LD)(CD)}$$

$$\cos \angle LDC = \frac{(4.82)^2 + (2.88)^2 - (2.75)^2}{2(4.82)(2.88)}$$

$$\angle LDC = 29.6^\circ$$



Consider ΔLDE

$\angle CDE = 120^\circ$, $DE = 1.39$ Å

$\angle LDE = \angle LDC + \angle CDE = 29.6^\circ + 120^\circ = 149.6^\circ$

$LE^2 = (LD)^2 + (DE)^2 - (\cos \angle LDE)(2)(LD)(DE)$

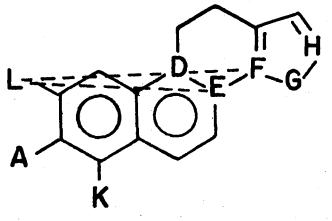
$LE^2 = (4.82)^2 + (1.39)^2 - (\cos\ 149.6^\circ)(2)(4.82)(1.39)$

$LE = 6.06$ Å

$$\cos \angle LED = \frac{(DE)^2 + (LE)^2 - (LD)^2}{2(DE)(LE)}$$

$$\cos \angle LED = \frac{(1.39)^2 + (6.06)^2 - (4.82)^2}{2(1.39)(6.06)}$$

$$\angle LED = 23.7$$



Consider ΔLEF

$\angle LEF = \angle LED + \angle DEF = 23.7^\circ + 120^\circ = 143.7^\circ$

$LF^2 = (LE)^2 + (EF)^2 - (\cos \angle LEF)(2)(LE)(EF)$

Figure 9 (Continued)

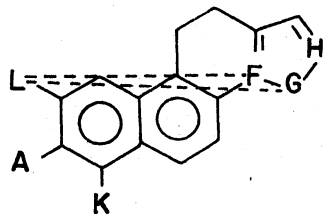
$LF^2 = (6.06)^2 + (1.49)^2 - (\cos 143.7^\circ)(2)(6.06)(1.49)^2$

$LF = 7.31\ \mathring{A}$

$$\cos \angle EFL = \frac{(EF)^2 + (LF)^2 - (LE)^2}{2(EF)(LF)}$$

$$\cos \angle EFL = \frac{(1.49)^2 + (7.31)^2 - (6.06)^2}{2(1.49)(7.31)}$$

$\angle EFL = 29.3^\circ$



Consider ΔLFG

$\angle LFG = \angle EFL + \angle EFG = 29.3^\circ + 133.5^\circ = 162.8^\circ$

$LG^2 = (LF)^2 + (FG)^2 - (\cos \angle LFG)(2)(LF)(FG)$

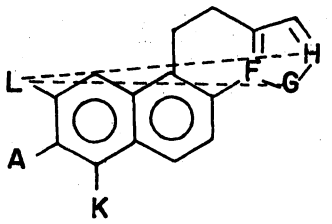
$LG^2 = (7.31)^2 + (1.34)^2 - (\cos 162.8^\circ)(2)(7.31)(1.34)$

$LG = 8.60\ \mathring{A}$

$$\cos \angle LGF = \frac{(LG)^2 + (FG)^2 - (LF)^2}{2(LG)(FG)}$$

$$\cos \angle LGF = \frac{(8.60)^2 + (1.34)^2 - (7.31)^2}{2(8.60)(1.34)}$$

$\angle LGF = 14.4^\circ$



Consider ΔLGH

$\angle LGH = \angle LGF + \angle LGH = 14.4^\circ + 112.8^\circ = 127.2^\circ$

Figure 9 (Continued)

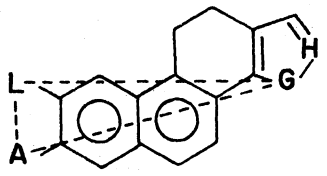
$$LH^2 = (LG)^2 + (GH)^2 - (\cos \angle LGH)(2)(LG)(GH)$$

$$LH^2 = (8.60)^2 + (1.34)^2 - (\cos 127.2^{\circ})(2)(8.60)(1.34)$$

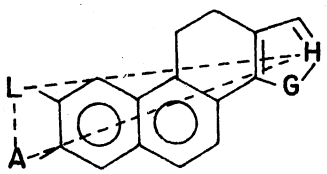
$$LH = 9.47 \text{ Å}$$

Figure 9 (Continued)

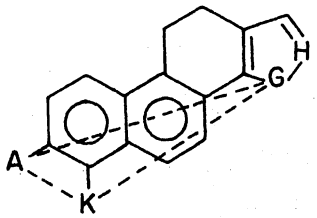
achieved by the same process used on the "model" compounds employing triangles ΔLAG in 191, ΔLAH in 192, ΔAGK in 193, and ΔAHK in 194. Results of these computations are given in Table XIV.



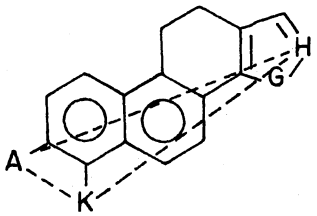
191



192

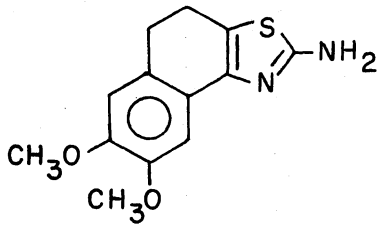


193



194

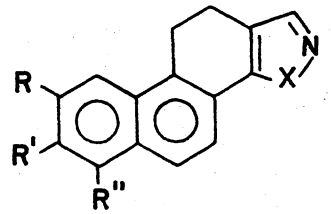
Because of the biological activity of 2-amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (111)[64] exhibited in both the microbial



111

TABLE XIII

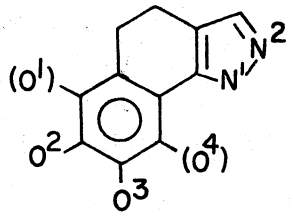
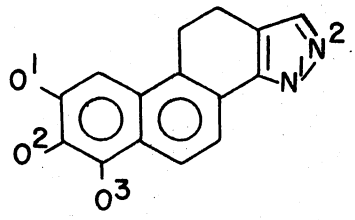
CALCULATED HETEROATOM DISTANCES (Å) IN PYRAZOLOSTEROIDS



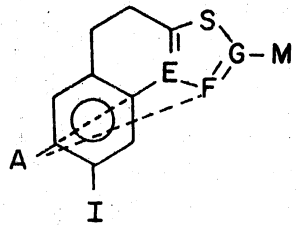
Cpd.	R	R'	R"	X	R'-R"	R-R"	R-X	R'-X	R"-X	R-N	R'-N	R"-N
110	CH_3O	CH_3O	H	N	2.75	-	8.60	8.62	-	9.47	9.91	-
106	CH_3O	CH_3O	CH_3O	N	2.75	4.76	8.60	8.62	7.27	9.47	9.91	8.55
204	CH_3O	CH_3O	H	O	2.75	-	8.61	8.76	-	9.42	9.99	-
107	CH_3O	CH_3O	CH_3O	O	2.75	4.76	8.61	8.76	7.27	9.42	9.99	8.54

TABLE XIV

TRIANGULATION ANGLES IN "MODEL" SYSTEMS AND PYRAZOLOSTEROIDS

Cpd. Reference	Specific	Value (°)	Specific	Value (°)
	O^1-N^1-O^2	24.5	O^1-N^2-O^2	20.5
	O^1-O^2-N^1	89.8	O^1-O^2-N^2	64.0
	O^2-O^1-N^1	65.7	O^2-O^1-N^2	95.5
	O^2-N^1-O^3	23.6	O^2-N^2-O^3	20.1
	O^2-O^3-N^1	104.8	O^2-O^3-N^2	103.2
	O^3-O^2-N^1	51.5	O^3-O^2-N^2	56.7
	O^3-N^1-O^4	14.5	O^3-N^2-O^4	10.4
	O^3-O^4-N^1	150.7	O^3-O^4-N^2	153.9
	O^4-O^3-N^1	14.8	O^4-O^3-N^2	15.7
	O^1-N^1-O^2	18.4	O^1-N^2-O^2	16.1
	O^1-O^2-N^1	80.4	O^1-O^2-N^2	72.8
	O^2-O^1-N^1	81.2	O^2-O^1-N^2	91.6
	O^2-N^1-O^3	17.4	O^2-N^2-O^3	14.9
	O^2-O^3-N^1	110.3	O^2-O^3-N^2	111.9
	O^3-O^2-N^1	52.3	O^3-O^2-N^2	53.2

and tissue culture screens, the heteroatomic distances of 111 were also computed. Calculations similar to the "model" pyrazole 109 were made using the following triangulations: ΔAEF in 195, ΔAFG in 196, ΔAGM in



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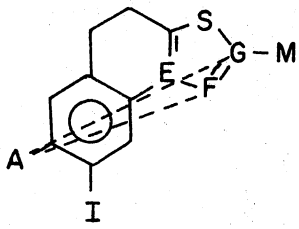

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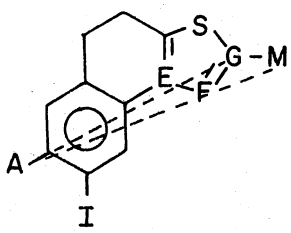

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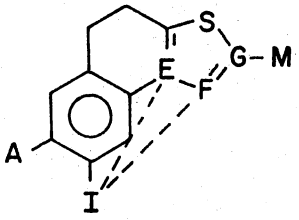

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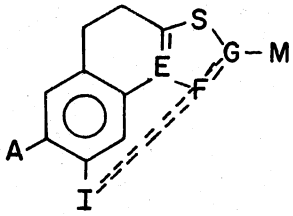

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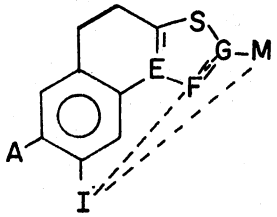
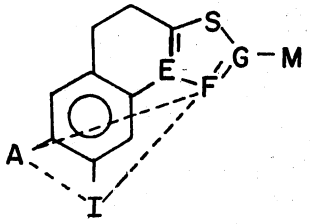


200



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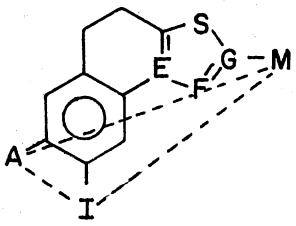


202

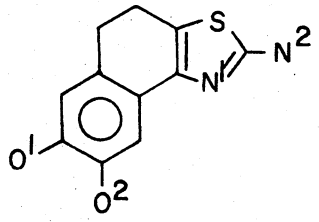
197, ΔIEF in 198, ΔIFG in 199, and ΔIGM in 200. Triangles ΔAFI in 201 and ΔAMI in 202 were used for determining O-N-O angles. Results of these calculations are shown in Table XV.

Correlation of Structure to Biological Activity

There has always been considerable interest in establishing the

TABLE XV

CALCULATED HETEROATOM DISTANCES AND ANGLES IN 2-AMINO-4,5-DIHYDRO-7,8-DIMETHOXYNAPHTHO[1,2-d]THIAZOLE (111)



Heteroatoms	Distance (Å)	Specific ∠	Value (°)
O^1-N^1	6.63	O^1-N^1-O^2	23.6
O^1-N^2	8.99	O^1-O^2-N^1	104.8
O^1-S	7.97	O^2-O^1-N^1	51.6
O^2-N^1	5.37	O^1-N^2-O^2	16.4
O^2-N^2	7.58	O^1-O^2-N^2	112.3
O^2-S	7.47	O^2-O^1-N^2	51.3

relationship of chemical structure to biological activity. Not only is an interpretation of this type fundamental to the understanding of the function of drugs, but also it is basic to the rational design of more effective analogs.

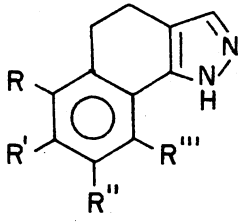
Pyrazoles were selected for this correlation due to the activity they exhibited in the growth studies of B. subtilis and the consequent tissue culture screening. Since the heterocyclic ring is identical in all cases, it is not unreasonable to assume that either the number and/or orientation of methoxy groups or the heteroatomic distances between the methoxy oxygen atoms and the pyrazole nitrogen atoms might be significant in the exhibited biological activity. Therefore, a study of such parameters was undertaken.

Table XVI gives a comparison of the percent of plating efficiency exhibited to the number and position of methoxy groups in "model" systems and the pyrazolosteroids. Because of the relatively large effort devoted to synthesis and the number of compounds purified (and analyzed), caution is required in making comparison of the number of methoxy groups present and the biological activity expressed at a given concentration of compound. However, with the data available, no direct correlation is apparent between the number of methoxy groups and the percent plating efficiency of KB cells. Obviously, for statistical significance one should include many more compounds and also the monomethoxy and tetramethoxy derivatives.

It is interesting that the dimethoxy pyrazolosteroid 110 did not exhibit any inhibitory effects on plating efficiency up to 150 µg./ml. The trimethoxy-substituted pyrazolosteroid 106 exhibited little effect at 50 µg./ml. (70% plating efficiency) but a more substantial effect was

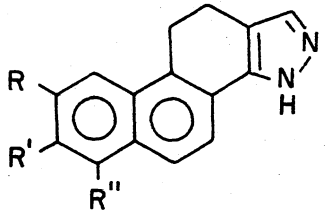
TABLE XVI

COMPARISON OF METHOXY ORIENTATION IN "MODEL" SYSTEMS AND PYRAZOLOSTEROIDS AND PERCENT PLATING EFFICIENCY AT DIFFERENT CONCENTRATIONS



Cpd.	R	R'	R''	R'''	% Plating Efficiency 25 µg./ml.	50 µg./ml.	150 µg./ml.
109	H	CH_3O	CH_3O	H	65	31	0
97	CH_3O	CH_3O	CH_3O	H	100	91	0
98	H	CH_3O	CH_3O	CH_3O	75	14	3

TABLE XVI (Continued)



Cpd.	R	R'	R"	% Plating Efficiency 25 µg./ml.	50 µg./ml.	150 µg./ml.
110	CH_3O	CH_3O	H	100	100	100
106	CH_3O	CH_3O	CH_3O	100	70	15

observed at 150 μg./ml. (15% plating efficiency, 85% inhibition). However, all of the "model" compounds were totally inhibitory at 150 μg./ml. This might indicate that size itself is important. Solubility differences might also be significant here as the "model" compounds are more water-soluble.

Comparisons of the ratios of heteroatomic distances (≥ 1) distinct for each compound and the percent plating efficiency are shown in Table XVII. For example, 4,5-dihydro-6,7,8-trimethoxy-1H-benz[g]indazole (97) contains three methoxy groups, yet only ratios $\frac{O^1\text{-}N^1}{O^2\text{-}N^1}$ and $\frac{O^1\text{-}N^2}{O^2\text{-}N^1}$ are distinct because the ratios $\frac{O^3\text{-}N^1}{O^2\text{-}N^1}$ and $\frac{O^3\text{-}N^2}{O^2\text{-}N^2}$ are also formed in 4,5-dihydro-7,8-dimethoxy-1H-benz[g]indazole (109) and 4,5-dihydro-7,8,9-trimethoxy-1H-benz[g]indazole (98). Ratios $\frac{O^3\text{-}N^1}{O^2\text{-}N^1}$ and $\frac{O^3\text{-}N^2}{O^2\text{-}N^2}$ are considered unique for 109 because no other possibilities exist. Although 111 is not a pyrazole, data for it are also included because of its somewhat related structure and biological activity. Only O-N distances are considered for this compound since none of the pyrazoles contain sulfur.

A graphical presentation of these data is given in Figure 10, where the $\frac{O^A\text{-}N}{O^B\text{-}N}$ ratios calculated are plotted against the precent plating efficiency of KB cells at a test compound concentration of 50 μg./ml. For three compounds (97, 98, and 109) maximum and minimum heteroatom distances ($O^1\text{-}N^1$, $O^2\text{-}N^1$, $O^3\text{-}N^1$, $O^3\text{-}N^1$) were calculated using standard deviation values from the x-ray data selected for bond lengths in the models used. Maximum and minimum ratios calculated from these data are represented by the three bar lines in Figure 10. There is no obvious reason to assume that the limits of the ranges for the remaining points would deviate significantly from what we have found for the ranges of

TABLE XVII

COMPARISON OF $\frac{O^A\text{-}N}{O^B\text{-}N}$ RATIOS OF PYRAZOLES AND 111 AND PLATING EFFICIENCY

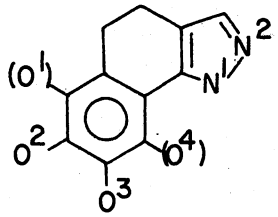
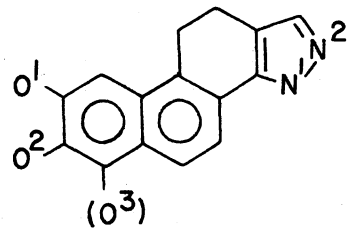
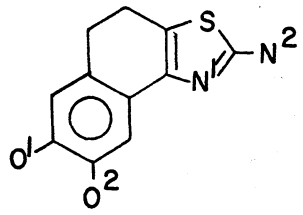
Cpd. Reference	Cpd.	Ratio Calc'd	% Pl. Eff. at 50 µg./ml.
	97	$\frac{O^1\text{-}N^1}{O^2\text{-}N^1} = .931$	91
	97	$\frac{O^1\text{-}N^2}{O^2\text{-}N^2} = .903$	91
	109	$\frac{O^3\text{-}N^1}{O^2\text{-}N^1} = .810$	31
	109	$\frac{O^3\text{-}N^2}{O^2\text{-}N^2} = .859$	31
	98	$\frac{O^4\text{-}N^1}{O^3\text{-}N^1} = .521$	14
	98	$\frac{O^4\text{-}N^2}{O^3\text{-}N^2} = .615$	14

TABLE XVII (Continued)

Cpd. Reference	Cpd.	Ratio Calc'd	% Pl. Eff. at 50 µg./ml.
	110	$\frac{O^1-N^1}{O^2-N^1} = .998$	100
	110	$\frac{O^1-N^2}{O^2-N^2} = .956$	100
	106	$\frac{O^3-N^1}{O^2-N^1} = .843$	70
	106	$\frac{O^3-N^2}{O^2-N^2} = .863$	70
	111	$\frac{O^2-N^1}{O^1-N^1} = .810$	56
	111	$\frac{O^2-N^2}{O^1-N^2} = .843$	56

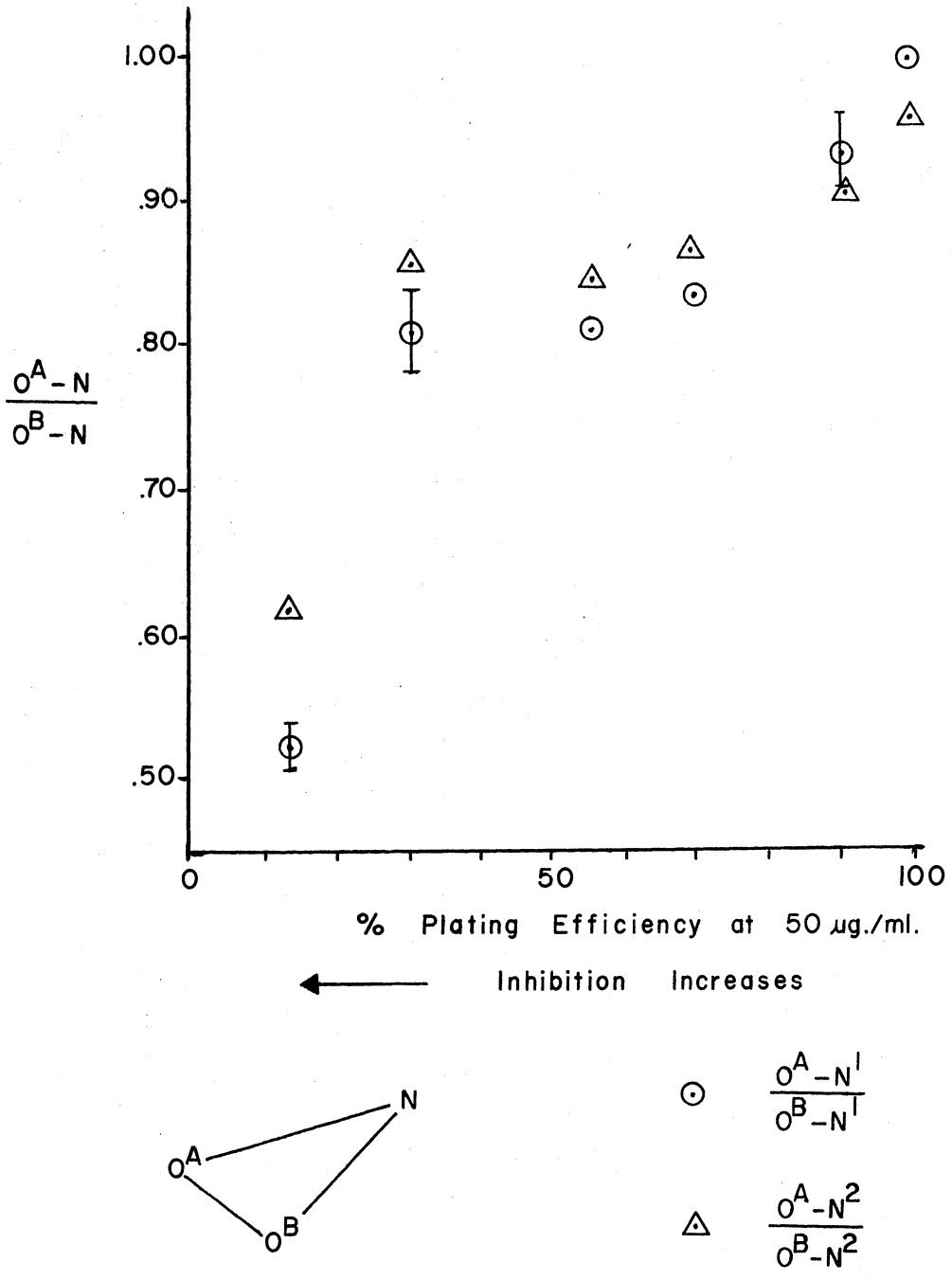


Figure 10. Relationship Between the $\frac{O^A-N}{O^B-N}$ Ratio from the Triangulation Process and the Plating Efficiency of KB Cells at 50 µg./ml.

the three points chosen.

Calculation of the correlation coefficient (r) using the equation given [where $\overline{X}$ and $\overline{Y}$ represent the mean values and X_i (ratio) and Y_i

$$r = \frac{\Sigma(X_i - \overline{X})(Y_i - \overline{Y})}{\sqrt{\Sigma(X_i - \overline{X})^2 \Sigma(Y_i - \overline{Y})^2}}$$

(plating efficiency) represent the individual values], indicates that a probable correlation exists. Consideration of only the $\frac{O^{A}\text{-}N^{1}}{O^{B}\text{-}N^{1}}$ points (n = 6) gave r = .914; consideration of only the $\frac{O^{A}\text{-}N^{2}}{O^{B}\text{-}N^{2}}$ points (n = 6) gave r = .855; consideration of all points (n = 12) gave r = .875. Confidence limits[107] (n = 6, $r \geq .815$, 95%; n = 6, $r \geq .920$, 99%; n = 12, $r \geq .575$, 95%; n = 12, $r \geq .710$, 99%) indicates a better than 95% probability of correlation. Although the sample size is small, there does seem to be a general trend in that as $\frac{O^{A}\text{-}N}{O^{B}\text{-}N}$ approaches 1, inhibition decreases (plating efficiency approaches 100%) and the more $\frac{O^{A}\text{-}N}{O^{B}\text{-}N}$ deviates from 1, the inhibition increases (plating efficiency approaches 0%). More specific examples are needed before this trend could really be deemed significant. Dimethoxy-substituted pyrazoles involve only two possible ratios. Thus, an exhaustive study might eliminate or prove the relevance of interaction of other groups on the activity. At the moment, we have not determined conclusively the effect of the remaining oxygen-nitrogen distance in the trimethoxy compounds.

A comparison of O-N-O angles as calculated from the triangulation process and the plating efficiency of KB cells at a test compound concentration of 50 μg./ml. is given in Figure 11. This graph would indicate that there is no correlation between the O-N-O angles and inhibition exhibited by these compounds on KB cell cultures. Again,

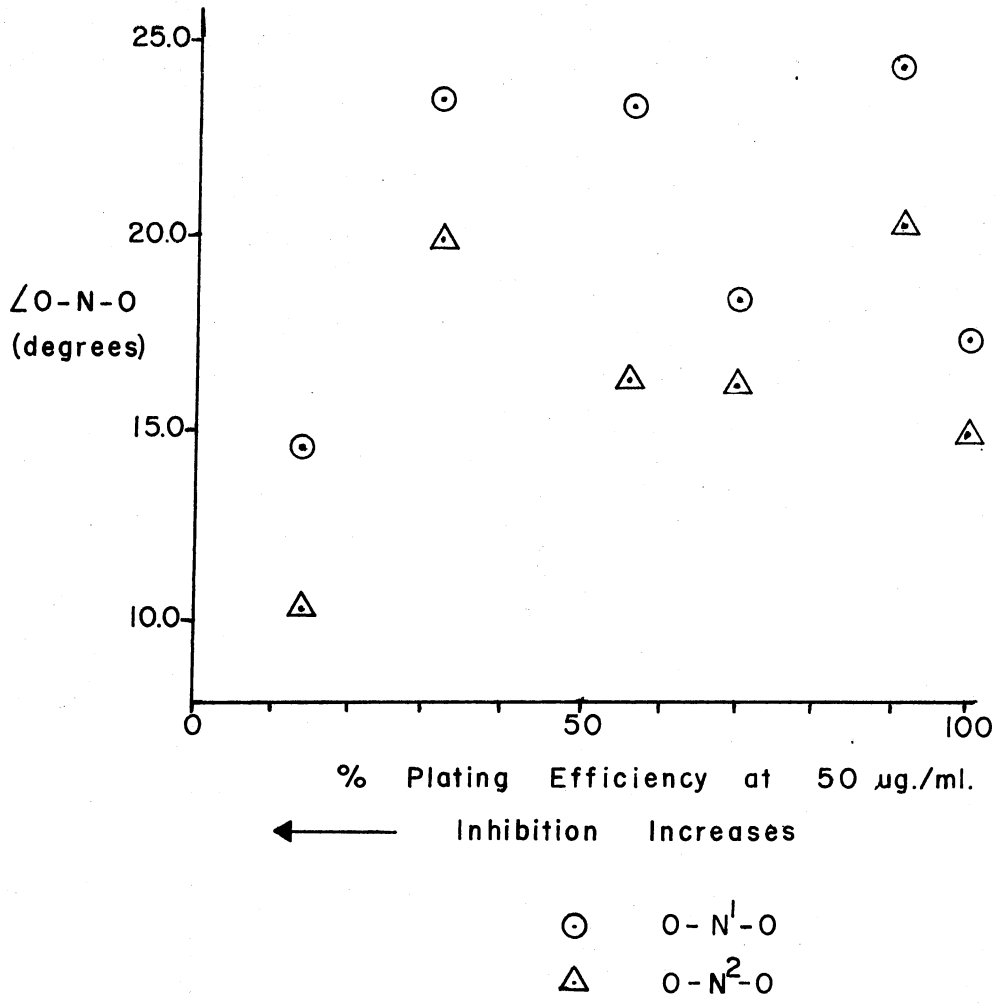


Figure 11. Relationship Between the O-N-O Angle from the Triangulation Process and the Plating Efficiency of KB Cells at 50 µg./ml.

care must be exercised in interpreting the lack of correlation of such data here on the basis of limited test compounds.

Cheng reported[154] a common triangulation process, consisting of one N atom and two O atoms, revealing a correlation existed among a wide variety of antileukemic agents of both synthetic and natural origin. This suggested that the arrangement of these atoms could be critical for binding to receptor sites on an enzyme, protein, etc., in vivo. However, it was found that the angles in the triangulation process were not critical,[27] which suggested another role for the heteroatoms besides binding (perhaps via a charge transfer complexation).[82]

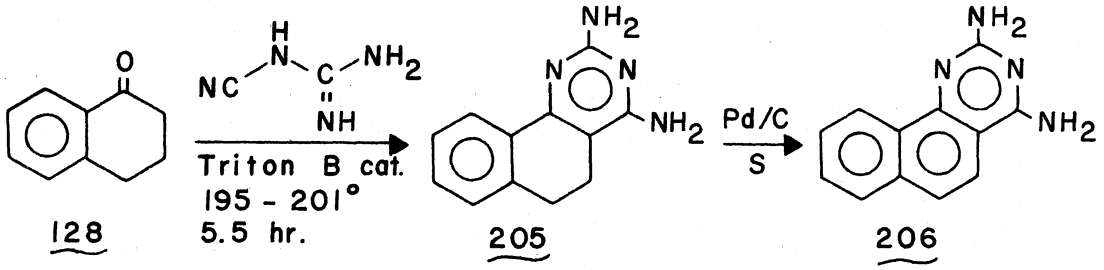
In our system, the observed biological activity of the pyrazoles and thiazole 111 appears to be somewhat dependent upon the $\frac{O^A\text{-}N}{O^B\text{-}N}$ ratio, but a relationship with the O-N-O angle is not apparent. However, it is certainly plausible that steric compression generated from repulsion of the three oxygen atoms bonded to three adjacent sp^2 carbon atoms in the arene ring could alter any O-O distance. Consequently, the basic length of the triangle (O-O distance) used in the calculations might vary from compound to compound. This, in turn, would change the expected O-N-O angle. Therefore, the O-N-O angle cannot be predicted accurately which would result in what appears to be a random relationship between $\angle$ O-N-O and plating efficiency. Also, there could be another role for the heteroatoms in addition to binding,[154] or the conformation at the binding site might be rather unrestricted.

Either of these hypotheses would be difficult to substantiate without an understanding of the inhibition mechanism. It is recognized that even in systems as simple as some of ours, additional mechanistic work at the molecular level is needed to determine the true cause of

inhibition. Thus, we are somewhat limited to date in our understanding of the role of heteroatoms in the pyrazoles in inhibiting KB cell plating, but we can infer that the heteroatom distances between oxygen and nitrogen atoms do have an effect on reactivity.

Suggestions for Further Work

The successful application of synthetic methods for the heterosteroids and "model" compounds herein discussed could be extended to the formation of similar compounds containing heterocyclic and trimethoxyarene functions. Sengupta and co-workers[125] report the preparation of the diaminopyrimidines 205 and 206 from the condensation of 1-tetralone (128) with dicyandiamide in the presence of Triton B.



128 205 206

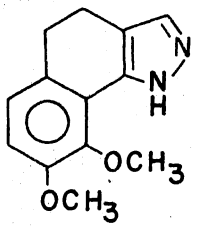
Realizing the importance of pyrimidines in biological systems,[28,29,30] by applying this method to the polymethoxytetralones and -phenanthrones one might conceivably prepare biologically active diaminopyrimidines.

Since 1,2-benzisoxazole (207) and 4,5,6,7-tetrahydro-1,2-benzisoxazole (208) undergo photoinduced transposition into either benzoxazole (209)[48] or 4,5,6,7-tetrahydrobenzoxazole (210)[48] (the latter

207 209 208 210

in almost quantitative yield), it is conceivable that the same process could be applied to the isoxazoles 99 and 100 for formation of the corresponding oxazoles.

For a more complete study of a possible correlation between the methoxy-heteroatom distances and biological activity, other possible ortho-methoxypyrazoles 211 and 212 and the tetramethoxy derivative 213



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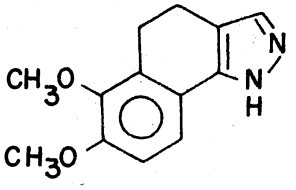

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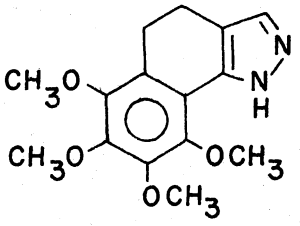
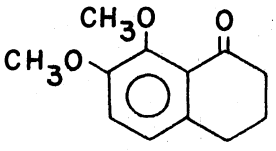


213

should be synthesized and screened. Tetralones 215 and 216 are known and could be easily prepared;[7,45] however, starting tetralone 214 has



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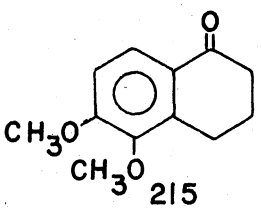
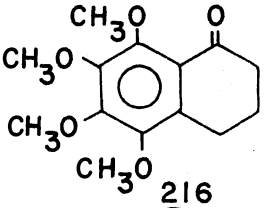


215



216

not been reported. This tetralone might be difficult to obtain by similar processes due to the steric hindrance of the methoxy group at C(8).

Pyridine hydrochloride is probably a commendable reagent for methoxy cleavage of the trimethoxy derivatives. However, it may not be successful on the isoxazoles due to their propensity to undergo ring opening.[59] Longer reaction times might be necessary for complete demethylation of the pyrazoles, but increased temperature might lead to decomposition.

To increase water solubility in ways other than cleavage of the methoxy groups, it is conceivable that hydrophilic groups (i.e., carboxylic or sulfonic acids or sugars, such as glucose or ribose) could be added to the pyrazoles or the hydrochlorides of the amino-pyrimidines could be formed.[17]

CHAPTER III

EXPERIMENTAL[a-f]

Preparation of 3,4-Dihydro-5,6,7-1(2H)-naphthalenone (28).[132] 1,2,3-Trimethoxybenzene (16.8 g., 0.1 mole) and 3-carbomethoxypropanoic acid (20 g., 0.15 mole) were stirred for 2.5 hr. in 230 g. of 115% PPA, the temperature being maintained at 45°. The mixture was then poured with stirring into 500 ml. of ice and water. The granular product was removed by filtration, washed with H_2O and 5% $NaHCO_3$, and dissolved in 100 ml. of diethyl ether. After the ethereal solution was dried ($MgSO_4$), it was concentrated to give an oil which crystallized upon standing

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[a]Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected.

[b]Proton magnetic resonance spectra were taken on a Varian XL-100 (15) high resolution NMR spectrometer using tetramethylsilane (TMS) as the internal standard.

[c]Infrared spectra were taken on a Beckman IR-5A spectrophotometer with samples as films on sodium chloride discs or in potassium bromide pellets.

[d]Low and high resolution mass spectra were obtained on a CEC 21-110 B double-focusing mass spectrometer.

[e]Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

[f]Commercially available reagents were used without further purification unless otherwise stated. Sodium methoxide was obtained from Research Organic/Inorganic Chemical Corporation, Belleville, New Jersey and 115% polyphosphoric acid (82.3% P_2O_5, guaranteed minimum) was obtained from FMC Corporation.

(25.2 g., 0.082 mole, 86% crude). Recrystallization of the solid (hot hexane) gave pure methyl 4-(2',3',4'-trimethoxyphenyl)-4-oxobutanoate (114), m.p. 48-49°, lit.[55] m.p. 48-49° (20.4 g., 0.072 mole, 72%); ir (KBr) μ: 5.77 (C=O), 6.02 (C=O); nmr ($DCCl_3$), δ 2.71 (t, 2, J_{HCCH} = 6 Hz, CH_2CH), 3.30 (t, 2, J_{HCCH} = 6 Hz, CH_2CO), 3.69 (s, 3, CO_2CH_3), 3.87, 3.90, and 3.99 [s, 9, Ar $(OCH_3)_3$], 6.71 and 7.53 [d(AB pattern), 2, J_{HCCH} = 4.5 Hz, ArH].

A sample of 114 (9.5 g., 0.032 mole), glacial acetic acid (60 ml.), and palladium on charcoal (10%, 4 g.) was shaken under a H_2 atmosphere (30-40 psi) in a Parr hydrogenation apparatus. The reaction temperature was maintained at ca 60°. Hydrogen uptake ceased after ca 30 min. (theoretical amount). The reaction mixture was cooled and filtered through a cake of filter aid. Solvent was removed to give crude methyl 4-(2',3',4'-trimethoxyphenyl)butanoate (115) (8.6 g., quantitative) as a pale yellow oil. An analytical sample was obtained by distillation, b.p.113-114°/20-30 mm.; ir (film) μ: 3.40 (C-H), 5.75 (C=O), 6.25 (Ar), 9.05 (OCH_3); nmr ($DCCl_3$), δ 1.85 (m, 2, $CH_2CH_2CH_2$), 2.34 (t, 2, J_{HCCH} = 6 Hz, $CH_2CH_2CH_2$), 2.60 [t, 2, J_{HCCH} = 7 Hz, $CH_2CH_2CH_2C(O)$], 2.65 (s, 3, CO_2CH_3), 3.81, 3.84, and 3.87 [s, 9, Ar $(OCH_3)_3$], 6.59 and 6.81 [d(AB pattern), 2, J_{HCCH} = 8 Hz, ArH].

Saponification of 115 (8.6 g., 0.032 mole) was achieved by boiling 115 in 100 ml of 5% NaOH for 5 hr. The cooled basic solution was extracted (ether, 3x, 50 ml) and the extracts were discarded. The aqueous portion was acidified with HCl (6N) and extracted (ether, 2x, 60 ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give 4-(2',3',4'-trimethoxyphenyl)butanoic acid (8.0 g., quantitative) as a clear oil; ir (film) μ: 2.9 (OH), 5.85 (C=O), 9.06 (OCH_3), 6.25

(Ar); nmr ($DCCl_3$), δ 1.95 (m, 2, $CH_2\underline{CH_2}CH_2$), 2.40 (t, 2, $\underline{J}_{HCCH}$ = 7 Hz, $\underline{CH_2}$-CO_2H), 2.63 (t, 2, $\underline{J}_{HCCH}$ = 7 Hz, Ar CH_2), 3.82, 3.86, and 3.88 [s, 9, Ar $(OCH_3)_3$], 6.58 and 6.82 [d(AB pattern), 2, $\underline{J}_{HCCH}$ = 8 Hz, Ar $\underline{H}$] and 10.98 (s, 1, CO_2H).

The crude trimethoxyphenylbutanoic acid (8.0 g., 0.032 mole) without further purification was treated with 115% PPA (80 g.) with stirring for 45 min. at 65-70°. The dark mixture was cooled to room temperature and poured into 200 ml of 50/50 ice/H_2O. After the mixture was thoroughly hydrolyzed, the product was filtered out, washed (2% $NaHCO_3$) and (air) dried to give crude 28. Sublimation (72-76°/0.0009 mm.) gave pure 28 (6.4 g., m.p. 74.5-76°, lit.[65] m.p. 74-74.5°, 84%). IR, NMR and mass spectral analyses (Plates I, II, and Table VIII) support the structure of 3,4-dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone.

Preparation of the Oxime of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (139).[123] To a solution of 0.5 g. (0.0073 mole) of hydroxylamine hydrochloride in 3 ml. of water was added 2 ml. of an aqueous 10% sodium hydroxide solution and 0.2 g. (0.0082 mole) of the trimethoxytetralone 28. Just enough 95% ethanol was added to dissolve the ketone. After the solution was heated on a steam bath for 15 min. and then cooled in an ice/H_2O bath, a white precipitate formed. Filtration and drying in vacuo gave 0.18 g. (51%) of the oxime 139, m.p. 102-103°. The structure of 139 is supported by IR and NMR spectra (Plates III and IV) along with mass spectral data (Table VIII).

Anal. Calcd. for $C_{13}H_{17}NO_4$: N, 5.58.

Found: N, 5.42.

Preparation of the Methoxime of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (140).[127] Methoxyamine hydrochloride (0.7 g., 0.0084 mole)

was dissolved in 3 ml. of water. Two ml. of aqueous 10% sodium hydroxide solution and 0.2 g. (0.00082 mole) of the tetralone 28 was added. Enough 95% ethanol was added to dissolve the tetralone. After heating on a steam bath for 15 min., the solution was cooled in an ice/H_2O bath. The methoxime 140 was collected (76 mg., 35%, m.p. 55-56.5°) and structural characterization was achieved via IR, NMR and mass spectral analyses (Plates V, VI and Table VIII).

Anal. Calcd. for $C_{14}H_{19}NO_4$: N, 5.28.

Found: N, 5.04.

Preparation of the Thiosemicarbazone of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (141).[127] Trimethoxytetralone 28 (2.0 g., 0.0085 mole) and 0.77 g. (0.0085 mole) of thiosemicarbazide were added to 50 ml. of methanol. The resulting solution was boiled for an hour, cooled overnight, and filtered. The white solid [m.p. 185-186° (decomp.), 1.6 g., 61%] is shown by IR, NMR and mass spectral data (Plates VII, VIII and Table VIII) to be 141.

Anal. Calcd. for $C_{13}H_{19}N_3O_3S$: N, 13.59.

Found: N, 13.48.

Preparation of the 2,4-Dinitrophenylhydrazone of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (136).[126] 2,4-Dinitrophenylhydrazine (0.4 g., 0.0020 mole) was added to 2 ml. of concentrated H_2SO_4. Three ml. of water was added with stirring until solution was complete; then 95% ethanol (10 ml.) was added. The trimethoxytetralone 28 (0.47 g., 0.0020 mole) was dissolved in 20 ml. of 95% ethanol. Immediate reaction occurred upon mixing the two solutions and the bright red solid precipitate was collected by suction filtration. Recrystallization from ethyl acetate/95% ethanol gave 0.55 g. (66%) of pure 136, m.p. 244-245°

(lit.[65] m.p. 245°). IR and NMR spectral data (Plates IX and X) support the structure of 136.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: N, 13.46.

Found: N, 13.44.

Preparation of 3,4-Dihydro-2-(hydroxymethylene)-5,6,7-trimethoxy-1(2H)-naphthalenone (142). A mixture of 4.63 g. (0.085 mole) of sodium methoxide and 6.30 g. (0.085 mole) of ethyl formate in 50 ml. of anhydrous benzene (reagent grade, dried over Na metal) was cooled under N_2 to 0-3° in an ice/H_2O bath. 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (28) (10.0 g., 0.0424 mole) was dissolved in 50 ml. of anhydrous benzene and slowly added through an addition funnel to the cooled reaction mixture (temperature between 0-3°). This yellow mixture was stirred (under N_2) at 0-3° for 1 hr. and then allowed to come to room temperature for 2 hr. The reaction mixture now was a yellow gel which was scooped out into 200 ml. of ice and stirred until the ice had dissolved. The organic layer was separated and washed twice with H_2O and once with 5% NaOH. These aqueous washings were added to the original aqueous layer and washed first with benzene then once with ether. The remaining aqueous layer was acidified (10% HCl) to pH 6.0 and washed (ether, 3x, 50 ml.). The ether layers were combined and the ether was evaporated leaving a dark brown oil. The oil was dissolved in hot hexanes and decolorized with activated charcoal. Upon cooling, cubic crystals formed, which were pure 142 (7.75 g., 69%), m.p. 74-76°. A mixed m.p. with 28 was taken, m.p. 55-64°. The proposed structure of 142 is confirmed, by IR, NMR, and mass spectral analyses (Plates XIII, XIV, and Tables VIII and IX).

Preparation of 4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole (97). The hydroxymethylene compound 142 (5.1 g., 0.0193 mole) was dissolved in 50 ml. of anhydrous methanol (distilled from Mg) and 5.0 ml. (5.0 g., 0.16 mole) of hydrazine (anhydrous, 97+%) was added. Being exothermic, the mixture was stirred (under N_2) for 3.5 hr. Water (80 ml.) was added and the resulting solution was cooled overnight. Tan crystals formed and were filtered out to give crude 97 (3.4 g., 68%). Recrystallization (benzene/hexane) gave pure 97, m.p. 94-95°. IR, NMR, and mass spectral analyses (Plates XV, XVI and Table VIII) support the proposed structure of 97.

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

Found: N, 10.64.

Preparation of 4,5-Dihydro-6,7,8-trimethoxynaphth[1,2-d]isoxazole (99). To a solution of 4.4 g. (0.017 mole) of the α-ketohydroxymethylene compound 142 in 50 ml. of glacial acetic acid was added a solution of 1.16 g. (0.017 mole) of hydroxylamine hydrochloride and 1.37 g. (0.017 mole) of sodium acetate in 4 ml. of water. The mixture was stirred (under N_2) and heated to 100° C for 1 hr. Cooling to room temperature caused deposition of a small amount of solid which was filtered off. The filtrate was cooled in an ice/H_2O bath and water was added until precipitation was complete. The dark reaction mixture was filtered and the brown solid was washed with 5 ml. of cold H_2O and air dried. The crude material was then sublimed (95°/7.5 x 10^{-4} mm.) to yield 2.9 g. (67%) of pure 99, m.p. 92-93°. IR, NMR, and spectral analyses (Plates XVII, XVIII and Table XVIII) support the proposed structure of 99.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36.

Found: C, 64.35; H, 5.88; N, 5.27.

Preparation of Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-oxo-2-naphthoate (148). Trimethoxytetralone 28 (11.1 g., 0.47 mole) was dissolved in 50 ml. of anhydrous dimethyl carbonate (distilled from NaH, b.p. 89-90°). Sodium methoxide (4.85 g., 0.090 mole) was added and the mixture was boiled (3 hr.). The solvent was evaporated off and 50 ml. of water was added to the residue. After acidification (pH 6.8) with 25% aqueous acetic acid, the solution was extracted with ether (2x, 30 ml.). Evaporation of the ether gave a mixture of the keto ester 148 and starting tetralone 28. Distillation of the mixture gave 10.2 g. (64%) of crude 148, b.p. 188-192°/0.4 mm., suitable for use in subsequent reactions. Crystallization of the slightly yellow oil from methanol gave a pure sample of 148, m.p. 71-74°. IR, NMR, and mass spectral analyses (Plates XIX, XX and Tables VIII and IX) support the proposed structure of 148.

Preparation of 4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole (101). The crude keto ester 148 (3.75 g., 0.0127 mole) was dissolved in 5 ml. of anhydrous methanol (distilled from Mg); hydrazine (4.1 ml., 4.1 g., 0.045 mole, anhydrous, 97+%) was added and the solution was heated at reflux (1 hr.). After the solution was cooled to room temperature, 30 ml. of water was added, and the mixture was chilled (ice/H_2O bath) until a precipitate formed. Filtration and recrystallization from 50/50 C_2H_5OH/H_2O gave a white crystalline product (0.58 g.), m.p. 74-76°, which proved on analysis [see IR, NMR, and mass spectral data (Plates XXI, XXII and Tables VIII and IX)] to be 149 rather than the expected indazole 101. Upon standing for a couple of days, the original filtrate produced a white precipitate. Filtration and

sublimation (192°/0.003 mm.) of this solid gave a pure white compound, m.p. 235-237° (1.19 g., 34%) which, when analyzed by IR, NMR, and mass spectral methods (Plates XXI, XXII and Tables VIII and IX), proved to be the expected pyrazolone 101.

Preparation of 2-Amino-5,6-dihydro-7,8,9-trimethoxybenzo[h]-quinazolin-4-ol (104). Guanidine hydrochloride (0.77 g., 0.0080 mole) and sodium methoxide (0.87 g., 0.016 mole) were dissolved in 40 ml. of absolute methanol (distilled from Mg). The keto ester 148 (2.34 g., 0.00795 mole) was dissolved in 20 ml. of absolute methanol and slowly added to the first solution. After heating under N_2 for 9 hr., the solvent was evaporated off and the residue was dissolved in 40 ml. of water. Treatment with Nuchar, followed by filtration through Celite filter aid, yielded a slightly brown solution. This was first washed with ether, cooled in an ice/H_2O bath, then acidified with glacial acetic acid to yield 1.035 g. of crude 104. Sublimation (186°/0.002 mm.) gave pure 104 (0.62 g., 26%) m.p. 255-257° (decomp.). NMR and IR analyses (Plates XXIII and XXIV) support the proposed structure of 104 as does mass spectral data (Table VIII).

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.41; H, 5.61; N, 13.86.
Found: C, 59.24; H, 5.75; N, 13.72.

Preparation of 5,6-Dihydro-2-mercapto-7,8,9-trimethoxybenzo[h]-quinazolin-4-ol (105). Thiourea (0.39 g., 0.0051 mole) and sodium methoxide (0.44 g., 0.010 mole) were dissolved in 50 ml. of 2-propanol. After addition of the keto ester 148 (1.50 g., 0.0051 mole), the reaction mixture was vigorously boiled under N_2 for 24 hr. The reaction mixture became increasingly cloudy during the reaction time owing to the water formed in the reaction. Evaporation of the solvent left a dirty

yellow residue which was dissolved in 40 ml. of water. Extraction with ether afforded a pale yellow aqueous layer which, upon cooling in an ice/H_2O bath and slow acidification with glacial acetic acid, yielded 0.183 g. (0.00057 mole, 11.2%) of pure 105, m.p. 206-207° (decomp.). The structure of 105 is supported by IR and NMR (Plates XXV and XXVI) data and mass spectral data (Table VIII).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: N, 8.75; S, 10.00.

Found: N, 8.27; S, 9.60.

Preparation of 2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one (102). A three-necked, round-bottom flask fitted with a mechanical stirrer and Friedrich condenser was purged with nitrogen and dried by heating with a flame. 5,6,7-Trimethoxy-1-tetralone (28) (10 g., 0.058 mole), 4 g. (0.089 mole) of sodium methoxide, and 100 ml. of anhydrous dimethyl carbonate (distilled from NaH, b.p. 89-90°) were added to the dry apparatus and the mixture was heated at reflux for 2 hr. A yellow suspension formed and was diluted with 200 ml. of anhydrous methanol (distilled from Mg, b.p. 64°). Iodomethane (10 ml., 22.7 g., 0.16 mole) was added and the reaction mixture was stirred at room temperature overnight. An additional 5 ml. of iodomethane (0.08 mole) was added, and the mixture was boiled for 1 hr. After coming to room temperature, the brown solution was acidified to pH 6.5 (2 N acetic acid) and extracted three times with ether (30 ml. each). The ether layer was washed once with H_2O. After the ether was evaporated, the residue was vacuum-distilled to yield 13.35 g. (71.5%) of slightly colored methyl 1,2,3,4-tetrahydro-5,6,7-trimethoxy-2-methyl-1-oxo-2-naphthoate (153), b.p. 160-170°/0.3-0.5 mm.

Structural characterization is supported by IR, NMR, and mass spectra analysis (Plates XXVII, XXVIII and Tables VIII and IX).

To 13.35 g. (0.046 mole) of this keto ester 153 was added 16.0 g. (0.50 mole) of 95% hydrazine (from Eastman Chemical Company) and 10 ml. of anhydrous methanol (distilled from Mg, b.p. 64°). The mixture was heated to 50° for 1 hr. and then stirred at room temperature for an additional 2 hr. The cooled mixture was poured onto 50 ml. of H_2O; a white precipitate formed immediately. After filtration, the crystals were triturated in ether, filtered out, and sublimed (172°/0.005 mm.) to yield 11.4 g. (84.5%) of pure 102, m.p. 186-188°. IR, NMR, and mass spectral analyses (Plates XXIX, XXX, and Table VIII) support the proposed structure of 102.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: N, 9.65.

Found: N, 9.69.

Preparation of 5,6,7-Trimethoxy-1-naphthalenebutyric Acid (130). A zinc (50 g., 0.76 g. at.) sheet 1/100 in. thick was cut into approximately 0.25 in. by 0.5 in. pieces and washed consecutively with dilute HCl (2x, 100 ml.), distilled H_2O (3x, 150 ml.), acetone (3x, 150 ml.), and anhydrous ether (3x, 150 ml.). The zinc was then dried in an oven at 100° for at least 0.5 hr. before use.

A 300-ml. flask equipped with a condenser, mechanical stirrer, and N_2 inlet was purged with N_2 and flamed dry before 20 g. (0.31 g. at.) of the treated zinc, 72 ml. anhydrous, reagent-grade benzene, and 1.3 g. (0.0055 mole) of anhydrous $HgCl_2$ were added. This mixture was stirred under N_2 purge for 0.5 hr. Freshly distilled methyl 4-bromocrotonate [Aldrich Chemical Co., b.p. 32-35°/0.08-0.1 mm. (lit.[5] b.p. 83-85°/13 mm.)] (17.6 g., 0.98 mole) and 25.0 g. (0.106 mole) of 5,6,7-trimethoxy-

1-tetralone (28) in 20 ml. of anhydrous benzene and 50 ml. of anhydrous ether, along with a crystal of iodine, were added at one time to the reaction flask.

After about 1 hr. of heating, the mixture turned first green and then red-orange in color. At 1.5-hr. intervals, 10 g. (0.15 g. at.) of treated zinc and 5.7 g. (0.032 mole) of methyl 4-bromocrotonate were added. This procedure was performed 3 times, the mixture being boiled and stirred under N_2 the whole period.

Heating and stirring were continued for 17 hr. after the last addition; the mixture was then cooled, poured into ice water, neutralized with acetic acid, and extracted with ether. The organic phase was extracted three times (50 ml. each) with 5% aqueous NH_4OH, once with water (60 ml.), and once with saturated aqueous NaCl (40 ml.); the resulting solution was dried ($MgSO_4$). After filtering, the solvents were evaporated on an aspirator and the residual oil was distilled *in vacuo*. A forerun, consisting primarily of unreacted 28, distilled at 148-160°/0.5 mm. The product, which is a viscous, red-orange oil, amounted to 15.2 g. (45% based on 28), of crude methyl 4-(5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate (217) (b.p. 200-220°/0.5 mm.).

Crude 217 (9.88 g., 0.031 mole) was heated to 260° with 1.78 g. of 10% Pd/C for 6 hr. under a CO_2 atmosphere. The mixture was then cooled, diluted with ether, filtered, and evaporated. The residue was heated at reflux for 12 hr. with 3.8 g. (0.082 mole) of KOH in 40 ml. of 50/50 ethanol/H_2O.

The resulting hydrolyzate was diluted (H_2O), extracted 3 times (30 ml. each) (ether), and acidified (dil. HCl). The acidic solution was

extracted 3 times with ether (40 ml. each), and the ether was evaporated to yield a brown solid. This solid was placed in a Soxhlet extraction thimble and extracted with hexanes for 11 hr. On cooling, the hexane solution deposited 7.65 g. (81% from crude ester 129) of white crystals 130 (m.p. 123-127°) suitable for use in the next step. A pure sample (m.p. 127-128°) of 130 was crystallized from hexane. IR and NMR spectral data (Plates XXXI and XXXII) support the reported structure for 130.

Preparation of 3,4-Dihydro-6,7,8-trimethoxy-1(2H)-phenanthrone (131). Polyphosphoric acid (30 g. of 115% PPA) was heated to 110° in a 100-ml. beaker. Compound 130 (5.8 g., 0.022 mole) was added and the mixture was stirred for 15 min. An additional 30 g. of PPA was added and the mixture was reheated to 110° and then allowed to cool with stirring to 60°.

The resulting, dark-brown syrup was poured into 150 ml. of 50/50 ice/H_2O, and the dark tar-like precipitate was dissolved in benzene. The resulting solution was passed through a 50-g. (15 cm. by 1 cm.) column of alumina (Merck active aluminum oxide, neutral, activity I). The column was washed with additional benzene until no further material was eluted. Evaporation of the benzene in vacuo yielded 2.01 g. (32.5%) of 131 as a light yellow powder (m.p. 135-137°) suitable for use in the next step. After sublimation of a small amount of the above material, a white, analytically pure sample of 131 was obtained (m.p. 137-139°). IR, NMR and mass spectral analyses (Plates XXXIII, XXXIV, and Table VIII) support the proposed structure.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.33; H, 6.29.

Found: C, 70.93; H, 6.23.

Preparation of 3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-phenanthrone (144). A mixture of 10 ml. of anhydrous, reagent benzene, 1.0 g. (0.023 mole) sodium methoxide, and 1.37 g. (0.0185 mole) of ethyl formate (under N_2) was cooled to 0-3° in an ice/H_2O bath. A solution of phenanthrone 131 (1.68 g., 0.00587 mole) in 15 ml. anhydrous benzene was slowly added to the cooled mixture (temperature between 0-3°). The yellow solution was stirred (under N_2) at 0-3° for 1 hr. and then at room temperature for 3 hr. Water (60 ml.) was added, and the resulting two layers were separated. After washing (H_2O) the organic layer, the combined water layers were acidified with 20% aqueous HCl (pH 6.5). Cooling in an ice/H_2O bath caused precipitation of a yellow solid 144 (1.68 g., 91%) which was pure enough to use in subsequent reactions. Sublimation (140°/0.05 mm.) yielded pure 144, m.p. 144.5-146.5°. IR, NMR and mass spectral data (Plates XXXV, XXXVI, and Table VIII) support the proposed structure for 144.

Preparation of 10,11-Dihydro-6,7,8-trimethoxy-3H-phenanthro[1,2-c]-pyrazole (106). The hydroxymethylenephenanthrone 144 (1.55 g., 0.00495 mole), 20 ml. of anhydrous methanol (freshly distilled from Mg), and 1.5 ml. (1.5 g., 0.48 mole) of hydrazine (Matheson, Coleman and Bell, anhydrous, 97+%) were stirred and boiled (under N_2) for 3.5 hr. After addition of 30 ml. of water, the mixture was heated for 20 min. and then cooled in the refrigerator. The resulting precipitate was recrystallized from methanol and then sublimed (155°/0.05 mm.) to yield 1.1 g. (72%) of pure 106 (m.p. 169-171°). IR, NMR and mass spectral analyses (Plates XXXVII, XXXVIII, and Table VIII) support the proposed structure of 106.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: N, 9.03.

Found: N, 9.20.

Preparation of 10,11-Dihydro-7,8,9-trimethoxyphenanthro[1,2-d]-isoxazole (107). A mixture of the hydroxymethylenephenanthrone 144 (1.03 g., 0.0033 mole) and 12.5 ml. of glacial acetic acid was added to a dry flask. Hydroxylamine hydrochloride (0.24 g., 0.0034 mole) and sodium acetate (0.27 g., 0.0034 mole) were dissolved in 1 ml. of water and added to the reaction flask. The resulting solution was heated to 100° for 1 hr. and then allowed to cool to room temperature. Distilled water was added with stirring, until precipitation ceased. The light tan solid was filtered out and washed with water. Recrystallization from C_2H_5OH/acetone yielded 0.88 g. (86%) of pure 107, m.p. 142-143°. IR, NMR and mass spectral analyses (Plates XXXIX, XL, and Table VIII) confirm the proposed structure of 107.

Anal. Calcd. for $C_{18}H_{17}NO_4$: N, 4.50.

Found: N, 4.41.

Preparation of 2,10,11,11a-Tetrahydro-6,7,8-trimethoxy-11a-methyl-1H-phenanthro[1,2-c]pyrazol-1-one (108). A mixture of 1.46 g. (0.00511 mole) of the phenanthrone 131, 20 ml. (21.4 g., 0.24 mole) of anhydrous dimethyl carbonate (freshly distilled from NaH), and 1.0 g. sodium methoxide was boiled (under N_2) for 15 min. The mixture solidified and could not be stirred. Anhydrous methanol (30 ml.) was added and the solid was broken up so stirring could be continued. Methyl iodide (3 ml., 6.8 g., 0.048 mole) was added and the mixture was stirred at reflux for 1 hr. After cooling, the mixture was neutralized (CH_3CO_2H), and most of the solvents were removed with a rotary evaporator. The residue was diluted with water and extracted with three 30-ml. portions of ether. The combined ether extracts were dried ($MgSO_4$) and the ether

was evaporated to yield 1.55 g. (84.5%) of crude ester 155. Sublimation (125°/0.05 mm.) yielded pure 155, m.p. 138-139°. IR, NMR and mass spectral data (Plates XLI, XLII and Table VIII) support the proposed structure of 155.

The crude ester 155 (1.03 g., 0.0029 mole), 0.9 ml. (0.9 g., 0.03 mole) of anhydrous, 97+% hydrazine, and 5 ml. of anhydrous methanol (distilled from Mg) were combined and heated to 60° under N_2 for 1 hr. The remaining solution was poured over 50/50 ice/water (30 ml.) and extracted with ether. Sublimation (165°/0.05 mm.) of the residue, after evaporation of the ether, yielded 56 mg. (32.2% from the phenanthrone 131) of pure 108, m.p. 205-206°. IR, NMR, and mass spectral analyses (Plates XLIII, XLIV, and Table VIII) support the proposed structure of 108.

Anal. Calcd. for $C_{19}H_{21}N_2O_4$: N, 8.24.

Found: N, 8.22.

Preparation of 3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (125).[153] To a cold (5° C) solution of 180 g. (4.5 mole) of sodium hydroxide in 1100 ml. of water was added 110 g. (0.647 mole) of gallic acid (117). After all of the acid had dissolved, dimethyl sulfate (295 ml., 392 g., 3.12 mole) was added; the ice/H_2O bath was removed, and the solution was stirred for 20 min. The solution was then boiled for 2 hr. In order to saponify the small amount of ester produced, an additional 44 g. (1.1 mole) of sodium hydroxide in 66 ml. of water was then added, and boiling was continued for 2 hr. After cooling, the mixture was acidified (dilute HCl); the precipitated trimethylgallic acid (118) was filtered out and washed well with cold water. Recrystallization from water yielded 88 g. (71%) of pure 118, m.p. 165-167° (lit.[93]

m.p. 167°).

Trimethylgallic acid (118) (41 g., 0.19 mole) was heated with 50 g. (0.42 mole) of thionyl chloride until the evolution of HCl and SO_2 ceased (2 hr.). Benzene (100 ml.) was added and the mixture was cooled. Rotary evaporation of the solvents, followed by recrystallization (1 ml. benzene/100 ml. petroleum ether-b.p. 65-75°), gave 28 g. (49%) of 3,4,5-trimethoxybenzoyl chloride (119) (m.p. 74-77°, lit.[108] m.p. 77-78°).

Ethyl (3,4,5-trimethoxybenzoyl)acetoacetate (120) was prepared by the method of Koo.[81] Sodium (31.5 g., 1.37 g. at.) was dissolved in 500 ml. of absolute ether and 121.5 g. (0.935 mole) of ethyl acetoacetate. After the mixture had been stirred for 10 min., one-half of a solution of 119 (104 g., 0.45 mole) in 680 ml. of absolute ether was added dropwise during 30 min. The remaining one-third of the sodium ethoxide solution was added 20 min. later. Ten min. later the rest of the solution of acid chloride was added, again over a 30-min. period. Stirring was continued overnight. A thick paste was collected by suction filtration and dissolved in 1500 ml. of water, and the resulting solution was acidified (pH ≈ 5) (temp. between 0-5°). Recrystallization from aqueous ethanol provided 80 g. (55%) of ethyl (3,4,5-trimethoxybenzoyl)-acetoacetate (120) (m.p. 78-81°, lit.[81] m.p. 83-85°) suitable for use in the next step.

A mixture of 60 g. (0.165 mole) of finely ground 120 and 100 g. (1.89 mole) of ammonium chloride was placed in a large flask; a homogeneous suspension resulted after the gradual addition of 500 ml. of warm water (35°) with shaking. Another 2000 ml. of water (35°) was added all at once, followed by 500 ml. of 15% aqueous ammonia. Most of

the starting material dissolved when the mixture was shaken vigorously; that which remained was crushed by a flattened glass rod. After 10 min., the mixture was chilled rapidly by adding ice and placed in the refrigerator for 2 hr. The colorless solid was collected and dried to yield 45 g. (85%) of ethyl (3,4,5-trimethoxybenzoyl)acetate (121), m.p. 88-89° (lit.[81] m.p. 93-94°).

Sodium (3.5 g., 0.15 g. at.) was dissolved in 250 ml. of absolute ethanol with stirring. While the solution was yet warm (40°), 28.2 g. (0.10 mole) of 121 was added. After stirring for 15 min., the solution was cooled in an ice/H_2O bath. Ethyl bromoacetate (6.0 g., 0.038 mole) was added and the solution was stirred for 1 hr. An additional 12.0 g. (0.0755 mole) of ethyl bromoacetate was added and the solution was stirred overnight. The mixture was cooled again, diluted with water, acidified (50% HCl), and extracted with ether. The ethereal extracts were washed twice with 100 ml. of H_2O and dried ($MgSO_4$); the ether was evaporated leaving a pale yellow oil. This oil was boiled in 250 ml. of 20% aqueous sulfuric acid for 45 hr. After cooling, the mixture was extracted with ether, the solvent was removed, and the residue was boiled with 200 ml. of 5% sodium hydroxide solution for 1 hr. Acidification of the filtrate (after filtration) produced 24 g. (90%) of β-(3,4,5-trimethoxybenzoyl)propionic acid (123), m.p. 117-119° (lit.[66] m.p. 121-122°). This process was repeated and the yield of acid was slightly increased (26 g., 97%).

The acid 123 (50 g., 0.19 mole), 500 ml. of glacial acetic acid, and 6.0 g. of 10% palladium on charcoal were shaken under H_2 atmosphere (30-40 psi) in a Parr hydrogenation apparatus (temperature ca 60°).

After hydrogen uptake ceased, the mixture was cooled and filtered through a cake of filter aid. Solvent was removed with a rotary evaporator.

The crude 4-(3',4',5'-trimethoxyphenyl)butanoic acid (124) was added to 500 g. of 115% PPA, and the resulting mixture was heated (65-70°) and stirred for 45 min. A dark mixture formed and was cooled to room temperature and poured into 1000 ml. of 50/50 ice/H_2O. After the mixture was thoroughly hydrolyzed, the product was filtered out, washed (2% $NaHCO_3$) and air dried to give crude 3,4-dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (125). Sublimation (110 /0.01 mm.) gave pure 125 [23.7 g. (53% from 120), m.p. 118-121°, lit.[65] m.p. 125°] IR, NMR and mass spectral analyses (Plates XLV, XLVI, and Table VIII) support the structure of 125.

Preparation of the 2,4-Dinitrophenylhydrazone of 3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (137). 6,7,8-Trimethoxy-1-tetralone (125) (0.172 g., 0.00073 mole) was dissolved in 10 ml. of 0.10 M solution of 2,4-dinitrophenylhydrazine[50] (prepared by dissolving 2.0 g. of 2,4-dinitrophenylhydrazine in 50 ml. of 85% phosphoric acid, heating, cooling and adding 50 ml. of 95% ethanol). After heating on a steam bath for 15 min., the mixture deposited a bright-red solid and was filtered. Recrystallization of the solid from 95% ethanol gave 0.128 g. (31%) of pure 137, m.p. 204-205°. The structure of 137 is supported by IR and NMR spectral data (Plates XLVII and XLVIII).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: N, 13.46.

Found: N, 13.41.

Preparation of 3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-naphthalenone (143). Sodium methoxide (1.4 g., 0.0031 mole),

ethyl formate (1.56 g., 0.0215 mole), and 10 ml. of anhydrous benzene were cooled under N_2 to 0-3° via an ice/H_2O bath. A solution of 2.5 g. (0.0106 mole) of 6,7,8-trimethoxy-1-tetralone (125) in 40 ml. of anhydrous benzene was added to the cooled mixture and immediately the mixture turned yellow, then green, and finally orange-yellow. The mixture was stirred under N_2 at 0-3° for 1 hr., and overnight at room temperature. The reaction mixture was then poured into 40 ml. of ice/H_2O and stirred until the ice had dissolved. The organic layer was separated and washed with H_2O (2x, 25 ml.) and 5% NaOH (1x, 25 ml.). The aqueous layers were combined and washed with benzene (1x, 50 ml.) and finally with ether. Acidification with 10% HCl and cooling produced 2.42 g. of crude 143. Recrystallization from hexane, followed by sublimation (71°/0.02 mm.), yielded 1.12 g. (38.5%) of pure 143, m.p. 69-71°. The structure proposed for 143 is supported by NMR, IR, and mass spectra (Plates XLIX, L, and Tables VIII and IX).

Preparation of 4,5-Dihydro-7,8,9-trimethoxy-1H-benz[g]indazole (98). The hydroxymethylene compound 143 (5.0 g., 0.019 mole) was dissolved in 20 ml. of anhydrous methanol (distilled from Mg); 6.8 g. (0.21 mole) of 95% hydrazine (from Eastman Chemical Company) was added and the resulting solution was heated (50°) for 2 hr. After returning to room temperature, the solution was stirred overnight. The resulting brown solution was poured into 40 ml. of 50/50 ice/H_2O and stirred until a precipitate formed. Isolation of the tan solid by filtration, followed by sublimation (150°/0.2 mm.) and recrystallization from methanol, gave 1.3 g. (26%) of pure 98, m.p. 159-161°. Structural characterization is supported by IR, NMR (Plates LI and LII) and mass spectral

values (Table VIII).

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

Found: N, 10.93.

Preparation of 4,5-Dihydro-7,8,9-trimethoxynaphth[1,2-d]isoxazole (100). The hydroxymethylene compound 143 (2.2 g., 0.0084 mole) was dissolved in 25 ml. of glacial acetic acid, and a solution of 0.69 g. (0.0084 mole) of sodium acetate and 0.58 g. (0.0084 mole) of hydroxylamine hydrochloride in 2 ml. of water was added. The resulting solution was heated (100°) under N_2 (1 hr.). After cooling, the mixture was filtered to remove the solid that had formed in trace amount. Addition of water to the filtrate gave crude 100 which was sublimed (100°/0.15 mm.) and gave 1.2 g. (55%) of pure 100, m.p. 128-130°. IR, NMR, and mass spectral data (Plates LIII, LIV and Table VIII) confirm the proposed structure of 100.

Anal. Calcd. for $C_{14}H_{15}NO_4$: N, 5.36.

Found: N, 5.26.

Preparation of 2,3a,4,5-Tetrahydro-7,8,9-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one (103). 6,7,8-Trimethoxy-1-tetralone (125) (2.5 g., 0.0106 mole) and 1.0 g. (0.0227 mole) sodium methoxide were dissolved in 25 ml. of anhydrous dimethyl carbonate (distilled from NaH). This mixture turned yellow, then orange-red, and finally brown within 10 min. Heating was initiated and the brown mixture was boiled under N_2 for 2 hr. The mixture was cooled (ice/H_2O bath) before adding 25 ml. of anhydrous methanol and 1.5 ml. (3.2 g., 0.022 mole) of methyl iodide. After stirring 1 hr. at 5°, the mixture was further stirred under N_2 overnight at room temperature. An additional 1.0 ml. (3.2 g., 0.022 mole) of methyl iodide was added and the mixture was boiled (1 hr.).

After cooling, the mixture was acidified (25% aqueous CH_3CO_2H); solvents were removed on a rotary evaporator. Water (25 ml.) was added to the residue, and the solution was extracted (ether, 3x, 25 ml.). Evaporation of the ether left crude ester 154, a slightly colored oil, which crystalized upon standing. Recrystallization from C_2H_5OH/H_2O and sublimation (95°/2 mm.) gave pure 154 (1.56 g., 48%), m.p. 82-84°. IR, NMR, and mass spectral analyses (Plates LV, LVI and Tables VIII and IX) support the proposed structure of methyl 1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-naphthoate (154).

The keto ester 154 (1.35 g., 0.0044 mole) was dissolved in 2 ml. of anhydrous methanol (distilled from Mg), and 1.4 g. (0.044 mole) of hydrazine (anhydrous, 97+%) was added. After heating (70°) the solution 30 min. under N_2, a solid formed. Water (7 ml.) was added and the mixture was cooled (ice/H_2O bath). Isolation of the solid by filtration followed by sublimation (196°/0.003 mm.) gave 1.15 g. (90% from keto ester) of pure 103, m.p. 224.5-225°. Support for the structure of 103 is provided by IR, NMR, and mass spectral data (Plates LVII, LVIII and Table VIII). Peak matching is shown in Table IX.

Preparation of Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthoate (150). 6-Methoxy-1-tetralone (132) (8.7 g., 0.0494 mole), 4.0 g. (0.074 mole) of sodium methoxide, and 40 ml. of anhydrous dimethyl carbonate (distilled from LiH, b.p. 89-90°) were mechanically stirred (under N_2) and boiled for 3 hr. Solvent was removed by evaporation and the residue was dissolved in ca 30 ml. of water. Acidification (pH ca 6) with 25% aqueous acetic acid and cooling in ice/H_2O produced a slightly tan solid. Filtration and drying in vacuo gave crude 150.

Recrystallization from methanol gave 8.75 g. (76%) of pure 150, m.p. 87-89° (lit.[74] m.p. 88-89°). IR, NMR and mass spectral analyses (Plates LIX, LX and Tables VIII and IX) support the proposed structure of 150.

Preparation of 2-Amino-5,6-dihydro-8-methoxybenzo[h]quinazolin-4-ol (151). β-Keto ester 150 (2.14 g., 0.00915 mole) was dissolved in 75 ml. of anhydrous methanol (distilled from Mg); guanidine hydrochloride (0.96 g., 0.010 mole) and sodium methoxide (1.08 g., 0.02 mole) were added and the mixture was boiled under N_2 (4 hr.). After cooling overnight, the solvents were removed (rotary evaporation). When aqueous 5% NaOH (100 ml.) was added, a blue solid formed which, after sublimation, proved to be starting tetralone 132. The filtrate was treated with Nuchar, filtered, and acidified (50/50 CH_3CO_2H/H_2O) to pH 6.3. Cooling (ice/H_2O bath) produced a fine grey solid; recrystallization from 50/50 DMSO/CH_3OH and sublimation (230°/0.006 mm.) gave 600 mg. (27%) of pure 151, m.p. 325-327° (dec.). IR, NMR and mass spectral analyses (Plates LXI, LXII and Table VIII) confirm the proposed structure of 151.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: N, 17.28.

Found: N, 17.28.

Preparation of 5,6-Dihydro-2-mercapto-8-methoxybenzo[h]quinazolin-4-ol (152). The keto ester 150 (2.14 g., 0.00915 mole) was added to a solution of thiourea (1.14 g., 0.015 mole) and sodium methoxide (0.81 g., 0.015 mole) in 50 ml. of anhydrous methanol (distilled from Mg). After boiling under N_2 (4 hr.), the mixture was stirred overnight. Evaporation of the solvents left a dark residue which was dissolved in 10% NaOH, treated with Nuchar, and filtered through filter aid. Acidification of the filtrate with 50/50 CH_3CO_2H/H_2O produced a powdery solid. Recrystallization (50/50 DMSO/CH_3OH) followed by sublimation (228°/0.006

mm.) gave 0.283 g. (12%) of pure 152, m.p. 290-294° (dec.). Structural support for 152 was provided by IR, NMR and mass spectral analyses (Plates LXIII, LXIV and Table VIII).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: N, 10.76; S, 12.30.

Found: N, 10.89; S, 12.03.

Attempted Preparation of 3-Methoxyphenethyl Bromide (158).[20,146] Utilizing the entrainment method for making Grignard reagents,[103,146] 17.3 g. (0.71 g. at.) of magnesium metal turnings and 50 g. (0.35 mole) of m-chloroanisole (156) were combined in 200 ml. of anhydrous ether. A solution of ethylene bromide (66.7 g., 0.35 mole) and 150 ml. of anhydrous ether was slowly added (∿ 1 drop/12 sec.) through a dropping funnel to the original mixture. After the solution was boiled gently overnight, 350 ml. of anhydrous benzene was added and the ether was distilled off. The reaction flask was cooled completely to 0-5° before a solution of 15.4 g. (0.35 mole) of ethylene oxide in 100 ml. of anhydrous ether was added (∿ 1 drop/5 sec.) through a dropping funnel to the Grignard. After all of the ethylene oxide solution had been added, the mixture was stirred at 0-5° for 1 hr., allowed to reach room temperature for 0.5 hr., and then boiled for 0.75 hr. The reaction mixture was again cooled to 0-5° and an additional 5.3 g. (0.12 mole) of ethylene oxide, dissolved in 30 ml. of cold ether, was slowly added (∿ 1 drop/5 sec.). Again the reaction mixture was stirred for 1 hr. at 0-5°, and then boiled for 20 min. After cooling to room temperature, the whole reaction mixture was poured onto 400 ml. of 50/50 ice/H_2O with stirring. The organic layer was decanted off, washed with H_2O (2x, 200 ml.), and dried ($MgSO_4$). The aqueous layer from the reaction mixture was filtered; the filtrate was extracted with ether (1x, 150 ml.) and the ether layer

was dried ($MgSO_4$). The solvents from the combined organic layers were removed via a rotary evaporator, and the residue was fractionally distilled in vacuo. Fraction I (24.8 g., 49%, b.p. 31-35°/1.7-2.5 mm.) proved by GLC (SE-40 column) to be primarily β-anisylethyl alcohol (157) with an impurity (∿ 20% of starting material, 156).

In the method of Buchta and Bayer,[20] crude 157 (13.6 g., 0.173 mole) was dissolved in 30 ml. of absolute CCl_4 and cooled to 0° in an ice/H_2O bath. Phosphorus tribromide (15.8 g., 0.058 mole) was added over a 1-hr. period while keeping the reaction temperature around 0°. After all of the PBr_3 was added, the mixture was stirred at 0° for 4 hr. and then stirred 20 min. at room temperature. The mixture was poured over 50 ml. of 50/50 ice/H_2O and stirred until the ice had all melted. Following separation of the two layers, the organic layer was washed with sat. $NaHCO_3$ (2x, 20 ml.), H_2O (1x, 30 ml.) and dried ($MgSO_4$). Evaporation of the solvents left a brown residue. Fractional distillation on the spinning band distilling column failed to separate product 158 from the alcohol 157 as deduced from GLC analysis.

Attempted Preparation of 7-Methoxy-1,2,3,4,9,10-hexahydrophenanthren-1-one (166). By means of the Reformatsky reaction via the method of Stork[130], methyl 4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate was prepared by first washing 141 g. (2.27 g. at.) of zinc metal, 0.25 in. by 0.5 in. pieces, with dilute HCl, water, acetone, and ether. The zinc was then dried in an oven (100°) for at least 0.5 hr. prior to use. To 56.5 g. (0.866 mole) of preconditioned zinc pieces in 210 ml. of anhydrous benzene was added 3.8 g. (0.016 mole) of dry mercuric chloride. After the mixture had been stirred (under N_2) for 0.5 hr. a solution of 56.1 g. (0.319 mole) of

6-methoxy-1-tetralone (132) and 52 g. (0.29 mole) of methyl 4-bromocrotonate in a mixture of 50 ml. of anhydrous benzene and 150 ml. of anhydrous ether was added all at once, followed by a crystal of iodine. Since no exothermic reaction took place immediately, the mixture was heated to boiling. After boiling for 2 hrs., additional portions of zinc (28.2 g., 0.432 mole) and bromo ester (17.3 g., 0.097 mole) were introduced. This was repeated at 1.5-hr. intervals until three additional portions had been added. Boiling was continued for 17 hr. after the last addition. The bright orange mixture was then cooled and poured on ice. The resulting mixture was acidified with acetic acid and extracted (ether, 2x, 150 ml. each). The organic solution was washed with 5% aqueous ammonia (3x, 60 ml. each), H_2O and saturated salt solution. Evaporation of solvents was accomplished with a rotary evaporator, and the bright red residue was distilled *in vacuo*. A forerun (b.p. 145-165°/1 mm.) consisted of unchanged 6-methoxy-1-tetralone (33 g.). The ester 164 was collected (b.p. 180-186°/1.5 mm.) as a viscous yellow oil (27.6 g., 0.106 mole, 33.4%).

A solution of 18.0 g. (0.0695 mole) of the ester 164 dissolved in 300 ml. of absolute ethanol containing 3 ml. of glacial acetic acid was hydrogenated in a Parr hydrogenation apparatus at atmospheric pressure and room temperature in the presence of 15 g. of freshly prepared Raney Ni catalyst, W-2.[99,144] After 20 min., hydrogen uptake ceased and the catalyst was removed by filtration through filter aid (the catalyst was deactivated with 10% HCl). The slightly yellow filtrate was added to 15 g. (0.15 mole) of potassium hydroxide dissolved in 1125 ml. water. The mixture was boiled under N_2 for 3 hr. and the alcohol was removed by rotary evaporation. The aqueous alkaline solution was extracted

three times (ether, 50 ml. each), made strongly acidic with conc. HCl, and then extracted three times (ether, 50 ml. each). The ether extracts were washed with water and dried ($MgSO_4$); the ether was evaporated to leave a light tan solid (15.9 g.), m.p. 66-75° C. This solid was transferred to a Soxhlet extractor and extracted for 12 hr. (petroleum ether, b.p. 65-75°). Upon cooling, a white crystalline material precipitated (8.4 g., m.p. 74-75°); its identity was confirmed by IR, NMR and mass spectral analyses as 4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid (168) (lit.[144] m.p. 76-78°) rather than the expected 4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid (165) required for the cyclization to 1-oxo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthren-1-one (166). Several attempts to prepare the correct acid 165 gave only the undesired saturated acid 168.

Spectral data for 168 are: ir (KBr) μ: 3.30-3.80 (-OH), 6.04 (-$\overset{O}{\overset{\|}{C}}$-), 6.35 (Ar stretching), 9.80, 11.75, 12.08, 12.38 (Ar C-H vibrations); nmr ($DCCl_3$) δ, 1.5-1.9 (m, 8, $CH_2\underline{CH_2}CHR$), 2.40 (m, 2, $\underline{CH_2}Ar$), 2.75 (m, 3, $CH_2\underline{CH}RCH_2$ and $\underline{CH_2}CO_2H$), 3.78 (s, 3, $-OC\underline{H_3}$), 6.60, 6.74, and 7.08 (m, 3, Ar-H); mass spectrum, m/e (70 ev) (rel. Intensity), 115 (24), 128 (18), 146 (17), 158 (21), 161 (100), 162 (38), 248 (28, molecular ion).

Attempted Preparation of 3,4-Dihydro-1(2H)-naphthalenone-5,6,7-triol (169). Trimethoxytetralone 28 (1.0 g., 0.0042 mole) was heated to 180° for 2 hr. in the presence of 2.25 g. (0.051 mole) of freshly fused pyridine hydrochloride. After cooling, the reaction mixture was dissolved in 40 ml. of 5% HCl. Following extraction with ether (5x, 20-ml. portions), the combined ether layers were washed (1x, 40 ml. H_2O) and dried ($MgSO_4$); the ether was evaporated leaving 0.40 g. of greenish residue. Sublimation (168°/0.1 mm.) yielded 0.15 g. (31%) of slightly

impure 169, m.p. 210-211°; ir (KBr) μ: 2.90-4.10 (OH), 6.11 (C=O); nmr (acetone-d_6), δ 1.88-2.16 (p, 2, J_{HH} = 6 Hz, $CH_2\underline{CH_2}CH_2$), 2.38-2.56 (t, 2, J_{HH} = 6 Hz, $\underline{CH_2}$), 2.72-2.92 [t, 2, J_{HH} = 6 Hz, $\underline{CH_2}$ C(O)], 3.10 (s, 1, O$\underline{H}$), 7.11 (s, 1, Ar-$\underline{H}$), 7.97 (s, 2, O$\underline{H}$).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.68, H, 5.15.

Found: C, 60.92, H, 5.11.

Preparation of 3,4-Dihydro-1(2H)-naphthalenone-6,7,8-triol (170). Dry pyridine hydrochloride (2.25 g., 0.015 mole) was freshly fused under nitrogen before 1.0 g. (0.0042 mole) of 6,7,8-trimethoxy-1-tetralone (125) was added. After heating (180°) for 2 hr., the reaction mixture was cooled and 40 ml. of 5% HCl was added. A precipitate formed and was filtered out. Sublimation (170°/0.1 mm.) gave 0.17 g. (20.9%) of pure 170, m.p. 185-186°; ir (KBr) μ: 2.88-3.80 (OH), 6.12 (C=O); nmr (acetone-d_6), δ 1.84-2.16 (p, 2, J_{HH} = 6 Hz, $CH_2\underline{CH_2}CH_2$), 2.48-2.65 (t, 2, J_{HH} = 6 Hz, $\underline{CH_2}$), 2.70-2.88 [t, 2, J_{HH} = 6 Hz, $\underline{CH_2}C(O)$], 3.00 (s, 1, O$\underline{H}$), 6.28 (s, 1, Ar$\underline{H}$), 8.00 (s, 1, O$\underline{H}$), 12.79 (s, 1, O$\underline{H}$).

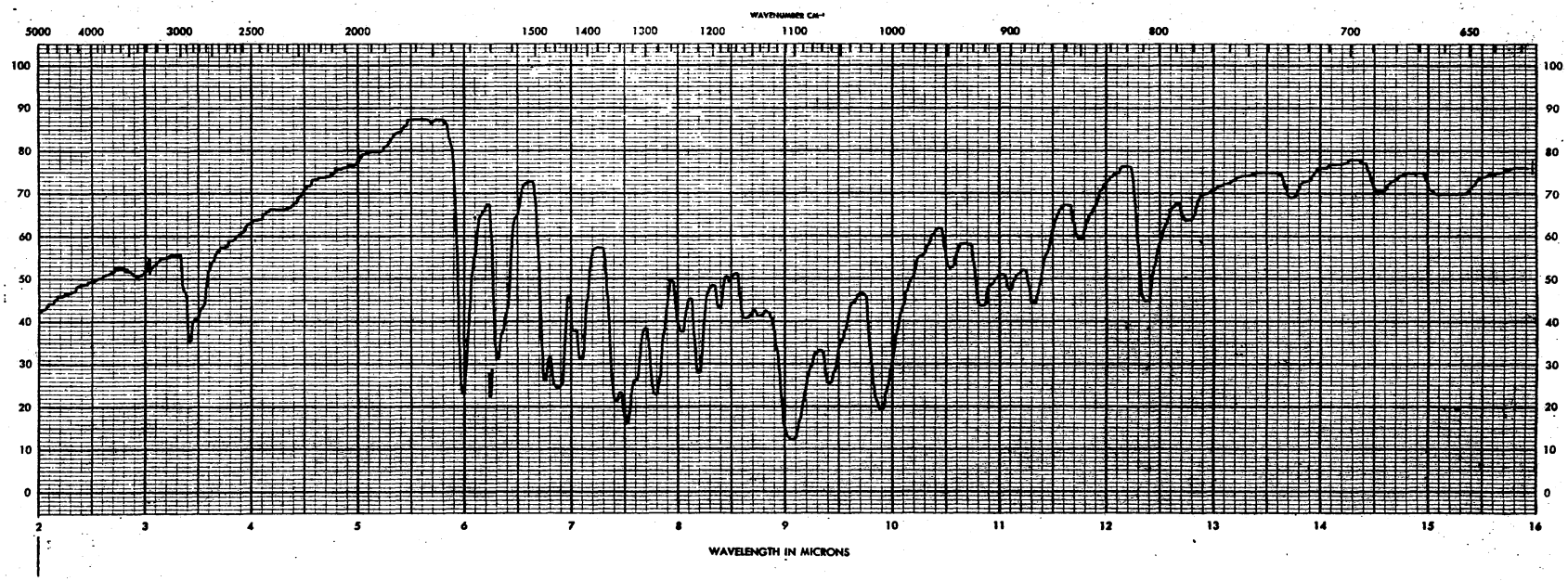
Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.86, H, 5.15.

Found: C, 61.80, H, 5.10.

Attempted Preparation of 4,5-Dihydro-1H-benz[g]indazole-6,7,8-triol (171). Pyrazole 97 (1.0 g., 0.00384 mole) was added to 3.0 g. (0.026 mole) of freshly fused pyridine hydrochloride and heated (180°) for 2 hr. under nitrogen. A precipitate formed as 40 ml. of 5% HCl was added. After cooling, the solid was filtered out, then sublimed (210°/0.1 mm.) to give 0.30 g. (35.8%) of partially cleaved 97 (crude), m.p. 235-240° (dec.); ir(KBr) μ: 2.90-3.25, 3.45-4.20 (OH), 6.25 (C=N); nmr (acetone-d_6), δ 2.42-2.80 (m, 4, $\underline{CH_2}\underline{CH_2}$), 3.78 (s, 3, OCH_3), 6.70 (s, 1, Ar$\underline{H}$), 7.27 (s, 2, O$\underline{H}$), 7.37 (s, 1, C$\underline{H}$).

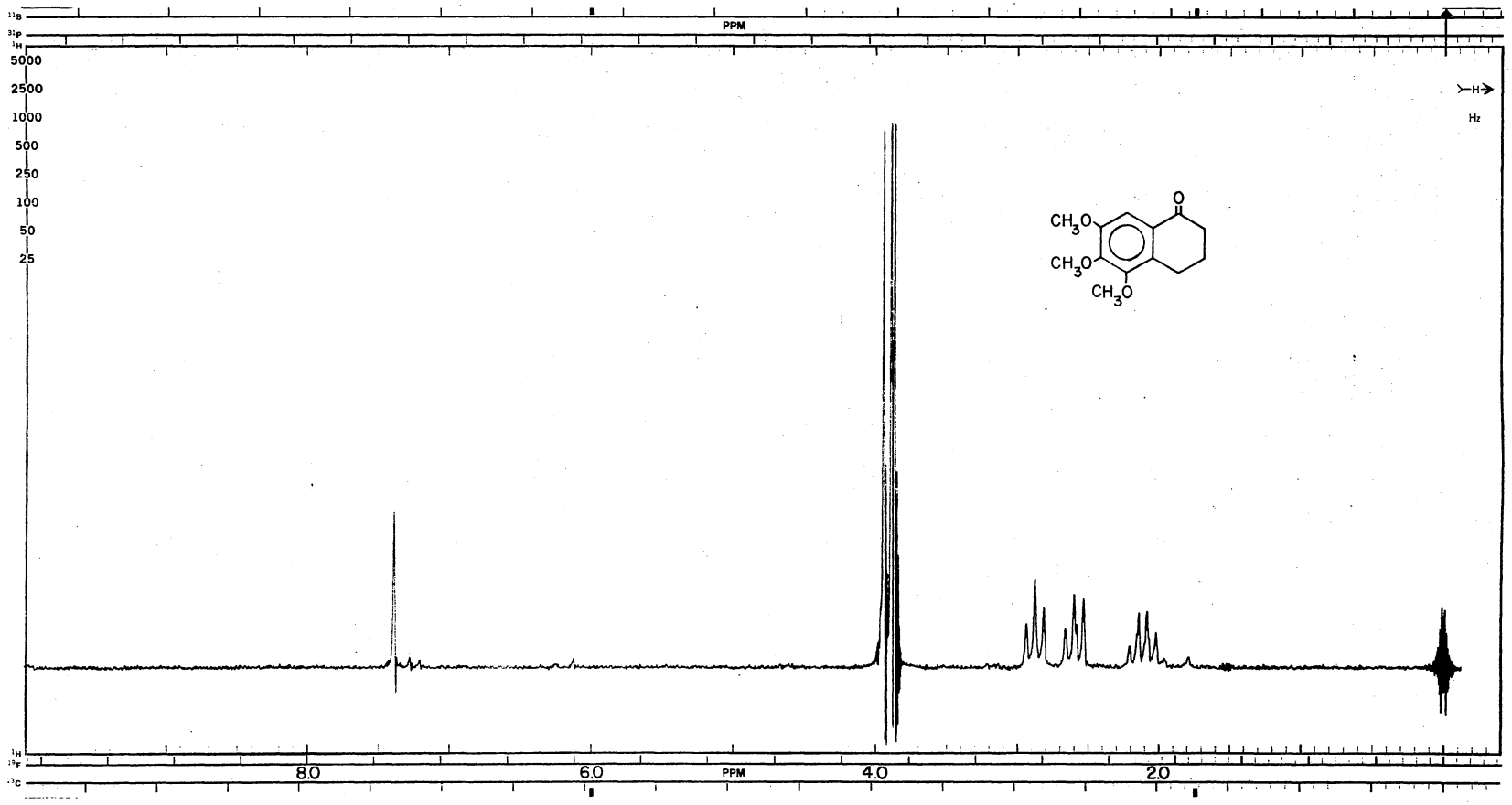
Attempted Preparation of 4,5-Dihydronaphth[2,1-d]isoxazole-6,7,8-triol (172). Isoxazole 97 (1.7 g., 0.0065 mole) was heated (180°) for 2 hr. in the presence of 3.5 g. (0.030 mole) of freshly fused pyridine hydrochloride. As the reaction progressed, the mixture darkened until it was black after 2 hr. Addition of 40 ml. of 5% HCl did not dissolve the black tar. Attempts at sublimation failed to yield any product.

PLATE I



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (28), KBr Pellet

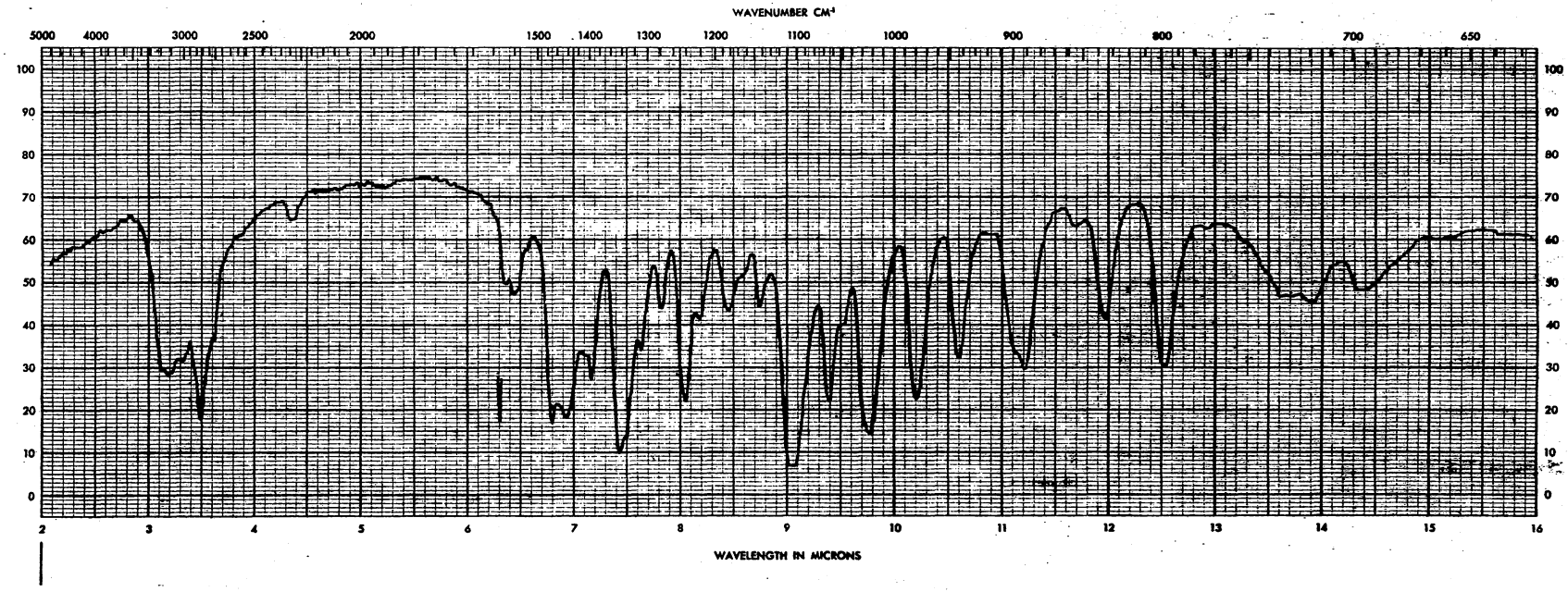
PLATE II



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (28)

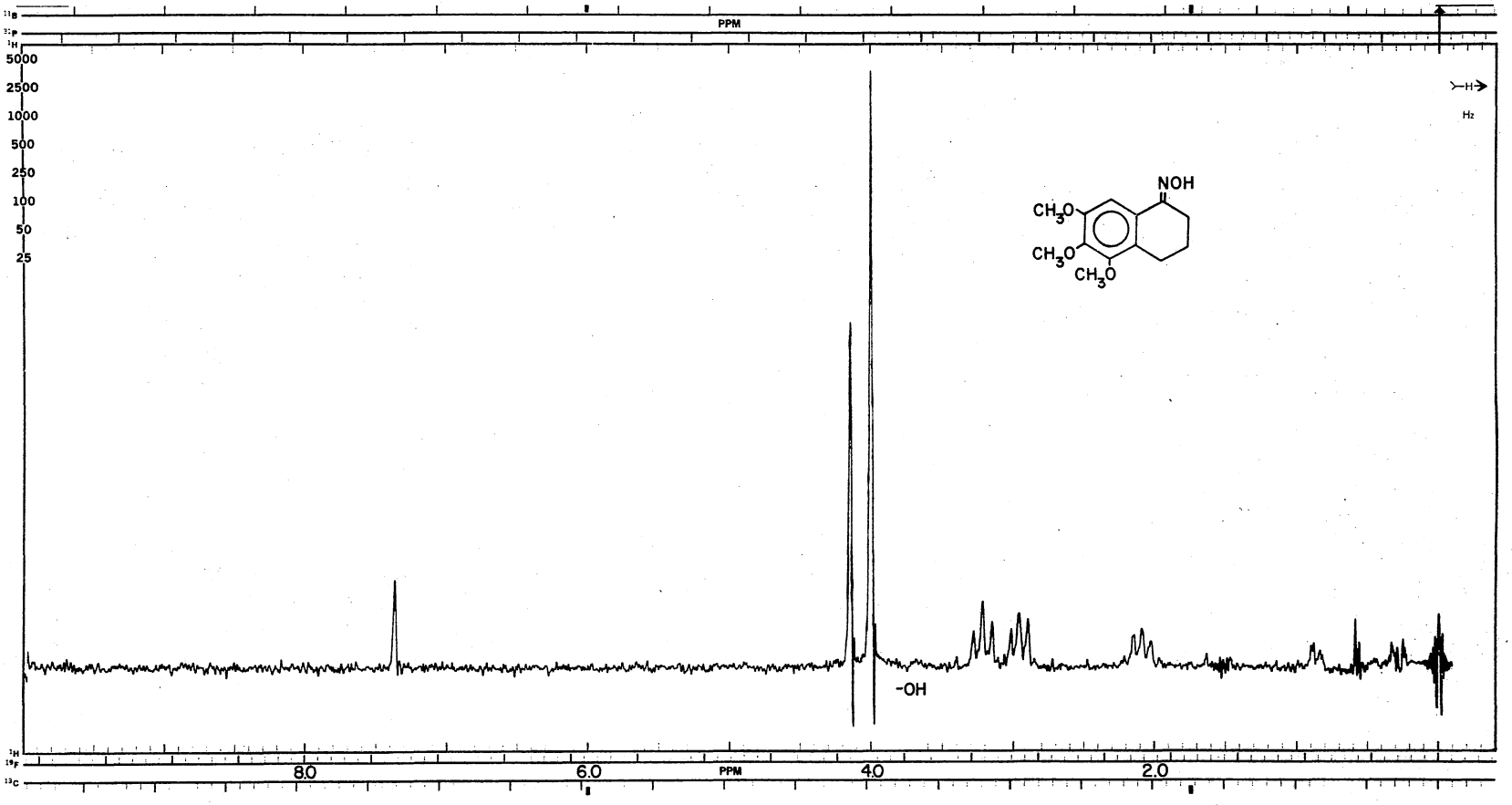
Solvent. . . $DCCl_3$	O.F. . . . 100.1 Hz	F.B. . . . . 2 Hz	R.F. . .64 dB
S.W. . . . 1000 Hz	S.T. . . . .500 sec	S.O. . . 83701 Hz	S.A. . . 2.0 Lock. .HOMO

PLATE III



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone, Oxime (139), KBr Pellet

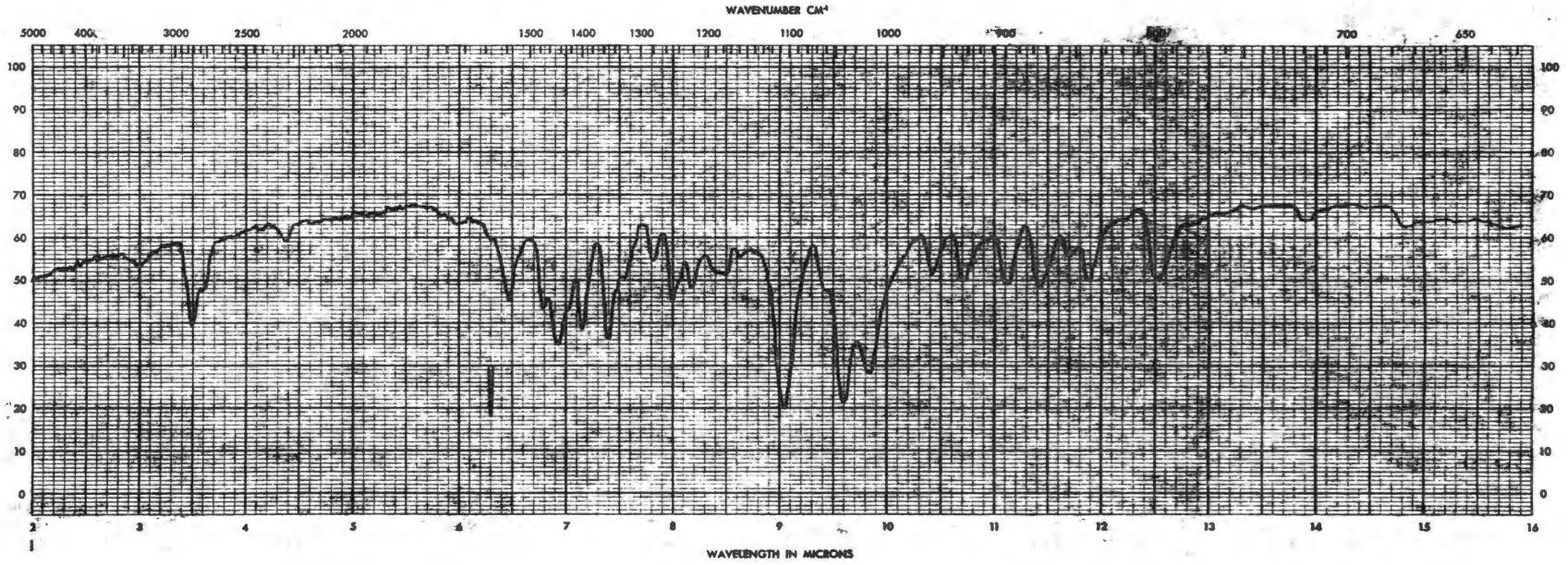
PLATE IV



Oxime of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (139)

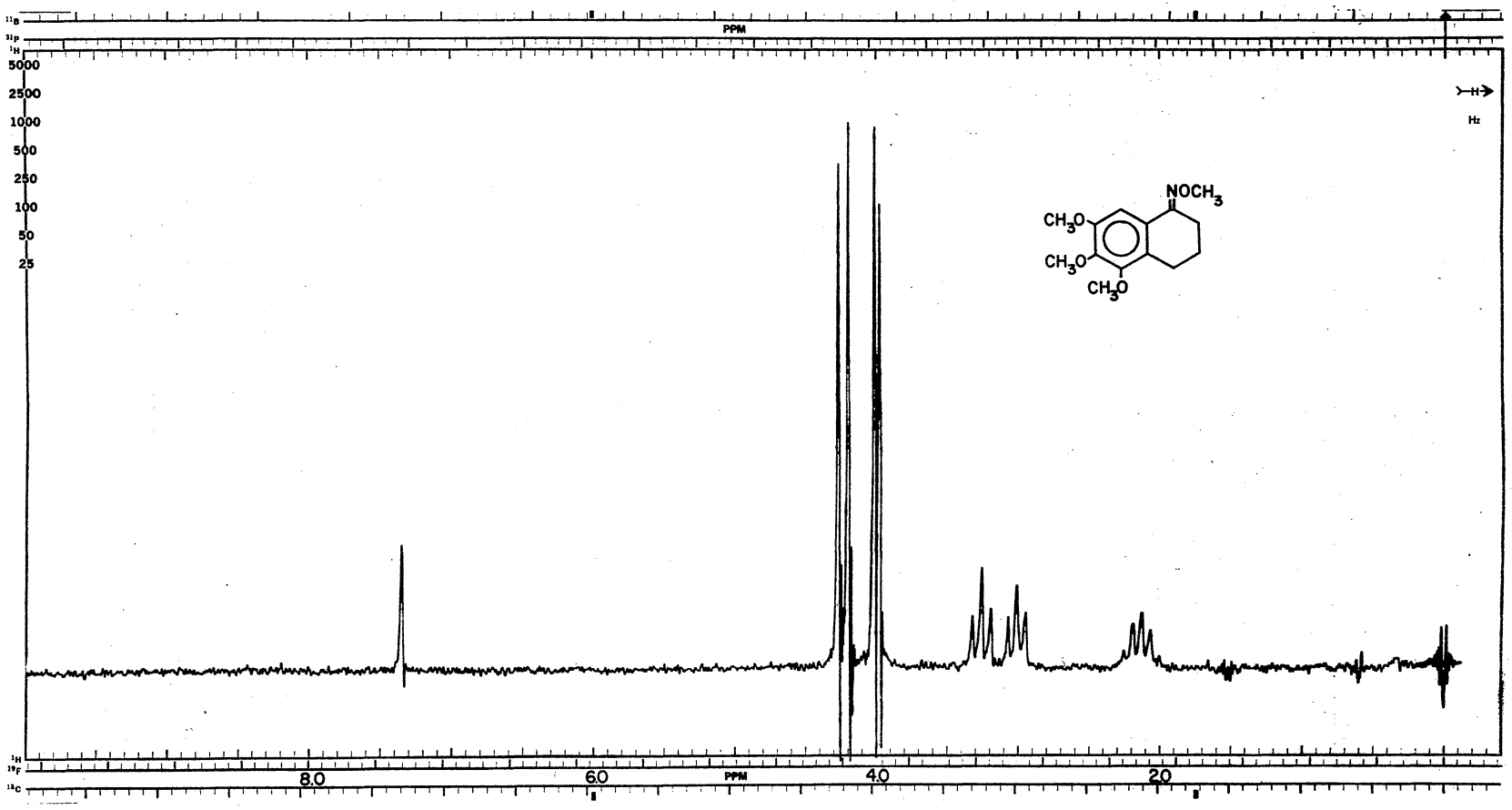
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . .65 dB
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 8.0 Lock. .HOMO

PLATE V



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone, Methoxime (140), KBr Pellet

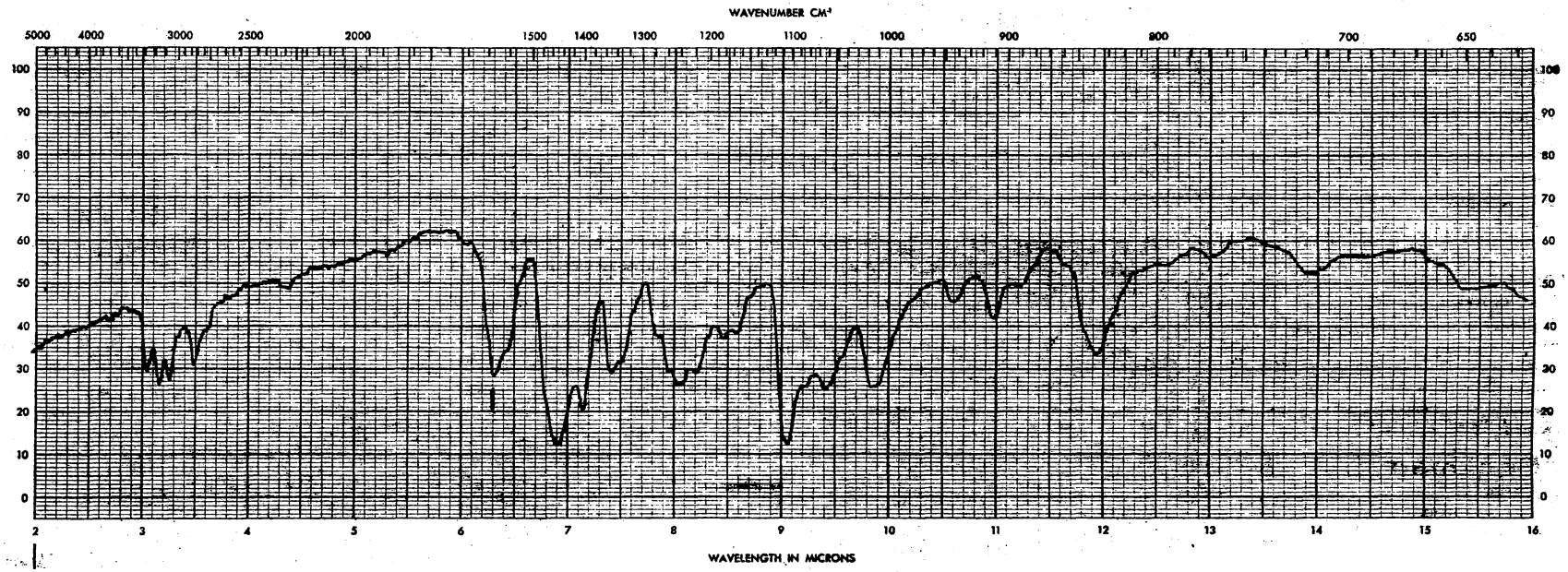
PLATE VI



Methoxime of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (140)

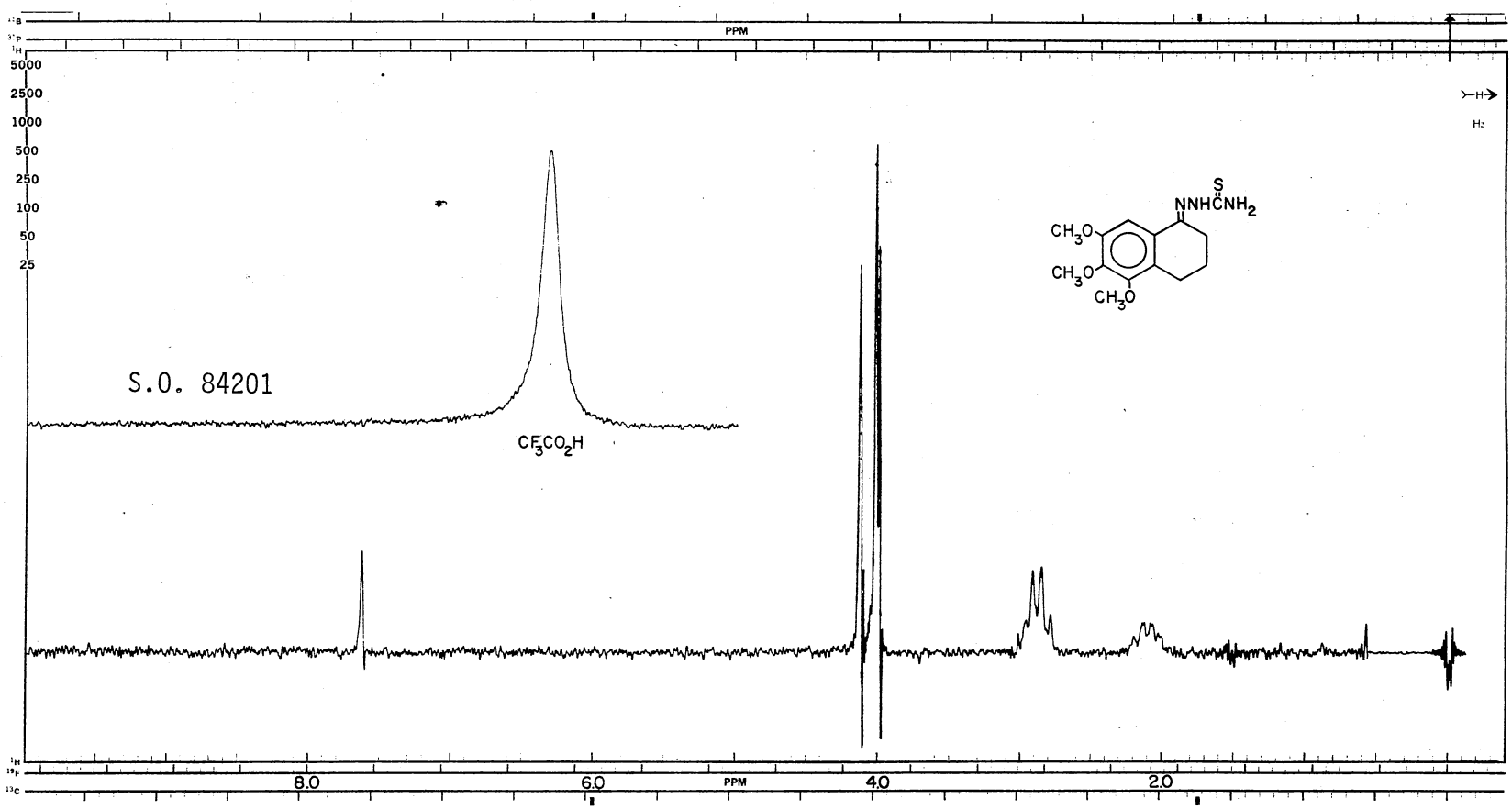
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . .65 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 6.3	Lock. .HOMO

PLATE VII



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone, Thiosemicarbazone (141), KBr Pellet

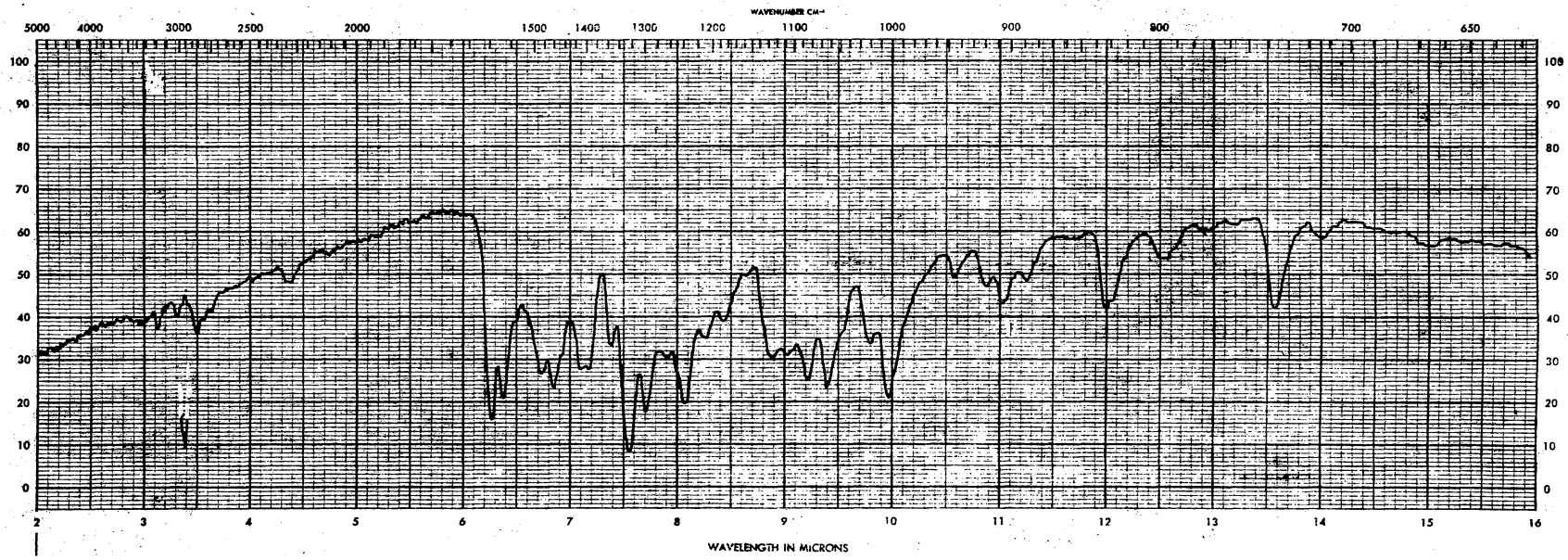
PLATE VIII



Thiosemicarbazone of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (141)

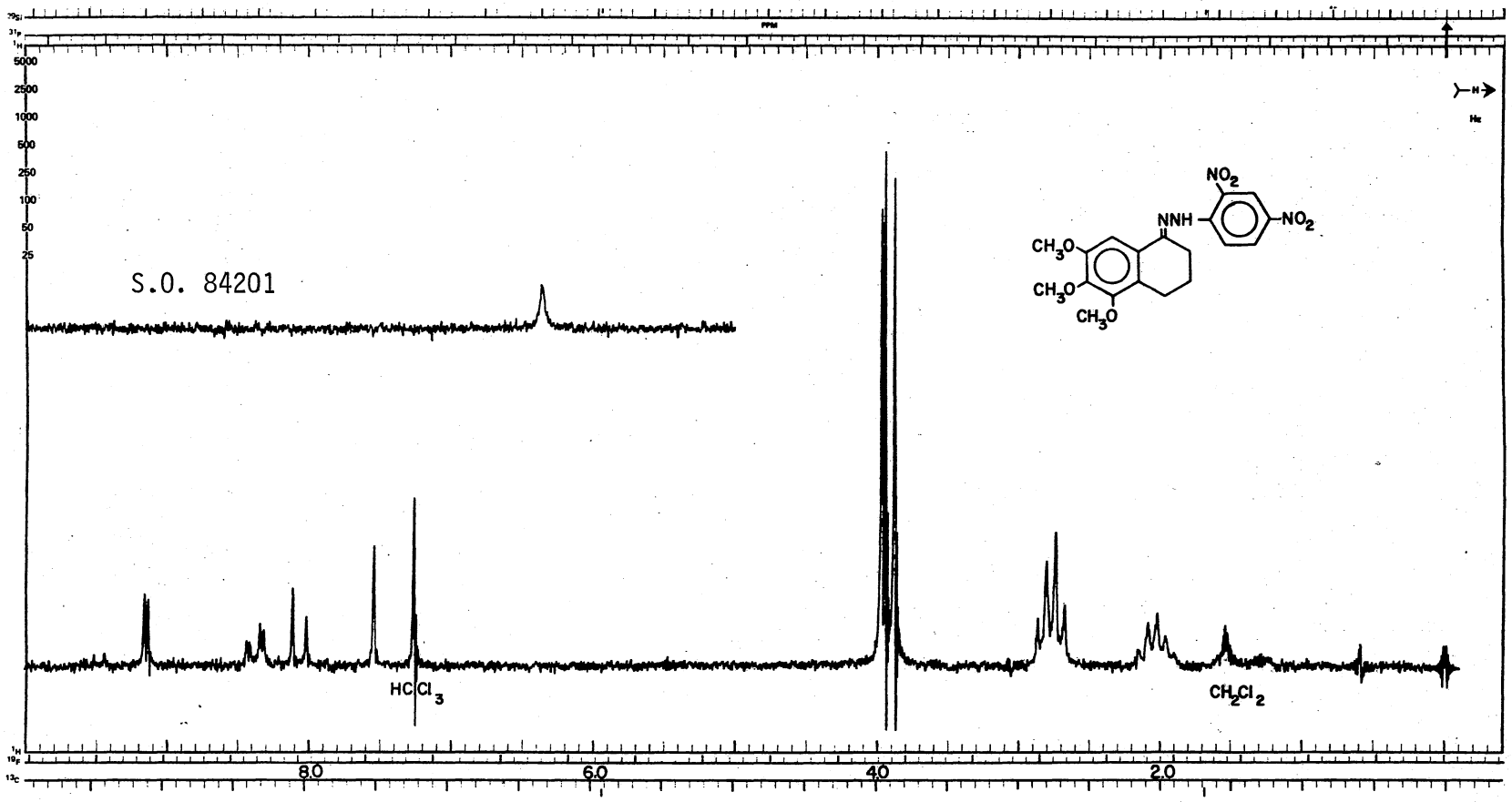
Solvent. . CF_3CO_2H	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 32 dB
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 8.0 Lock. .HOMO

PLATE IX



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone, 2,4-Dinitrophenylhydrazone (136), KBr Pellet

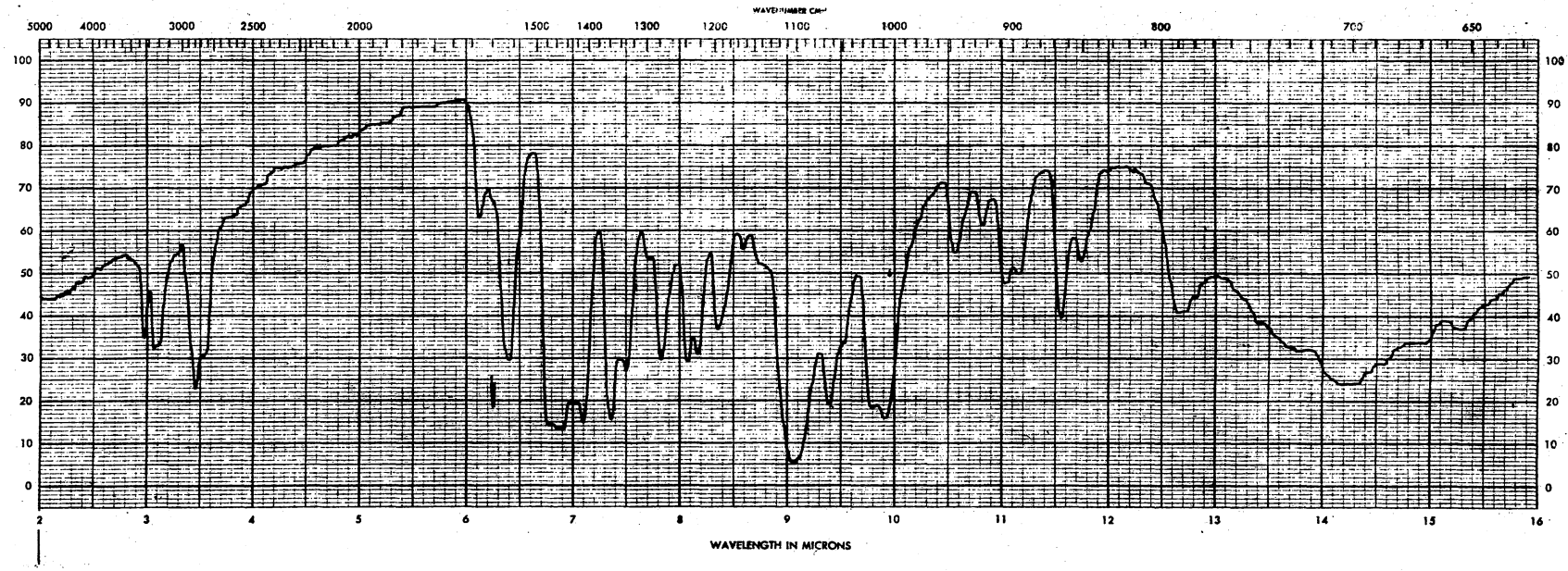
PLATE X



2,4-Dinitrophenylhydrazone of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (136)

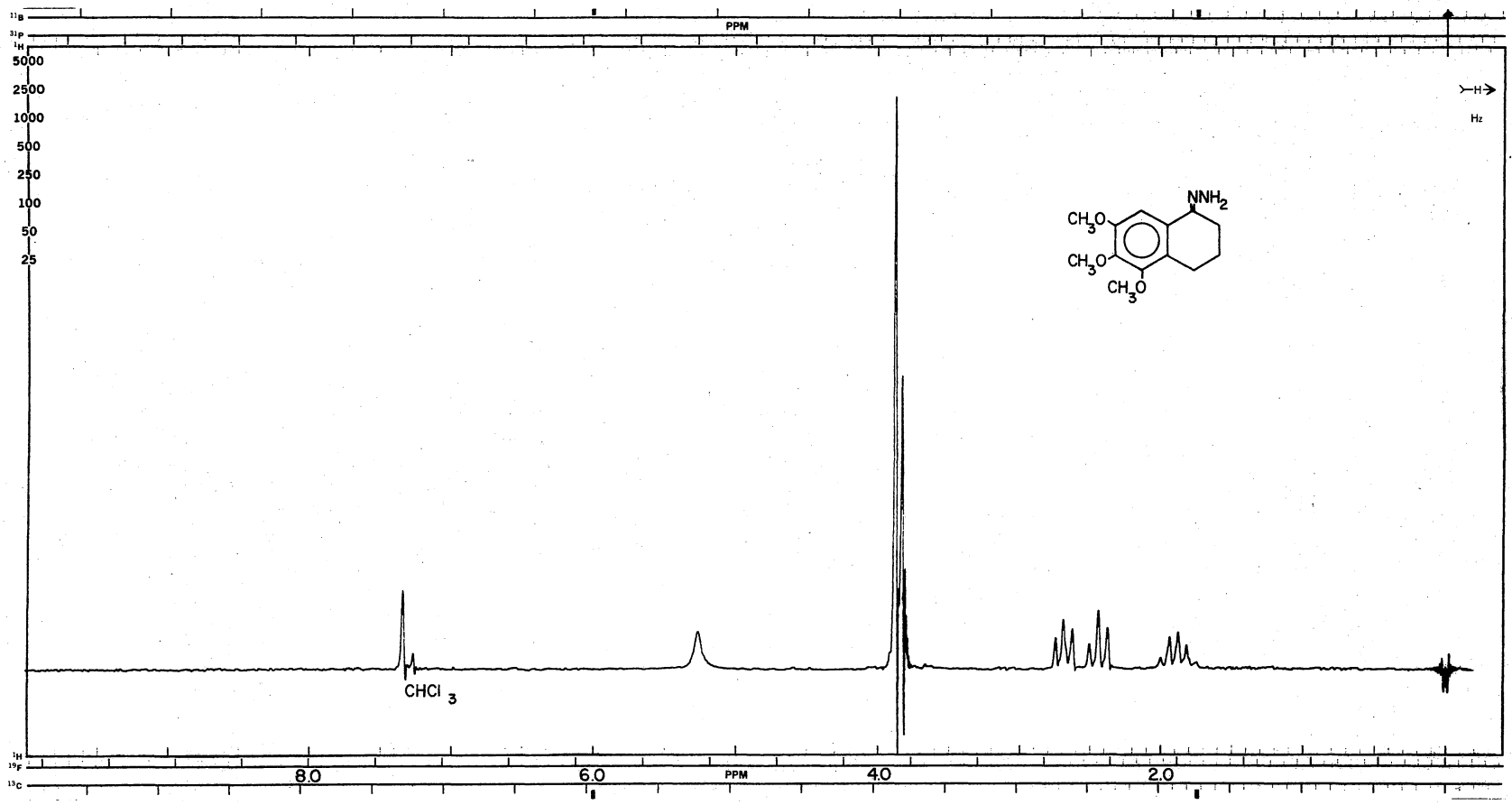
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 67 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . 12.5	Lock. .HOMO

PLATE XI



3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone, Hydrazone (149), KBr Pellet

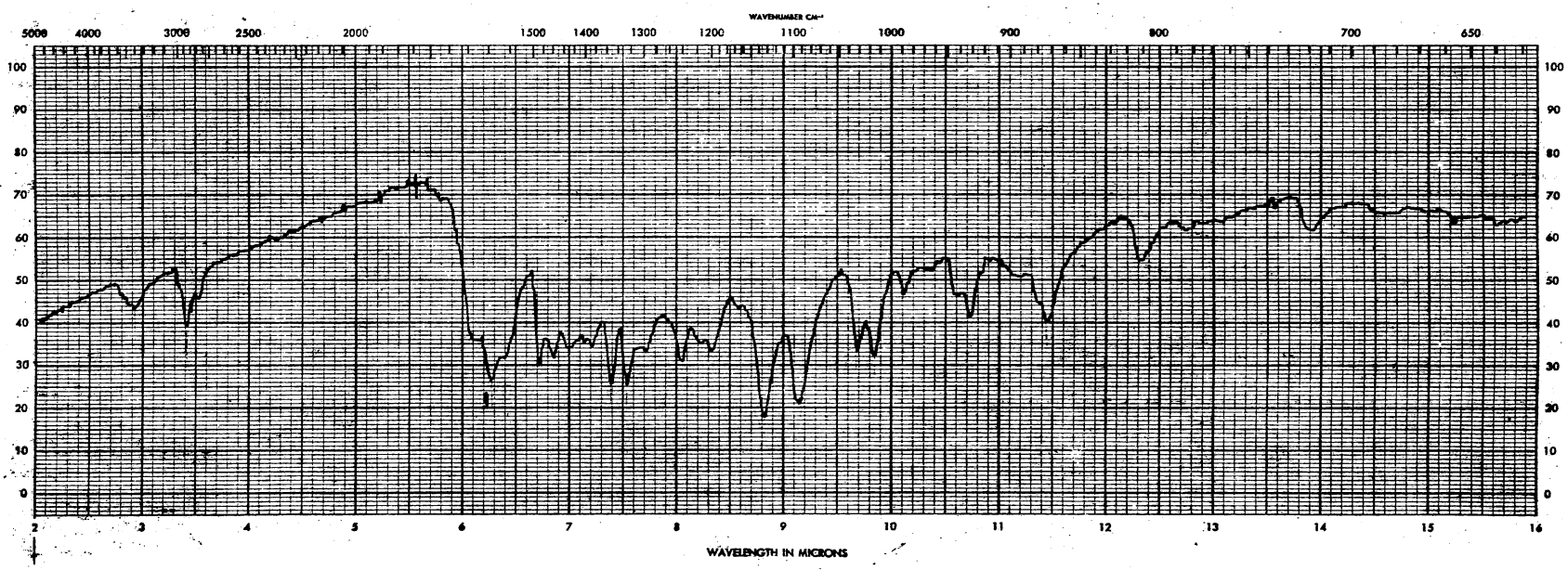
PLATE XII



Hydrazone of 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone (149)

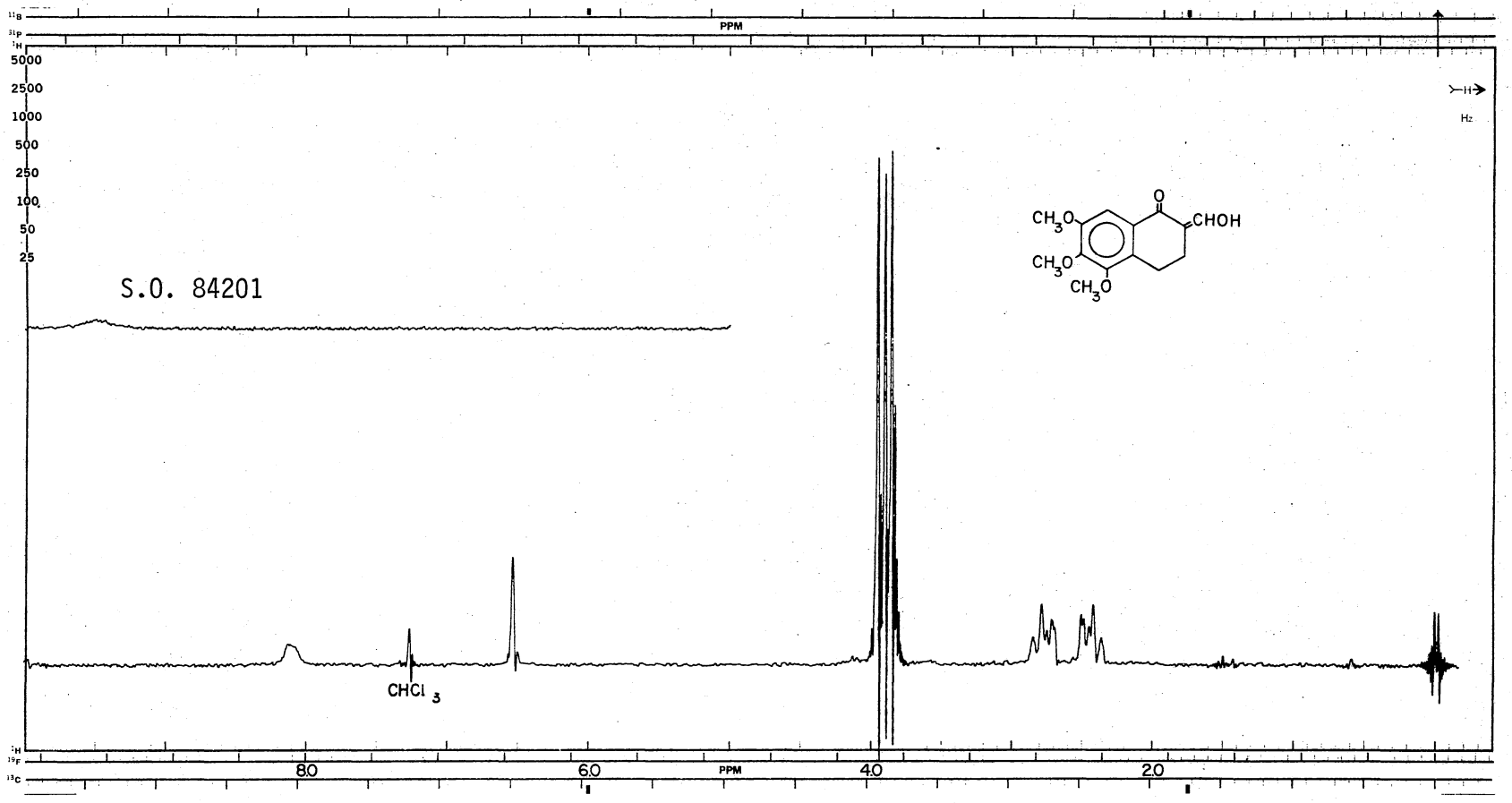
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 64 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . 1.25 Lock. .HOMO

PLATE XIII



4,5-Dihydro-2-(hydroxymethylene)-5,6,7-trimethoxy-1(2H)-naphthalenone (142), KBr Pellet

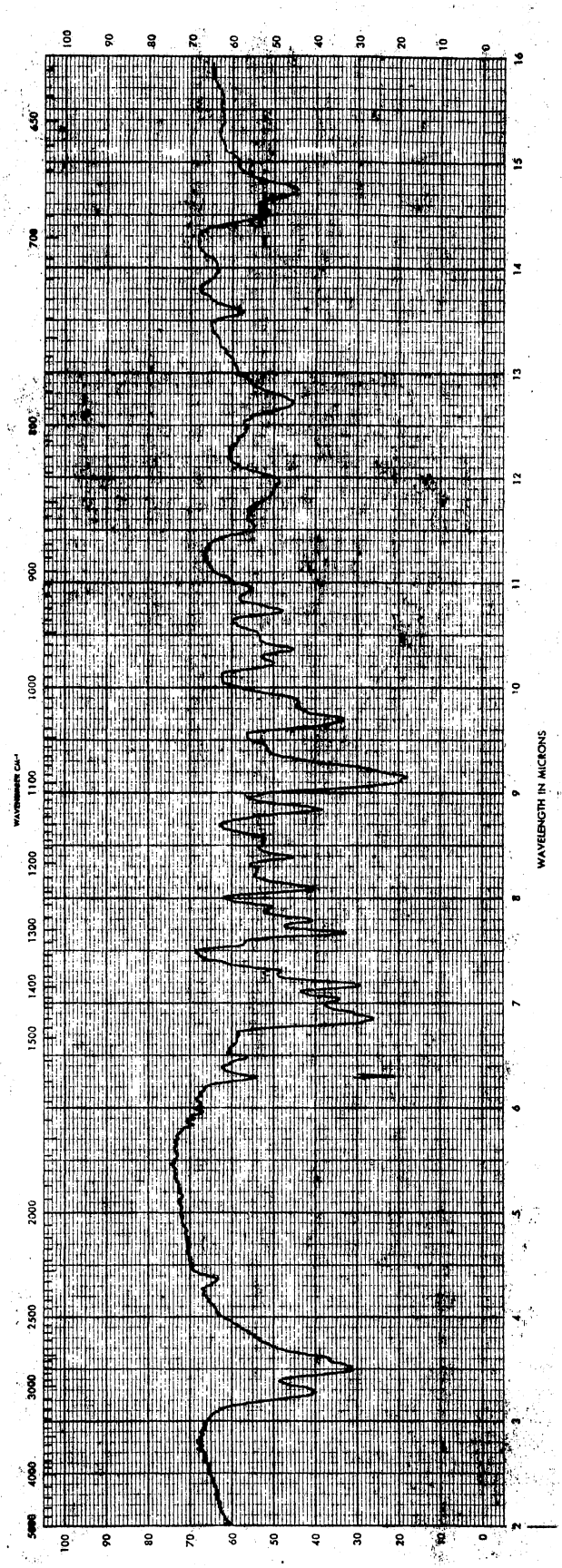
PLATE XIV



3,4-Dihydro-2-(hydroxymethylene)-5,6,7-trimethoxy-1(2H)-naphthalenone (142)

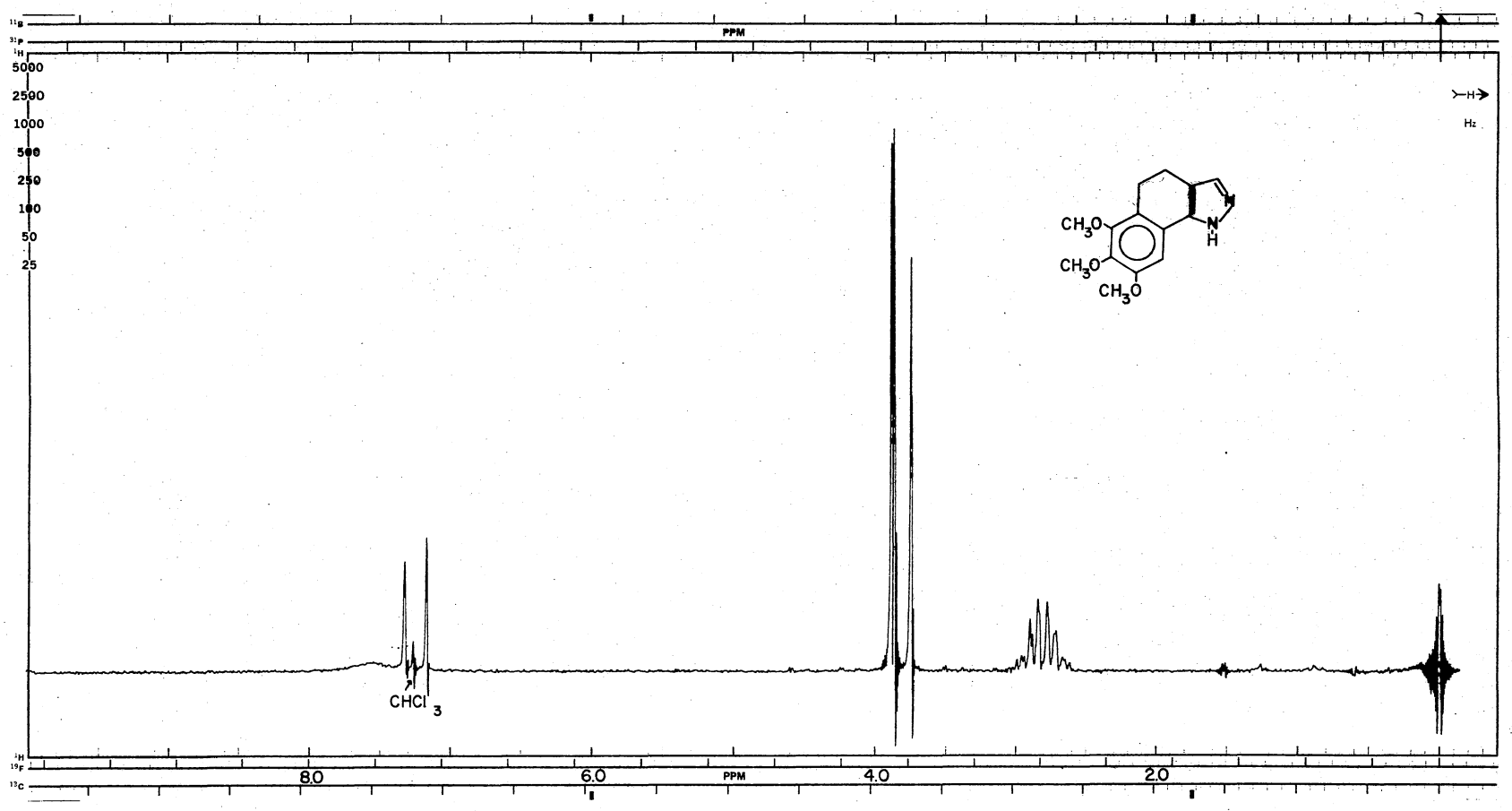
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 67 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 2.0	Lock. .HOMO

PLATE XV



4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole (97), KBr Pellet

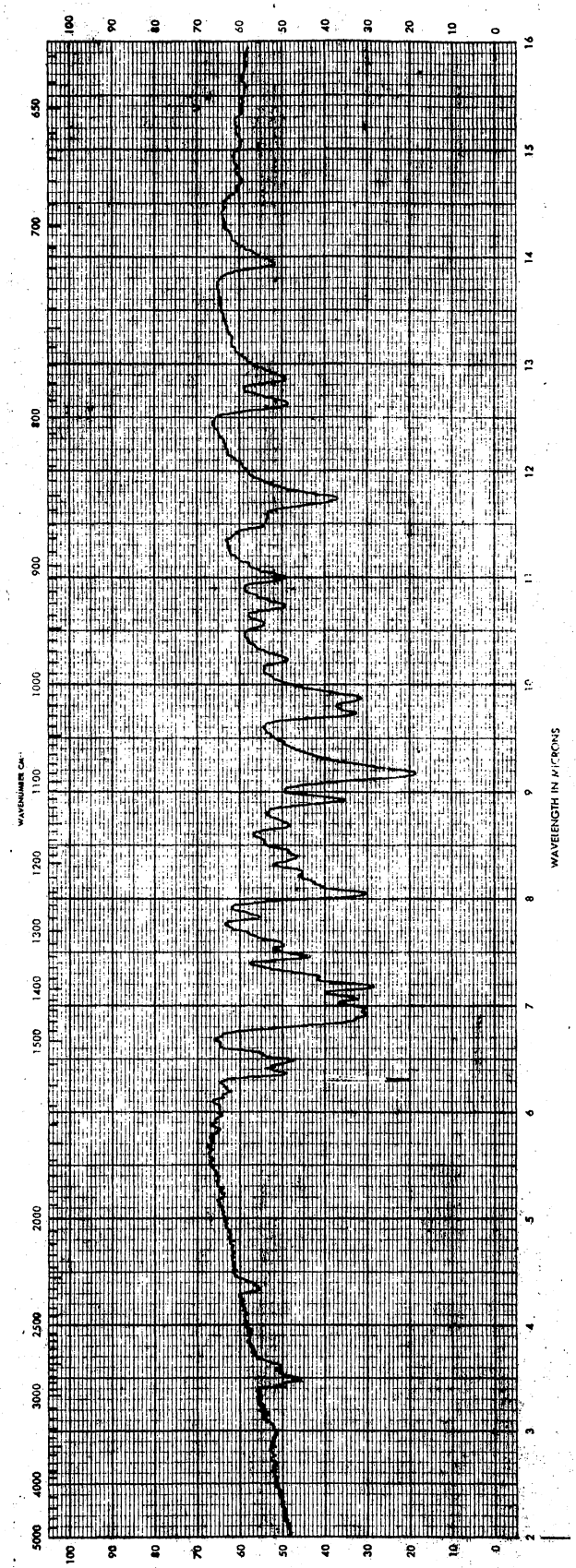
PLATE XVI



4,5-Dihydro-6,7,8-trimethoxy-1H-benz[g]indazole (97)

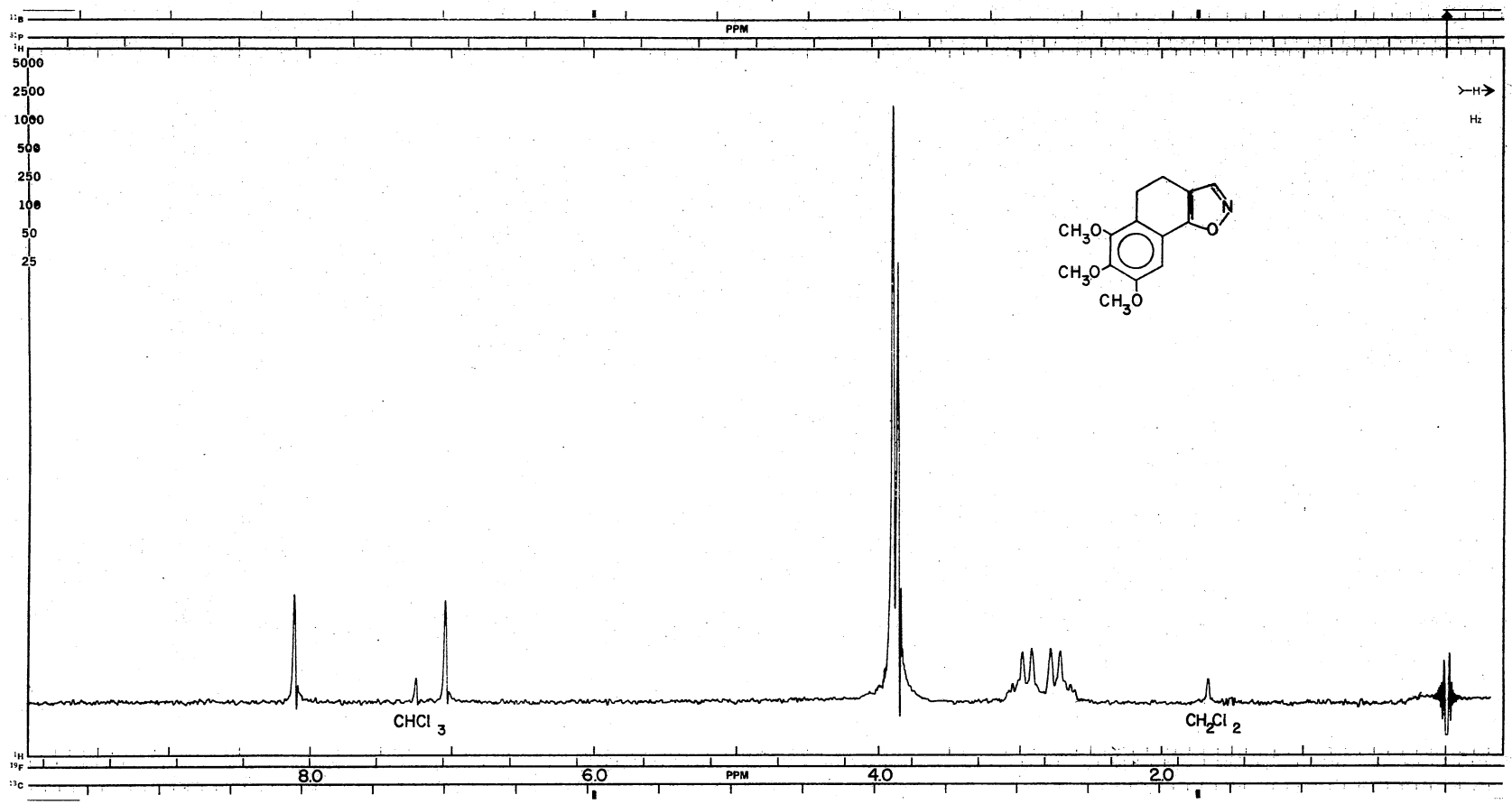
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 64 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 2.0	Lock. . HOMO

PLATE XVII



4,5-Dihydro-6,7,8-trimethoxynaphth[1,2-d]isoxazole (99), KBr Pellet

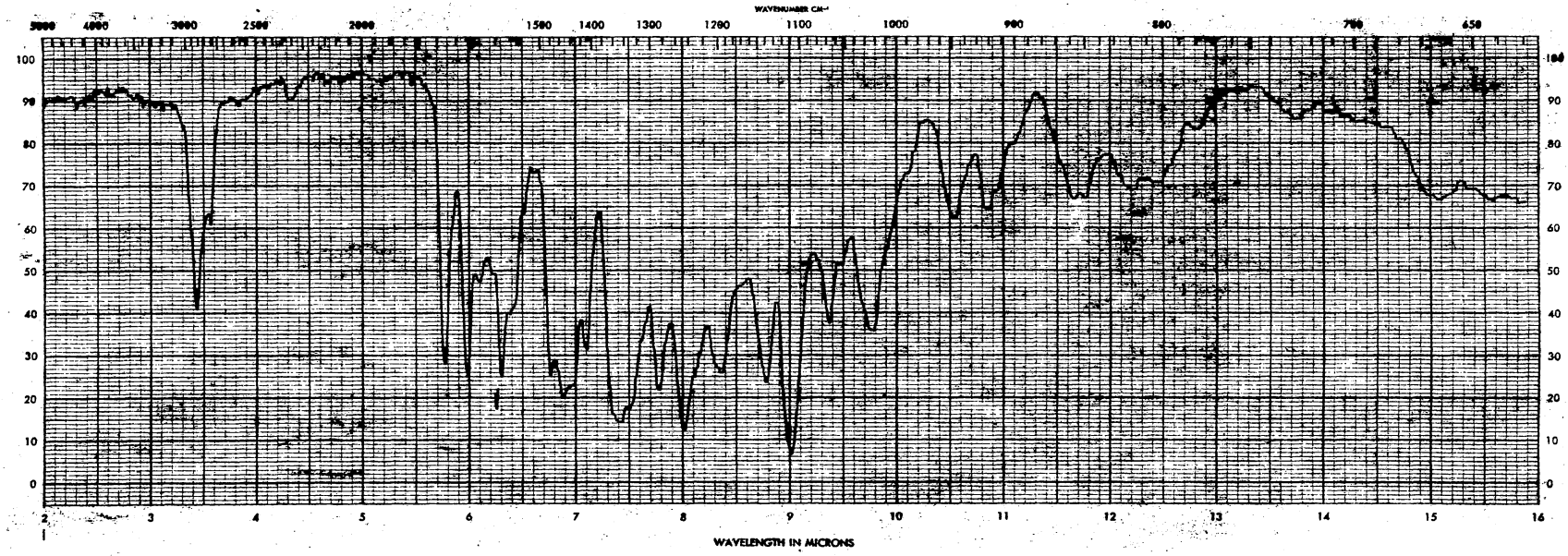
PLATE XVIII



4,5-Dihydro-6,7,8-trimethoxynaphth[1,2-d]isoxazole (99)

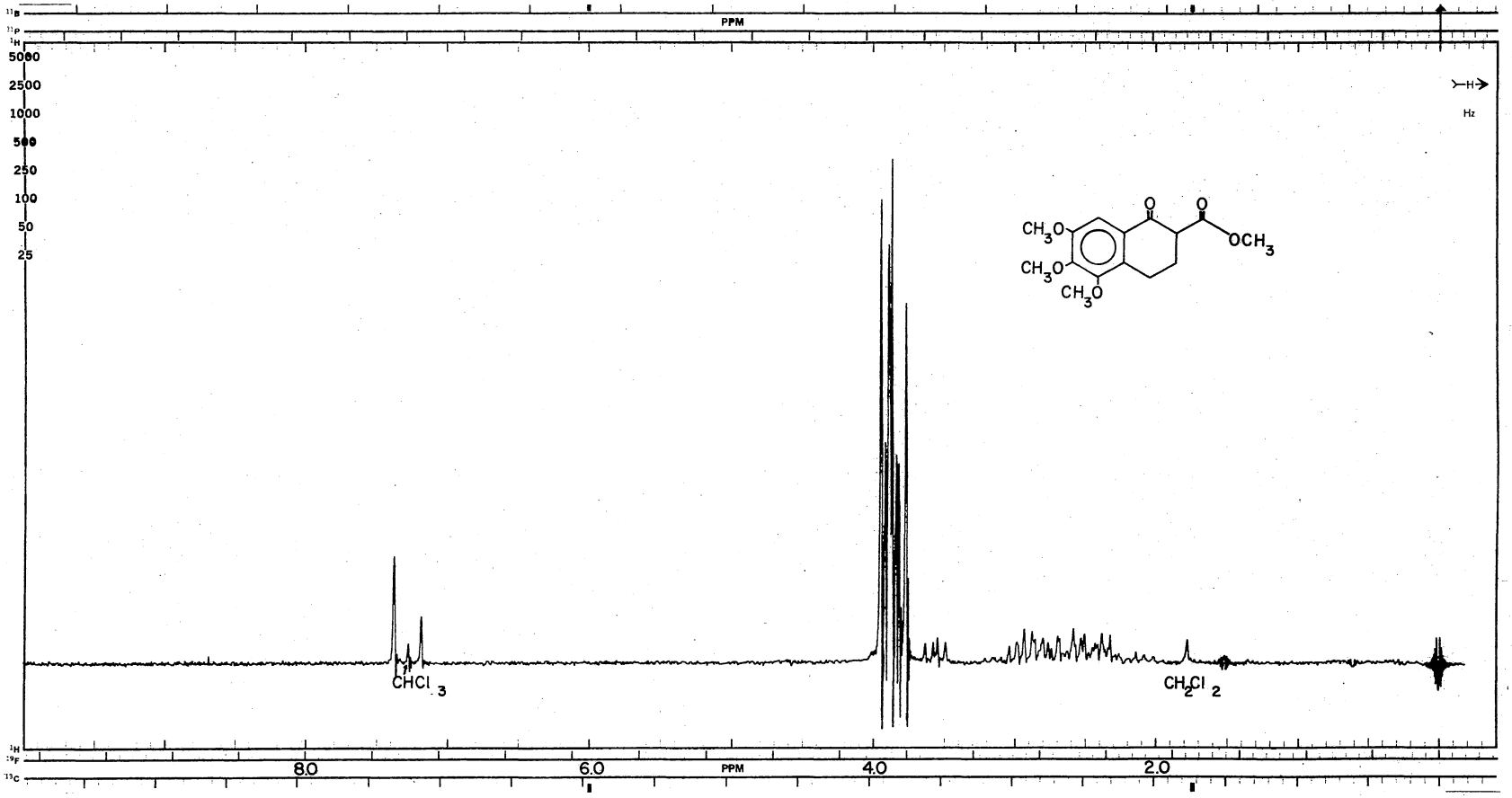
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 67 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . 12.5 Lock. .HOMO

PLATE XIX



Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-oxo-2-naphthoate (148), Film

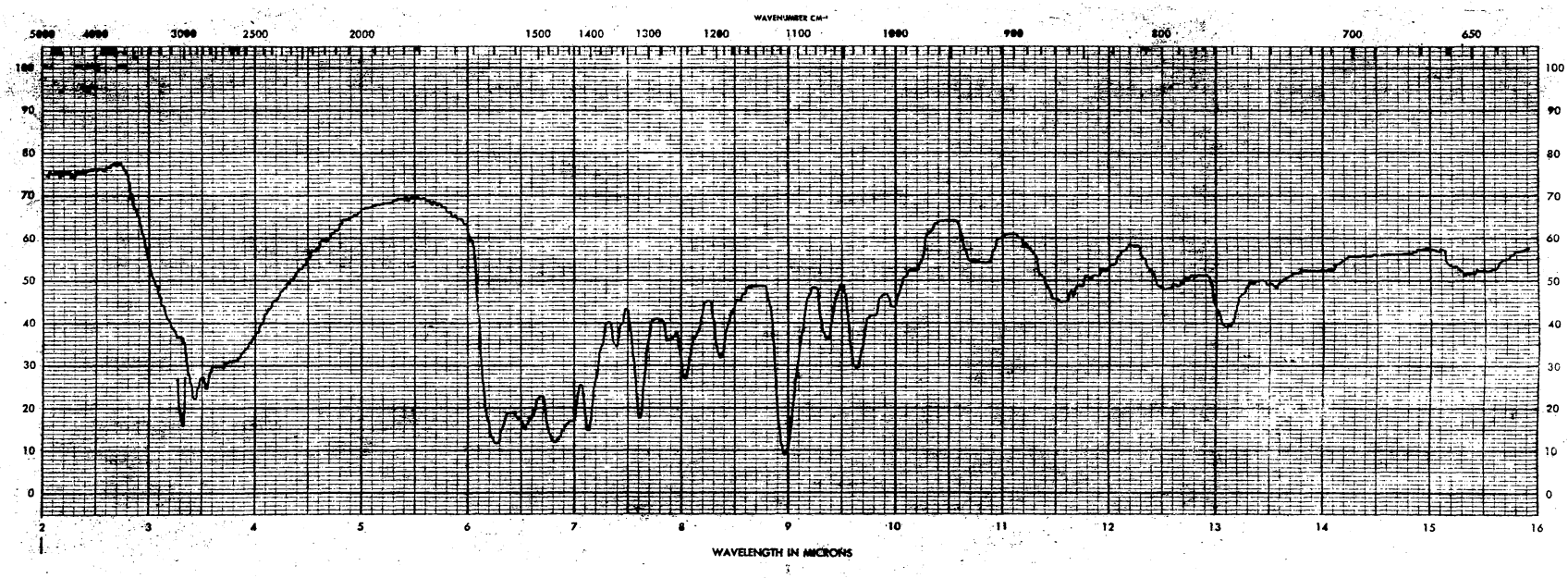
PLATE XX



Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-oxo-2-naphthoate (148)

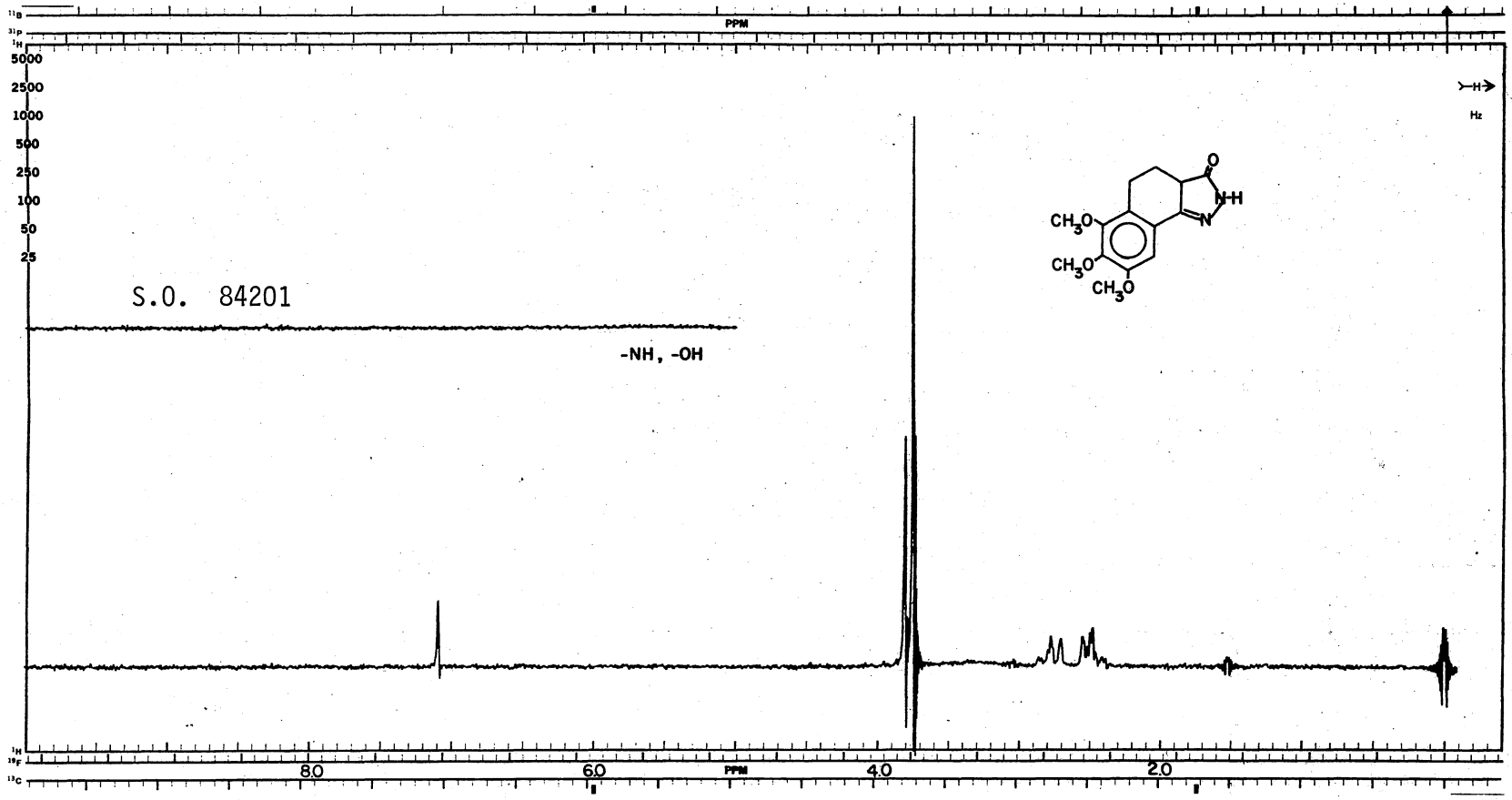
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 53 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 2.5	Lock. .HOMO

PLATE XXI



2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3H-benz[g]indazol-3-one (101), KBr Pellet

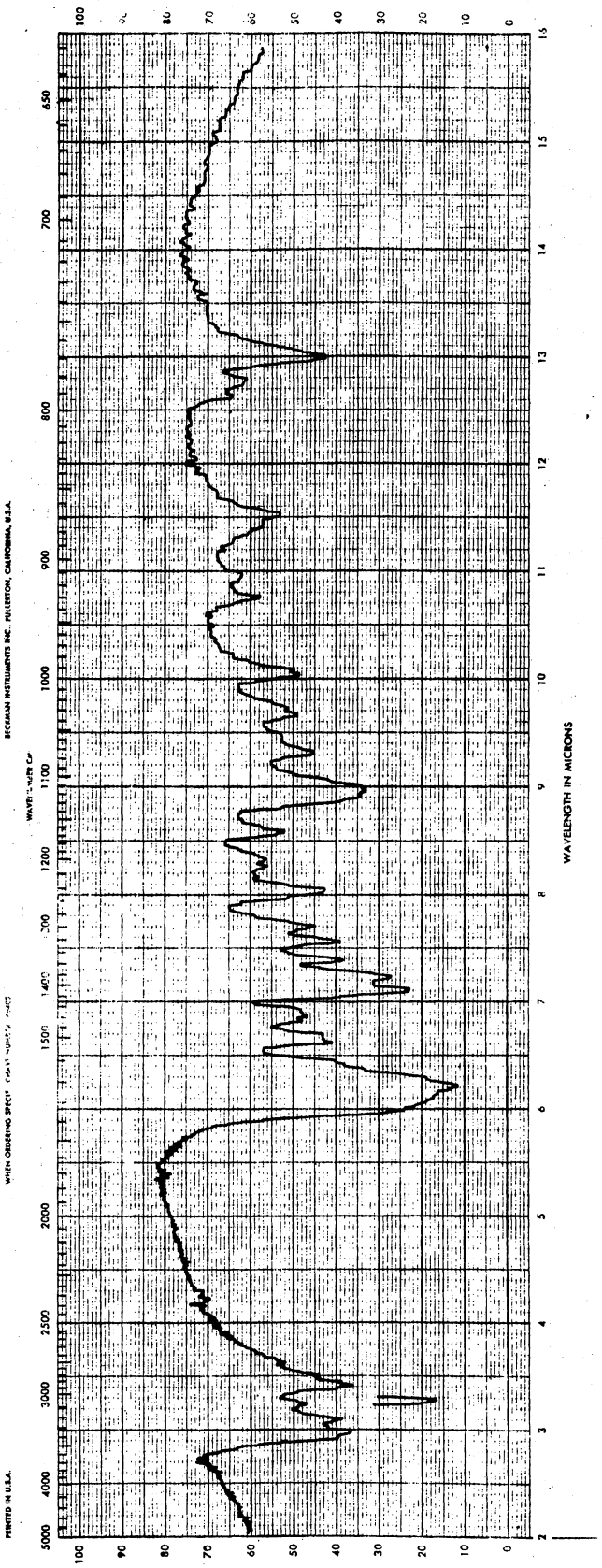
PLATE XXII



2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3H-benz[g]indazol-3-one (101)

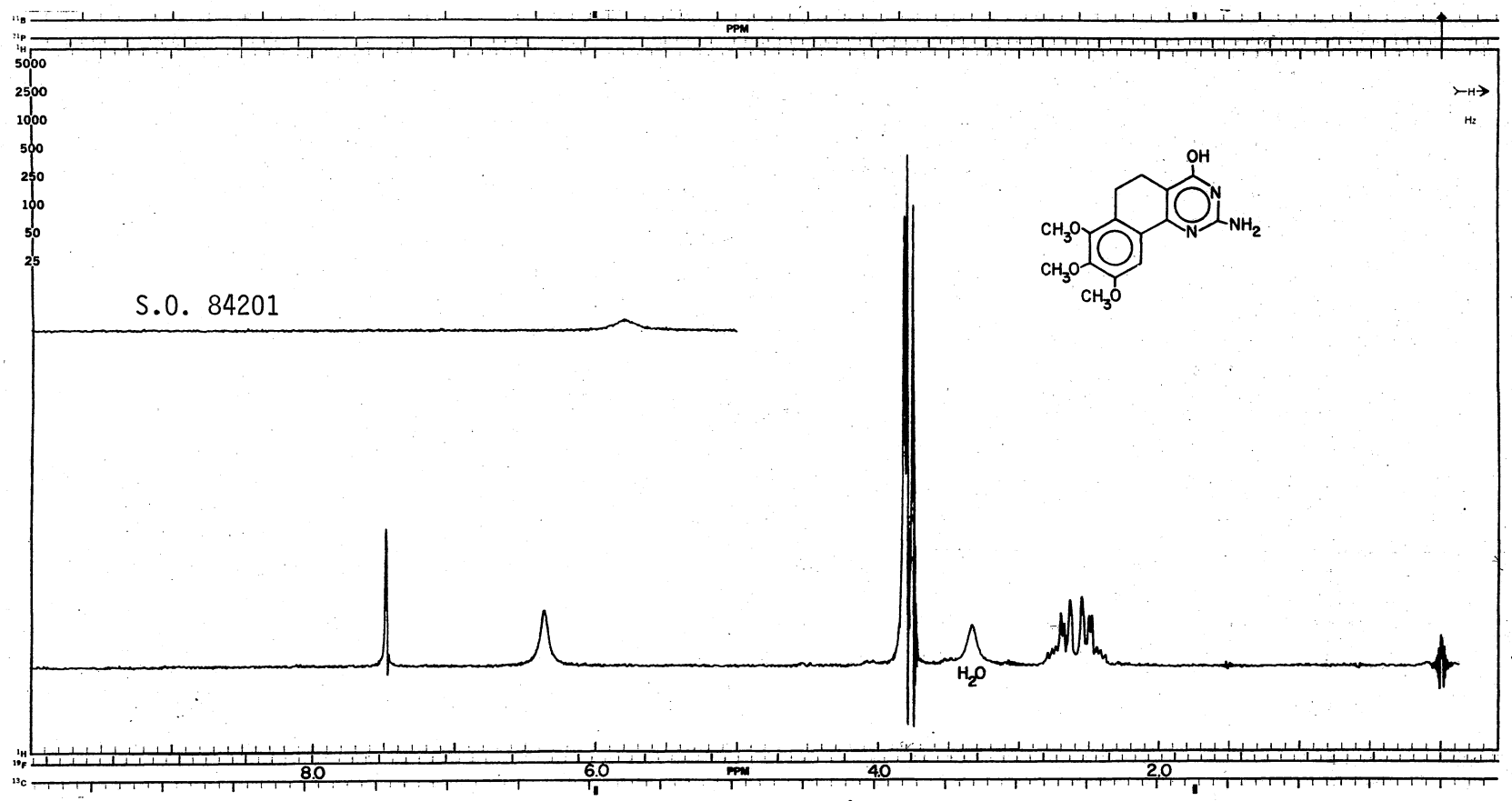
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 70 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 3.2	Lock. .HOMO

PLATE XXIII



2-Amino-5,6-dihydro-7,8,9-trimethoxybenzo[h]quinazolin-4-ol (104), KBr Pellet

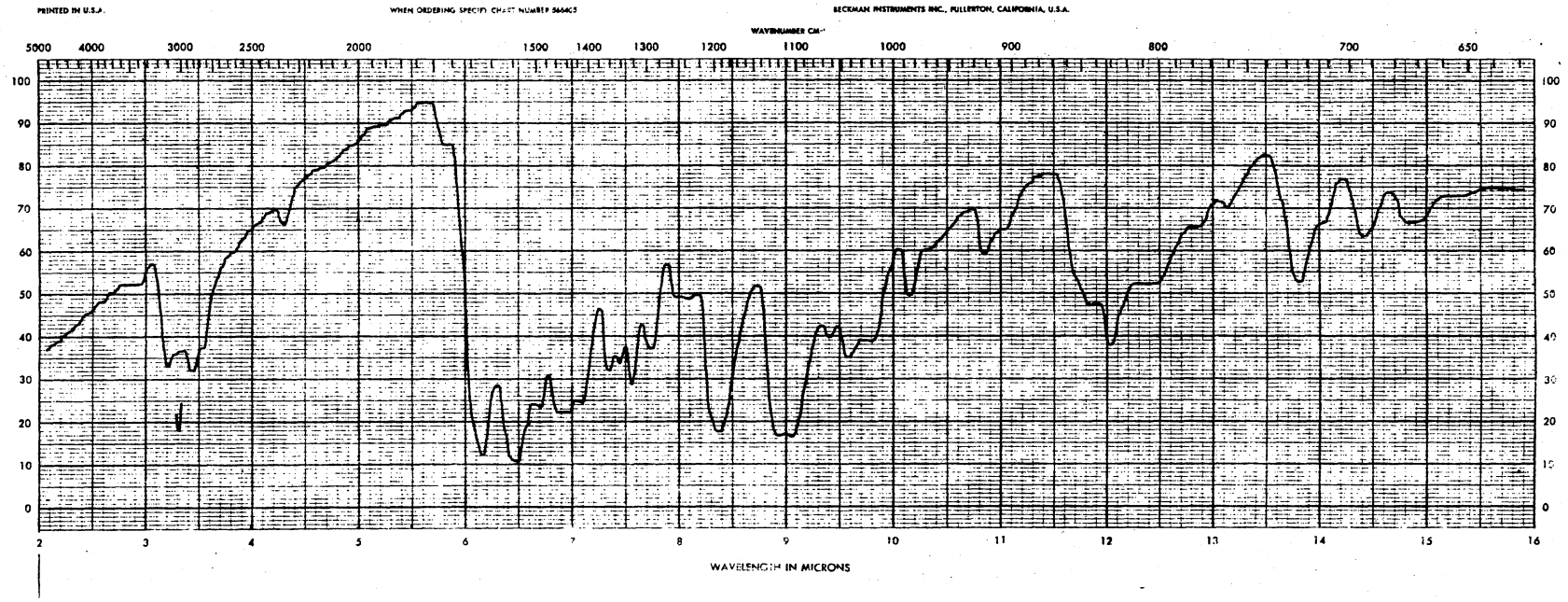
PLATE XXIV



2-Amino-5,6-dihydro-7,8,9-trimethoxybenzo[h]quinazoline-2,4-diol (104)

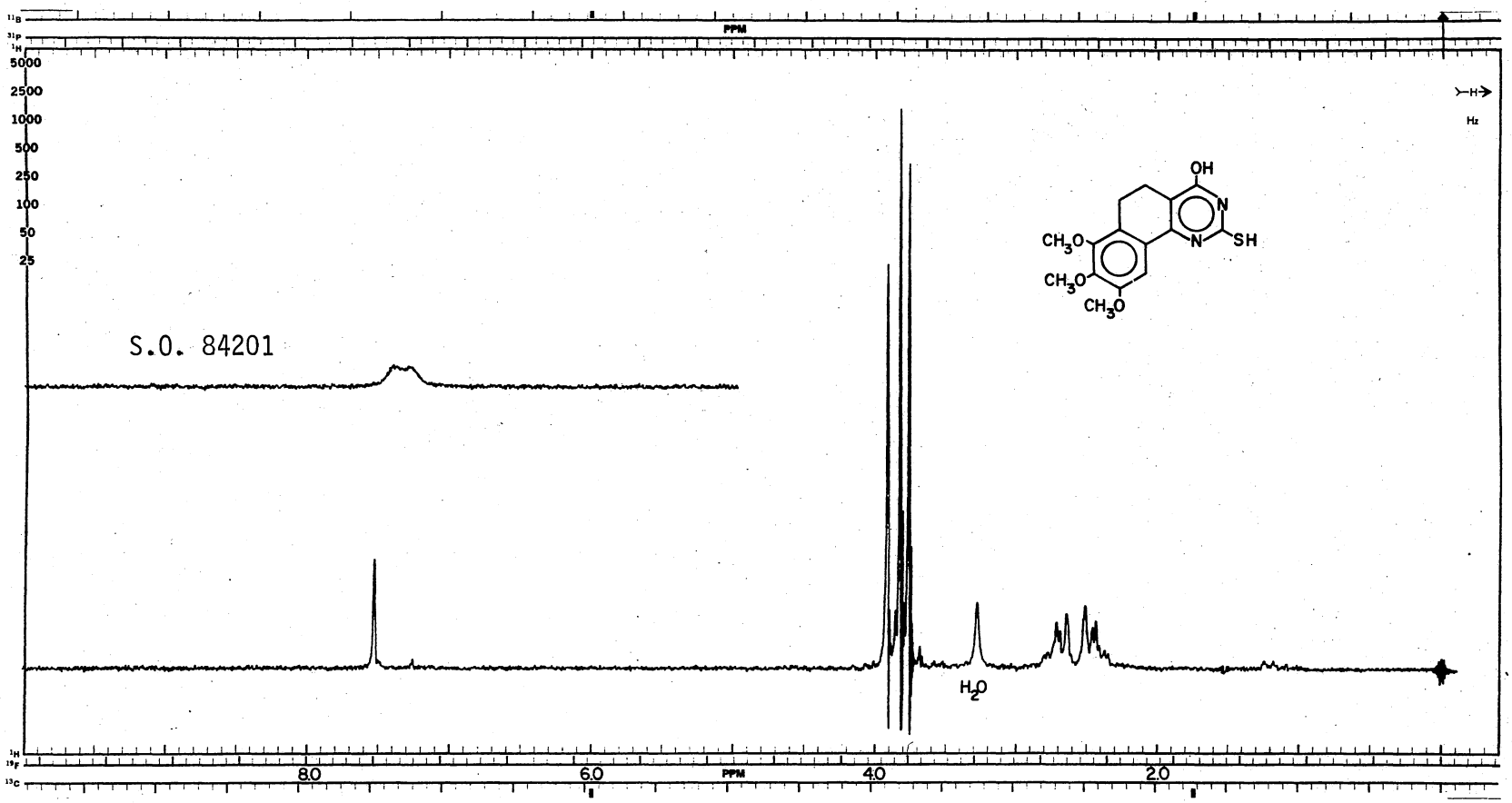
Solvent. . DMSO-d_6	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 66 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 1.6	Lock. .HOMO

PLATE XXV



5,6-Dihydro-2-mercapto-7,8,9-trimethoxybenzo[h]quinazolin-4-ol (105), KBr Pellet

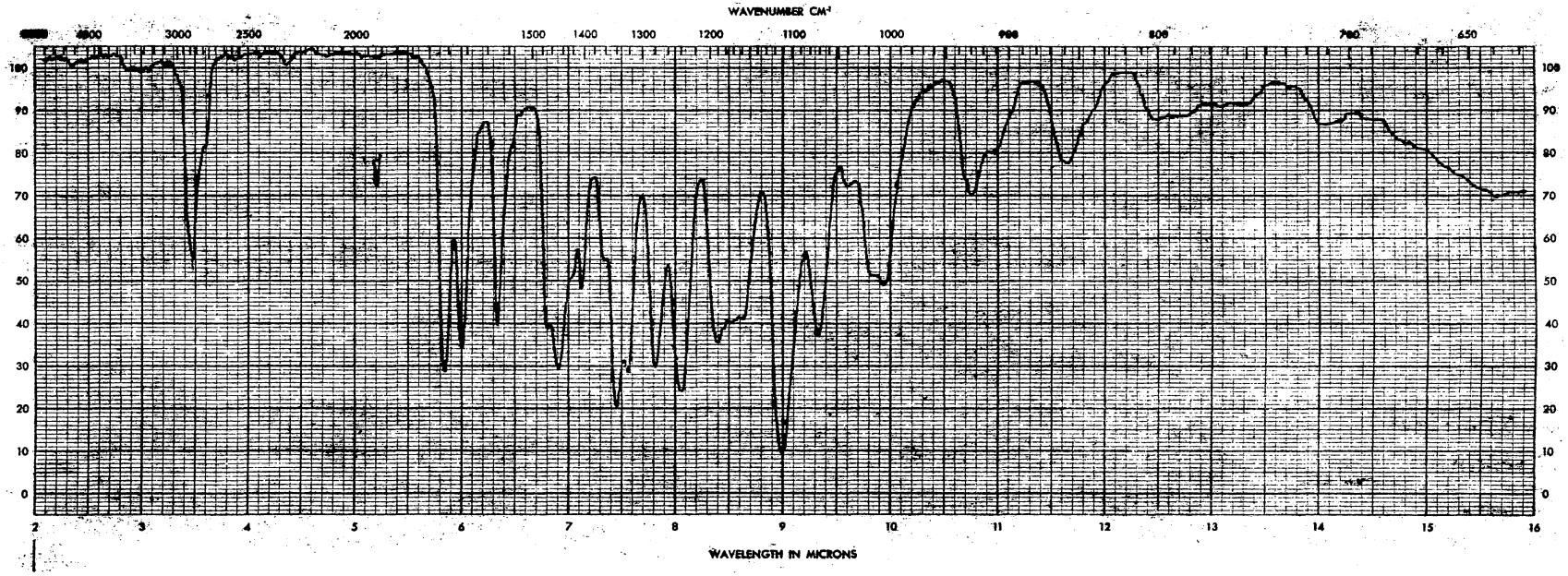
PLATE XXVI



5,6-Dihydro-2-mercapto-7,8,9-trimethoxybenzo[h]quinazolin-4-ol (105)

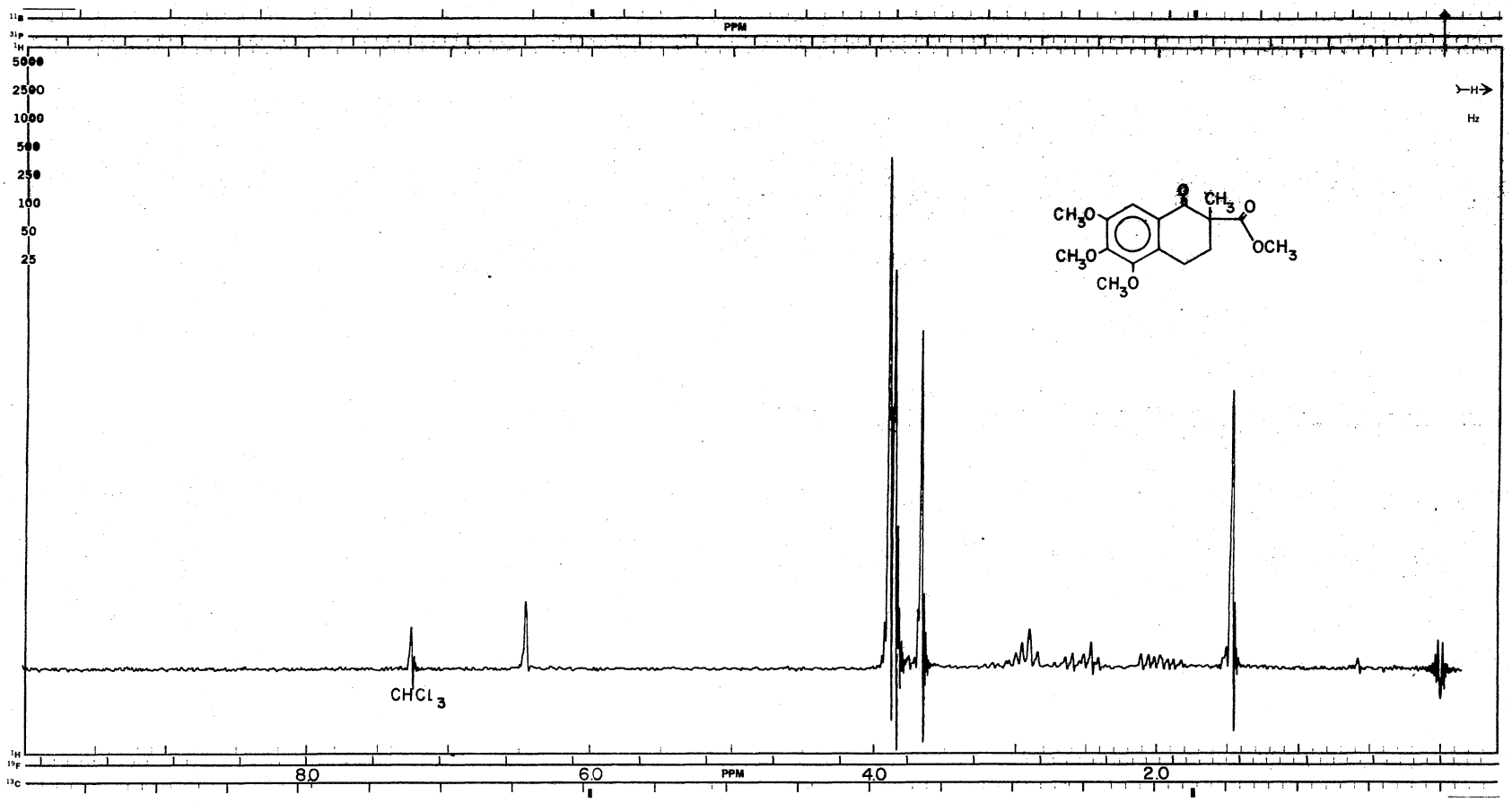
Solvent. . DMSO-d_6	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 71 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 3.2	Lock. .HOMO

PLATE XXVII



Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methyl-1-oxo-2-naphthoate (153), KBr Pellet

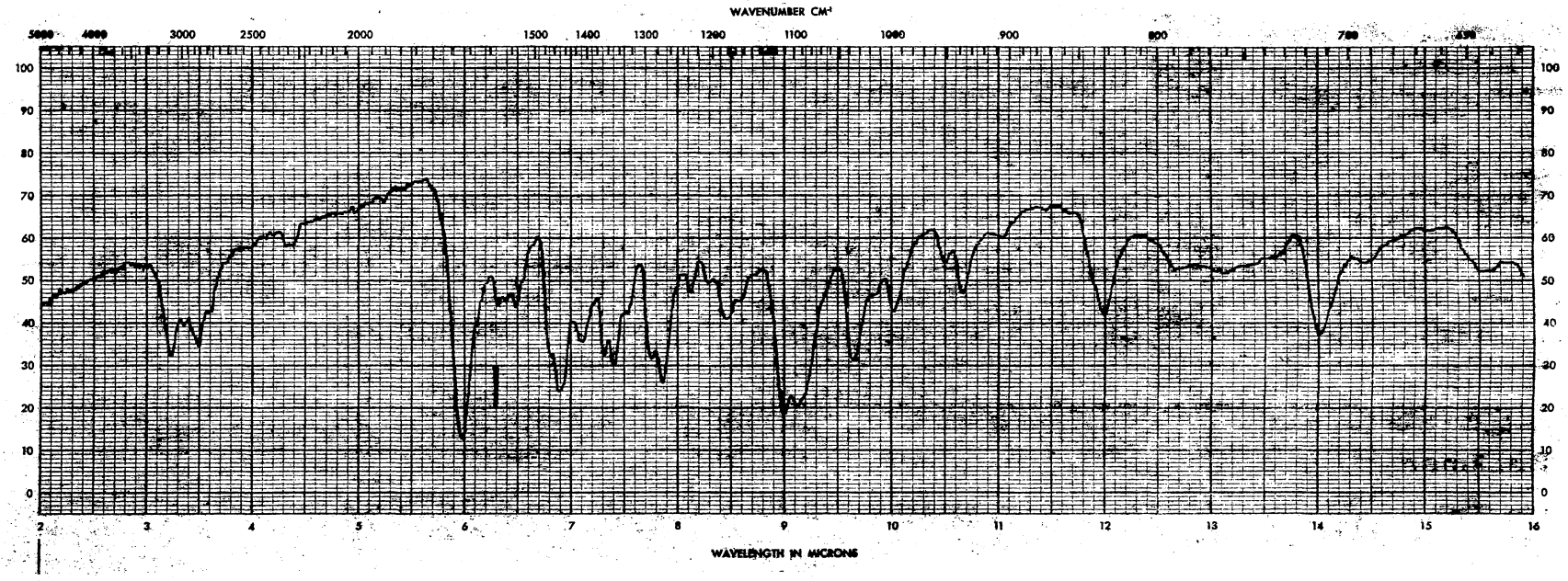
PLATE XXVIII



Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methyl-1-oxo-2-naphthoate (153)

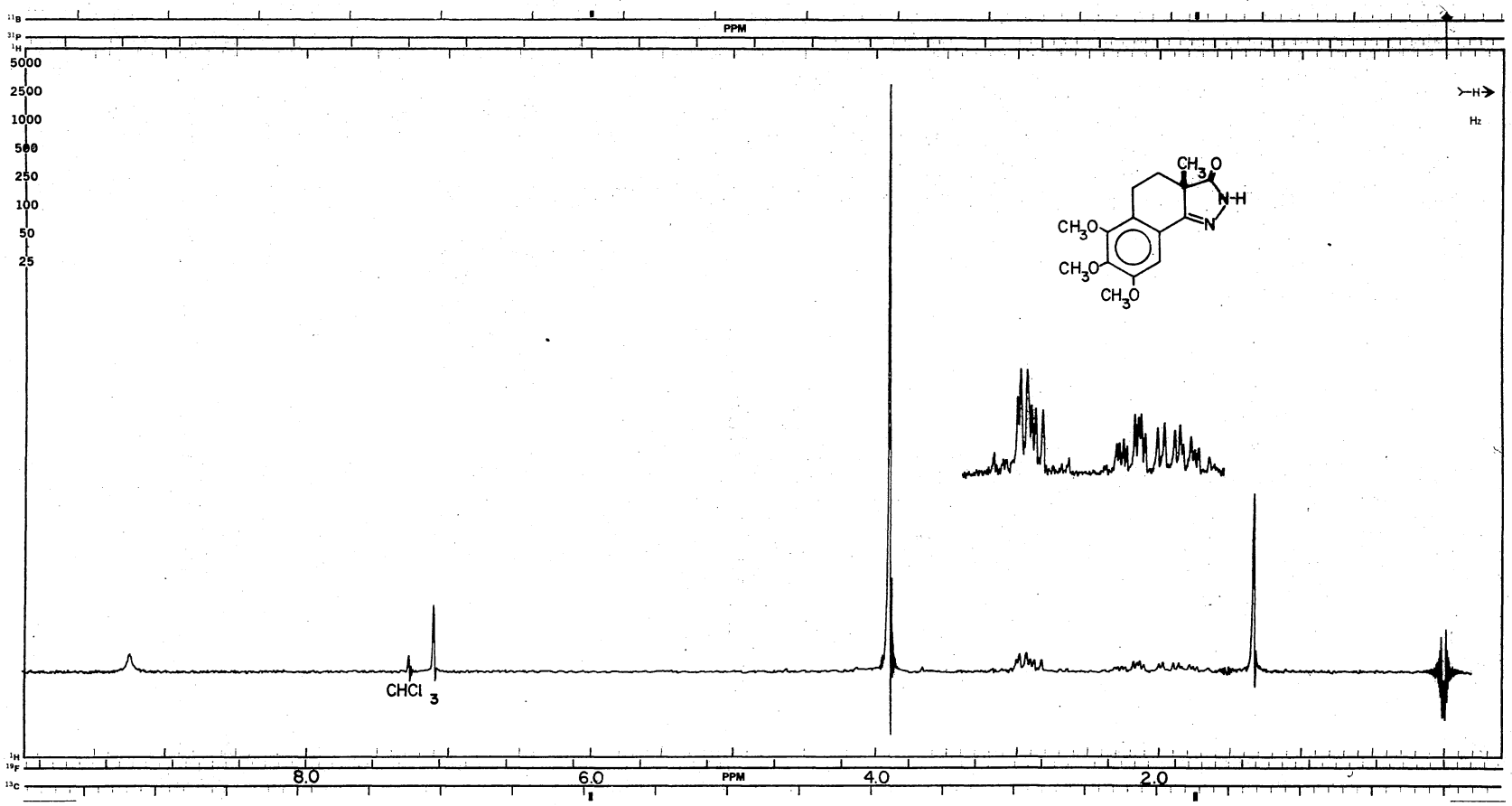
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 69 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 2.0	Lock. . HOMO

PLATE XXIX



2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one (102), KBr Pellet

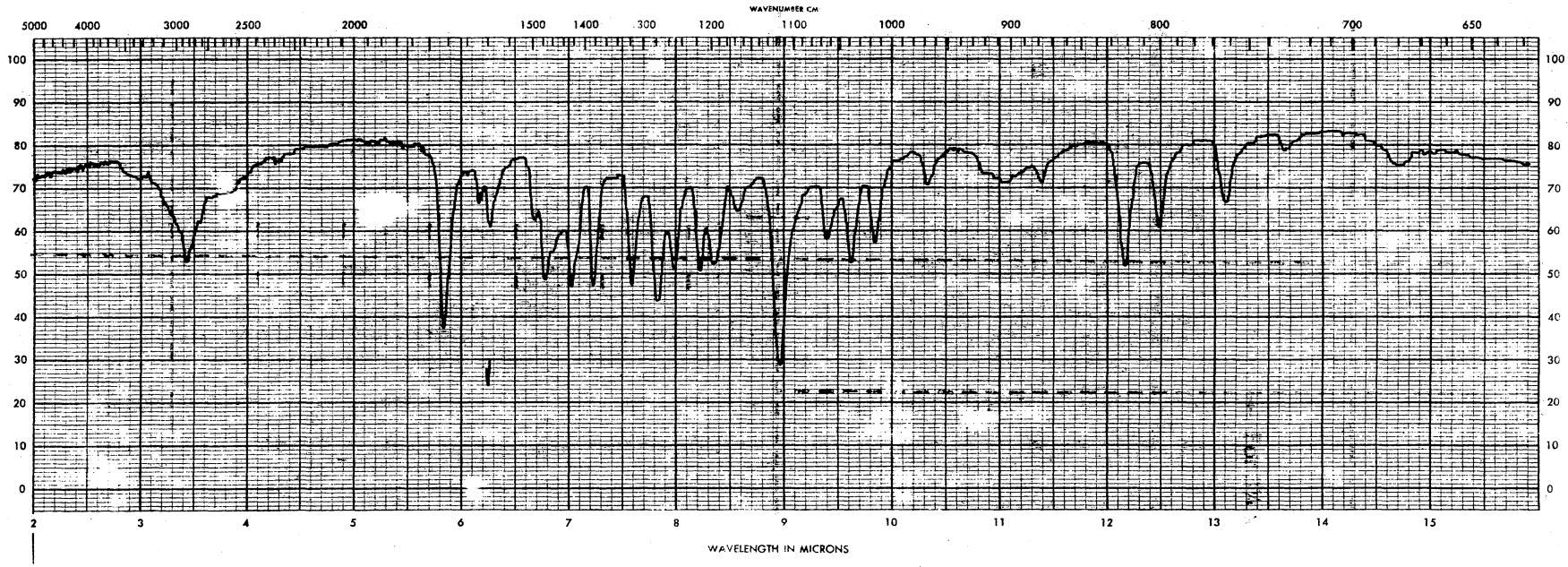
PLATE XXX



2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one (102)

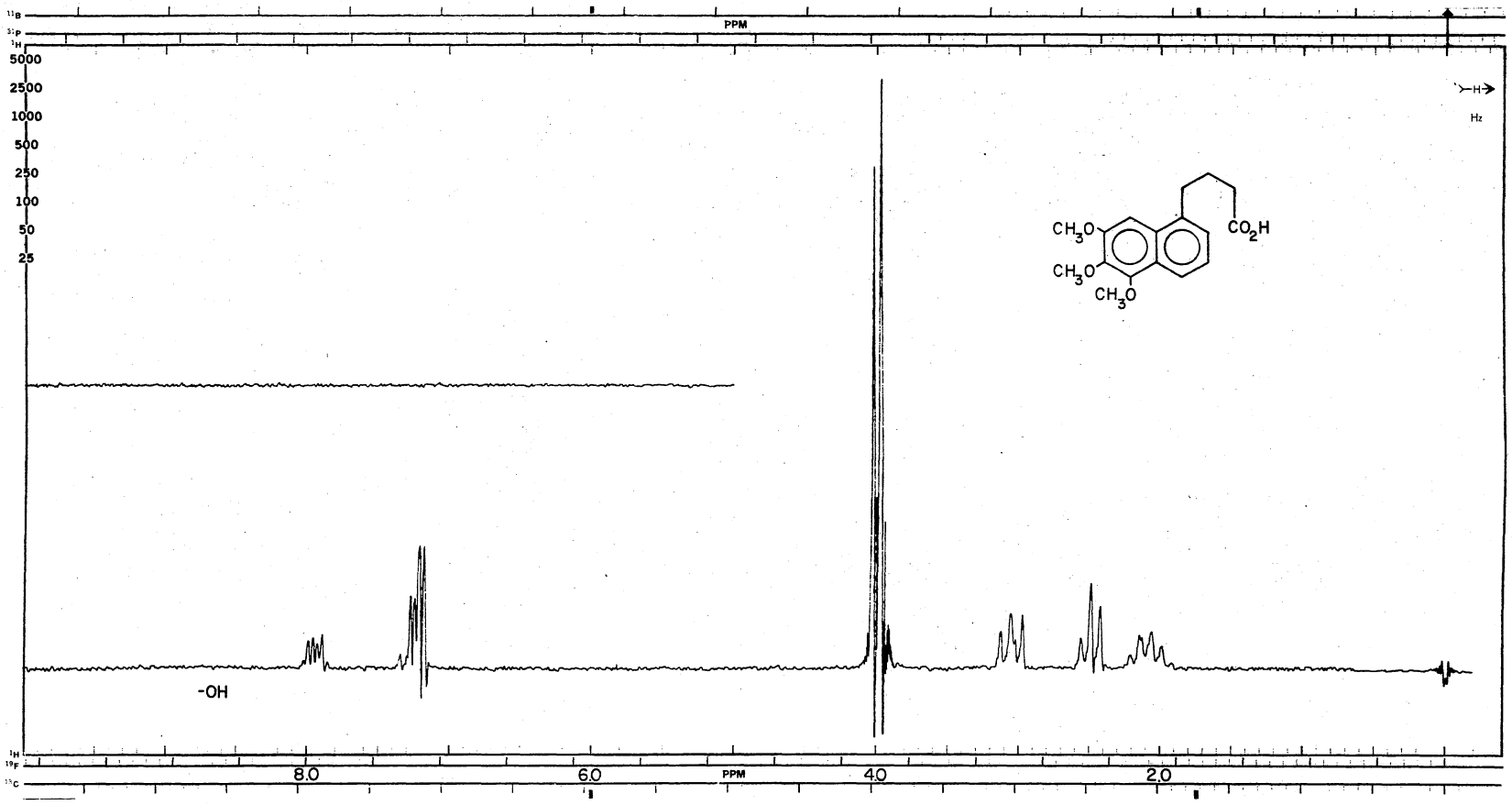
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 60 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 1.6	Lock. .HOMO

PLATE XXXI



5,6,7-Trimethoxy-1-naphthalenebutyric Acid (130), KBr Pellet

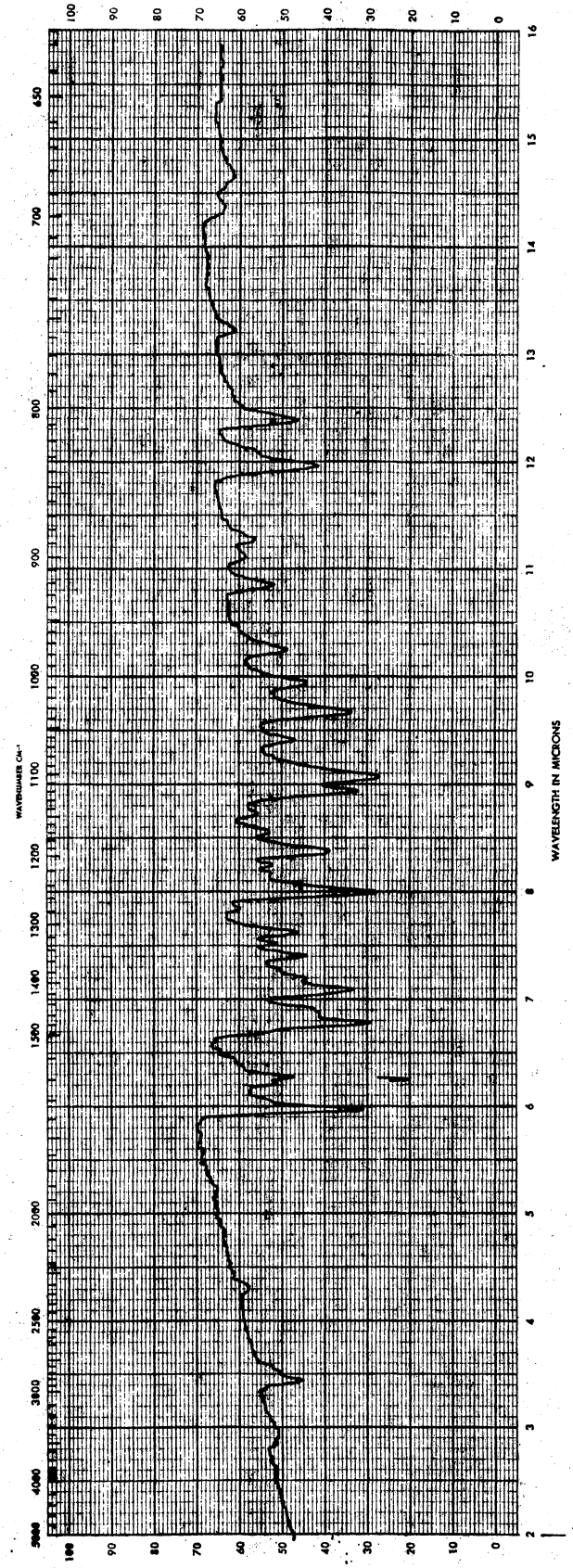
PLATE XXXII



5,6,7-Trimethoxy-1-naphthalenebutyric Acid (130)

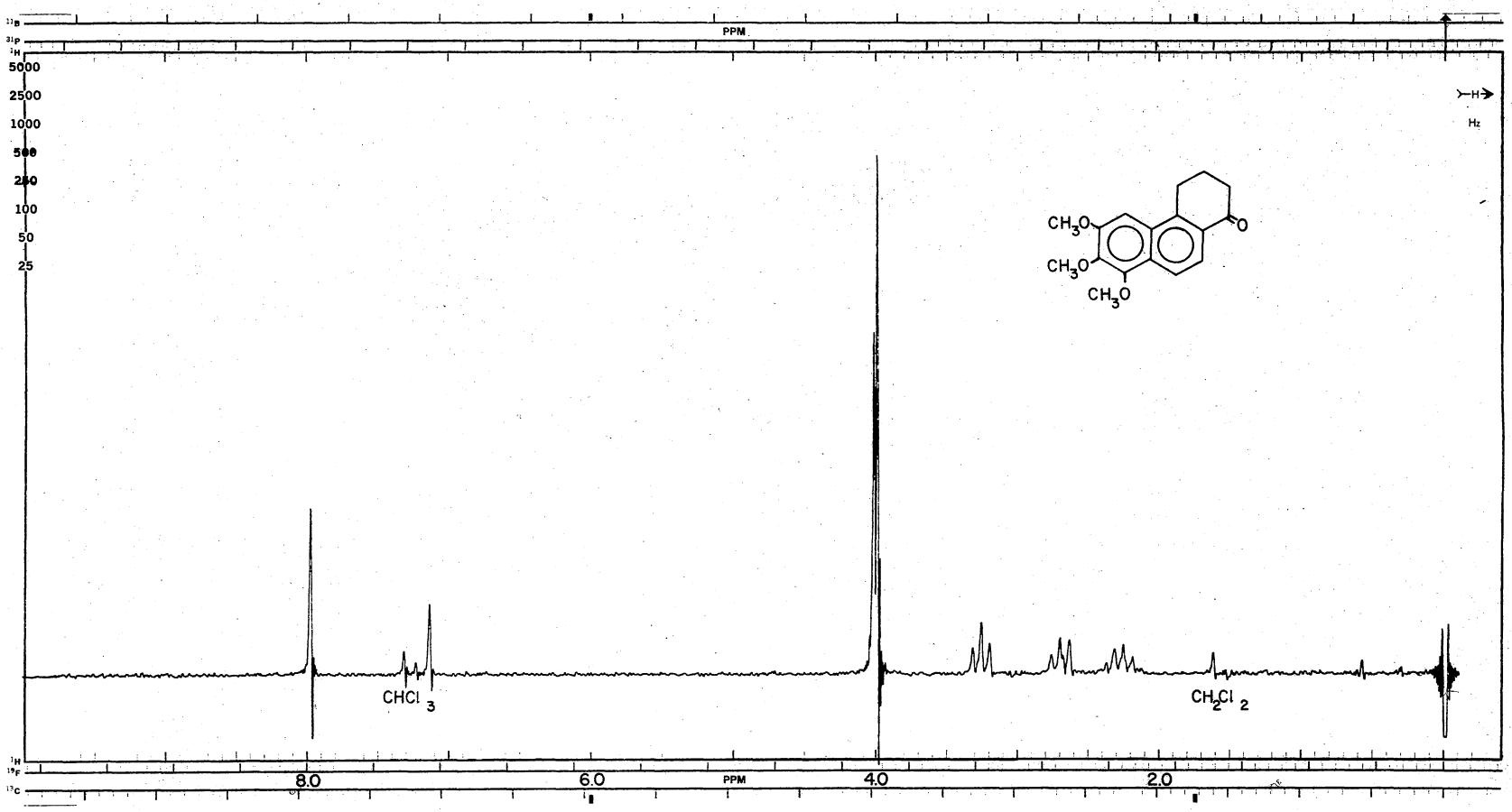
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 66 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . .32 Lock. .HOMO

PLATE XXXIII



3,4-Dihydro-6,7,8-trimethoxy-1(2H)-phenanthrone (131), KBr Pellet

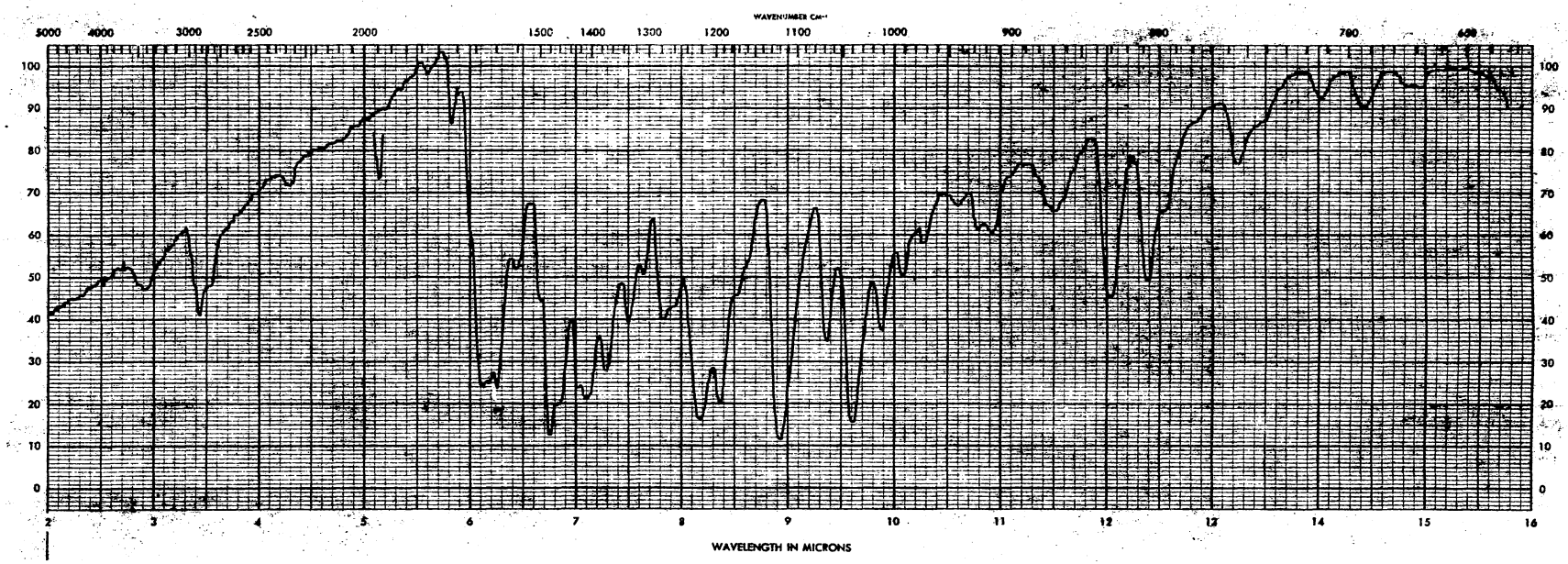
PLATE XXXIV



3,4-Dihydro-6,7,8-trimethoxy-1(2H)-phenanthrone (131)

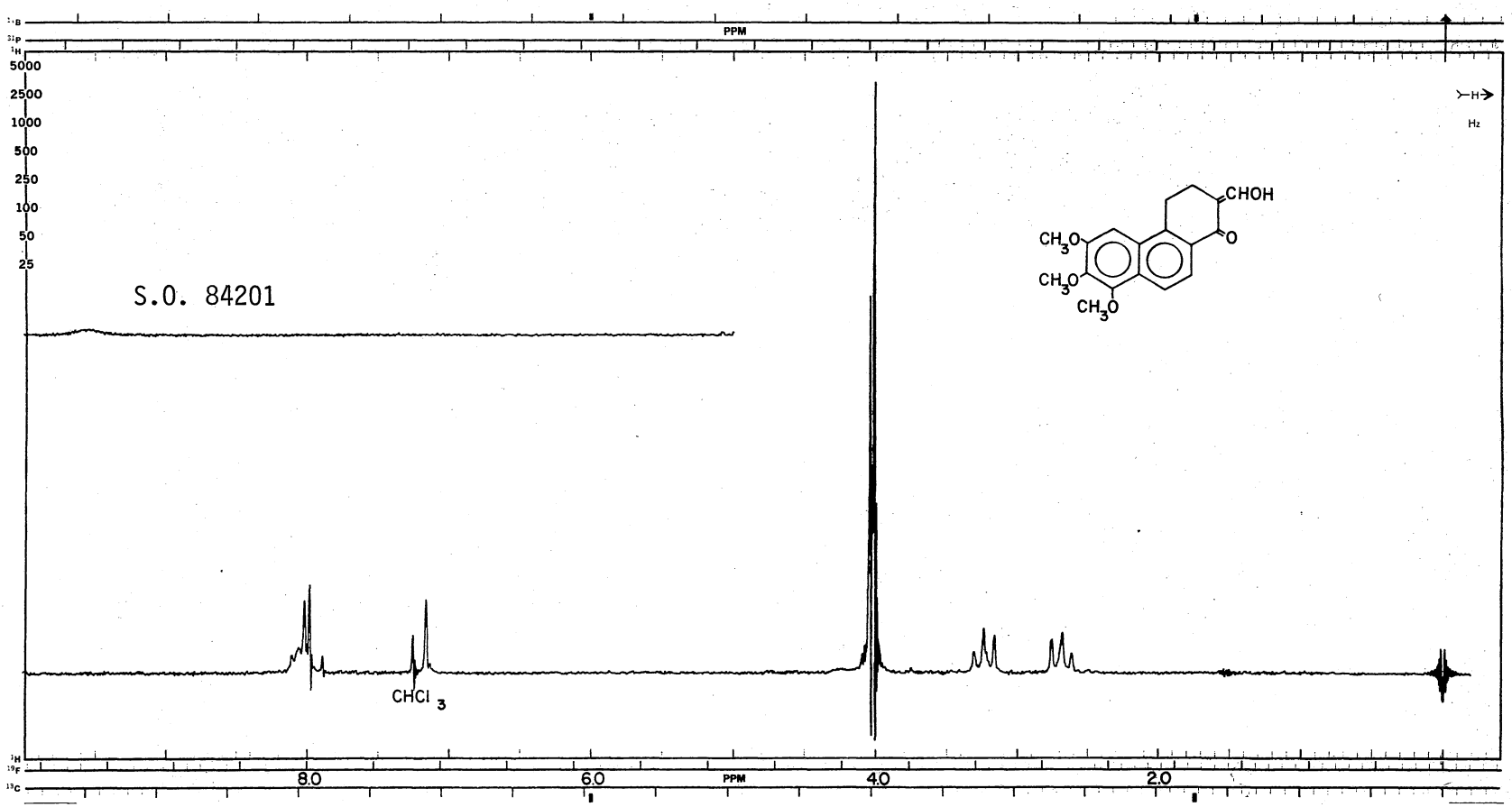
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 65 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 2.5 Lock. .HOMO

PLATE XXXV



3,4-Dihydro-2(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-phenanthrone (144), KBr Pellet

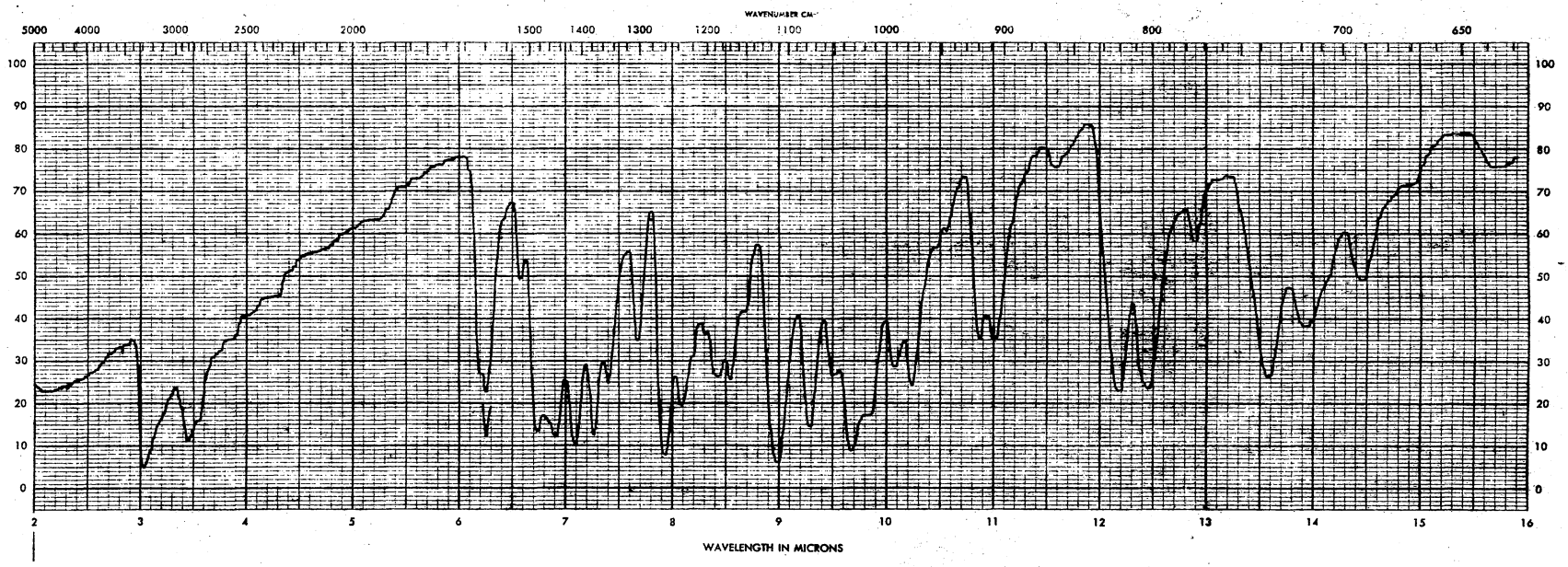
PLATE XXXVI



3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-phenanthrone (144)

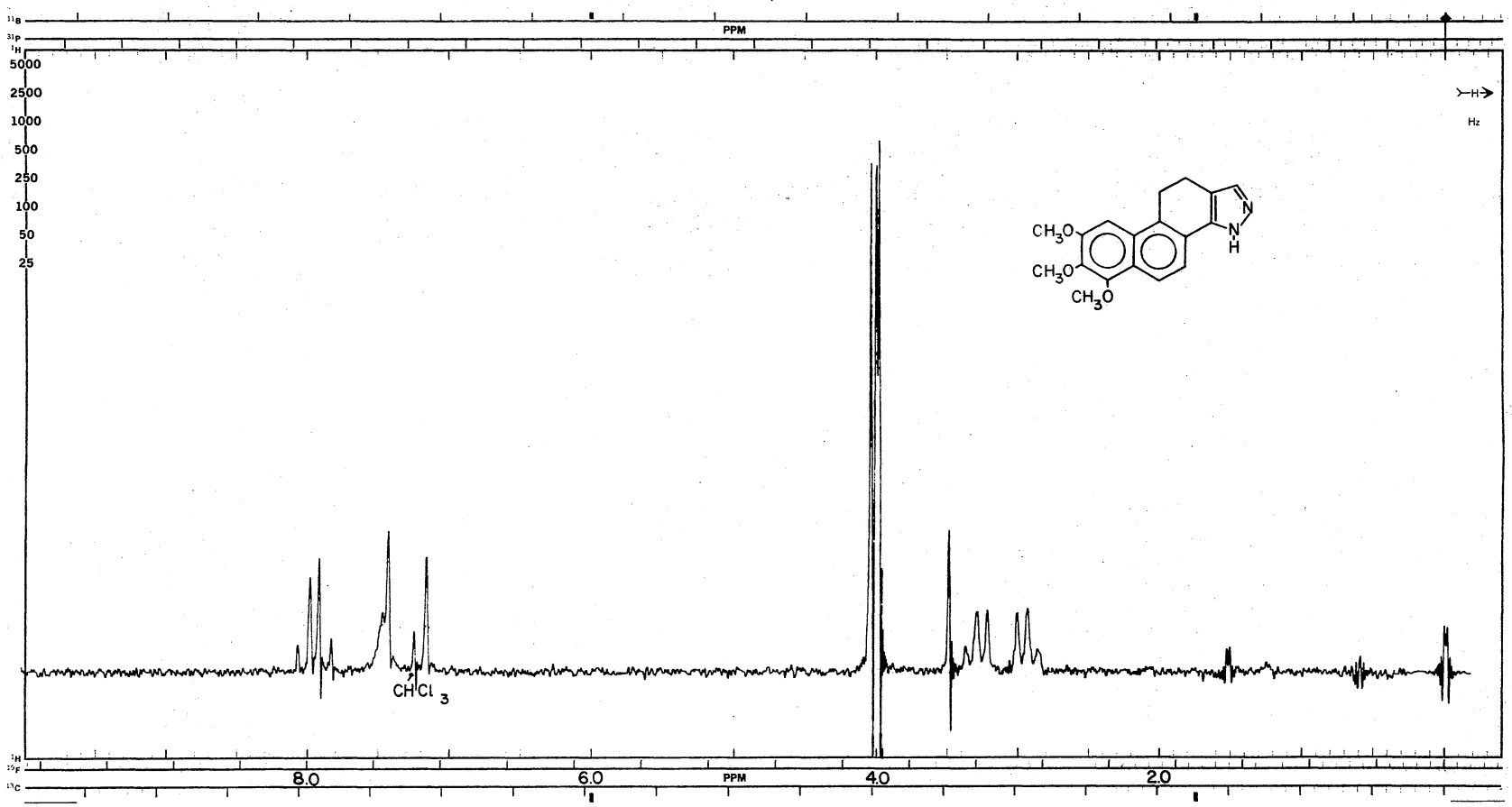
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 65 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 2.0	Lock. .HOMO

PLATE XXXVII



10,11-Dihydro-6,7,8-trimethoxy-3H-phenanthro[1,2-c]pyrazole (106), KBr Pellet

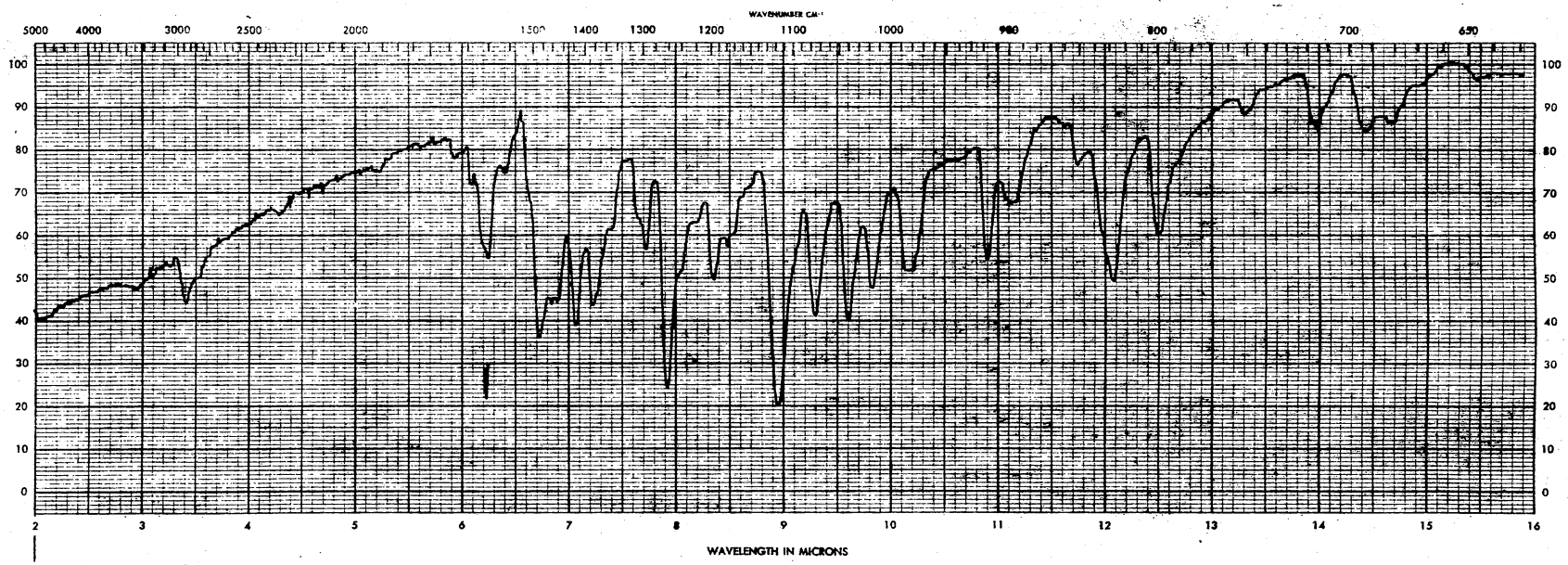
PLATE XXXVIII



10,11-Dihydro-6,7,8-trimethoxy-3H-phenanthro[1,2-c]pyrazole (106)

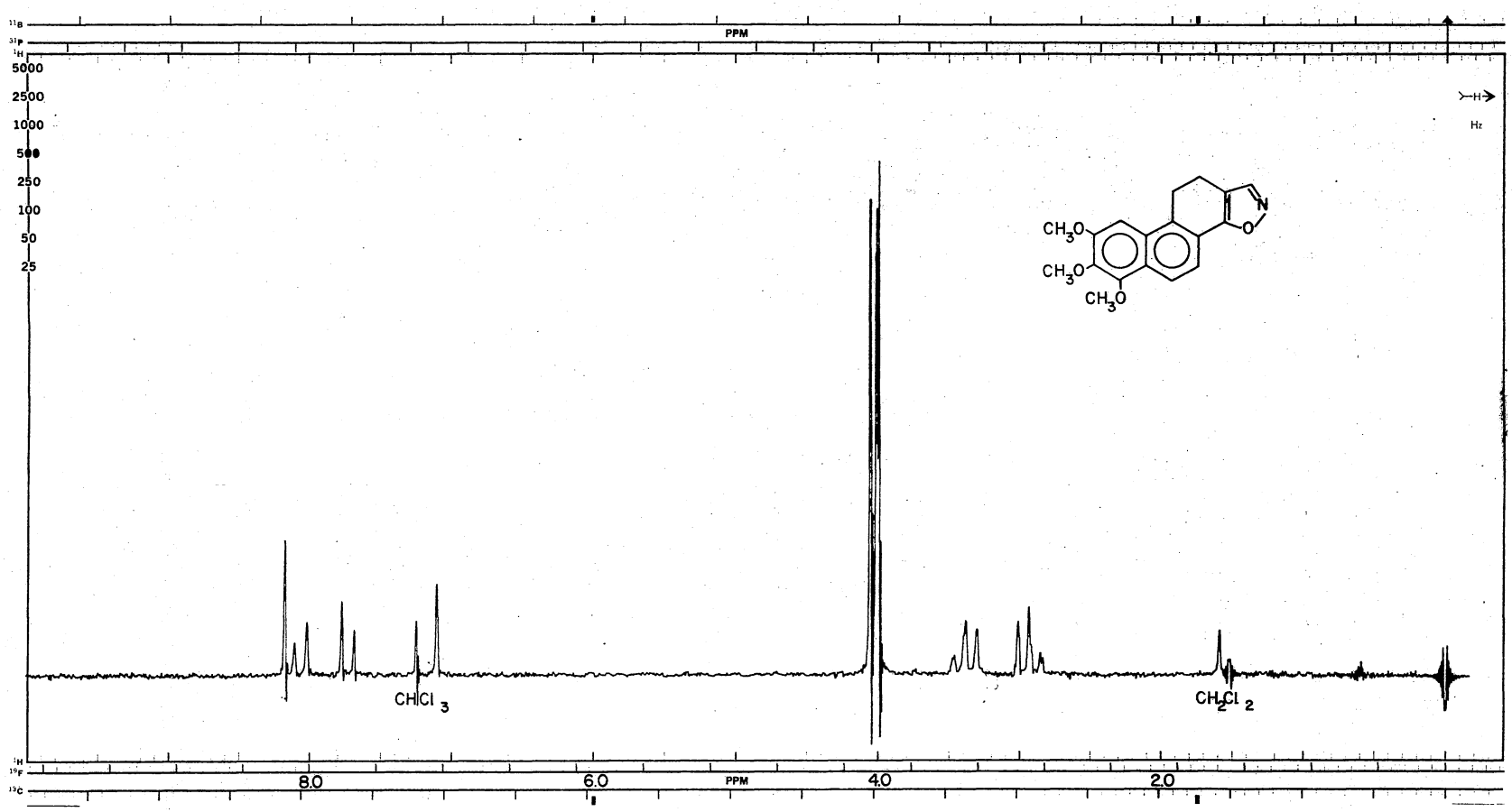
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 60 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 6.3 Lock. .HOMO

PLATE XXXIX



10,11-Dihydro-6,7,8-trimethoxyphenanthro[1,2-d]isoxazole (107), KBr Pellet

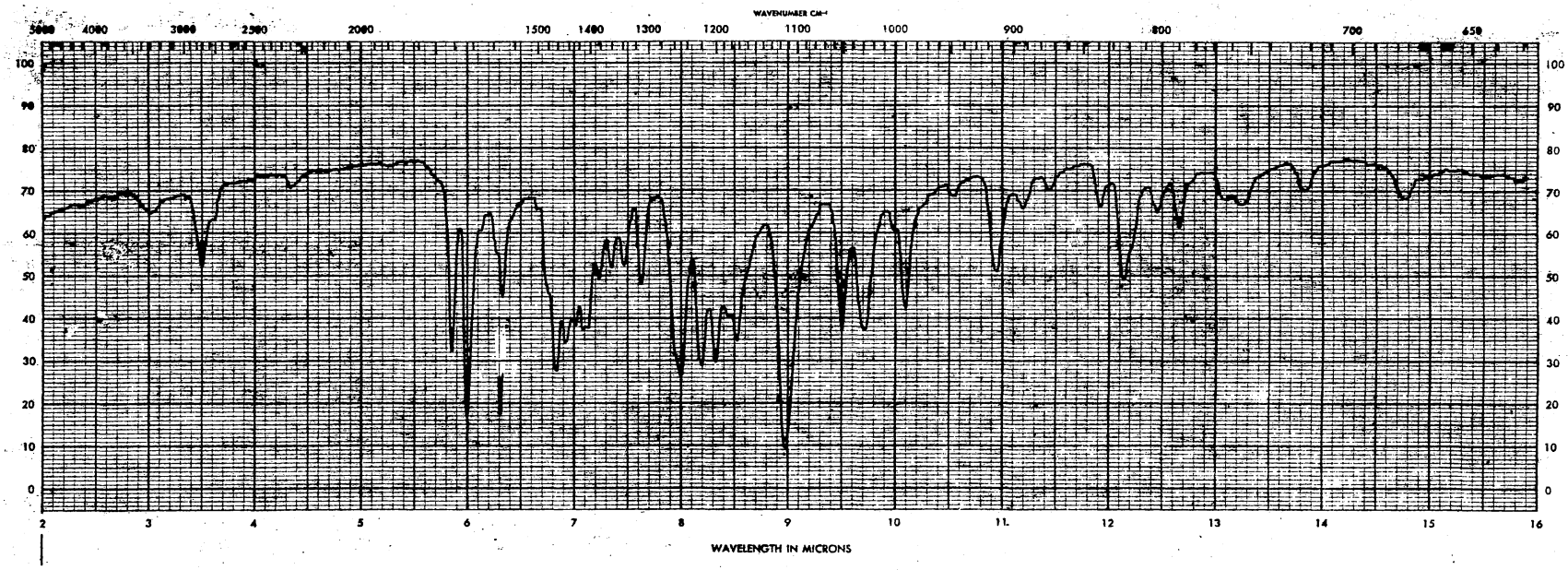
PLATE XL



10,11-Dihydro-7,8,9-trimethoxyphenanthro[1,2-d]isoxazole (107)

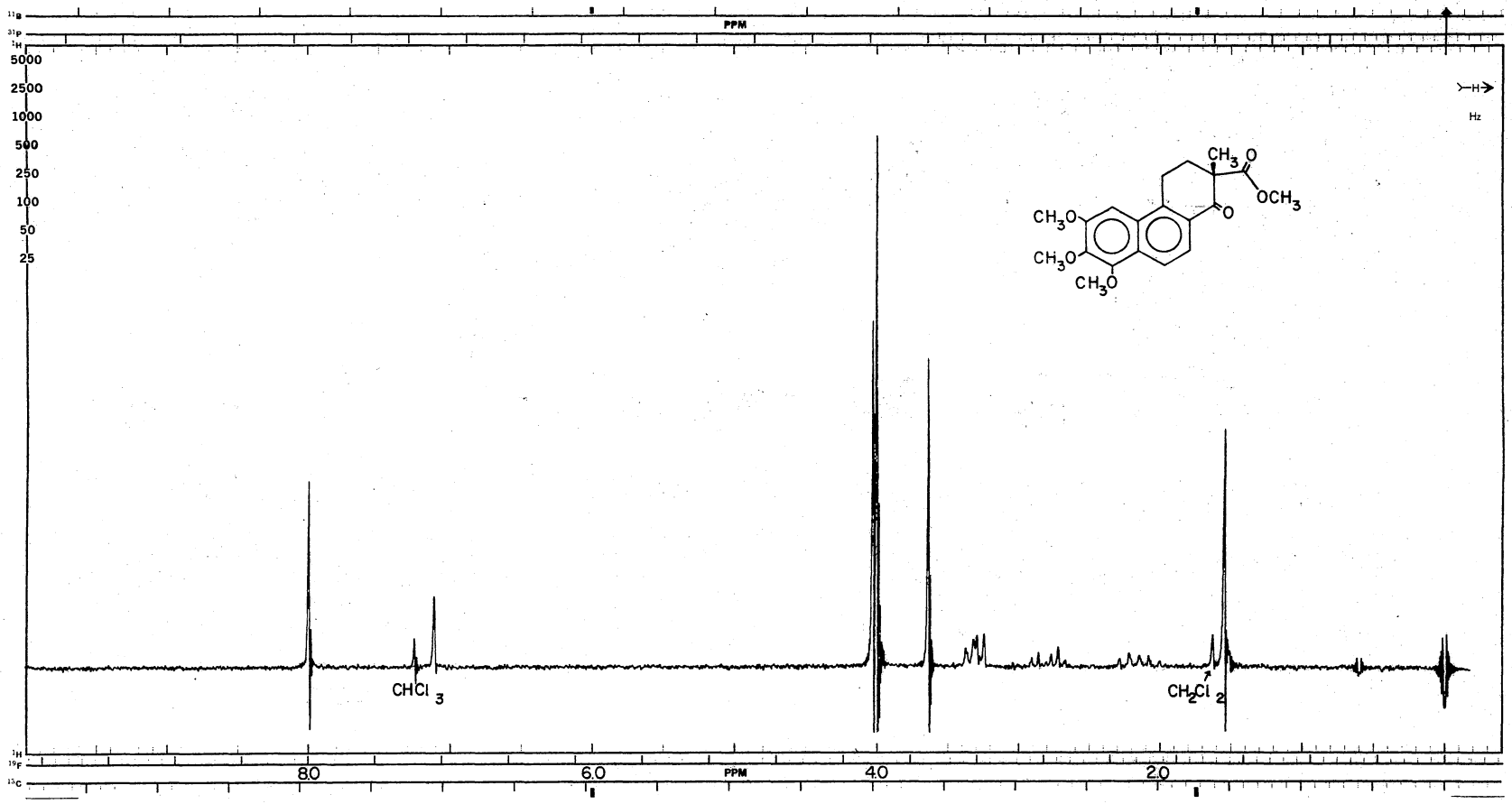
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 66 dB
S.W. . . . 1000 Hz S.T. . . . . 500 sec S.O. . . 83701 Hz S.A. . . . 4.0 Lock. .HOMO

PLATE XLI



Methyl 1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-phenanthrenecarboxylate (155), KBr Plate

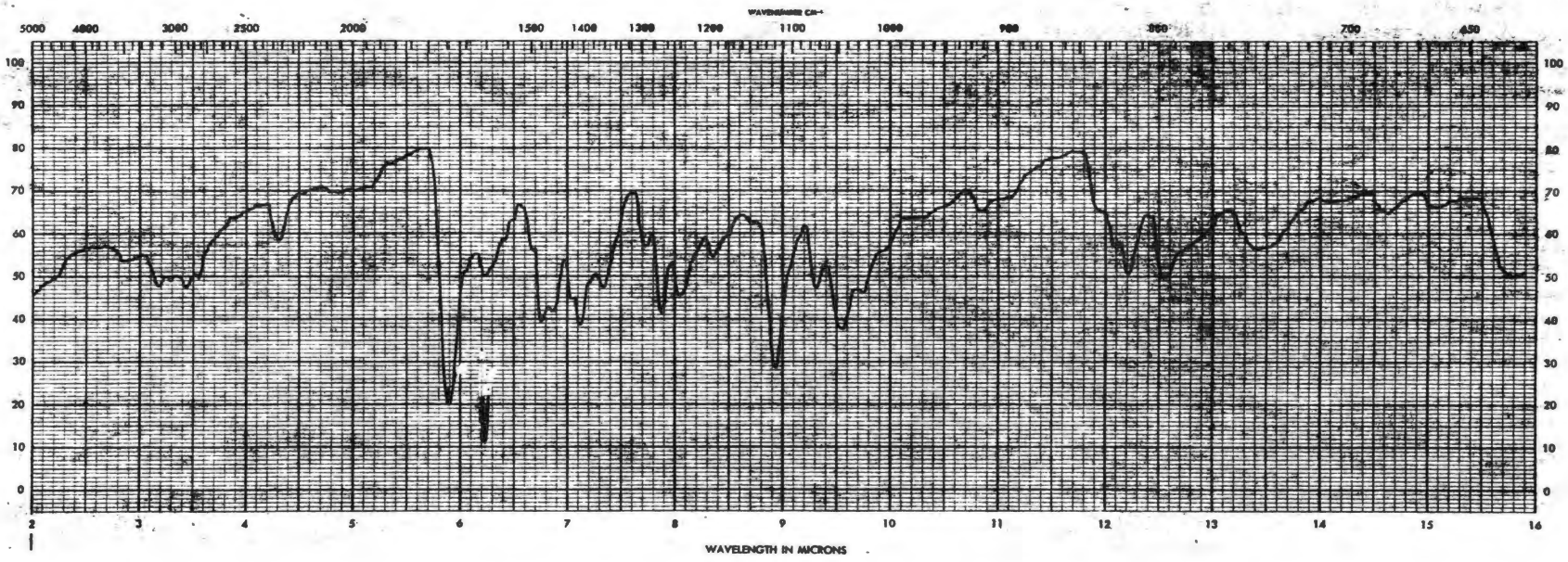
PLATE XLII



Methyl 1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-phenanthrenecarboxylate (155)

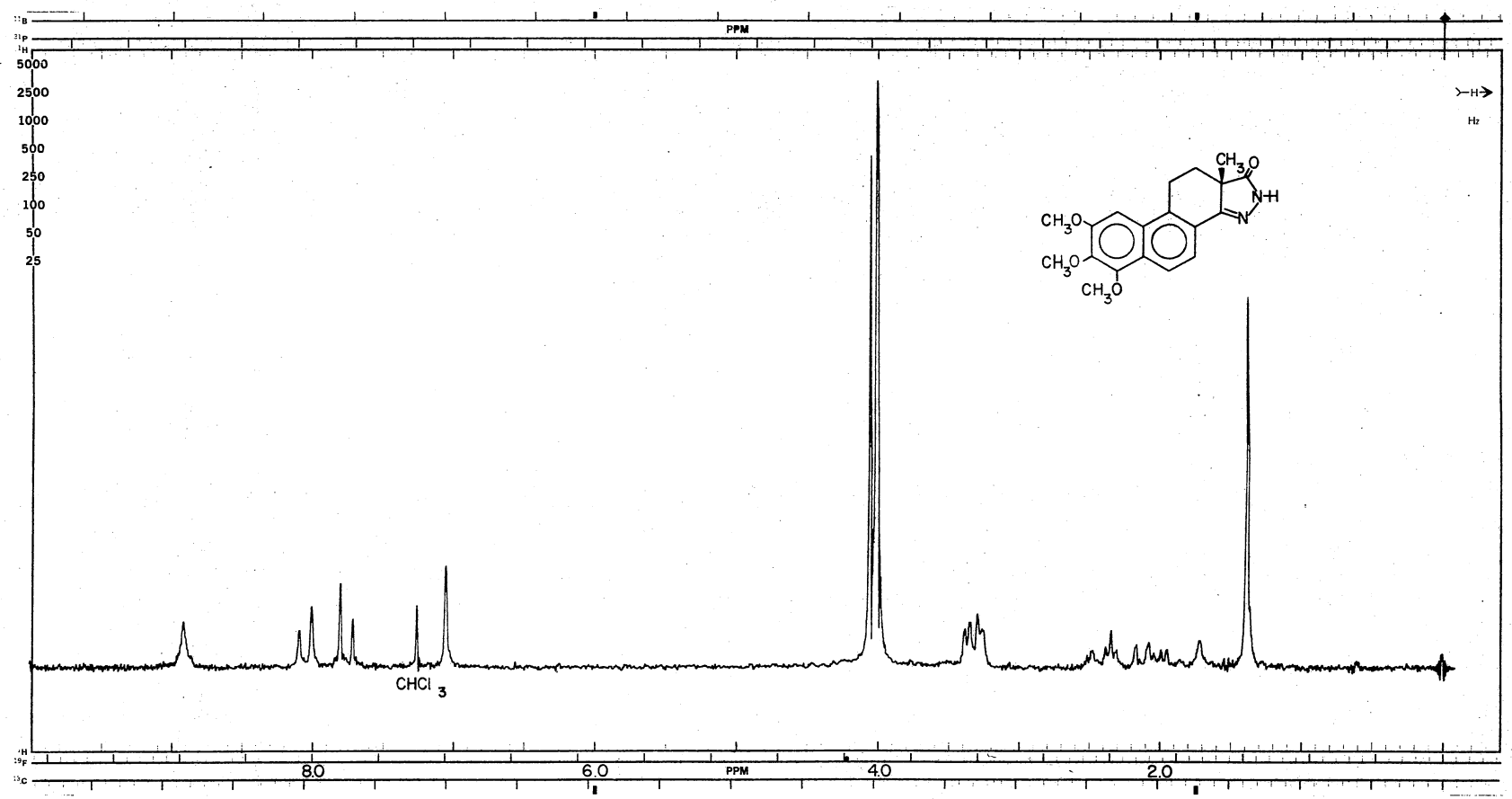
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 61 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 3.2	Lock. .HOMO

PLATE XLIII



2,10-11,11a-Tetrahydro-6,7,8-trimethoxy-11a-methyl-1H-phenanthro[1,2-c]pyrazol-1-one (108), KBr Pellet

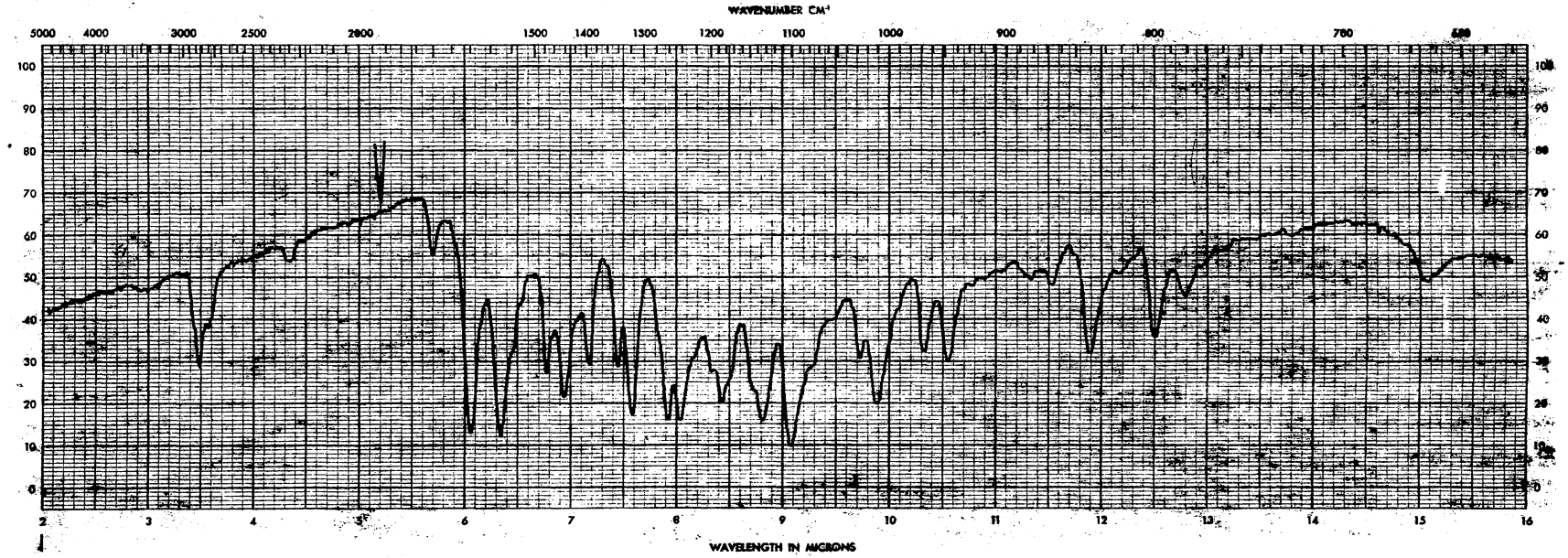
PLATE XLIV



2,10,11,11a-Tetrahydro-6,7,8-trimethoxy-11a-methyl-1H-phenanthro[1,2-c]pyrazol-1-one (108)

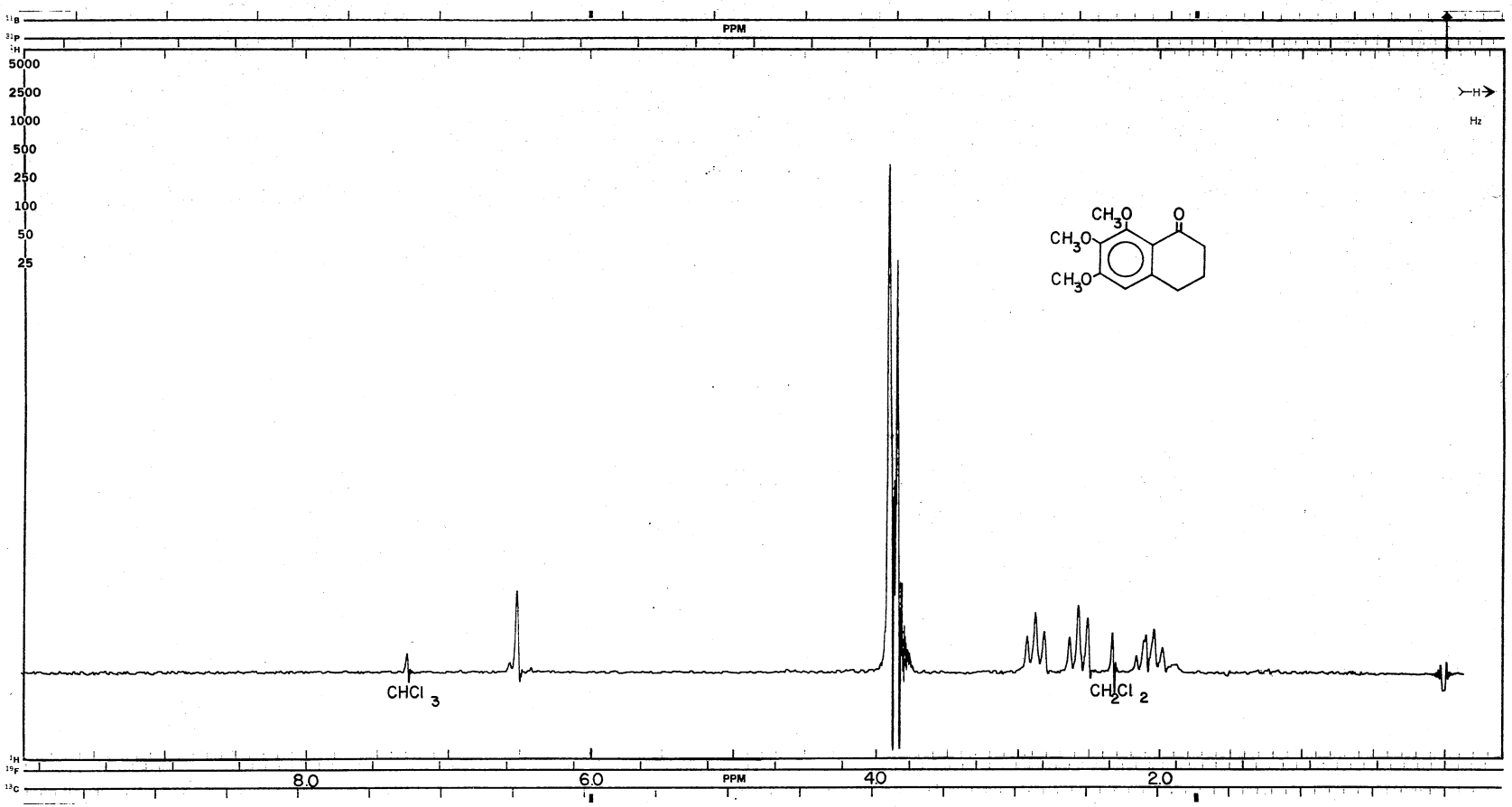
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 70 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 5.0	Lock. .HOMO

PLATE XLV



3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (125), KBr Pellet

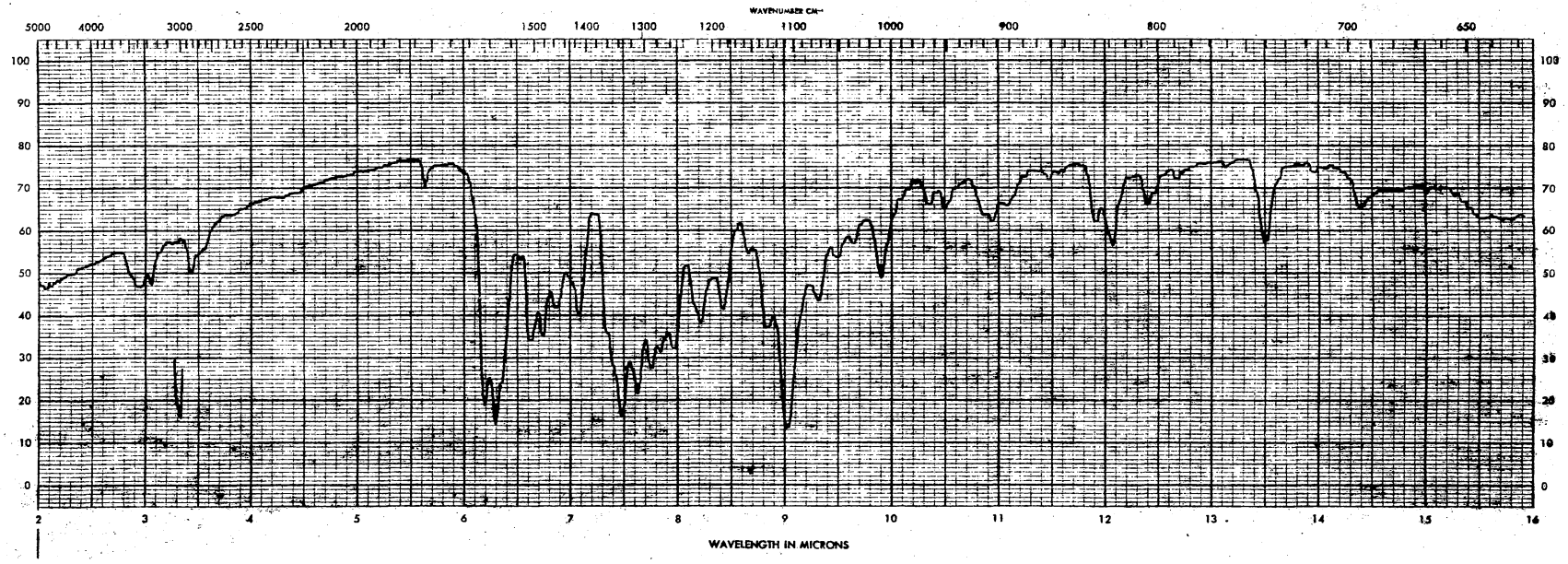
PLATE XLVI



3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (125)

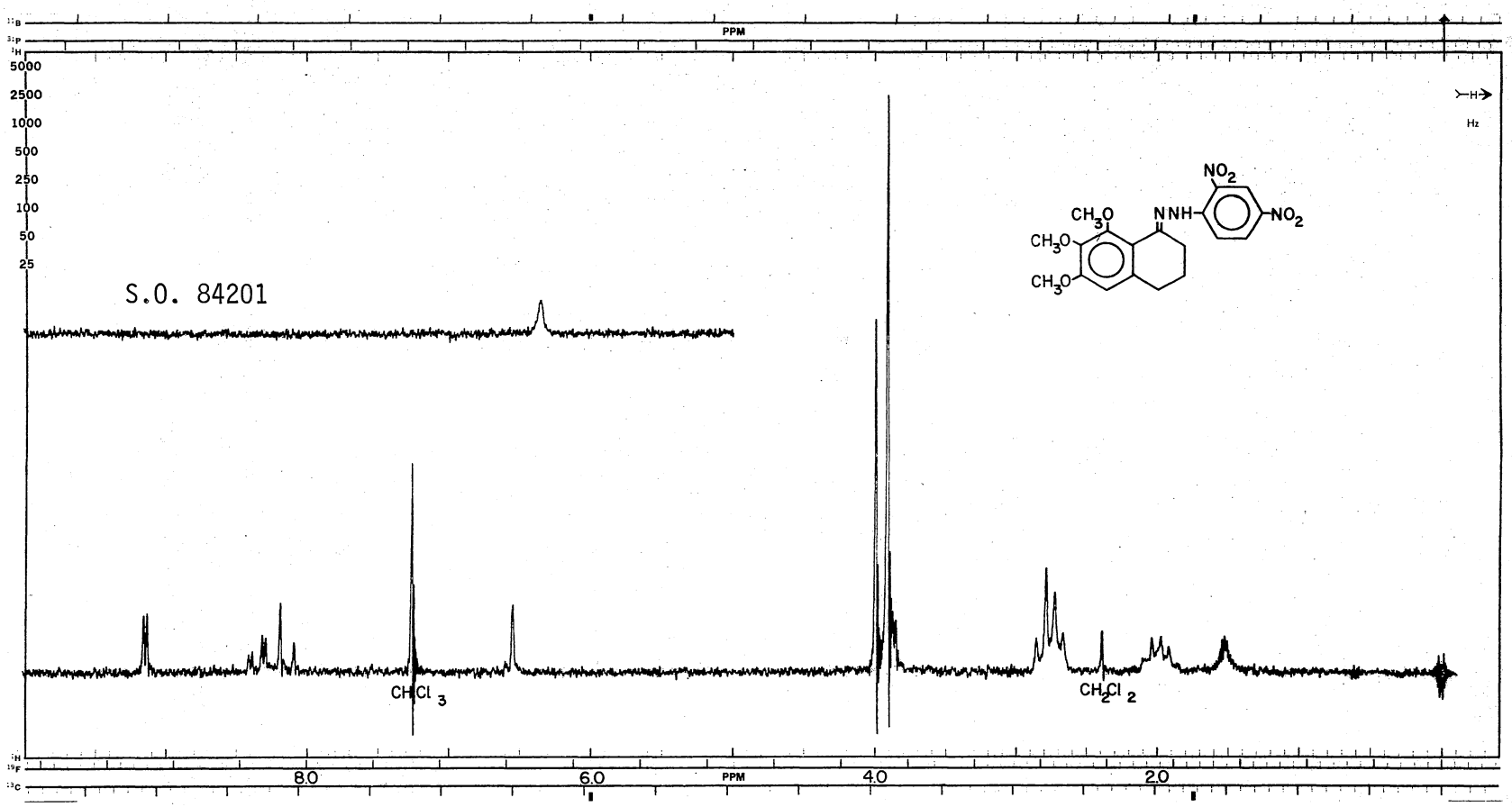
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 66 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 2.0 Lock. .HOMO

PLATE XLVII



3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone, 2,4-Dinitrophenylhydrozone (137), KBr Pellet

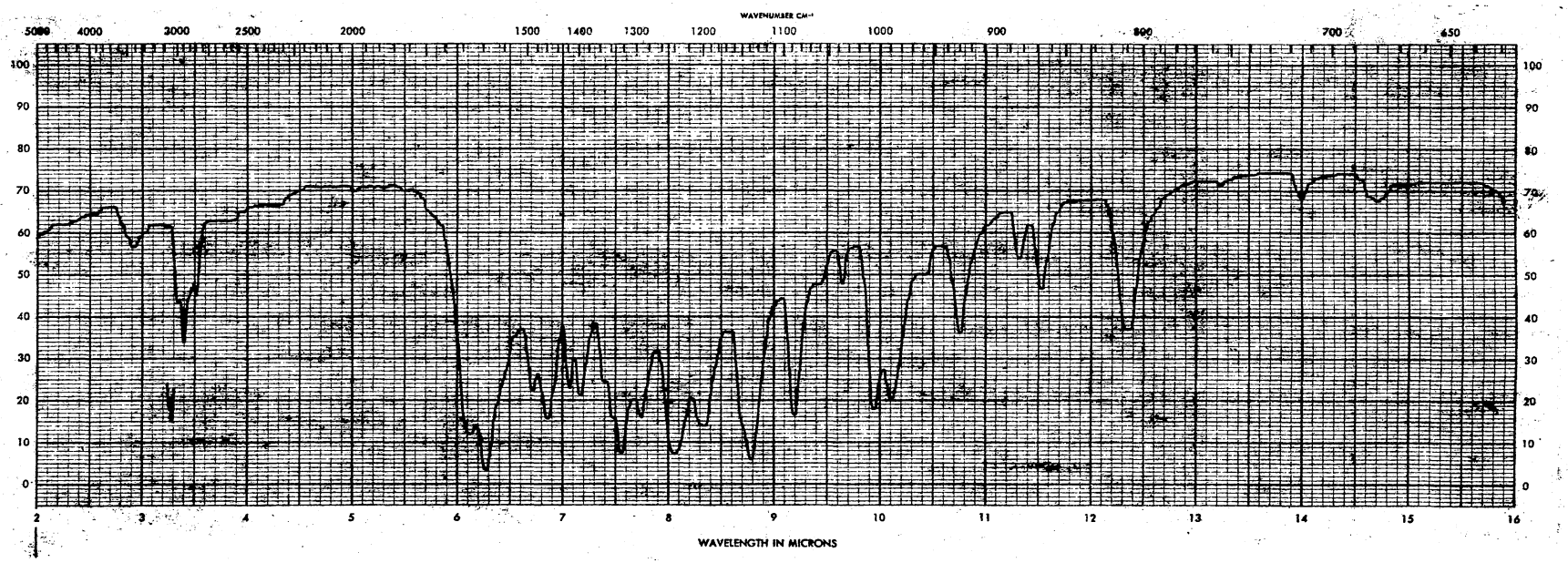
PLATE XLVIII



2,4-Dinitrophenylhydrazone of 3,4-Dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (137)

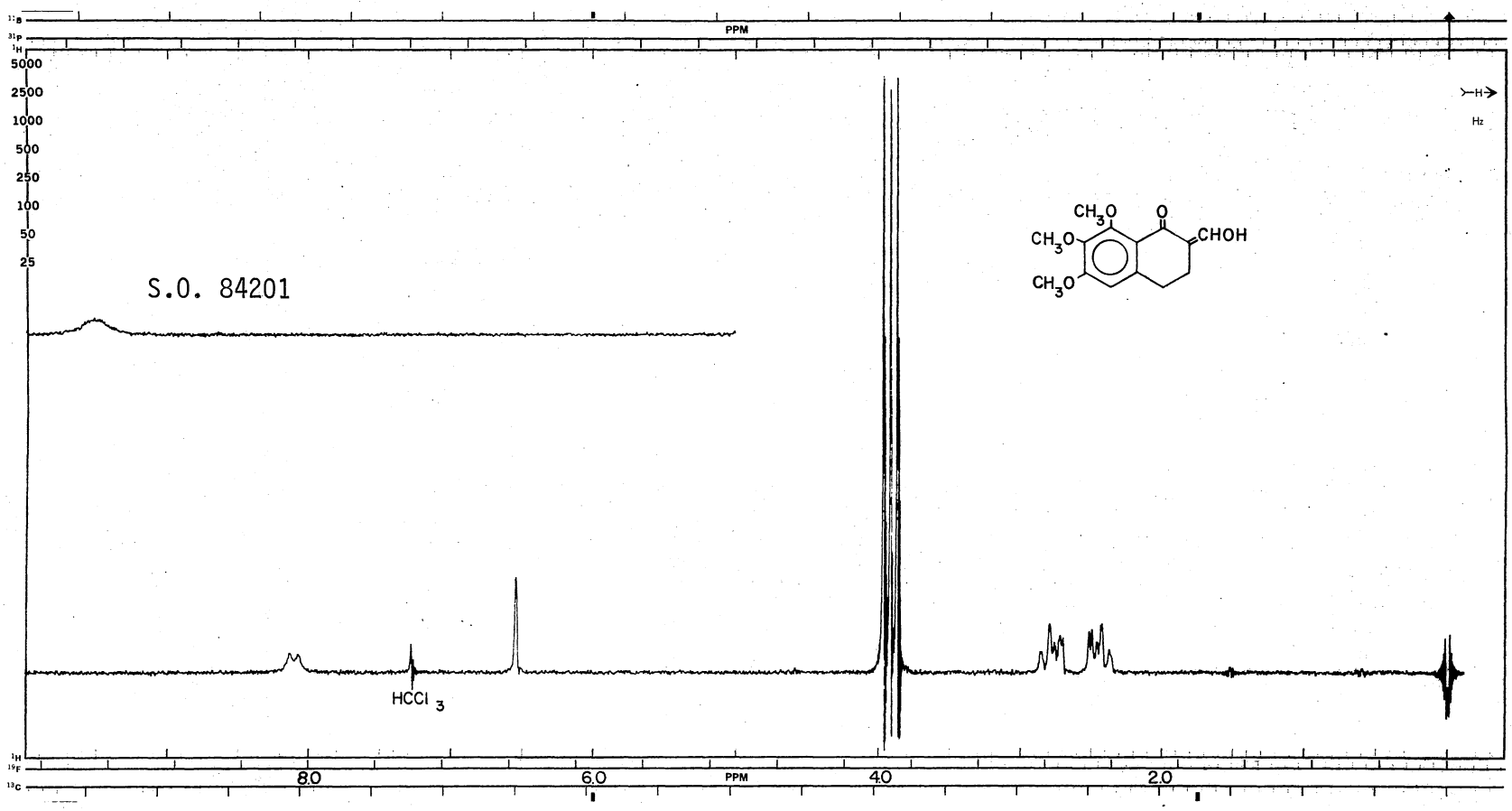
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 72 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 6.3	Lock. .HOMO

PLATE XLIX



3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-naphthalenone (143), KBr Pellet

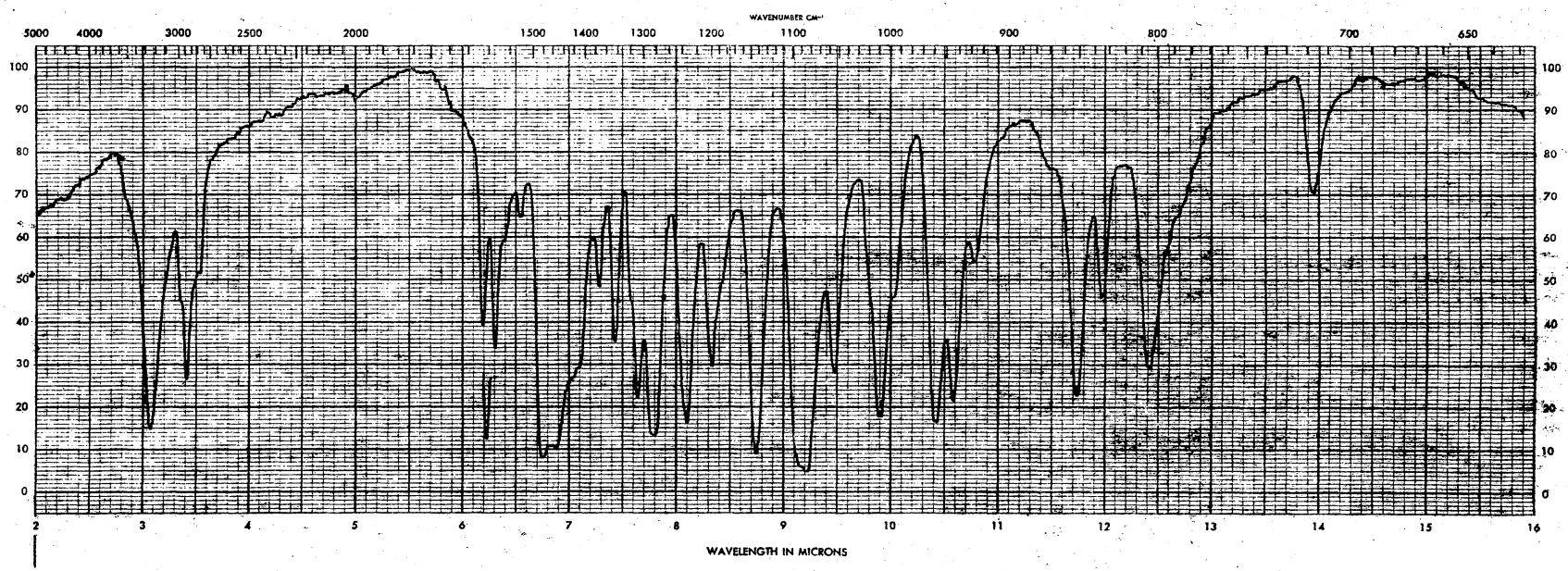
PLATE L



3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2H)-naphthalenone (143)

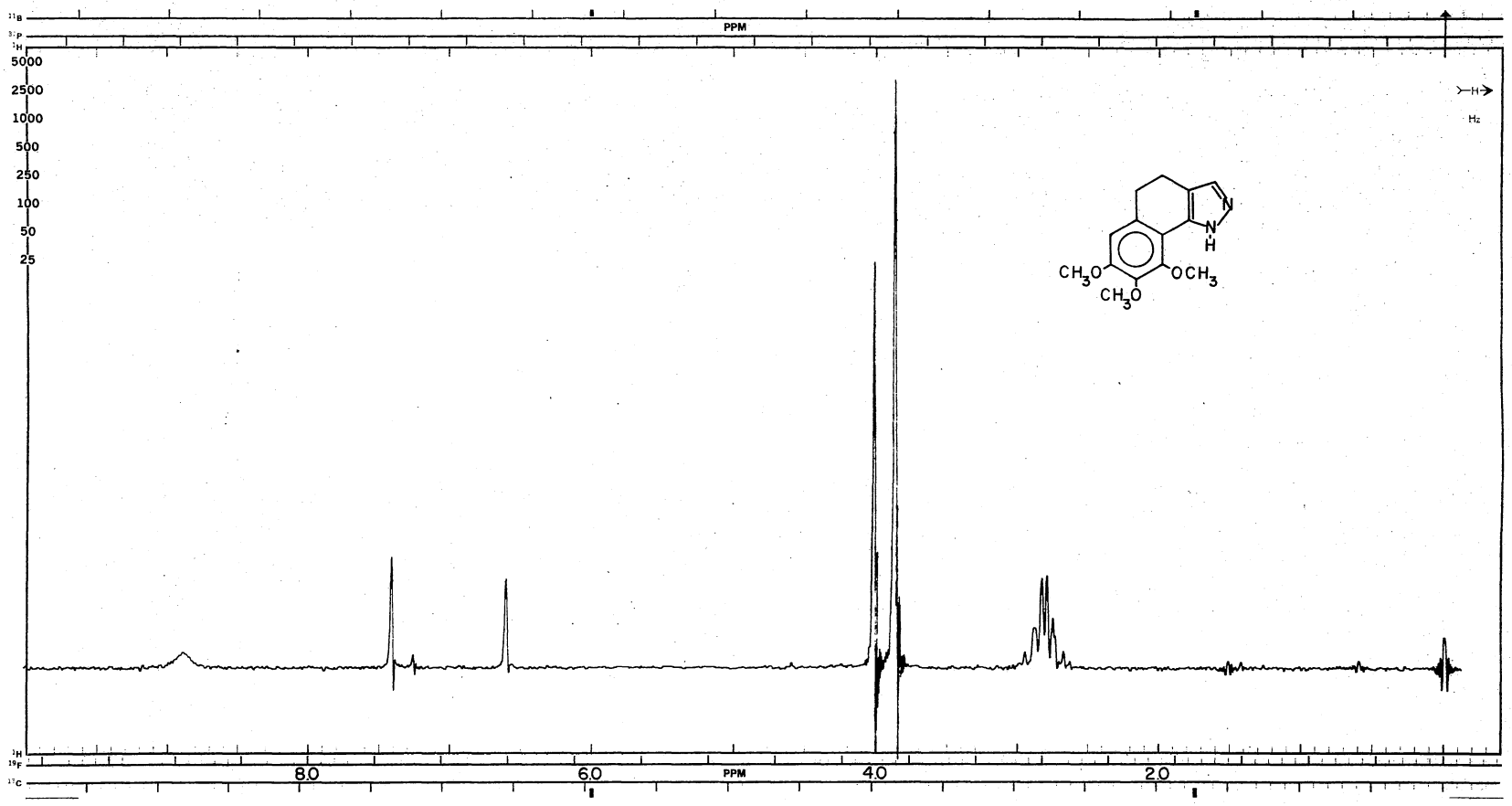
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 60 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 2.5	Lock. .HOMO

PLATE LI



4,5-Dihydro-7,8,9-trimethoxy-1H-benz[g]indazole (98), KBr Pellet

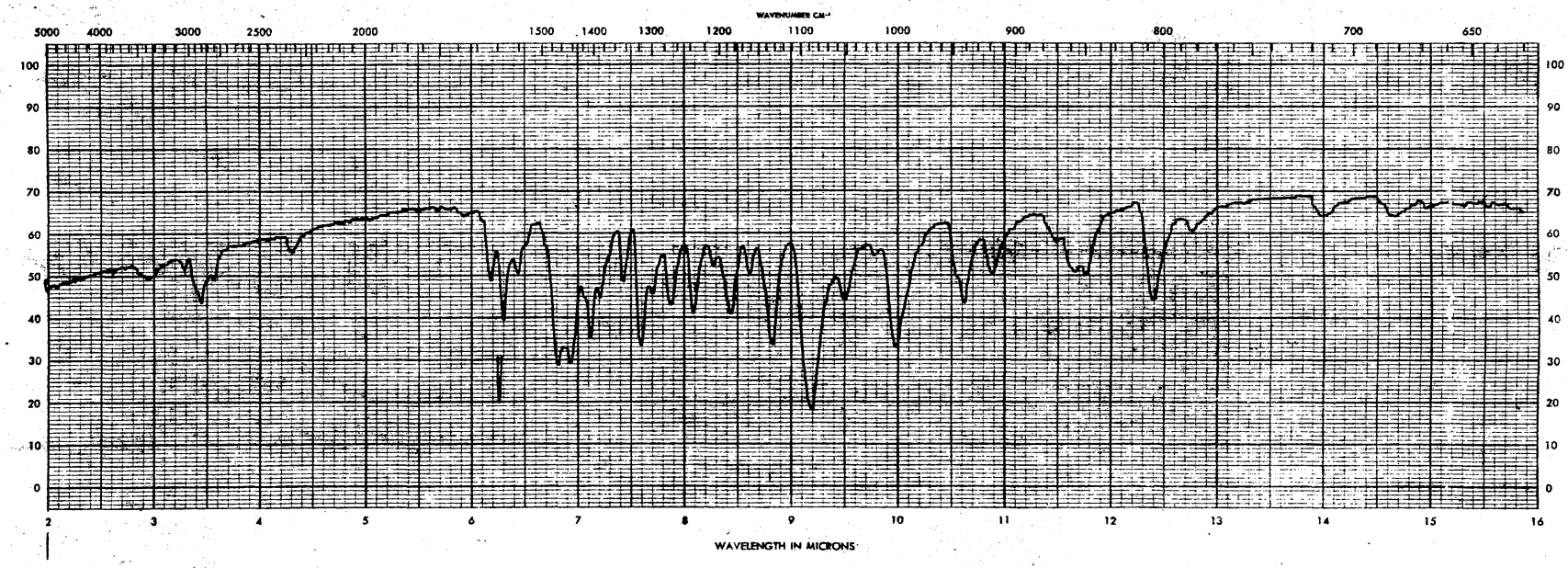
PLATE LII



4,5-Dihydro-7,8,9-trimethoxy-1H-benz[g]indazole (98)

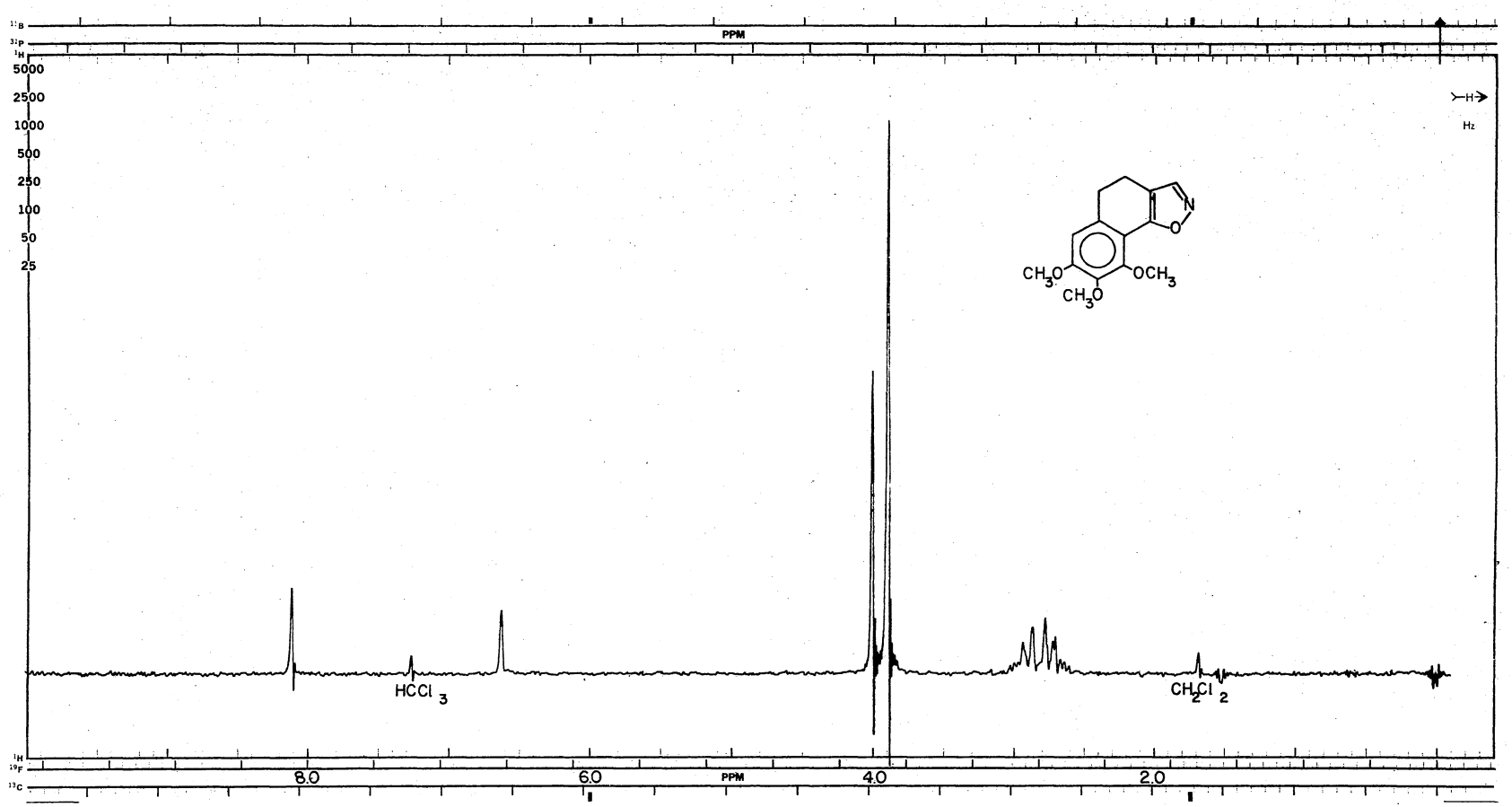
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 60 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 2.5 Lock. .HOMO

PLATE LIII



4,5-Dihydro-7,8,9-trimethoxynaphth[1,2-d]isoxazole (100), KBr Pellet

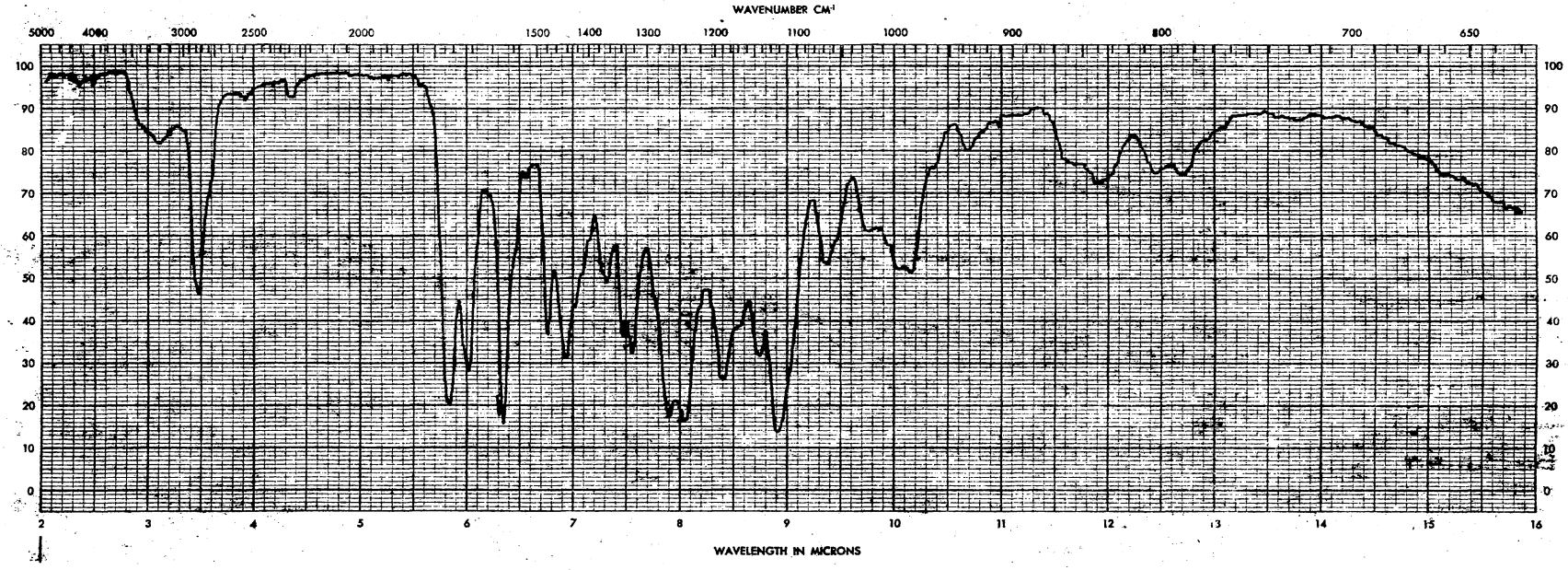
PLATE LIV



3,4-Dihydro-7,8,9-trimethoxynaphth[1,2-d]isoxazole (100)

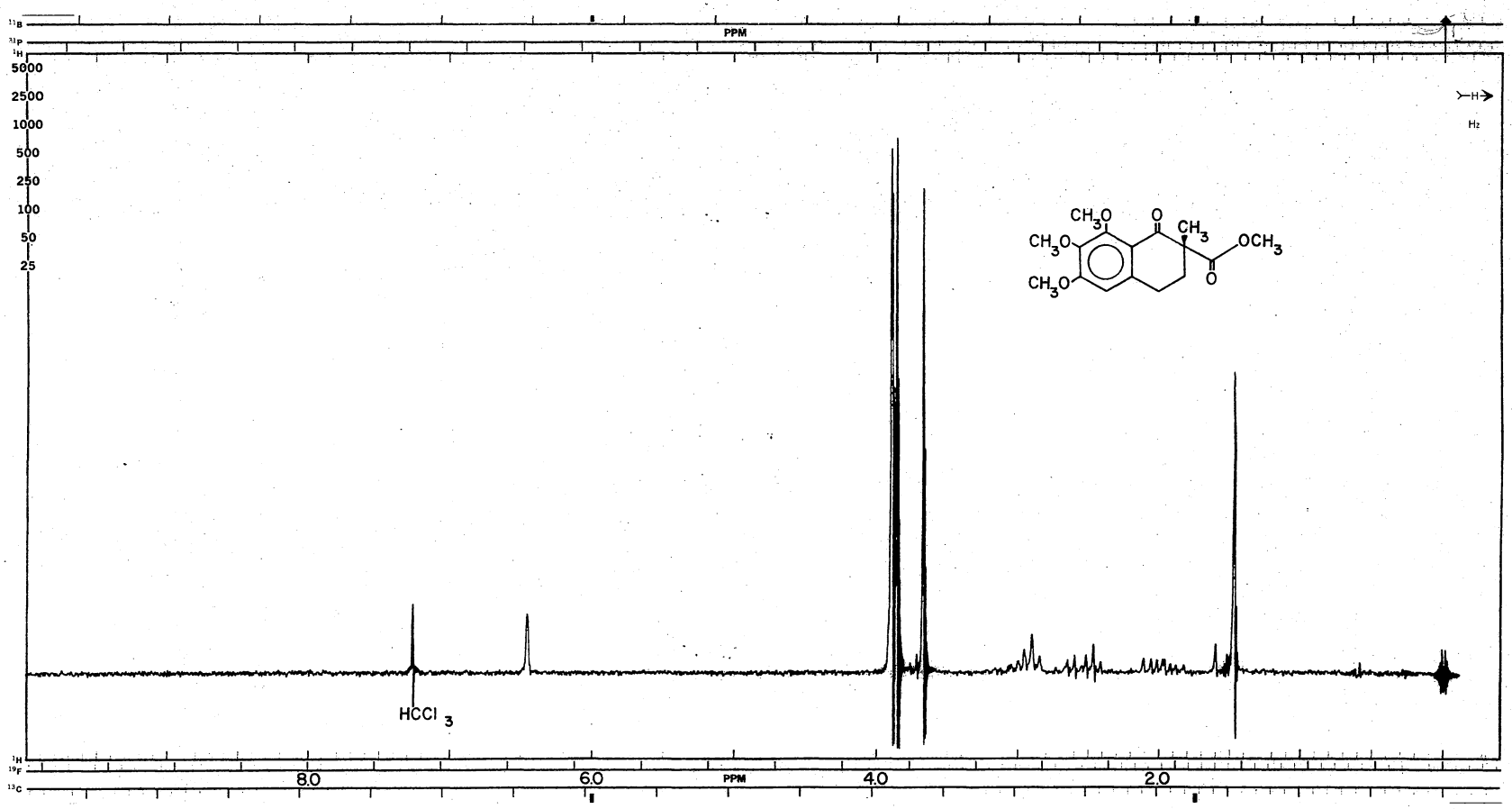
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 61 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 3.2	Lock. .HOMO

PLATE LV



Methyl 1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-naphthoate (154), Film

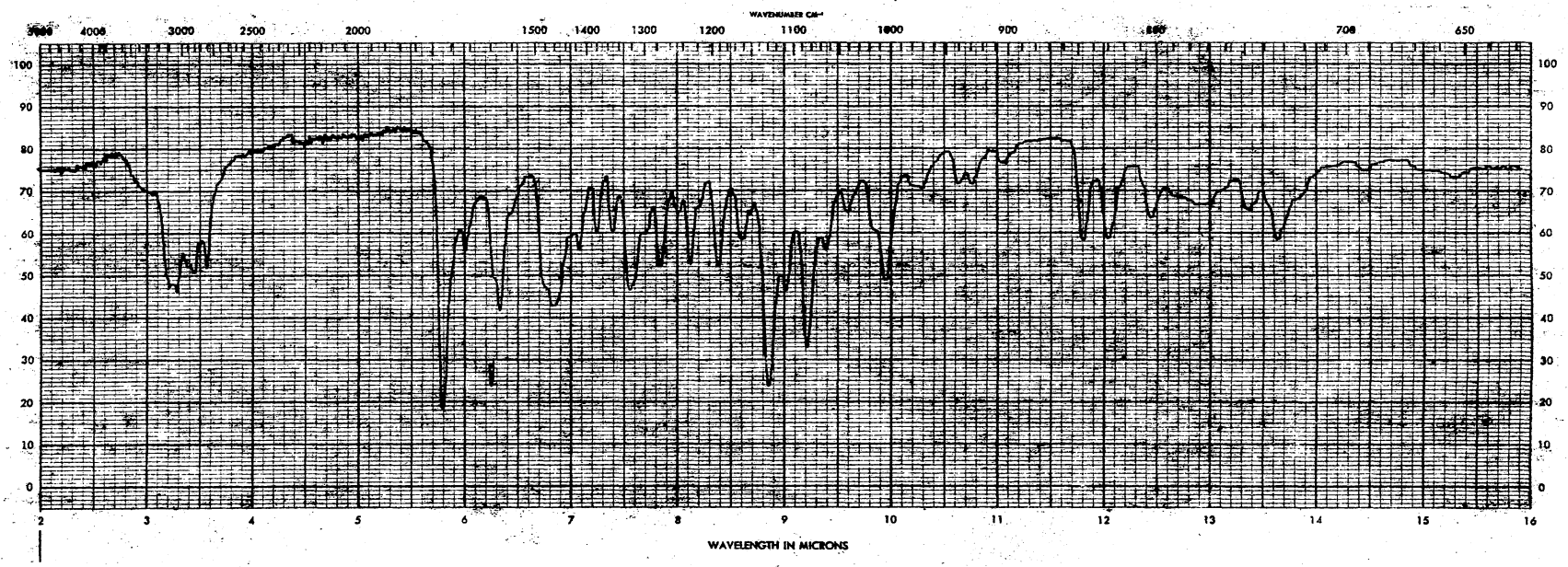
PLATE LVI



Methyl 1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-naphthoate (154)

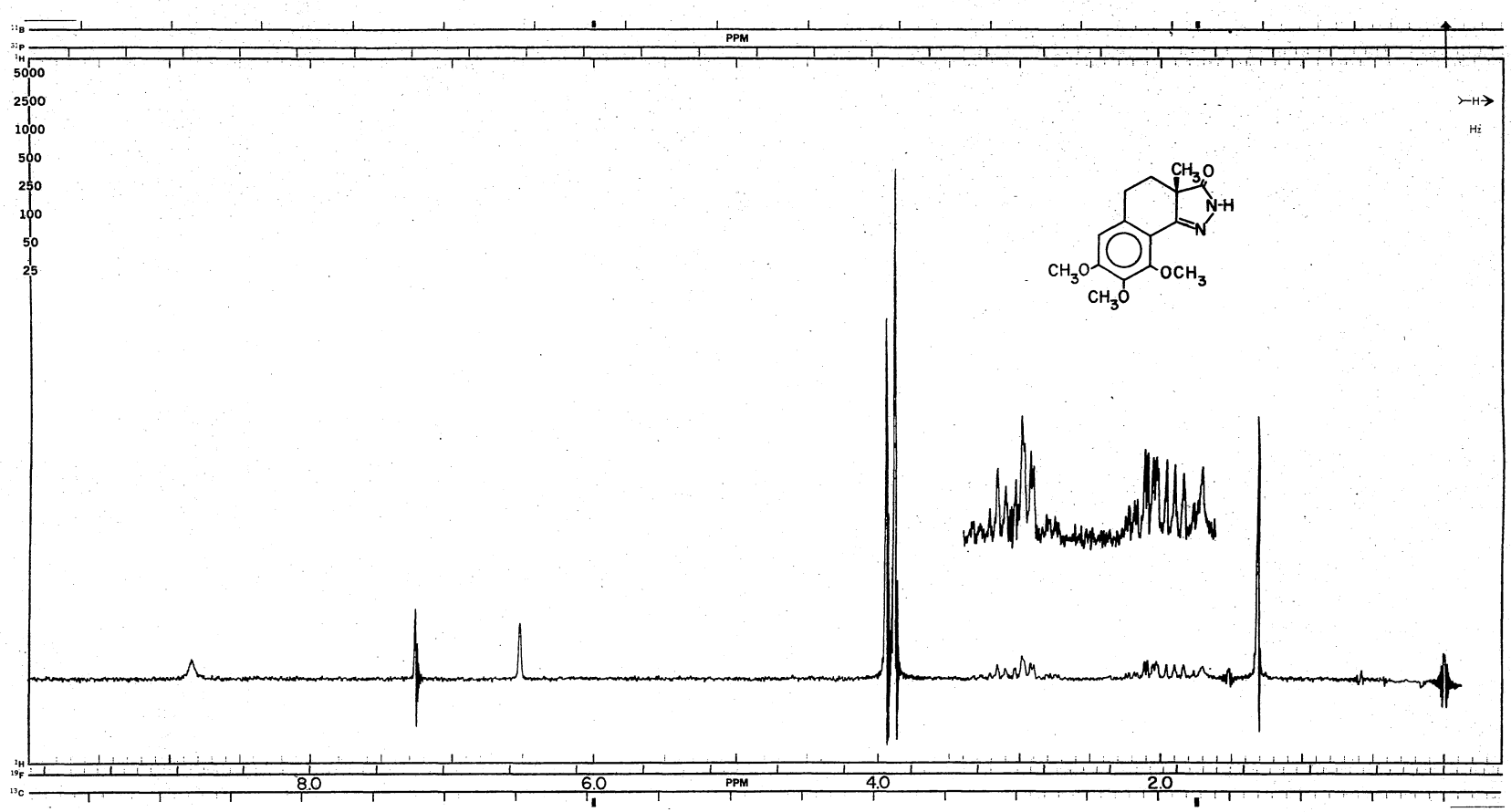
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 65 dB
S.W. . . . 1000 Hz S.T. . . . . 500 sec S.O. . . 83701 Hz S.A. . . . 3.2 Lock. .HOMO

PLATE LVII



2,3a,4,5-Tetrahydro-7,8,9-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one (103), KBr Pellet

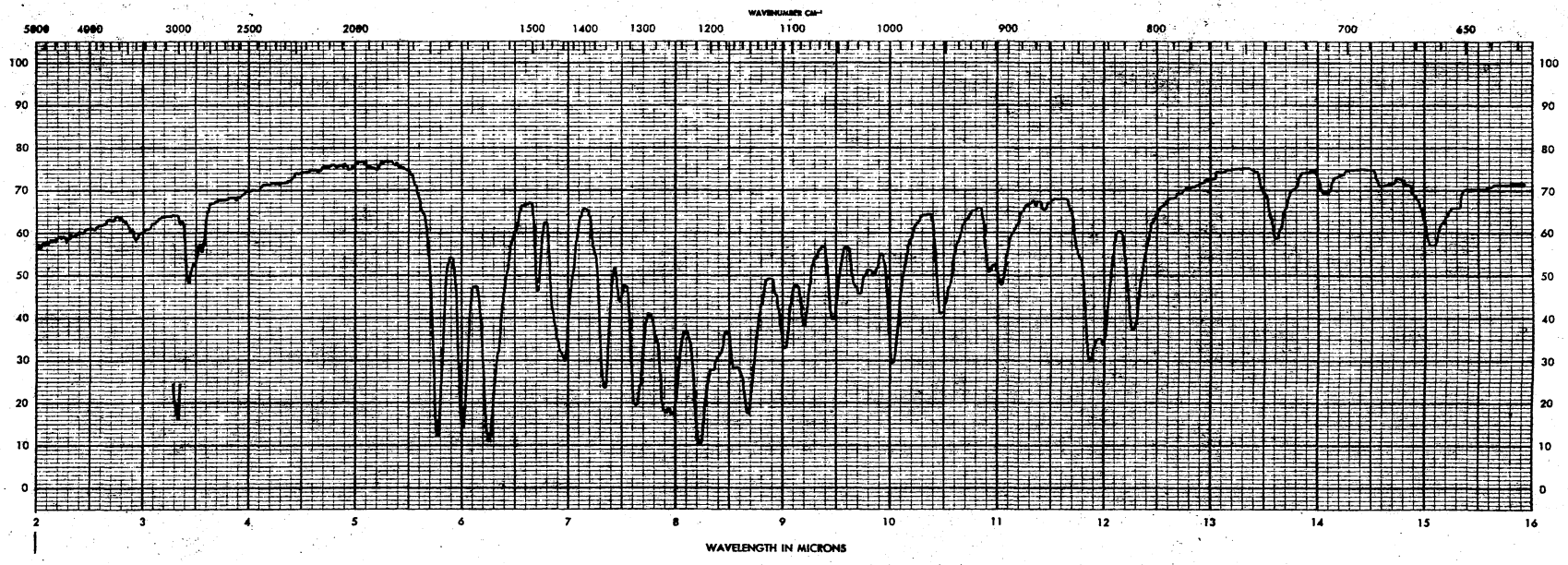
PLATE LVIII



2,3a,4,5-Tetrahydro-7,8,9-trimethoxy-3a-methyl-3H-benz[g]indazol-3-one (103)

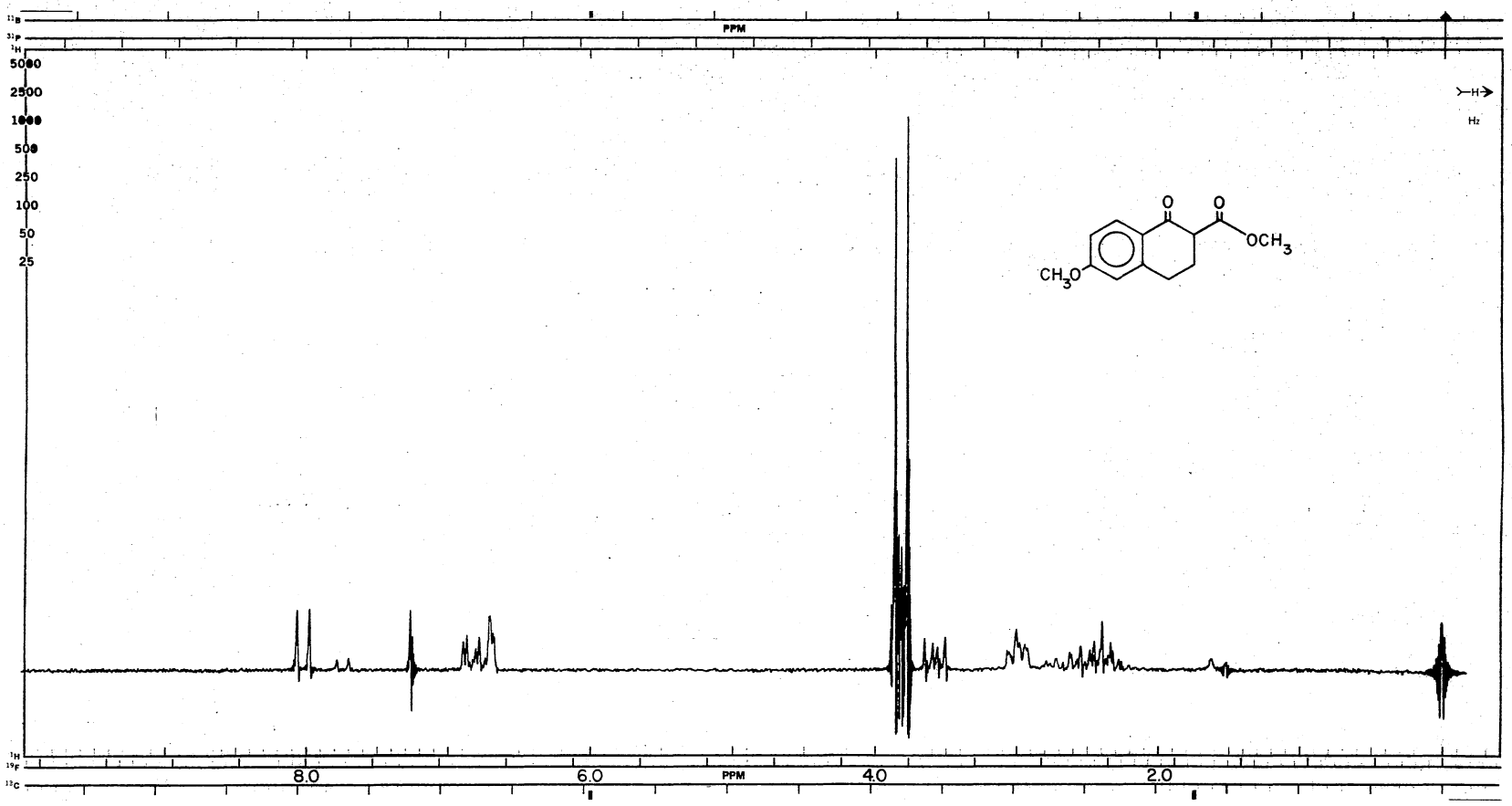
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 66 dB
S.W. . . . 1000 Hz S.T. . . . . 500 sec S.O. . . 83701 Hz S.A. . . . 3.2 Lock. .HOMO

PLATE LIX



Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthoate (150), KBr Pellet

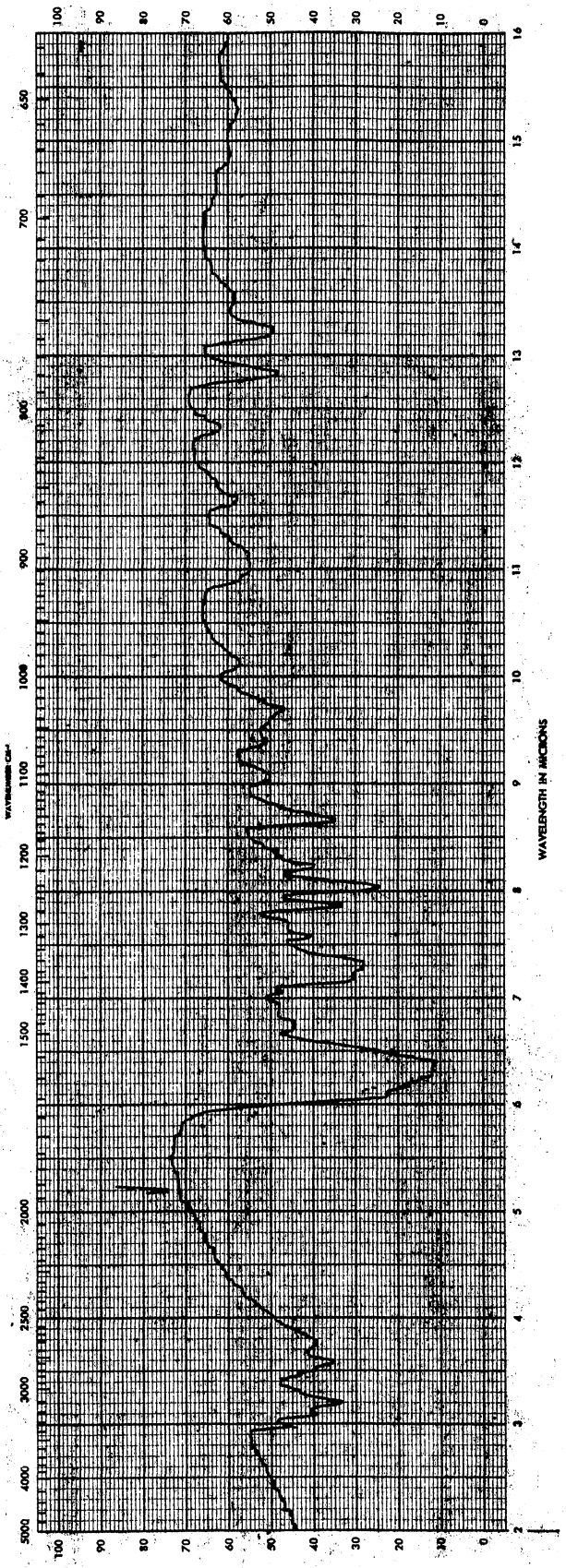
PLATE LX



Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthoate (150)

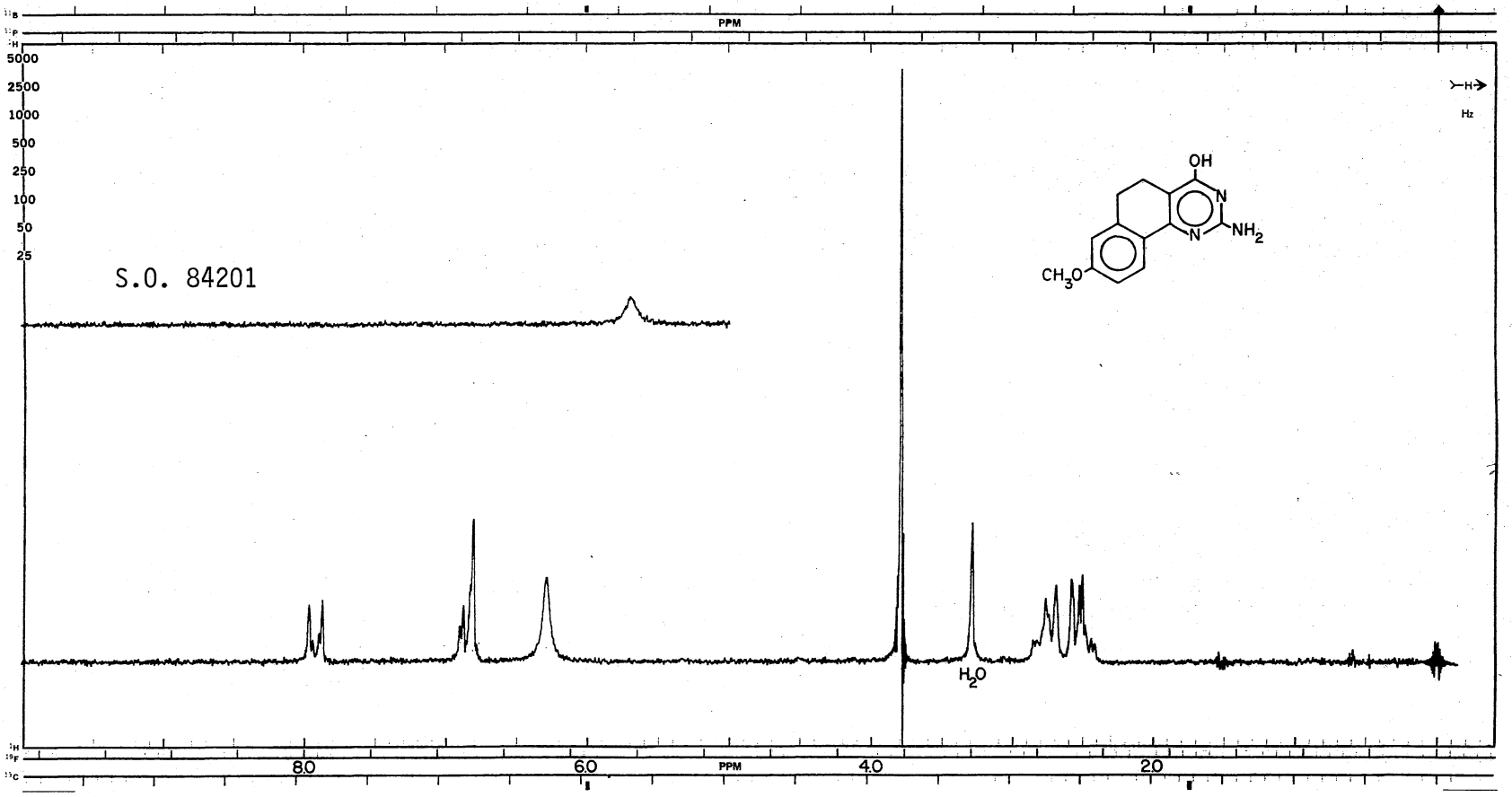
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 68 dB
S.W. . . . 1000 Hz S.T. . . . . 500 sec S.O. . . 83701 Hz S.A. . . . 2.0 Lock. .HOMO

PLATE LXI



2-Amino-5,6-Dihydro-8-methoxybenzo[h]quinazolin-4-ol (151) KBr Pellet

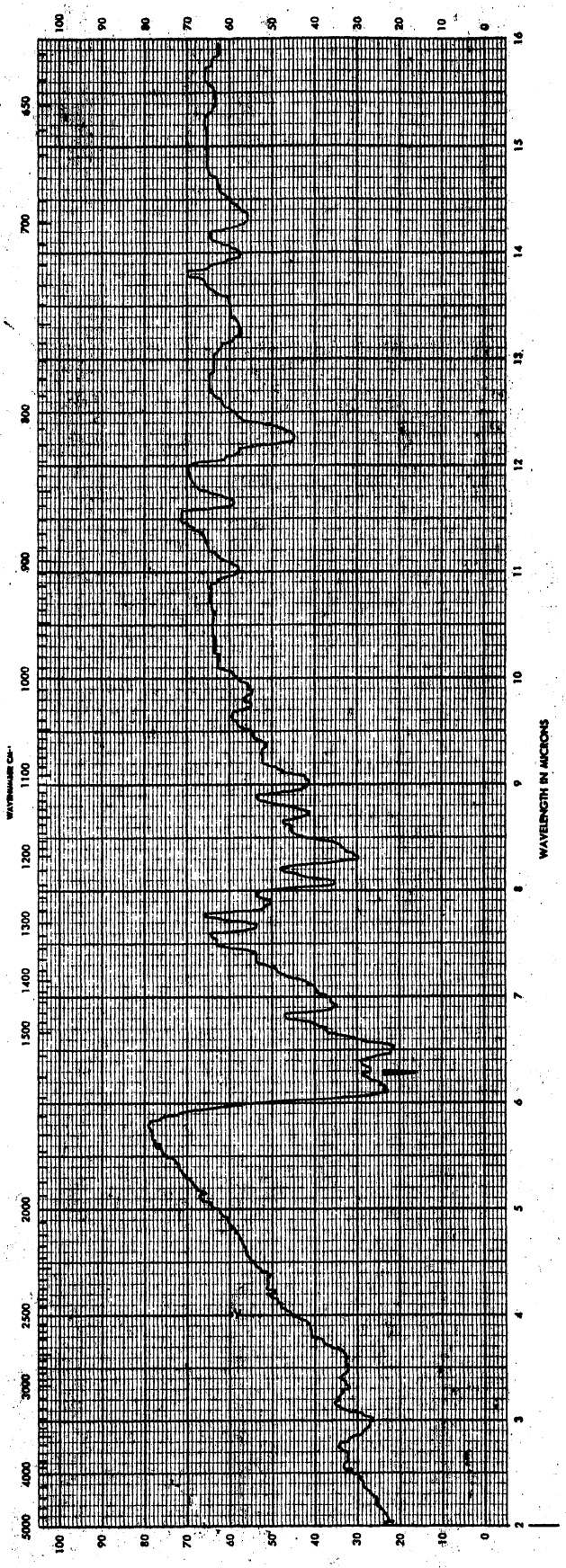
PLATE LXII



2-Amino-5,6-dihydro-8-methoxybenzo[h]quinazolin-4-ol (151)

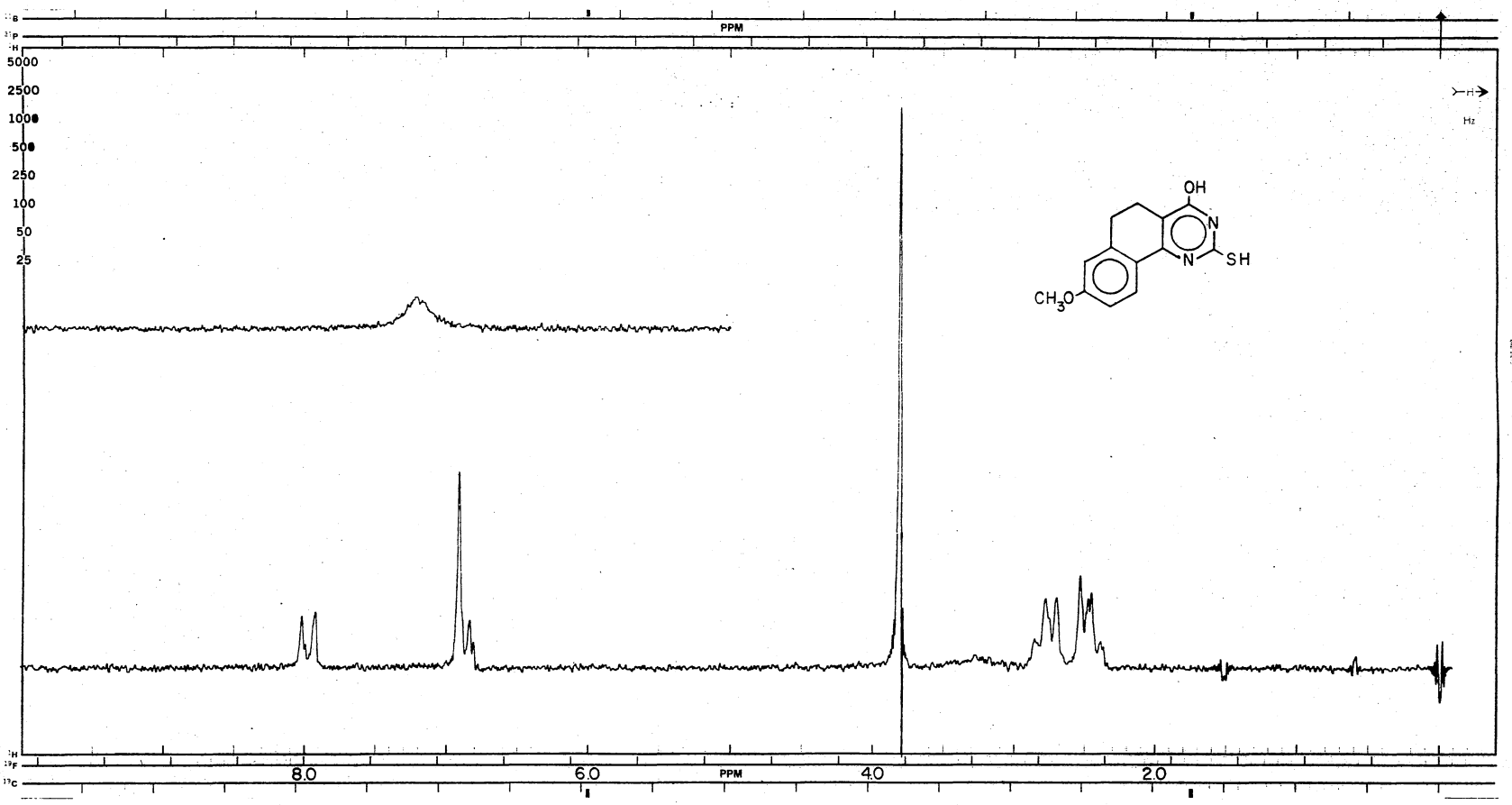
Solvent. . DMSO-d_6	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 50 dB	
S.W. . . . 1000 Hz	S.T. . . . . 500 sec	S.O. . . 83701 Hz	S.A. . . . 4.0	Lock. .HOMO

PLATE LXIII



5,6-Dihydro-2-mercapto-8-methoxybenzo[h]quinazolin-4-ol (152), KBr Pellet

PLATE LXIV



5,6-Dihydro-2-mercapto-8-methoxybenzo[h]quinazolin-4-ol (152)

Solvent. . DMSO-d_6 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. . . . 5.0 Lock. .HOMO

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