SYNTHETIC APPROACHES TO 15-AZASTEROIDS AND 15,16-DIAZASTEROIDS--NAPHTH[1,2-g] INDOLES AND NAPHTH[1,2-g]INDAZOLES AND RELATED COMPOUNDS

By

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1966

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
May, 1971

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ACKNOWLEDGEMENTS

I wish to express my gratitude for the encouragement and patience demonstrated by Dr. K. Darrell Berlin during the sometimes difficult course of this study, in addition to the valuable assistance which he has rendered in the preparation of this manuscript.

I gratefully acknowledge the receipt of a three-year NDEA Fellowship (1966-1969) and an American Cancer Society Grant (IN-91A) for the final year of study (1969-1970).

I wish to express my appreciation to Dr. Norman Durham and Mr. Robert Chesnut, without whom the biological testing program described herein would not have been possible. In addition, I wish to thank Dr. E. J. Eisenbraun and Dr. James M. Springer, who at certain times in the course of this research provided valuable counsel and material assistance.

Finally, I wish to recognize the various and assorted faculty, staff, students, and other residents of Stillwater who helped to make four and one-half years in this town a genuine educational experience.

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CHAPTER I

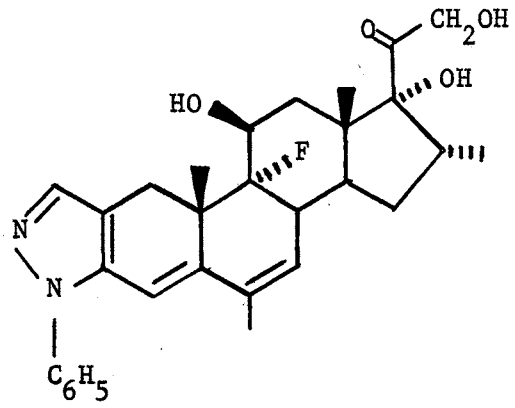
HISTORICAL

The wide range of biological function exhibited by the steroids and the variety of activities shown by specific individual steroids make this class of compounds one of the most studied in medicinal chemistry. Chemical modifications of the basic cyclopentaphenanthrene nucleus have provided many synthetic steroidal derivatives; among these are the azasteroids--compounds which incorporate the nitrogen atom in their molecular structures.

Steroid nuclei containing nitrogen heteroatoms have been shown to possess a wide range of physiological activities.[3,37,45] The vast majority of these azasteroids are derived by the modification of naturally occurring steroids, most probably owing to the relative ease of these syntheses. Also, it is reasonable to assume that the products derived from biologically active precursors are more likely to be active themselves than are the products of de novo synthesis routes.

Five representative examples of azasteroids with pronounced biological activity are listed in Figure 1 below. Note the pyrazole functions in 1, 4 and 5, characteristic of the naphthindazole title compounds in this study.

The [3,2-c]-2'-phenylpyrazole of 9α-fluoro-6,16α-dimethyl-Δ^6-hydrocortisone (1) is claimed to be the most potent anti-inflammatory steroid known--over 2000 times as powerful as hydrocortisone itself.[37]



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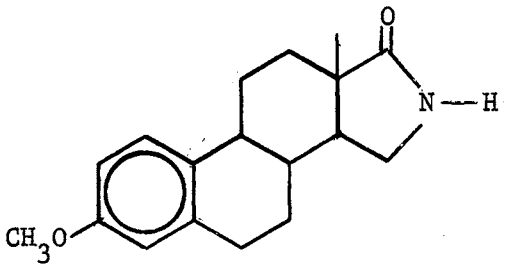

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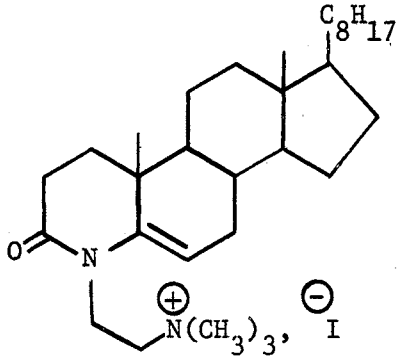

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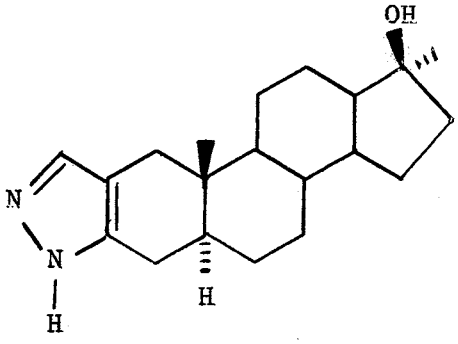

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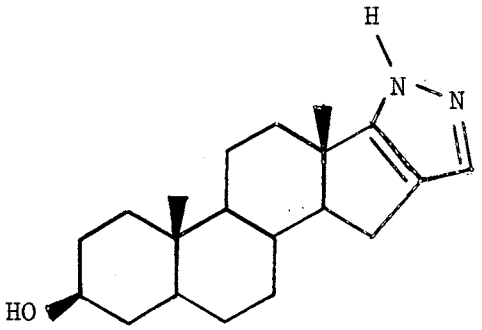


5

Figure 1. Some Azasteroids of Medicinal Significance

The O-methyl ether of 16-azaestrone (2) exhibited significant hypocholesterolemic activity but possessed less than 0.01% of the estrogenic activity of the parent estrone.[8]

4-Dimethylaminoethyl-4-aza-5-cholesten-3-one methiodide (3) irreversibly inhibits the growth of B. subtilis cultures at concentrations as low as 1 μg./ml.[51] 17β-Hydroxy-17α-methylandrostano[3,2-c]pyrazole (4) possesses a very favorable anabolic-to-androgenic activity ratio and has undergone clinical study.[3] 3β-Hydroxyandrostano[17,16-c]pyrazole (5) exhibits an antiovulatory activity one-fifth of that observed for norethisterone when administered orally in rats.[3]

A literature search of Chemical Abstracts through 1968 using the keyword "azasteroids" provides a general, if not completely comprehensive, survey of the frequency with which nitrogen has been substituted for carbon in the various positions in the steroid nucleus. Figure 2 is a summary of this information in bar-graph form.

As Figure 2 indicates, the two positions for which no examples of azasteroids are indexed are the methyl-bearing bridgehead, (C-10), and position 15. A comprehensive literature survey through May, 1970, reveals the existence of only 16 distinct 15-azasteroid "type" structures.[10,36,15,33,34,36,42] These structures are listed in Figure 3.

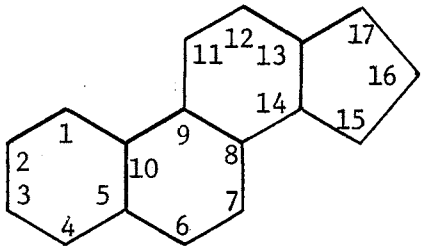
Of these 16 structures, 12 are of the 15,16-diazasteroid naphthindazole type, while 4 structures have only the 15 position substituted. Of the former, 6 and 6a were intermediates in studies for the synthesis of 6b. Compound 6b was tested as a carcinogen with inconclusive results.

Compounds 7-7c are described as "novel 15,16-diazasteroids"--no physiological activity is reported.[36] The syntheses of 8 and 8a by Scheigh and Popp[42] and Jones and Wood[33] were incidental to their research

into the preparation of 9-azasteroids.

Compounds 10-10b were three of a number of fused, pyrazole-type structures obtained by the treatment of the p-nitrophenylhydrazones of certain aryl methyl ketones with polyphosphoric acid; again, no physiological data was provided.[12]

Of the monoazasteroids, 5a was synthesized in the 1930's as a "synthetic decarboxylase,"[34] and 9-9b are all derivatives of 4,4-dimethyl-5α-androst-14-ene and are intermediates in steroid-terpene structure corre-



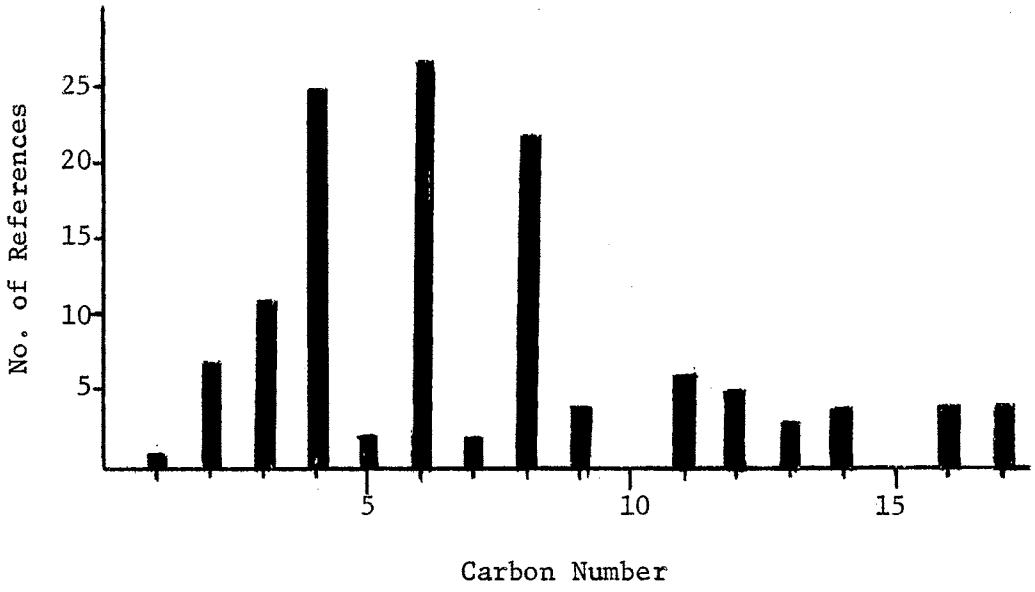
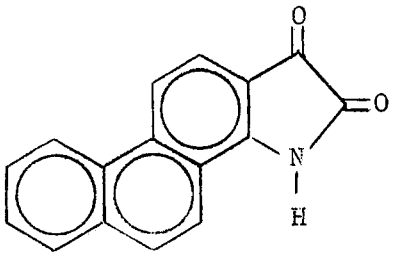
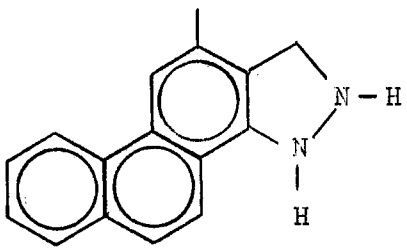


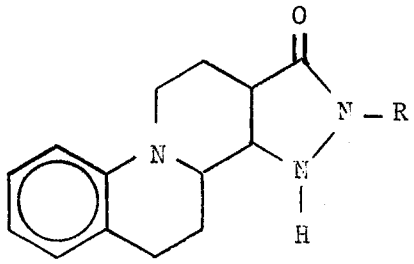
Figure 2. Frequency of Nitrogen Substitution vs. Position for Azasteroids Described in the Literature



5a

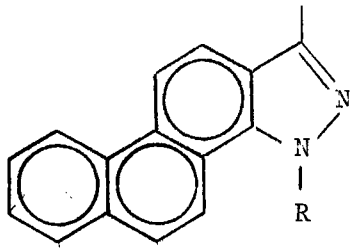


6b



8 R = H

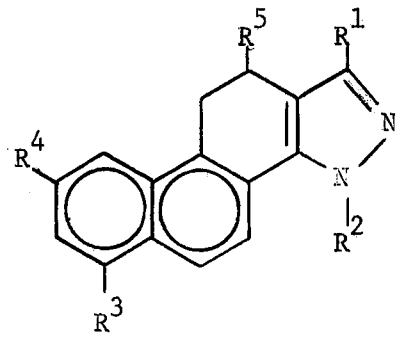
8a R = C_6H_5



10 R = H

10a R = p-$NO_2C_6H_4$

10b R = p-$NH_2C_6H_4$



6 R^1,R^2,R^3,R^4 = H; R^5 = CH_3

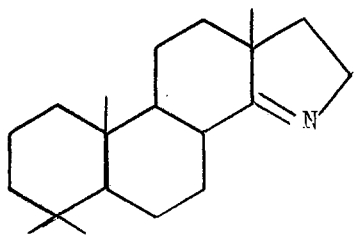
6a R^1,R^2,R^5 = H; R^3,R^4 = CH_3

7 R^1,R^2,R^3,R^4,R^5 = H

7a R^1,R^3,R^4,R^5 = H; R^2 = C_6H_5

7b R^2,R^3,R^4,R^5 = H; R^1 = CO_2Et

7c R^3,R^4,R^5 = H; R^1 = CO_2Et
R^2 = C_6H_5



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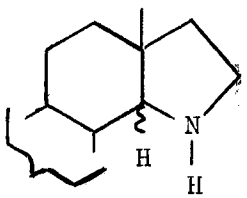
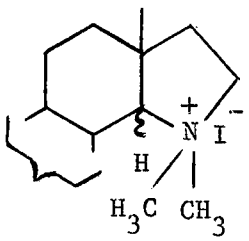


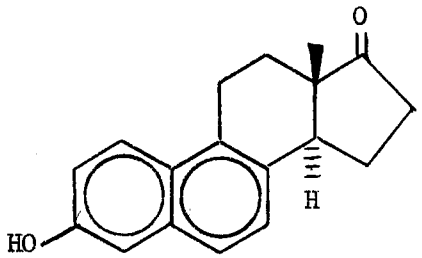
9a



9b

lations.[15] It is therefore apparent that the 15,16-diazasteroids and especially the 15-monoazasteroids have been little studied, despite the fact that this latter class of compounds combines the steroid nucleus with the often biologically active indole nucleus in a single structure.

Equilenin (11), the model for the azasteroids produced in this study, is a female sex hormone, originally isolated from mare pregnancy urine, and, more recently, found to be of interest in human physiology because of its isolation from human adrenal cortical carcinoma.[39]

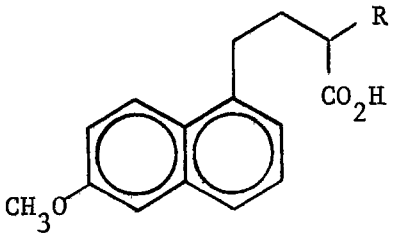


11

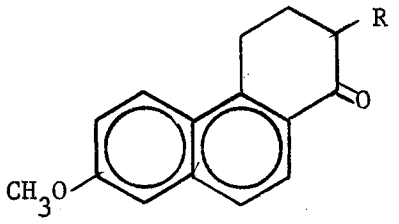
This naphtholic steroid offers two main advantages as a model for azasteroid synthesis: 1) it is a relatively simple molecule (for a steroid), containing only two optically active centers (i.e., existing in four potentially stereoisomeric forms), and 2) elegant de novo syntheses[17] of 11 by Bachmann and coworkers[5], and by Stork[47] afford intermediates of use in azasteroid synthesis.

Key intermediates in the synthesis of 11, which find application in the present work, are the naphthalenebutyric acids 12 and 12a, the derived phenanthrones 13 and 13a, and 14, the hydroxymethylene derivative of 13.

Acid 12 was first synthesized by Haberland and Blanke[21] by condensing the sodium salt of diethyl malonate with β-(6-methoxy-1-naphthyl)

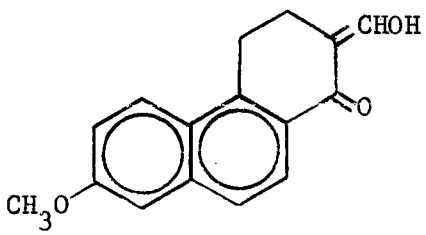


12 R = H
12a R = CH_3



13 R = H
13a R = CH_3

ethyl bromide and hydrolyzing the resulting diester, followed by decarboxylation. Acid 12a was synthesized by an analogous route using sodium diethyl methylmalonate.[21] Wilds and Close[54] used a similar method for producing 12a, an intermediate in their syntheses of steroids related to equilenin. Their method is a modification of that of Bachmann and coworkers[5], and is outlined in Figure 4 below.



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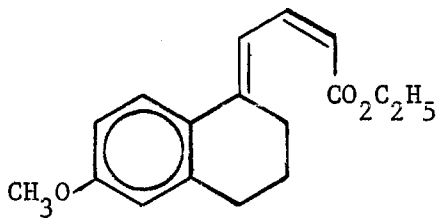


15

Stork[47] made a considerable improvement on the above method of synthesizing 12 when he found that a Reformatsky-type reaction between 6-methoxy-1-tetralone (46) and methyl 4-bromo-2-butenoate (47) provided a dienic ester 15, which upon isomerization and subsequent hydrolysis yielded the desired 12. (See Figure 13, p. 23, for an outline of the general method).

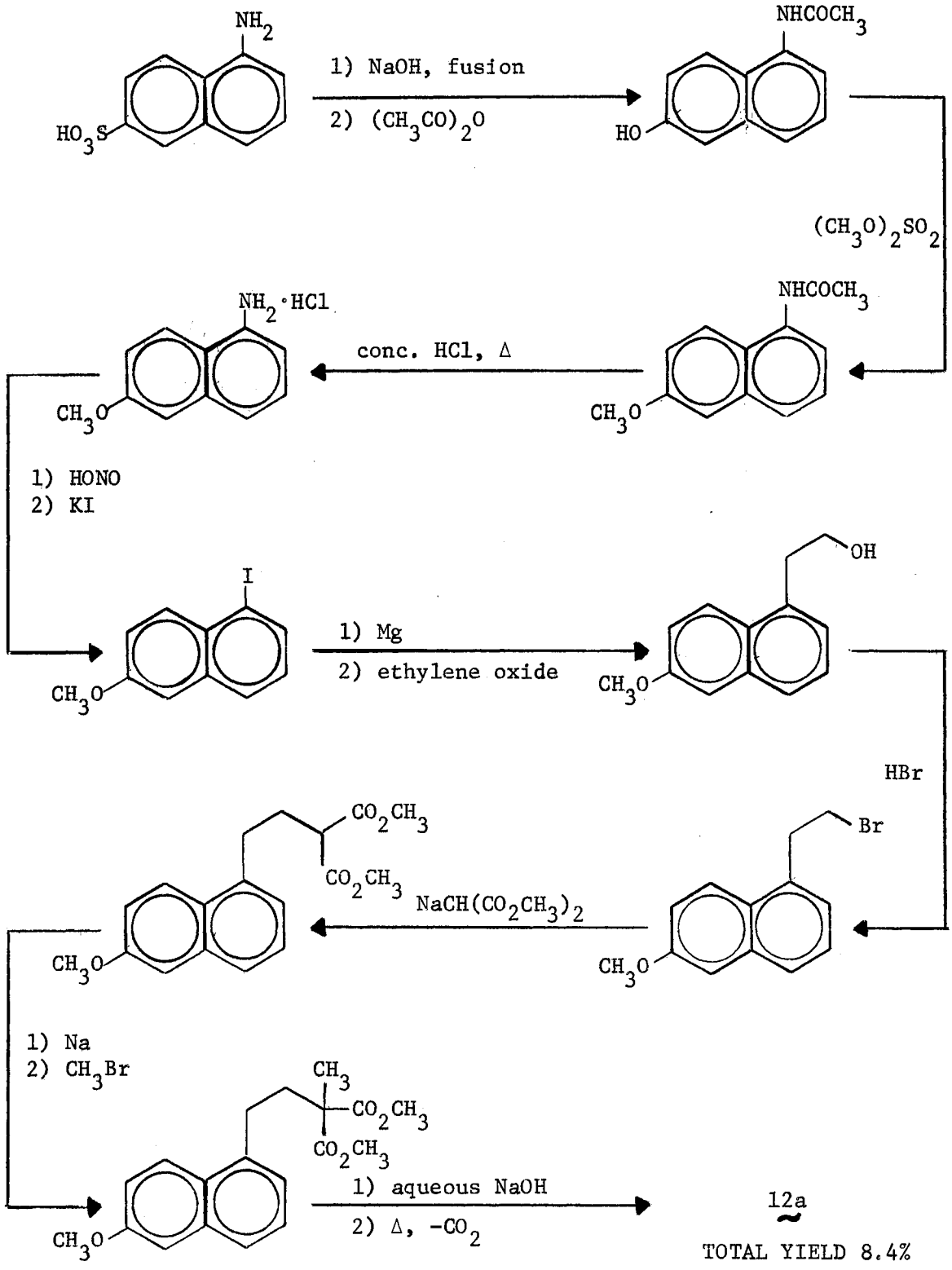
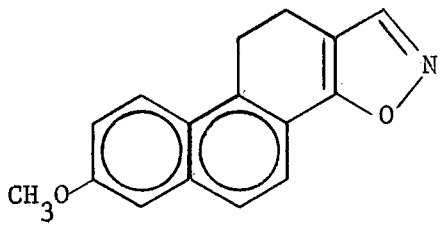


Figure 4. Reaction Sequence for the Synthesis of 6-Methoxy-α-methyl-1-naphthalenebutyric Acid (12a) by Bachmann and Coworkers[5]

Acids 12 and 12a have been converted to the corresponding phenanthrones 13 and 13a by a variety of reagents which include 90% H_2SO_4,[21] $SOCl_2$/pyridine followed by $SnCl_4$[54], and anhydrous HF.[47]

Phenanthrone 13 was methylated by Bachmann and coworkers[5] in a rather lengthy procedure to provide 13a. The method is outlined in Figure 5. A similar monomethylation which avoids the decarbonylation step[41] is included in Figure 9.

Condensation of 13 with ethyl formate in the presence of a basic catalyst yields the hydroxymethylene derivative 14, an important intermediate in the present study. The synthesis of 14 was originally accomplished by Johnson and coworkers[30] and it was an intermediate in the preparation of the isoxazole 16.[31] This latter chemical was then used in the synthesis of equilenin and related derivatives.[32] Compound 14 (among others) has been screened for inhibitory effect on sarcoma 37 in mice--"any tumor-inhibiting effect takes place at or near toxic levels."[35]



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Hydroxymethylene ketones can be intermediates in the successful monomethylation of ketones. Ireland and Marshall[28] condensed 2-hydroxymethylene-6-phenylcyclohexanone (17) with 1-butanethiol in the presence of p-toluenesulfonic acid (PTSA) to yield 88% of the thioether 18. Compound 18 was reductively desulfurized with Raney nickel to give 2-methyl-

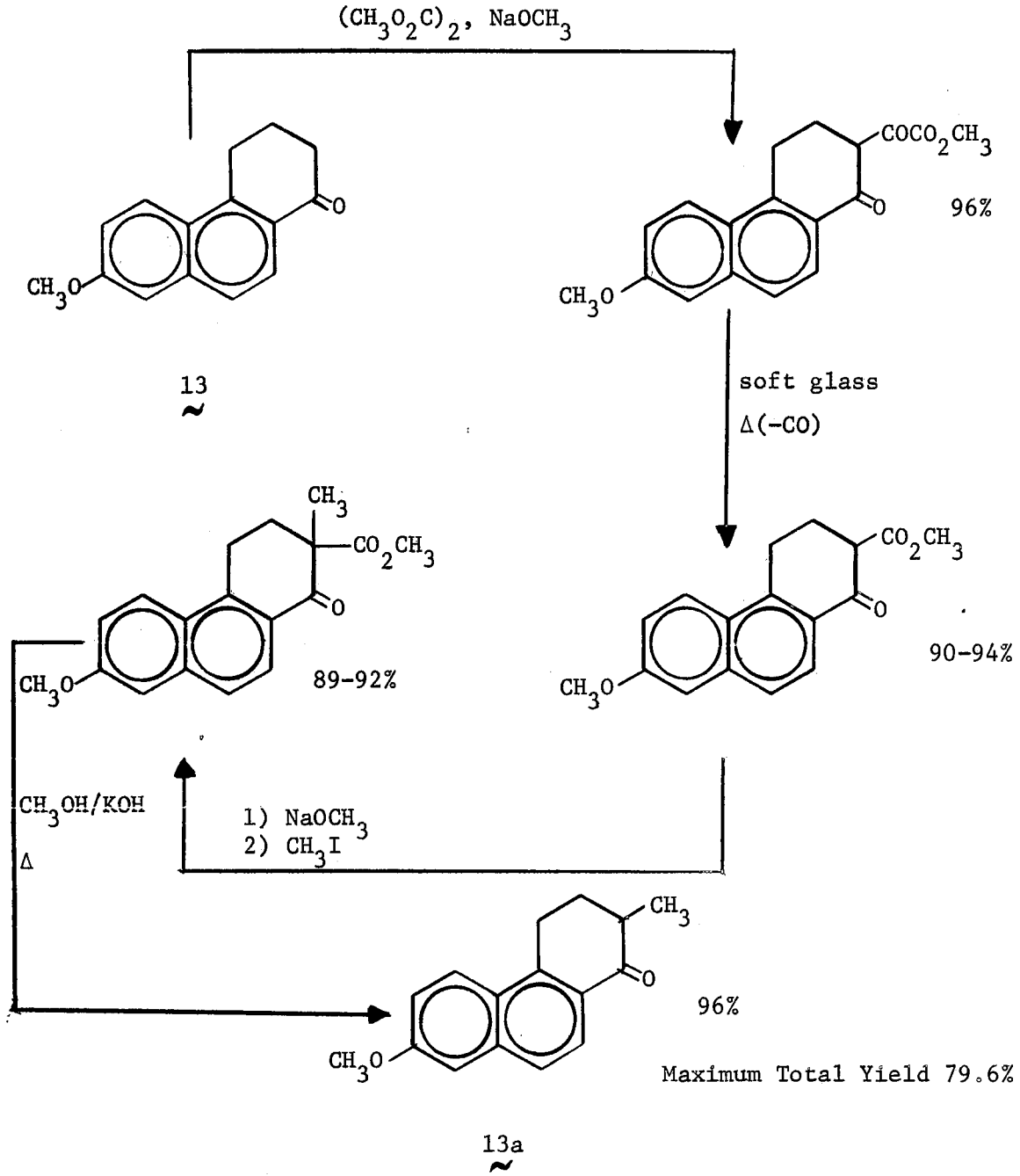
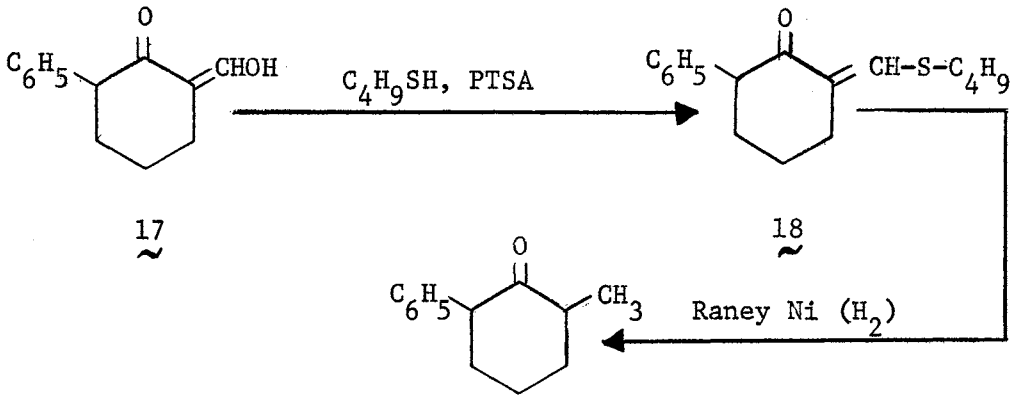


Figure 5. Methylation of 3,4-Dihydro-7-methoxy-1(2H)-phenanthrone (13)

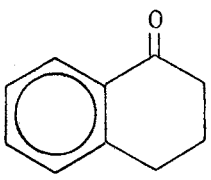
6-phenylcyclohexanone (19) in 94% yield. This procedure is outlined in Figure 6.



17 18 19

Figure 6. Ketone Monomethylation by Reductive Desulfurization of a 2-(n-Butylthiomethylene)cyclohexanone

Hattersley and coworkers[23] reported the successful direct monomethylation of 1-tetralone (20) to produce 2-methyl-1-tetralone (21) in 76% yield. These authors treated ketone 20 with sodium t-butoxide followed by methyl iodide. This thesis reports the failure of the above method (p. 68), which is probably unreliable in view of our results (see Experimental).



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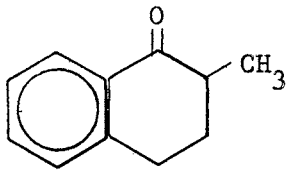

21

1-Oxo-2-phenanthrenepropionic acids have been synthesized and employed by a number of authors.[4,19,48,50] Green and Hey[19] prepared 1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-phenanthrenepropionic acid (22). Compound 22 is a very close analog of an important intermediate in this study, the acid 23. Their method is outlined in Figure 7.

Tsuda and Hayazu[50] have produced 15-aza-D-homosteroids using a phenanthrenepropionic acid intermediate. Their procedure and products are diagrammed in Figure 8. The azasteroid 24 is claimed to have "cardiotonic" activity.[25]

Ketones may be cyanoethylated, i.e., condensed with acrylonitrile in the presence of basic catalysts, common ones being potassium hydroxide or alkoxide in alcohols,[18] and Triton B in 1,4-dioxane.[9] The 1-oxo-2-naphthalenepropionic acid 25 is another analog of 23. The preparation of 25 illustrates a good monomethylation procedure plus the introduction of the 2-propionic acid group by cyanoethylation[41] (Figure 9).

Weinstock[53] pioneered the development (Figure 10) and use of a modified Curtius reaction which avoids the usual strenuous conditions necessary for the formation of acyl halide intermediates. In his method, the acid is condensed at 0° with ethyl chloroformate to yield a mixed ester-anhydride which is next allowed to react with aqueous NaN_3, still at 0°. The resulting azide undergoes rearrangement in hot toluene to the amine end-product. The entire sequence is completed without work-up or purification of the numerous intermediates. By this method, Weinstock achieved the conversion of cis-2-phenylcyclopropanecarboxylic acid to cis-2-phenylcyclopropylamine in 77% overall yield.

Fetizon and Golfier[15] applied the methods of Weinstock to the

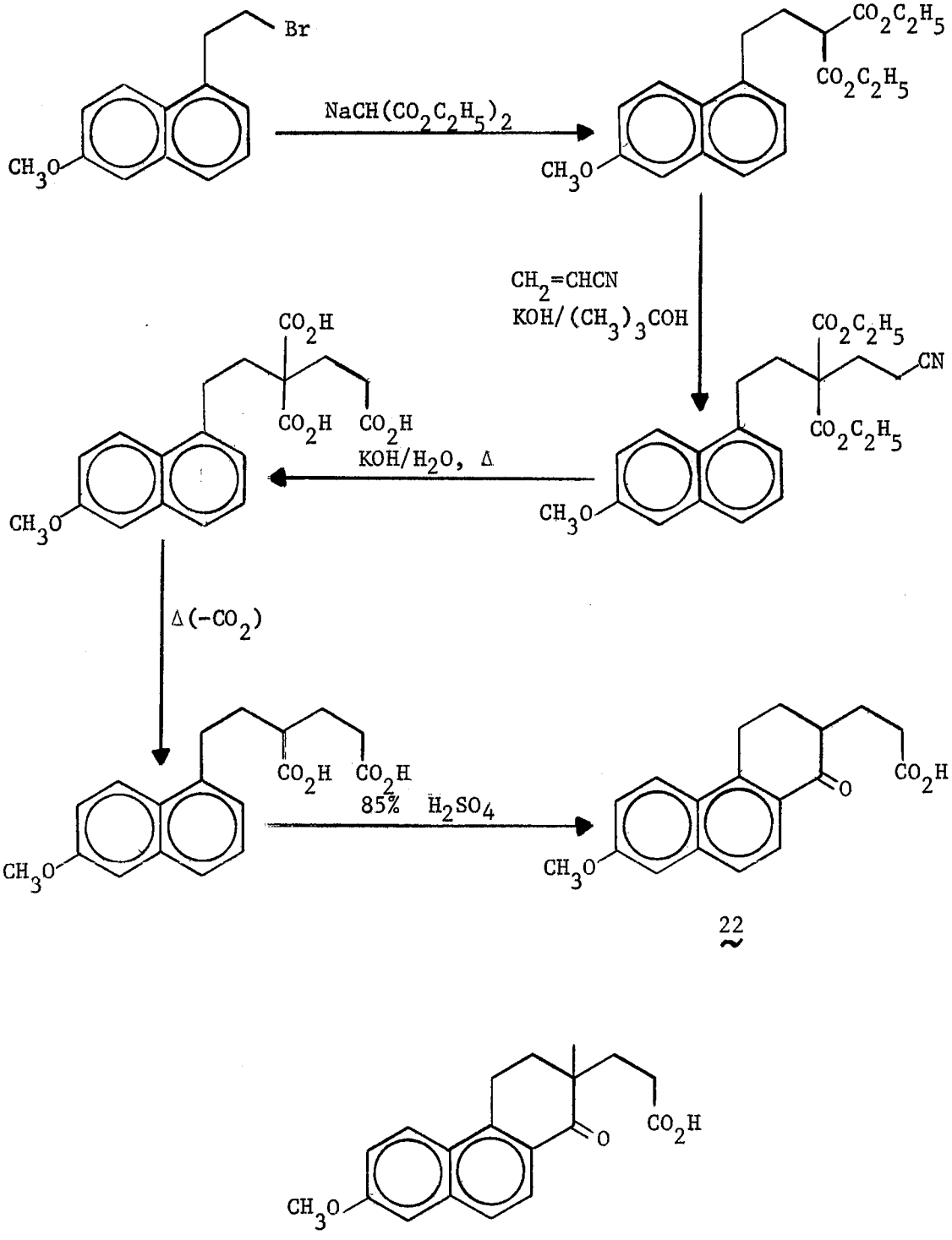

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Figure 7. Preparation of 1,2,3,4-Tetrahydro-7-methoxy-1-oxo-2-phenanthrenepropionic Acid (22)

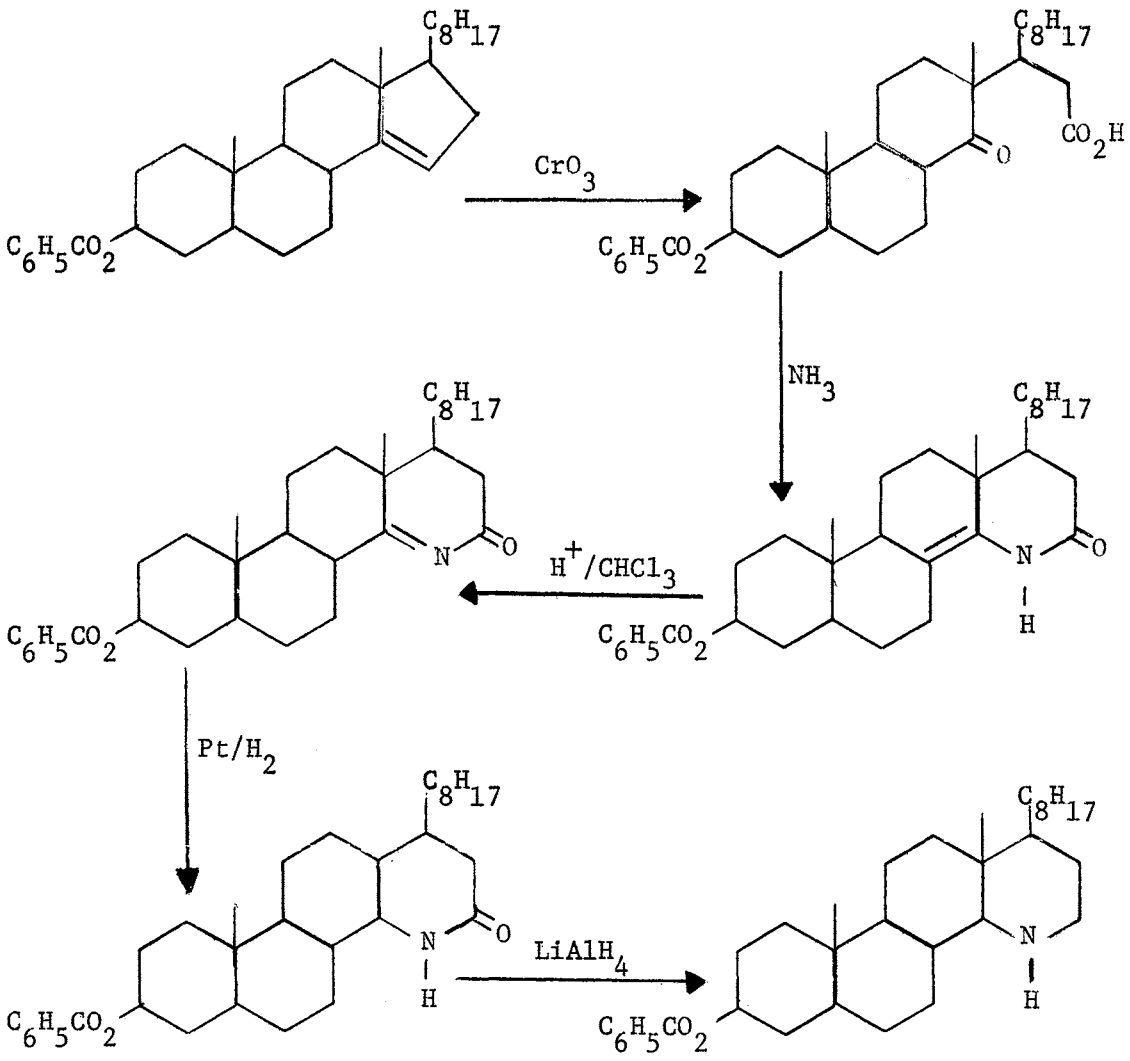


Figure 8. Conversion of a 14,15-Unsaturated Steroidal Alkene to a Series of 15-Aza-D-homosteroids

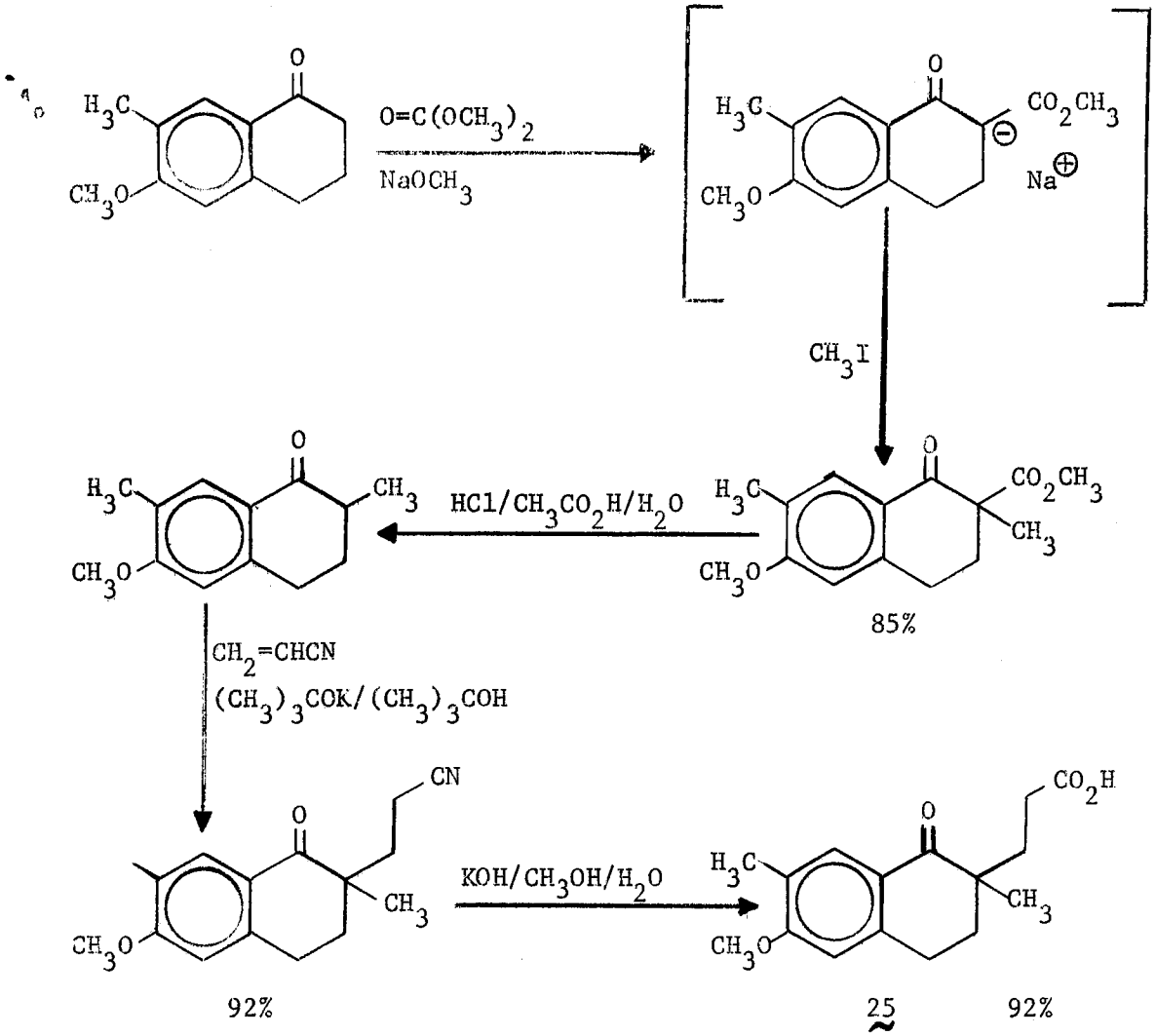


Figure 9. Preparation of 1,2,3,4-Tetrahydro-6-methoxy-2,5-dimethyl-1-oxo-2-naphthalenepropionic Acid (25)

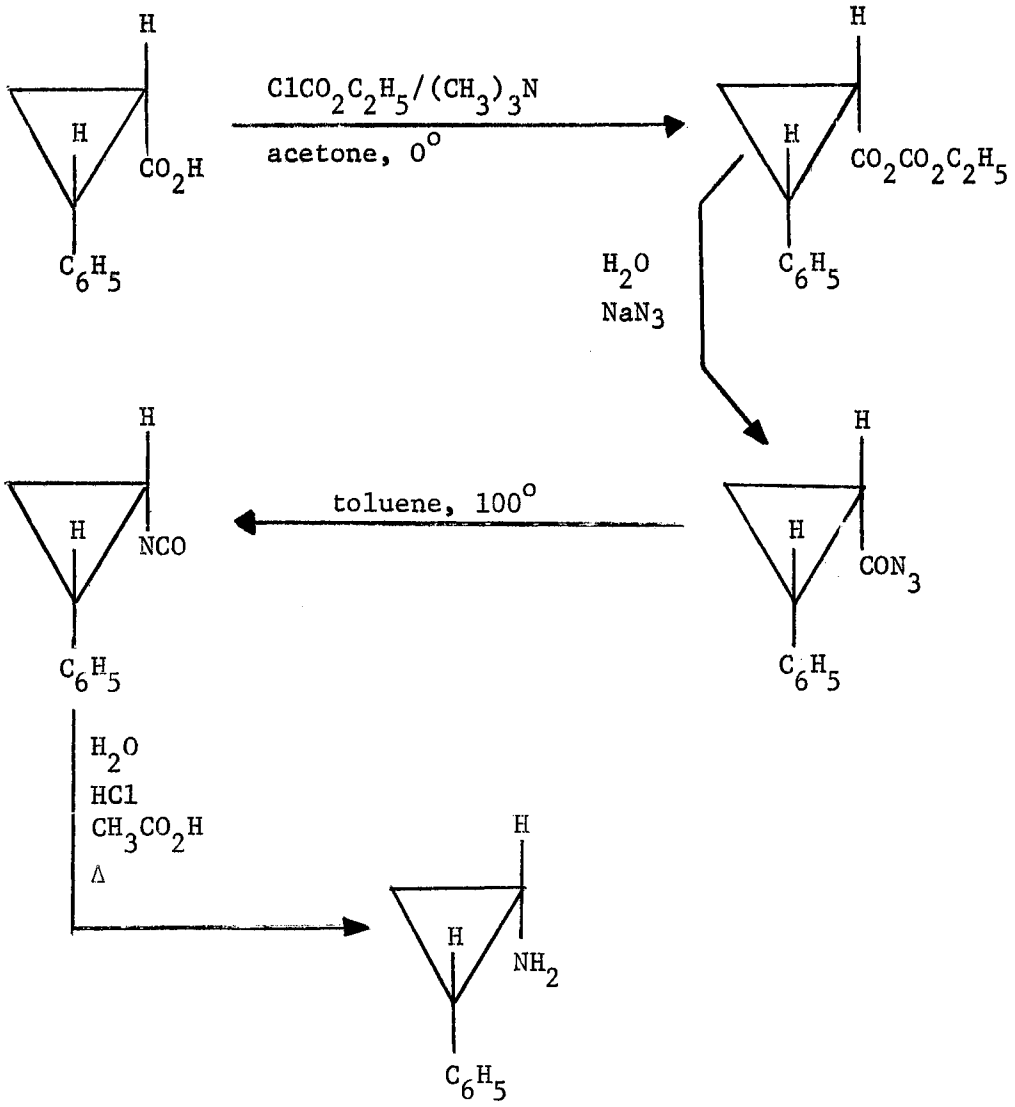
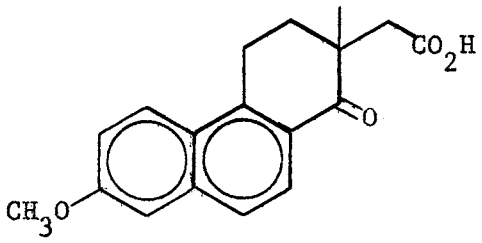


Figure 10. Conversion of cis-2-Phenylcyclopropanecarboxylic Acid to cis-2-Phenylcyclopropylamine by the Method of Weinstock[53]

1-oxo-2-phenanthrenepropionic acid 26 derived from 4,4-dimethyl-5α-androst-14-ene to produce 4,4-dimethyl-15-aza-5α-androst-14-ene (27). Imine 27 was subsequently reduced to amine 28. These procedures are outlined in Figure 11.

The naphthaleneacetic acid 29 can be obtained in 76% yield by the basic condensation of phenanthrone 13a with methyl bromoacetate.[54] Acid 29 is another homolog of 23. Djerassi's review[13] contains a large number of references to the preparation of steroidal cyclic amides and imides from keto-acid precursors. These products include one D-ring amide 30.[7]



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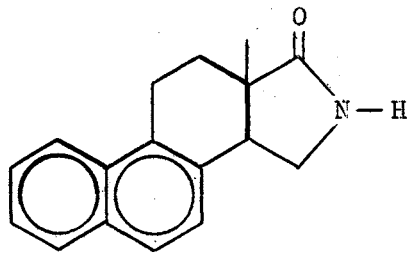

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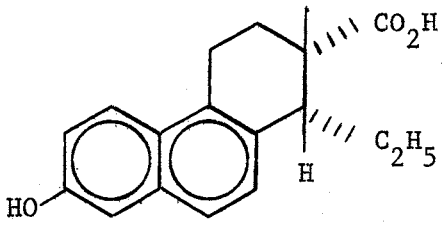
The presence of the D, or even the C, ring is apparently not necessary for pronounced hormonal activity in steroid-related materials. Compounds 31 and 32 both have high estrogenic activity, at least in rats.[46] The intermediates employed in this study may thus be viewed as possessing potential biological applications.



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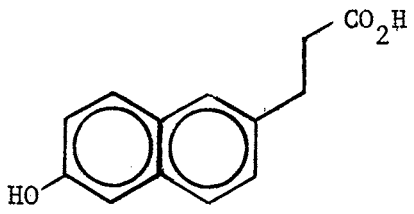

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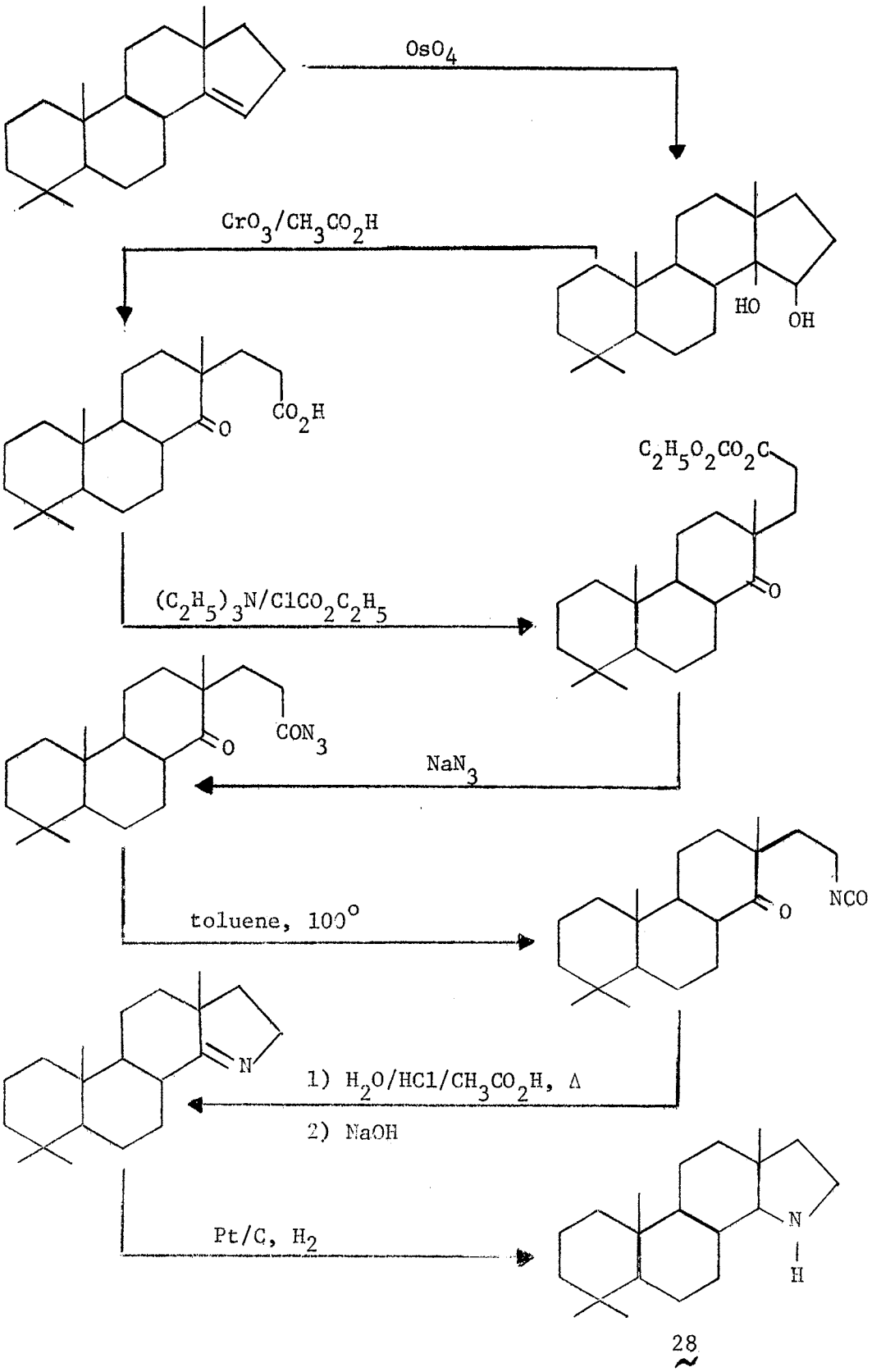

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Figure 11. Conversion of a 14,15-Unsaturated Steroidal Alkene to a 15-Azasteroid

CHAPTER II

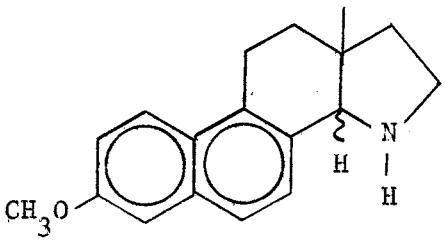
RESULTS AND DISCUSSION

As indicated earlier, the 15-azasteroids are an almost totally neglected class of compounds despite the fact that their combination of the steroid nucleus with the indole-type structure might reasonably be expected to confer on them pronounced biological activity. Equilenin (11) was chosen as the model steroid for this study by reason of its structural simplicity and biological activity, in addition to the fact that useful intermediates for the synthesis of equilenin-type structures were readily available.

This study reports the complete synthesis and characterization of a 17-deoxo-15-azaequilenin derivative, 1,2,3a,10,11,11a-hexahydro-7-methoxy-11a-methyl-3H-naphth[1,2-g]indole (34), as well as 1,10,11,11a-tetrahydro-11a-methyl-2H-napth[1,2-g]indol-7-ol (35) and the methyl ether of 35, i.e., 36. Naphtholic amine 37 has been prepared in impure form and characterized spectrally.

In addition, the steroidal pyrazoles 38 and 39 are reported here for the first time, as well as two novel benzindoles (40 and 41) and a benzindazole 42 produced in "model systems" studies.

Several of these novel azasteroids and "model" compounds have demonstrated significant biological activity, at least in microbiological systems. The results of this testing program are summarized at the end of this chapter.



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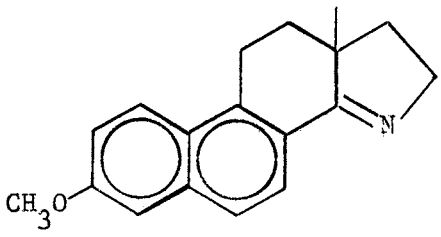

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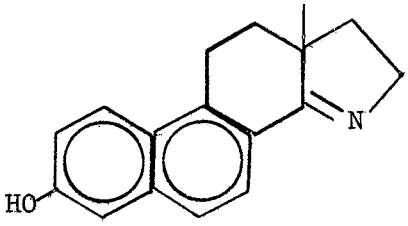

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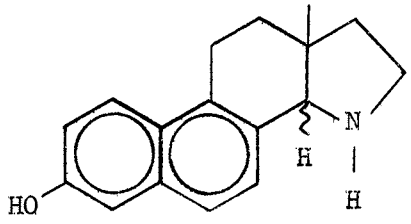

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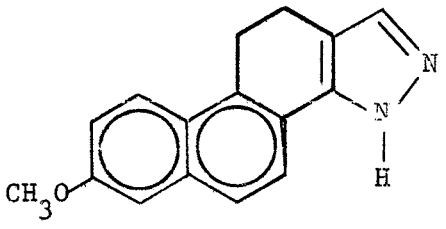
The first step in the synthesis of the azasteroids 34-37 required



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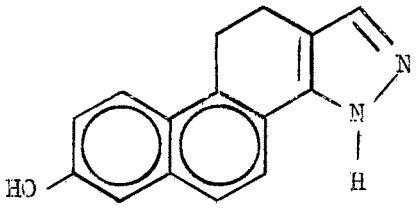

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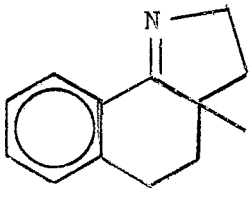

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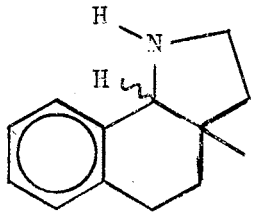

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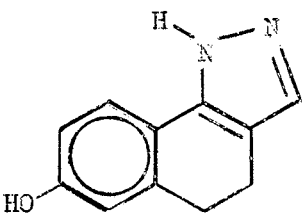

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an unsaturated halogenated ester, methyl 4-bromotiglate (43). The synthesis of 43, in turn, required tigic acid (44), which may be ob-

tained commercially (Aldrich) or synthesized by the method of Buckles and Mock[11] (see Figure 12). Acid 44 is conveniently methylated by the procedure of Harrison and coworkers[22] to produce methyl tiglate (45).

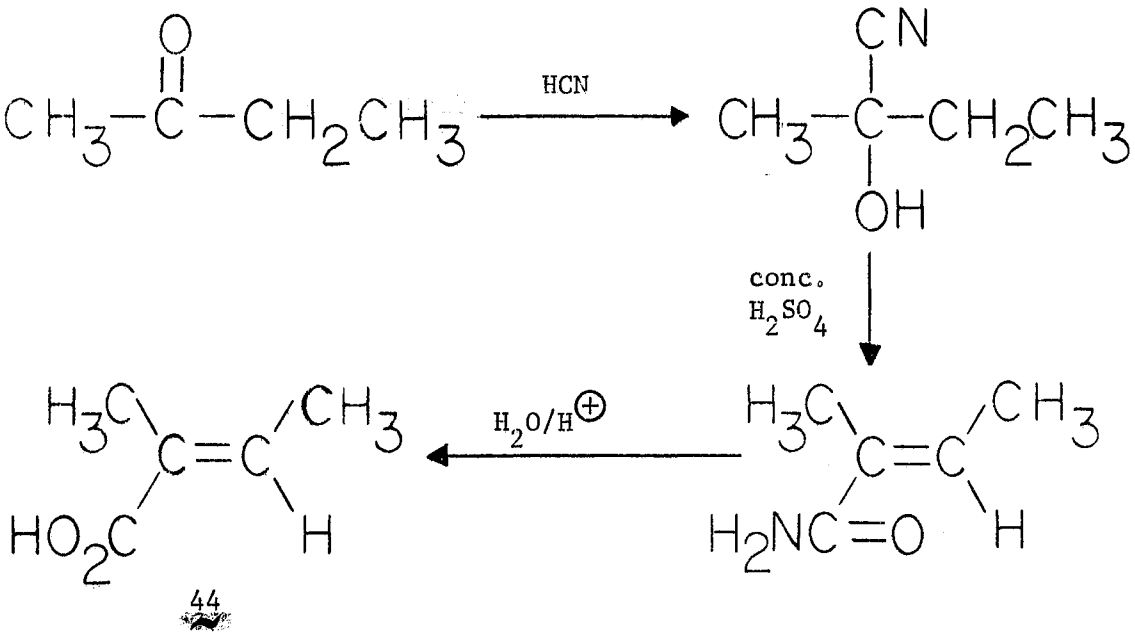

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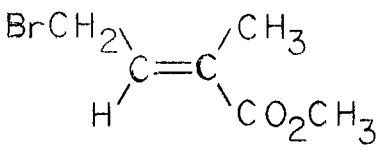
Figure 12. Synthesis of Tiglic Acid (44)

Inhoffen and coworkers[27] reported the bromination of 45 with N-bromosuccinimide (NBS) to produce 43 in 64% yield. When the work was repeated in this Laboratory (substituting benzoyl peroxide for light as a promoter) the product was found by GLC to consist of 2 major and 2 minor components. This product distribution is reasonable in view of the fact that the two distinct allylic methyl groups in 45 should give rise to 4 different monobromination products (43-43c) from the 2 possible free radical intermediate hybrids 45a and 45b. Bromination of the terminal methyl should be favored owing to the conjugation with the



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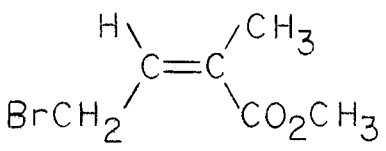

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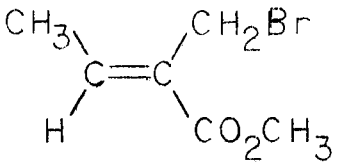

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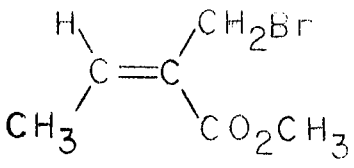

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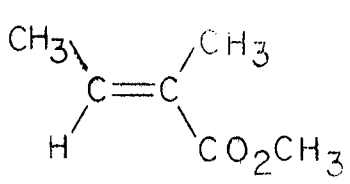

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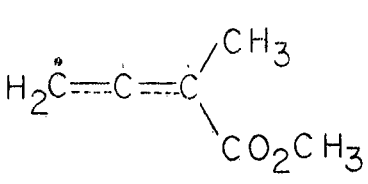

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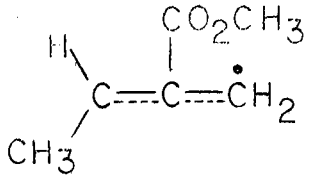


45b

ester function. In any case, the bromo ester mixture produced proved satisfactory for use in the next step.

Bromo ester 43 was condensed with the commercially available 6-methoxy-1-tetralone (46) according to the method of Stork.[47] In Stork's original procedure, the unsaturated halo ester used was the now commercially available ethyl 4-bromocrotonate (47). This study employed both 43 and 47, the method being outlined in Figure 13.

The above procedure differs from that of Stork only in the use of 10% Pd/C in place of 30% Pd/C. The yields of dienic ester for the 2 series of compounds are comparable--37.8% for 15, 35.6% for 15a, 26% for 12, and 24% for 12a respectively, all based on 46. During the isolation by distillation of 15 and 15a, nearly 50% of the starting ketone 46 is in-

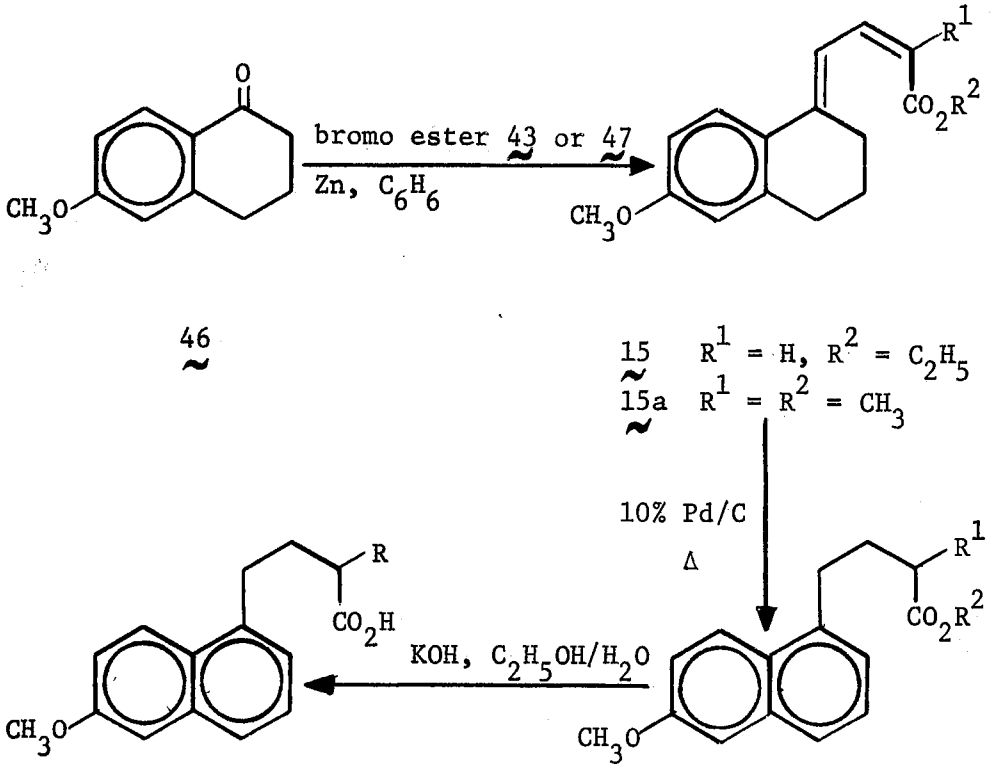
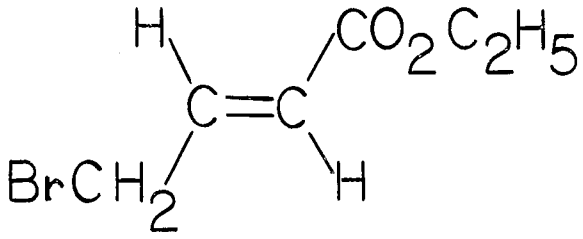


Figure 13. Synthesis of 1-Naphthalenebutyric Acids by the Method of Stork[47]

evitably recovered, despite the fact that an almost 2:1 excess of the bromo esters are employed. This inefficiency of the reaction with re-



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spect to the utilization of bromo ester is probably due to hydrolysis of the labile bromide by water produced in the course of the reaction, in addition to loss of bromo ester in coupling reactions.

This Reformatsky-type method of producing 12a is recorded here for the first time and is clearly superior in terms of simplicity and total yield to the methods historically employed (see p. 7). The dienic ester 15a is a novel compound unique to this study, but it was not fully purified or characterized.

The naphthalenebutyric acids 12 and 12a were cyclized to the phenanthrones 13 and 13a with 115% polyphosphoric acid (PPA).[46] This method has much to recommend it over the historical methods of cyclic acylations (p. 9) because of the extreme simplicity of the reaction and work-up procedures. Acid 12 melts well above the reaction temperature employed (151° vs. 100°) and must be converted to a microcrystalline powder (by precipitation from an aqueous solution of its salt) if one is to avoid unreacted acid in the product. Acid 12a (m.p. 85°) is easily and completely converted to the corresponding phenanthrone without a trace of base-soluble material remaining, regardless of the original physical form of the acid.

Whenever possible in this study, chromatography of concentrated solutions of crude products on alumina or silica gel was substituted for crystallization as a method of removing high molecular weight impurities. In most cases this method proved satisfactory for efficiently converting crude products to a usable state of purity.

Phenanthrone 13a was condensed with acrylonitrile by means of both KOH in t-butyl alcohol[18,44] (Figure 14) and Triton B in 1,4-dioxane[9] as basic reaction systems. The first procedure is definitely the method of

choice, since in the second method almost a third of the starting ketone is recovered unreacted. The limited solubility of 13a in alcohols is a difficulty in the use of t-butyl alcohol as a solvent, but if the reaction is run in dilute solutions (circa 3% phenanthrone) at a somewhat

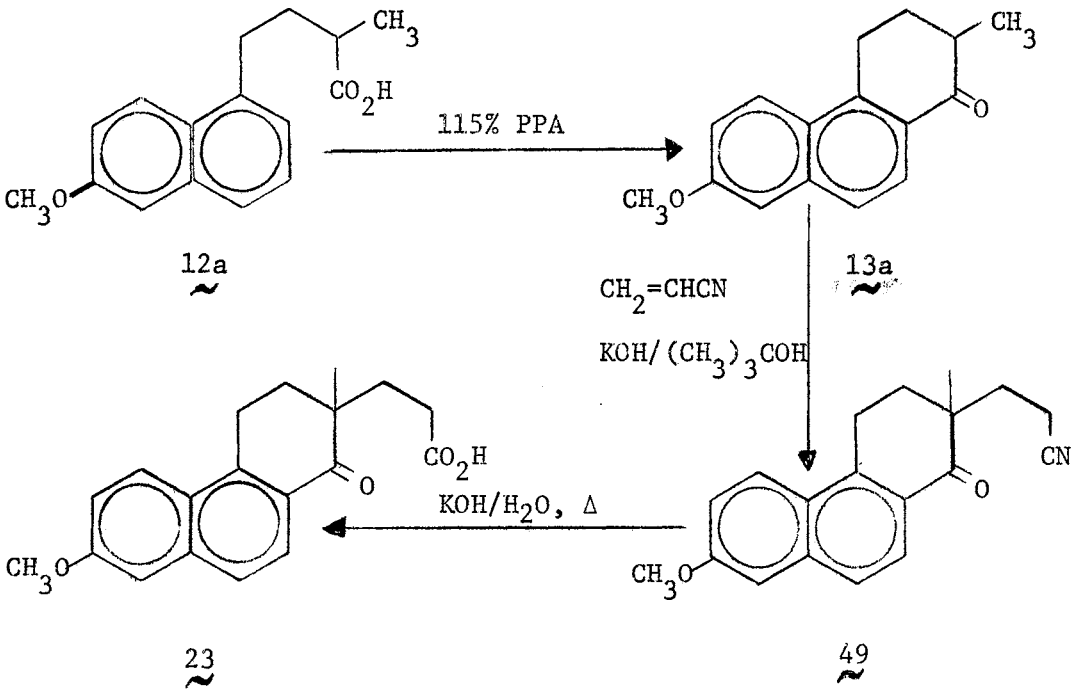


Figure 14. Conversion of an α-Methylnaphthalenebutyric Acid to a 2-Methyl-1-oxophenanthrenepropionic Acid

elevated temperature (60° vs. 40° maximum recommended[18]), the novel phenanthrenepropionic acid 23 may be obtained in 94% (crude) or 57% (analytical purity) yield. The nitrile 49 is unique to this study, but it was not purified or characterized.

2-Methyl-1-tetralone (21) was used as a model compound in the cyanoethylation procedure described above. Ketone 21 was prepared from 1-tetralone (20) in an exploratory series of reactions involving the

monomethylation of cyclic arylalkyl ketones. The method used was that of Ireland and Marshall[28], namely the reductive desulfurization of the alkylthiomethylene derivative 51. An "inactive" Raney nickel prepared according to Fieser and Fieser[16] and recommended for desulfurizations was used to minimize the possibility of reducing the benzene ring. The method succeeded for the benzene derivative 51 but failed when applied to the naphthalene derivative 54, presumably owing to partial reduction of the naphthalene ring system. This method of reductive methylation was abandoned in favor of the synthetic schemes described earlier. The reactions and products involved are listed in Figure 15. The nitrile 52 and the acid 53 have not been previously described in the literature and they were not purified or characterized in this study.

The hydro-oxoarylpropionic acids 23 and 53 were subjected to the modified Curtius rearrangement of Weinstock[53] (see Figure 16) and the resulting novel cyclic imines were isolated and characterized. Hydrolysis of isocyanate 55 by boiling for 24 hours with 1:1:1 HCl:CH_3CO_2H:H_2O yields the methoxy imine 34 and the phenolic imine 35 in a 2:1 ratio. Decreasing the heating time to 6 hours effects the complete hydrolysis of the isocyanate while producing only trace amounts of the base-soluble naphthol. Imines 40 and 34 are a colorless oil and a crystalline solid, respectively, which show no tendency to discolor or decompose even on prolonged standing. Naphtholic imine 35 shows some tendency to air oxidation, especially in solution.

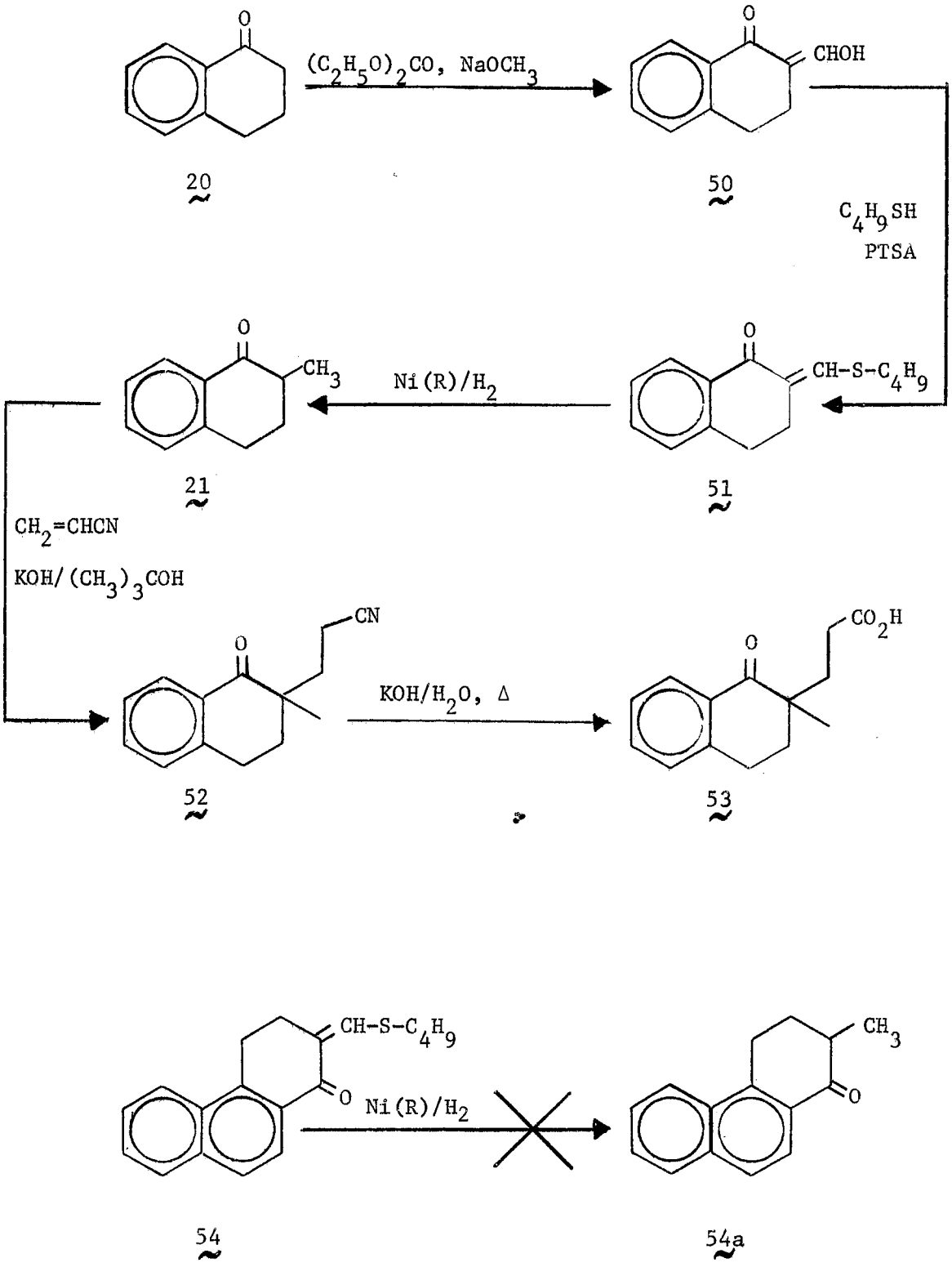


Figure 15. Methylation by Reductive Desulfurization as Applied to Cyclic Arylalkyl Ketones Plus Cyanoethylation of 2-Methyl-1-tetralone (21)

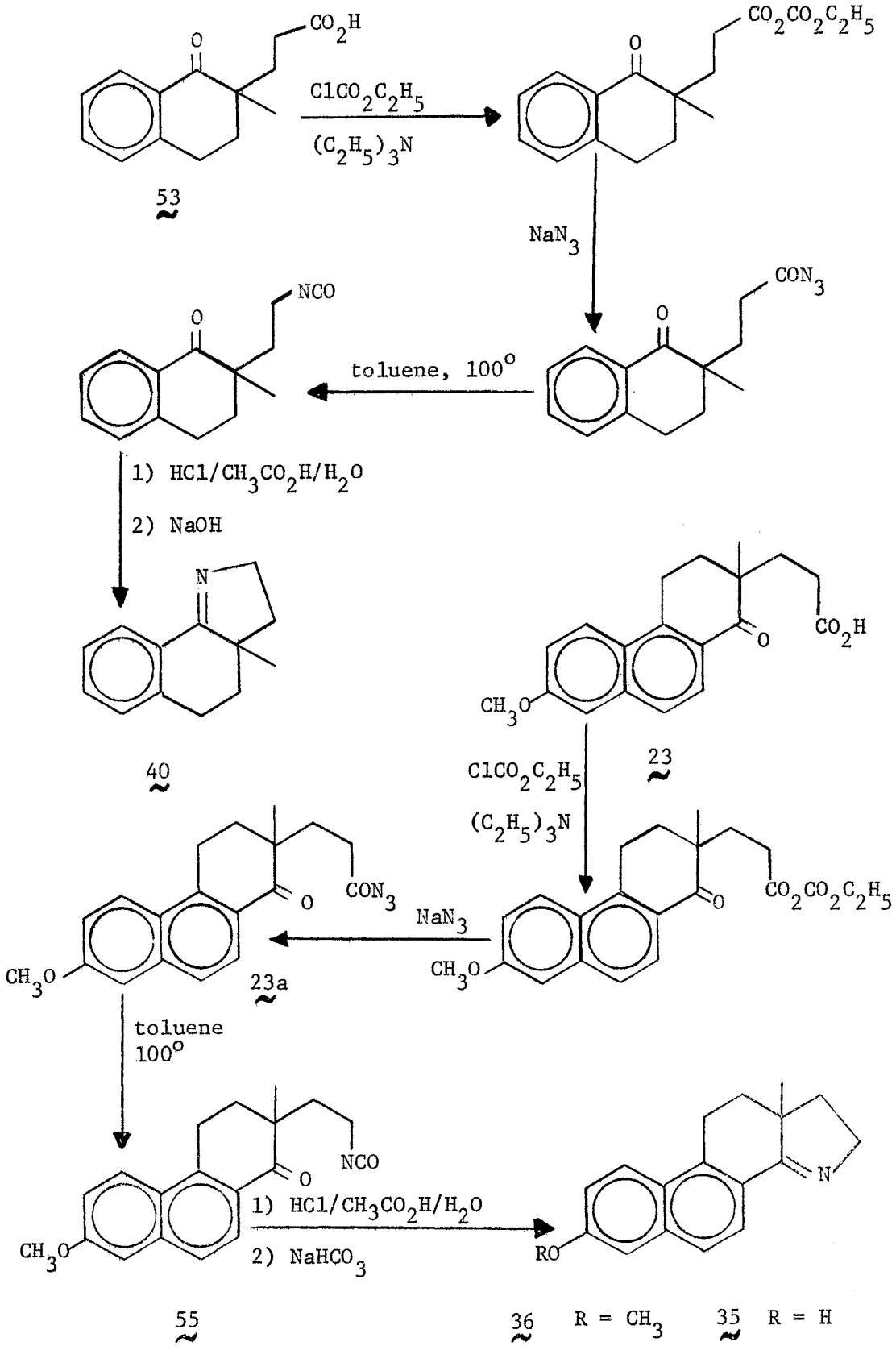
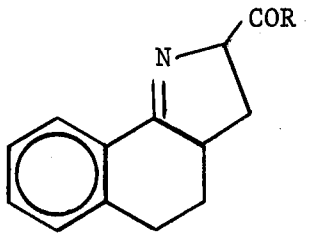


Figure 16. Conversion of 1,2,3,4-Tetrahydro-1-oxo-2-areneprop-ionic Acids to Cyclic Imines

Only one reference to 2H-benz[g]indoles (i.e., compounds similar to 40) is recorded in the literature.[20]



56 R = OH
56a R = OCH_3
56b R = NH_2

Compounds 56-56b are reported to be adrenolytic central nervous system depressants and analgetic agents.[20]

The imines 40 and 36 were reduced to the corresponding amines 41 and 34 using the method of Schmitt and coworkers[43] for the $NaBH_4$ reduction of steroidal imines (see Figure 17). The method was somewhat less than totally satisfactory since repeated application of large excesses of $NaBH_4$ was required and in the case of the steroidal imine 36, total reduction was never achieved. These reductions produced, in both cases, mixtures of the two possible diastereoisomers 41a, 41b, 34a, and 34b.

Amines 41a and 41b can be resolved by GLC employing a 5% SE-30 column. The retention time of the starting imine 40 overlaps that of the minor isomer but the absence of any unreacted imine is established by NMR and IR analysis of the product. The NMR spectrum (Plate XXXI)

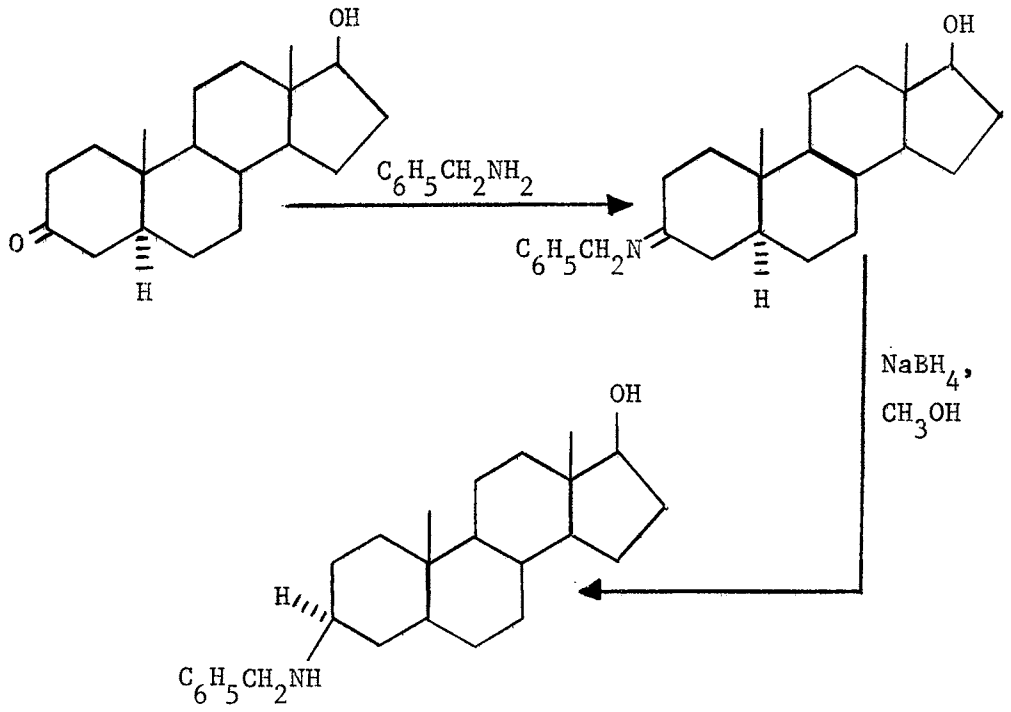
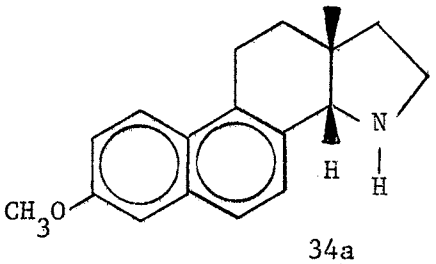
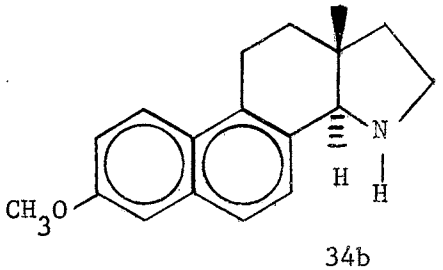


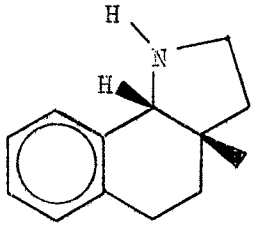
Figure 17. $NaBH_4$ Reduction of a Steroidal Imine



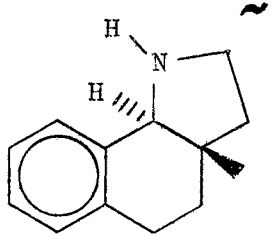
34a



34b

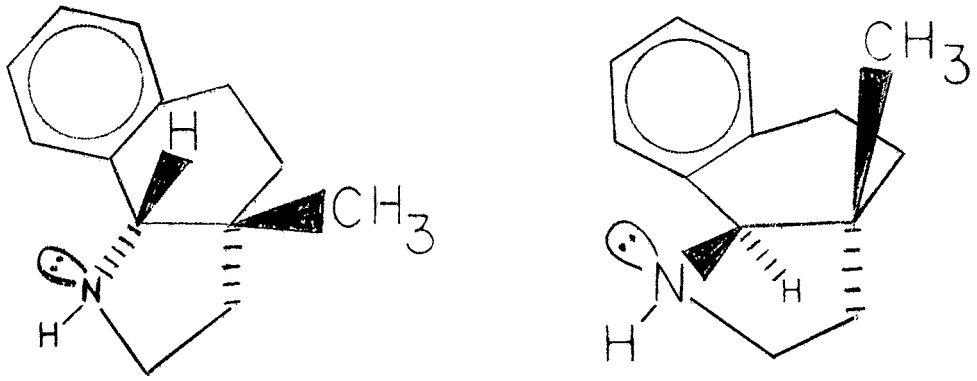


41a



41b

of the mixture of amines 41 indicates the presence of the two isomers in 81:19 ratio by integration of the methyl singlets at δ 0.90 and δ 0.45, respectively. The minor isomer (with high field methyl group) is assigned the trans configuration (41b) since examination of molecular models shows that one would expect the methyl group in the trans isomer to be shielded by the benzene ring relative to the methyl group in the cis isomer (see Figure 18).



41a (cis) 41b (trans)

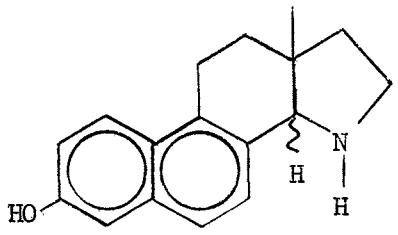
Figure 18. Conformations of the cis and trans Isomers of 2,3,3a,4,5,10-Hexahydro-3a-methyl-1H-benz[g]indole (41)

Moreover, the mobile cis-6,5 ring fusion would be expected to be thermodynamically favored over the strained, rigid trans ring juncture. This supposition is consistent with the product ratios, plus the fact

that, under the basic reaction conditions, the product corresponding to the upfield peak (trans compound) is observed to undergo isomerization to the downfield isomer (cis compound).

Similar observations hold for the steroidal amines 34a and 34b. Here, despite repeated treatments with $NaBH_4$, 10% of the starting imine remained unreduced. The isomers were only partially resolved by GLC and again the imine 36 and minor amine isomer 34b were not separated. Moreover, in the NMR spectrum, the absorption of the tertiary methyl group of the imine 36 and that of the major amine isomer 34a coincided; in the IR spectrum, the skeletal stretching frequency for the naphthalene ring overlapped with the expected band for imine 36. Fortunately, the steroidal imine 36 and amine mixture 34 could be identified and separated by TLC, and preparative TLC technique afforded an analytical sample of the amine mixture 34.

Despite repeated efforts, no system was found which would resolve the isomers 34a and 34b. Crude methoxy amine 34 was hydrolyzed with HBr to the naphtholic amine 37 in hopes that the isomers of this material would prove separable; however, this was not the case. Crude 37 was characterized by NMR (Plate XXII) and not examined further.



37

In the course of this study, several hydroxymethylene derivatives of the various available phenanthrones and tetralones were prepared as intermediates in the methylation studies. Enol ketones of this type were known to have been cyclized to hydroindazoles by treatment with hydrazine.[2,30,49] When phenanthrone 13 was treated in this manner, a novel 15,16-diazasteroid[38] resulted (see Figure 19).

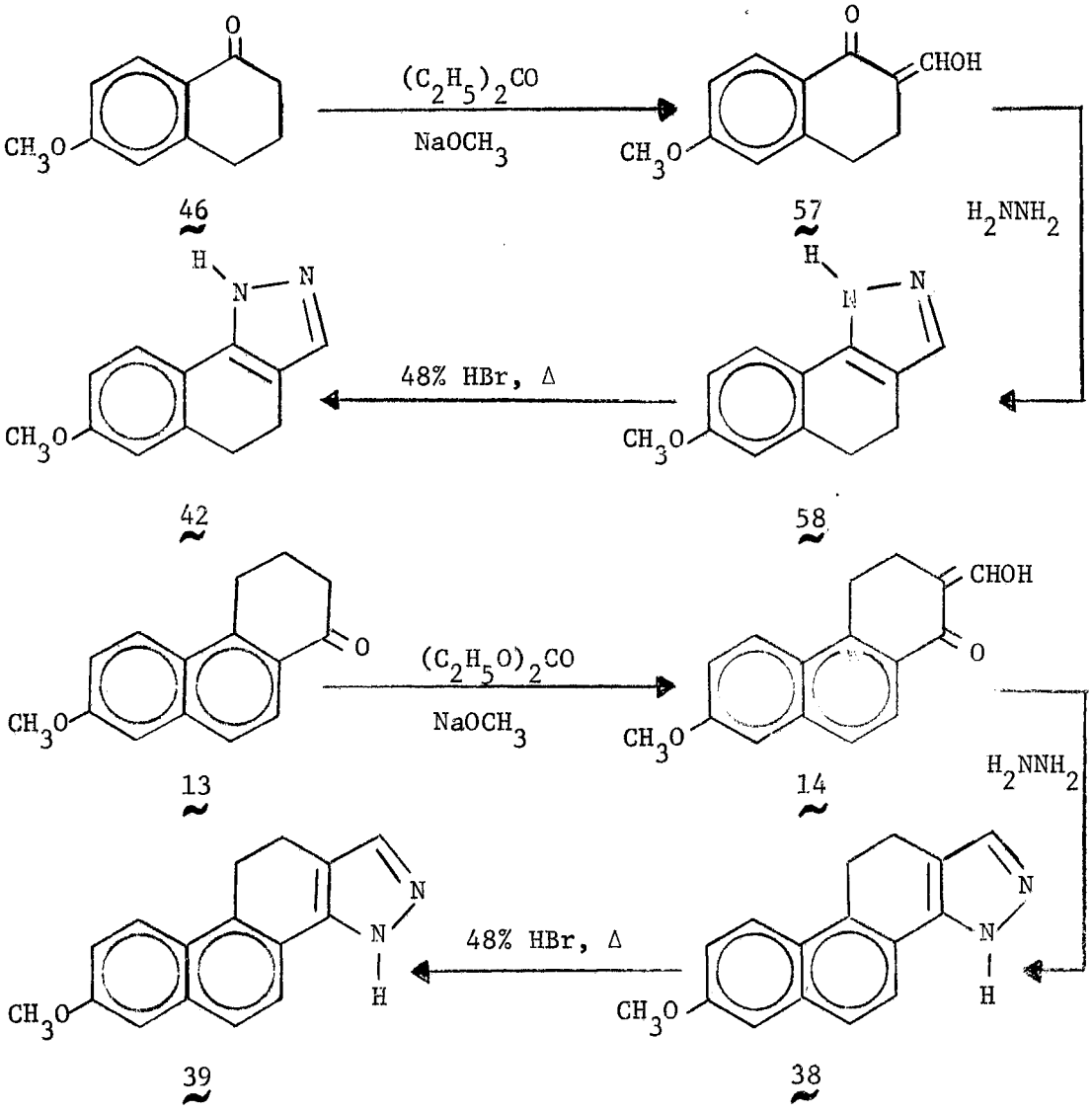
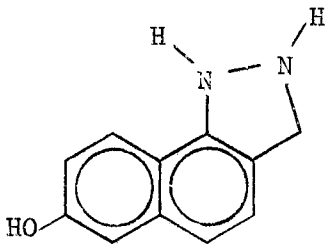


Figure 19. Synthesis of Steroidal Pyrazoles and Related Compounds

The methoxybenzindazole 58 is a known compound, having been synthesized and fully characterized by Taylor and coworkers.[49] Interestingly, although reference 49 reports the use of enol ketone 57 in the preparation of 58, no data is provided on 57 itself. References 29 and 30 are provided for compound 57 but although the general method for ethyl formate condensations is outlined in 29 and 30, no specific reference to 57 is made in either reference.

When 58 is boiled with 48% HBr for 12 hours, the benzindazolol 42 is formed and no isomerization to the naphthalene form 42a is observed. This is despite the fact that similar compounds (e.g., 6, p. 5) undergo such isomerizations under the influence of metal catalysts.[10] When the steroidal pyrazole 38 is treated likewise with HBr, the naphthindazolol 39 results.



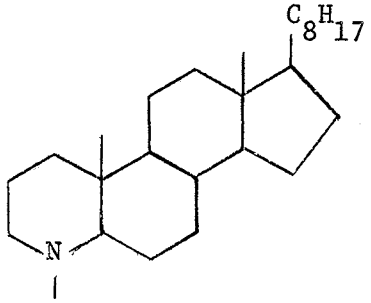
42a

Dr. Norman N. Durham and Mr. Robert Chesnut of the Microbiology Department at this University subjected title compounds 35, 36, and 39, as well as "model" indazoles 42 and 58, to a program of testing as antibiotics. A saturated aqueous solution of 58 inhibits the growth of Flavobacterium sp., while 42 inhibits the growth of Escherichia coli, Bacillus subtilis, Staphylococcus aureus, and Rhodospirillum rubrum, as well as Flavobacterium. Retardation of growth rates by 42 was observed at concentrations of 50 µg./ml. Unusual and excessive chaining of

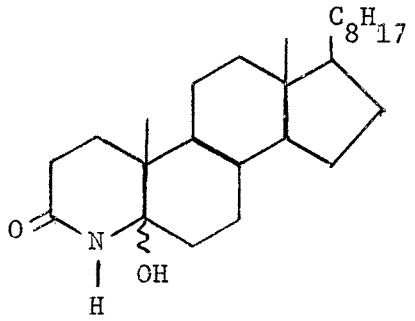
B. subtilis was observed with 42 at concentrations as low as 12 µg./ml. and growth initiation for B. subtilis was stimulated by 42 at concentrations of 12-14 µg./ml. compared to controls.

Azasteroid 36 (50 µg./ml.) produced lysis in B. subtilis and inhibited the growth of Flavobacterium, E. coli and Pseudomonas fluorescens. Normally, P. fluorescens is extremely resistant to many antibiotics. Compound 35 is similar in activity to 36 but growth recovery following lysis is more rapid, indicating 35 may be destroyed in the media more rapidly than 36 (Figure 20). A further program of biological testing for the above compounds and others is anticipated. The materials will be submitted either to NIH or one of the commercial drug houses. A program of animal toxicology studies by the College of Veterinary Medicine is contemplated.

Doorenbos and coworkers[14,51] have reported that compounds 3 (see p. 2), 58, 59, and 60 show activity against certain gram-positive bacteria, namely B. subtilis and Sarcina lutea. These compounds demonstrate surfactant properties, and 3, by ^{14}C studies, was shown to bind well with B. subtilis. Compound 3 causes rapid lysis of B. subtilis at

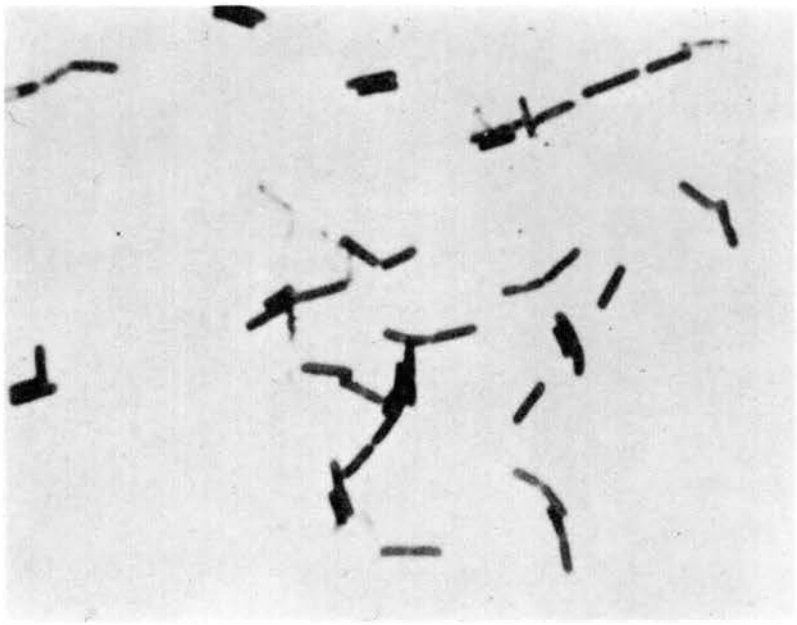


58 R = CH_3
59 R = C_2H_5

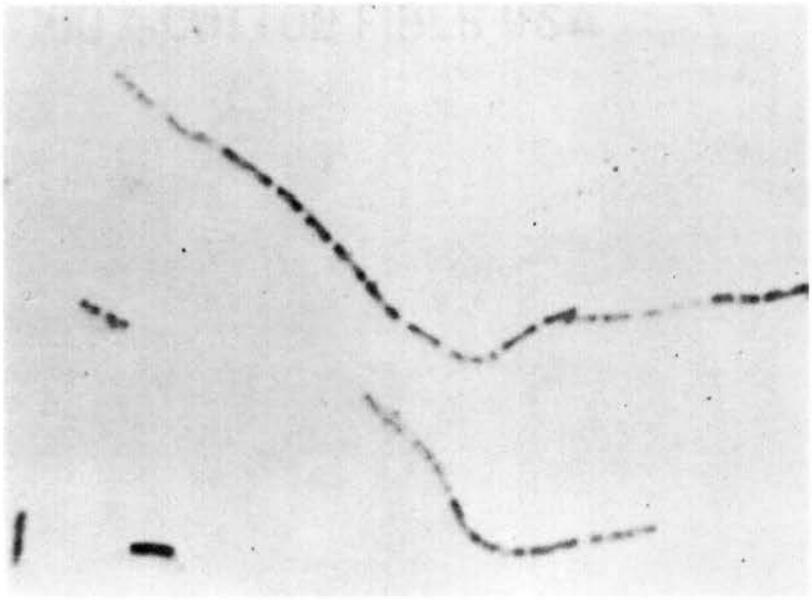


60

concentrations as low as 1 µg./ml. (1.7×10^{-6} M); at this concentration,



Bacillus subtilis W_{23} grown 2.5 hr. in glucose salts minimal medium after addition of H_2O control solution. (Total mag. 10,400x).

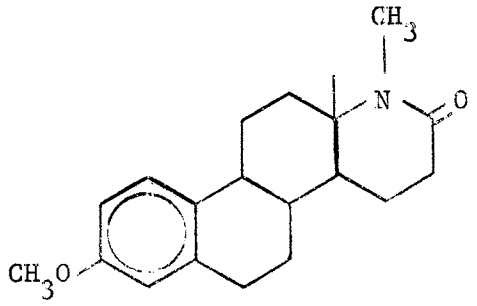


Same as above, except azasteroid 35 at a concentration of 38 µg./ml. was added in place of the H_2O control solution.

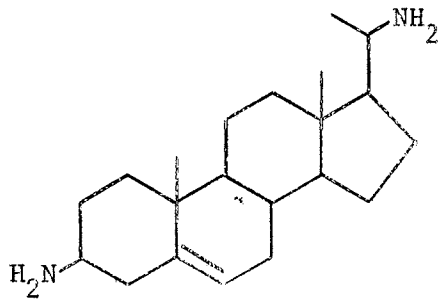
Figure 20. Cell Lysis of B. subtilis in the Presence of Azasteroid 35

growth of the bacteria was completely inhibited. Although a D-ring amide 61 was reported in one article, no testing results were presented.[51]

In a very recent report,[44] diamino steroid 62 clearly shows a marked effect on the permeation of cell membranes by potassium and acriflavine. It seems reasonable that the 15-azasteroids and related compounds reported in this thesis may function, in part at least, to control cell growth by regulation of the uptake of metabolites.

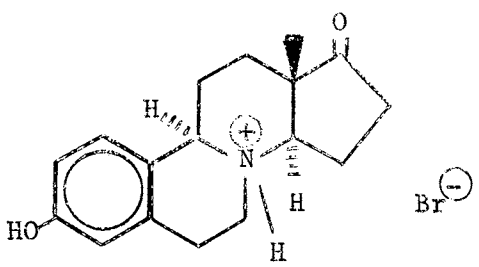


61



62

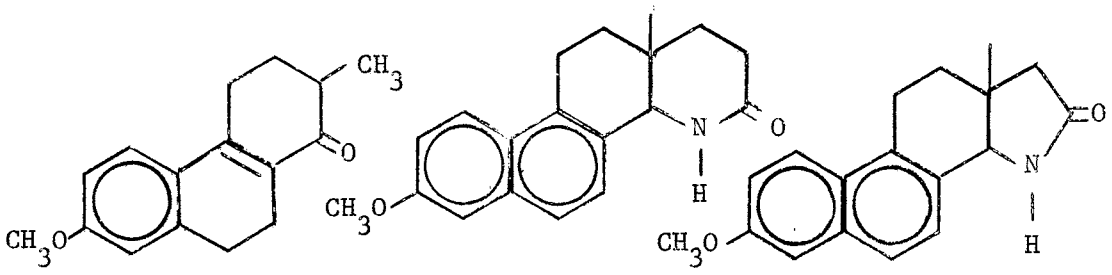
The possible value of azasteroids in medicinal chemistry has prompted x-ray analysis of 63.[38] Quite probably, an azasteroid's stereochemistry will govern its binding properties with respect to a cell, and hence influence cell permeability.



63

So very little work has been done with 15-azasteroids that the field is an extremely fertile area as far as the synthesis of novel compounds is concerned. In many cases, the intermediates necessary are readily available from other synthetic routes, and only one or two additional steps would be necessary to achieve the creation of some very interesting materials.

For instance, ketone 64 is preparable by literature methods.[6] Reduction of the double bond at C-10 and application of the methods described in this study would yield a series of 15-azaestrone-type materials. Application of the methods of Hayazu[25,50] (p. 12) or of Bachmann and Ramirez[7] (p. 17) to the acid 23 would yield 15-aza-D-homoequilenin derivatives such as 65. Cyclization of the phenanthreneacetic acid 29 (p. 17) by the same methods would provide the novel D-ring imide 66.



64 65 66

In view of the biological activity evident in the 15-azasteroids produced in this, the first directed effort made in the field, further investigations along these lines would certainly seem warranted.

TABLE I

NMR CHEMICAL SHIFTS FOR PRODUCTS

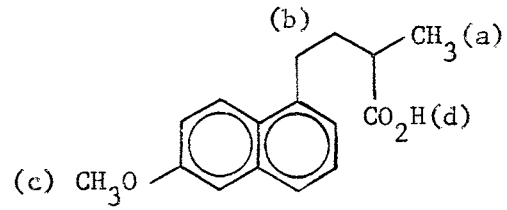
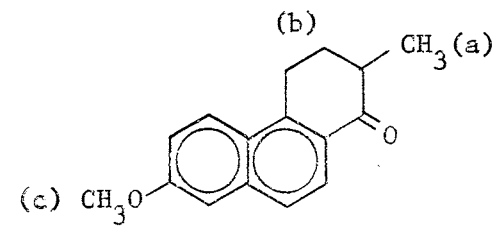
Compound[a]	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XVI	1.26 (d)	2.85	3	CH_3 (a)
		1.67-3.27 (m)	4.95	5	CH_2,CH (b)
		3.82 (s)	3.06	3	OCH_3 (c)
		6.98-8.05 (m)	6.1	6	Ar-H
		11.5 (s)	1.0	1	CO_2H (d)
	XVII	1.29 (d)	2.98	3	CH_3 (a)
		1.56-3.44 (m)	5.29	5	CH_2,CH (b)
		3.89 (s)	2.96	3	OCH_3 (c)
		7.05-8.18 (m)	4.76	5	ArH

TABLE I (Continued)

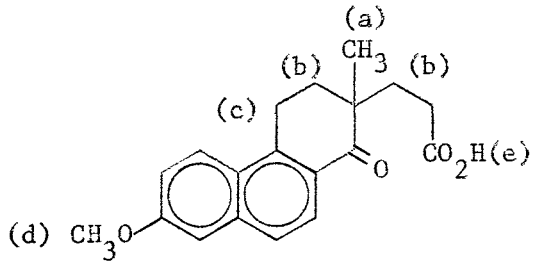
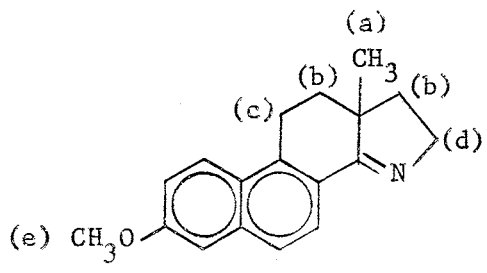
	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XVIII	1.22 (s)	3.00	3	CH_3 (a)
		1.76-2.67 (m)	5.94	6	CH_2 (b)
		3.13-3.47(bt)	2.01	2	$ArCH_2$ (c)
		3.90 (s)	2.85	3	OCH_3 (d)
		7.00-8.20 (m)	4.94	5	ArH
		11.41 (s)	0.91	1	CO_2H (e)
	XIX	1.11 (s)	3.0	3	CH_3 (a)
		1.65-2.50 (m)	4.1	4	CH_2 (b)
		2.94-3.47 (m)	2.2	2	$ArCH_2$ (c)
		3.78-4.25 (m)	4.9	5	$C{=}NCH_2$ (d)
		3.90 (s)			OCH_3 (e)
		7.06-8.27 (m)	5.1	5	ArH

TABLE I (Continued)

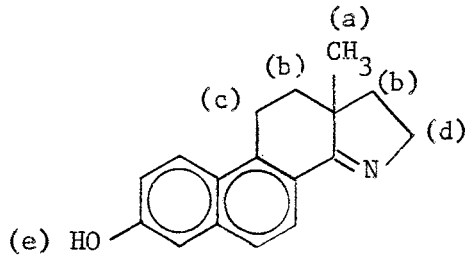
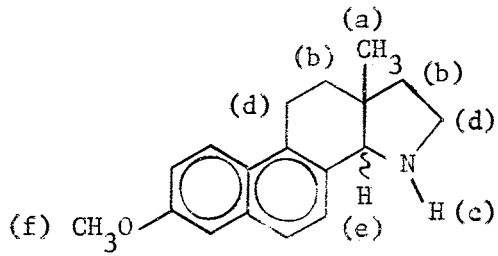
	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XX	1.00 (s)	3.00	3	CH_3 (a)
		1.33-2.33 (m)	4.09	4	CH_2 (b)
		2.96-3.46 (m)	1.88	2	$ArCH_2$ (c)
		3.68-4.49 (m)	2.08	2	$C{=}NCH_2$ (d)
		7.10-8.90 (m)	5.10	5	ArH
		11.5-12.5 (b)	0.84	1	ArOH (e)
	XXI[c]	0.62,1.09 (s)	3.22	3	CH_3 (a)
		1.50-2.06 (m)	3.82	4	CH_2 (b)
		2.45 (s)	1.38	1	NH (c)
		2.82-3.40 (m)	3.53	4	$ArCH_2$, NCH_2 (d)
		3.62,3.71 (s)	0.85	1	ArCH (c)
		3.88 (s)	3.01	3	OCH_3 (f)
		7.00-8.23 (m)	5.20	5	ArH

TABLE I (Continued)

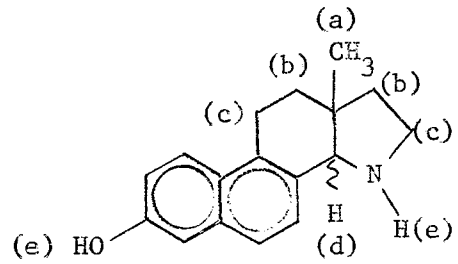
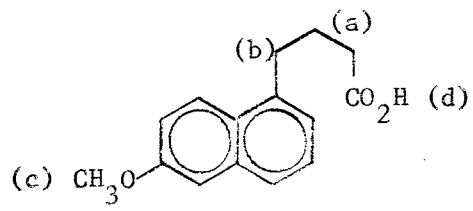
	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XXII[c]	0.71,1.01 (s)	3.00	3	CH_3 (a)
		1.33-2.11 (m)	3.79	4	CH_2 (b)
		2.78-3.40 (m)	3.08	4	$ArCH_2$, NCH_2 (c)
		3.76 (s)	0.93	1	ArCH (d)
		6.30 (s)	3.00	2	OH,NH (e)
		7.17-8.85	5.19	5	ArH
	XXIII	1.68-2.68 (m)	4.39	4	CH_2 (a)
		2.90-3.27(bt)	2.07	2	$ArCH_2$ (b)
		3.91 (s)	2.92	3	OCH_3 (c)
		7.01-8.11 (m)	5.78	6	ArH
		10.9 (s)	0.92	1	CO_2H (d)

TABLE I (Continued)

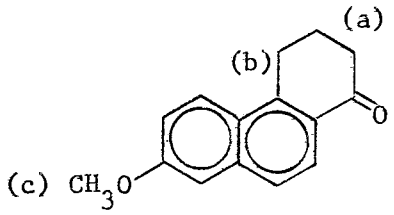
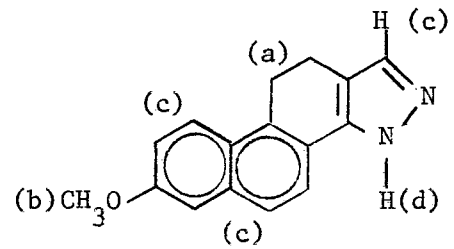
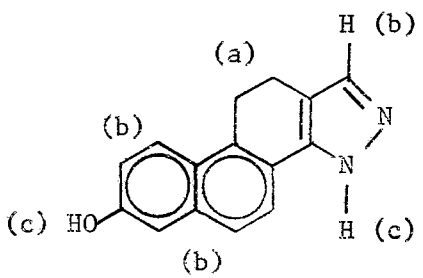
	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XXIV	1.85-2.81 (m)		4	CH_2 (a)
		2.92-3.28 (bt)		2	$ArCH_2$ (b)
		3.83 (s)		3	OCH_3 (c)
		6.85-8.09 (m)		5	ArH
	XXV	2.76-3.57 (m)	3.95	4	CH_2 (a)
		3.81 (s)	2.93	3	OCH_3 (b)
		7.17-8.85 (m)	6.42	6	ArH,N=CH(c)
		13.5-14.9 (b)	0.70	1	NH (d)
	XXVI[c]	2.70-3.59 (m)	3.23	4	CH_2 (a)
		7.16-8.82 (m)	6.88	6	ArH,N=CH(b)
		12.1-14.1 (b)	1.89	2	OH,NH (c)

TABLE I (Continued)

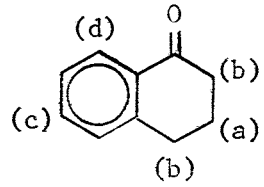
	Plates	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XXVII	1.62-2.18 (m)	1.87	2	CH_2 (a)
		2.31-2.93 (m)	3.96	4	$ArCH_2$, $O{=}CCH_2$ (b)
		6.95-7.53 (m)	3.04	3	ArH (c)
		7.83-8.08 (m)	1.15	1	ArH (d)

TABLE I (Continued)

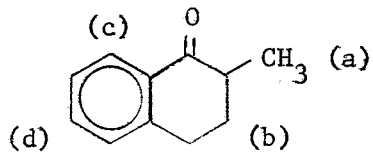
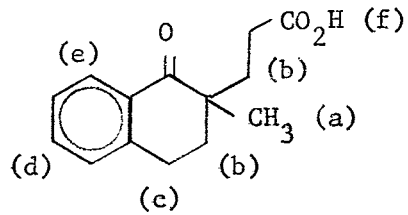
	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XXVIII	1.20 (d)	2.89	3	CH_3 (a)
		1.40-3.04 (m)	4.89	5	CH_2,CH (b)
		6.95-7.53 (m)	3.28	3	ArH (c)
		7.81-8.05	0.94	1	ArH (d)
	XXIX	1.18 (s)	2.80	3	CH_3 (a)
		1.76-2.61 (m)	5.96	6	CH_2 (b)
		2.80-3.13(bt)	2.38	2	$ArCH_2$ (c)
		7.02-7.61 (m)	2.73	3	ArH (d)
		7.87-8.11 (m)	0.97	1	ArH (e)
		10.4 (s)	1.17	1	CO_2H (f)

TABLE I (Continued)

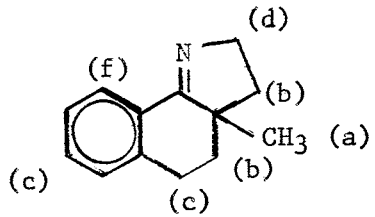
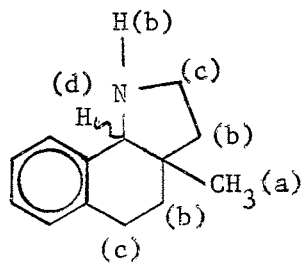
	Plate	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XXX	0.88	2.85	3	CH_3 (a)
		1.15-2.17 (m)	4.10	4	CH_2 (b)
		2.20-3.15 (m)	2.09	2	$ArCH_2$ (c)
		3.50-4.20 (m)	2.04	2	$C{=}NCH_2$ (d)
		6.76-7.23 (m)	2.96	3	ArH (c)
		7.88-8.22 (m)	0.97	1	ArH (f)
	XXXI	0.45,0.90 (s)	2.93	3	CH_3 (a)
		1.16-1.84 (m)	5.36	5	CH_2,NH (b)
		2.33-3.13 (m)	3.98	4	$ArCH_2$, NCH_2 (c)
		3.33 (s)	0.89	1	ArCH (d)
		6.66-7.27 (m)	3.85	4	ArH

TABLE I (Continued)

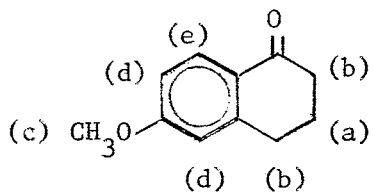
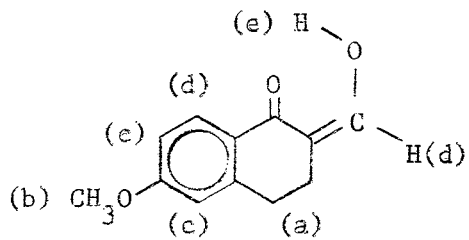
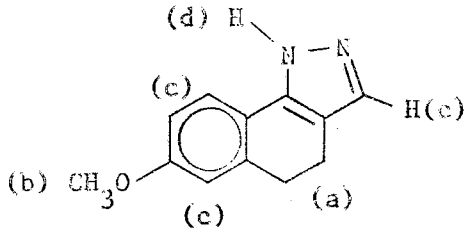
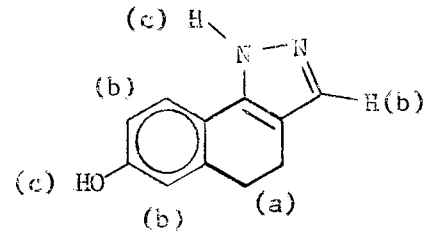
	Plate	δ(p.p.m.)[b]	Integration Found.	Theor.	Assignment
	XXXII	1.78-2.33 (m)	2.00	2	CH_2 (a)
		2.38-3.19 (m)	4.16	4	$ArCH_2$, $O{=}CCH_2$ (b)
		3.81 (s)	2.92	3	OCH_3 (c)
		6.60-6.92 (m)	1.94	2	ArH (d)
		7.81-8.13 (m)	1.00	1	ArH (e)
	XXXIII	2.24-2.99 (m)	4.28	4	CH_2 (a)
		3.79 (s)	3.05	3	OCH_3 (b)
		6.61-6.92 (m)	2.02	2	ArH (c)
		7.77-8.06 (m)	1.95	2	ArH,C=CH(d)
		14.5-15.1 (b)	0.70	1	C=COH (e)

TABLE I (Continued)

	Plates	δ(p.p.m.)[b]	Integration Found.	Integration Theor.	Assignment
	XXXIV	2.51-3.09 (m)	3.84	4	CH_2 (a)
		3.72 (s)	3.13	3	OCH_3 (b)
		6.51-7.74 (m)	4.02	4	ArH,N=CH(c)
		10.8-11.4 (bs)	1.03	1	NH (d)
	XXXV	2.78 (bs)	3.92	4	CH_2 (a)
		6.78-8.12	4.16	4	ArH,N=CH(b)
		12.4 (bs)	1.92	2	OH,NH (c)

[a] See spectral plates for solvent and concentration.

[b] Chemical shifts are measured downfield from TMS. The multiplicity is as follows: singlet, s; doublet, d; triplet, t; multiplet, m; broad, b.

[c] Impure samples and the dilute solutions employed produced inferior integration data for these compounds.

CHAPTER III

EXPERIMENTAL[a-e]

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

Preparation of Tiglic Acid (44).[11] A mixture of 1788 ml. (1440 g., 20 moles) of 2-butanone and 20 ml. of saturated aqueous KCN was warmed to 35° and 620 g. (23 moles) of HCN was bubbled into the mixture. The HCN was generated by introducing a solution of 1150 g. (23 moles) of NaCN in 3 liters of H_2O (dropwise) beneath the surface of a stirred

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

[b] Proton nuclear magnetic resonance spectra were determined on a Varian A-60 high resolution spectrometer. Tetramethylsilane was used as an internal standard.

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

[d] Microanalysis were performed by Galbraith Laboratories, Knoxville, Tennessee and by Midwest Microlabs, Inc., Indianapolis, Indiana.

[e] Gas chromatography analyses were performed using a Varian-Aerograph 1720-50 employing a thermal conductivity detector. The column used was a 5% SE-30 on 100/120, acid-washed, DMCS-treated Chromosorb G (6 ft. by 0.25 in.).

[f] Mass spectral analyses were performed on an LKB-9000 prototype unit.

solution of 2032 g. (24 moles) of H_2SO_4 in H_2O (50% v/v).

Since the reaction was exothermic, the rate of generation of the HCN was controlled so as to keep the temperature in the reaction vessel near 70°. After completion of the addition, the mixture was cooled to 0° and 20 ml. of conc. H_2SO_4 was added to suppress cyanohydrin decomposition. This crude cyanohydrin was added dropwise to 2540 g. (30 moles) of rapidly stirred 100% H_2SO_4. The reaction was exothermic and the rate of addition was controlled to keep the temperature around 80°.

After completion of the addition, the mixture was heated to 130° for 1 hr., cooled and treated with 1.4 liters (80 moles) of H_2O. This mixture was boiled 2 hr.; 1 kg. of anhydrous Na_2SO_4 was added and the mixture was steam-distilled. The distillate was filtered to provide 630 g. (32%) of crude 44 as an oily solid, m.p. 52-60° (lit.[11] m.p. 62-64°) (the impurity may be the isomeric angelic acid.)

Preparation of Methyl Tiglate (45).[11,22] Tiglic acid (44) (100 g., 1.0 mole) [Aldrich Chemical Co., m.p. 61-64° (lit.[11] m.p. 62-64°)], 180 g. (5.6 moles) of methanol, and 3 ml. of concentrated H_2SO_4 were placed in a 500-ml., r.b. flask fitted with a Soxhlet extractor and condenser. Molecular Sieve (160 g, Linde 3-A) was placed in the Soxhlet apparatus. The mixture was boiled, and the methanol was allowed to reflux through the Soxhlet cup 24 hr. The mixture was then cooled and 5.8 g. (0.055 mole) of anhydrous Na_2CO_3 was added; the resulting mixture was stirred and filtered. Fractional distillation of the mixture at atmospheric pressure through a 10-cm. Vigreux column gave 77 g. (67%) of 45, b.p. 135-137° (lit.,[11] b.p. 138-140°/760 mm.).

Preparation of Methyl 4-Bromo-2-methyl-2-butenoate (43).[27] Methyl tiglate (45) (77 g., 0.66 mole), 250 ml. of CCl_4, 125 g. (0.70 mole) of

N-bromosuccinimide, and 0.6 g. of benzoyl peroxide were placed in a 2-necked, 500 ml., r.b. flask fitted with a N_2 inlet and condenser. The mixture was boiled 7 hr. under N_2 purge, cooled to -18° overnight, and filtered. The precipitated succinimide was washed three times with 25-ml. portions of cold CCl_4.

The CCl_4 was evaporated by use of an aspirator and the residue was fractionally distilled at 5-10 mm. An 8.5 g. forerun (b.p. 30-40°/10 mm.) of unreacted 45 was collected. The yield of crude bromo ester 43 (b.p. 90-94°/10 mm.) was 82.4 g. (68%).

Analysis of crude 43 by GLC and NMR indicated the presence of several isomers, but 43 nevertheless proved satisfactory for use in the next step.

Preparation of 6-Methoxy-α-methyl-1-naphthalenebutyric Acid (12a).[47]

A zinc strip 1/100 in. thick (270 g., 4.1 moles) was cut into approximately 0.25 in. by 0.5 in. pieces and washed consecutively with dilute HCl, distilled H_2O, acetone, and anhydrous ether. The zinc was then dried at 100° in an oven for about 0.5 hr. before use.

The zinc, 700 ml. of anhydrous, reagent-grade benzene and 18.0 g. of anhydrous $HgCl_2$ were placed in a 5-liter flask equipped with a condenser and N_2 inlet. This mixture was stirred under N_2 purge for 0.5 hr. The crude bromo ester 43 (260 g., 1.34 moles) and 260 g. (1.48 moles) of 6-methoxy-1-tetralone (46) [Aldrich Chemical Co., m.p. 76-78° (lit.,[47] m.p. 78.4-79°] in 700 ml. of ether and 300 ml. benzene, along with a crystal of iodine, was added at one time to the reaction flask.

An exothermic reaction ensued accompanied by vigorous boiling of the solvent. At 1.5-hr. intervals, 140 g. (2.15 g. at. of zinc, 87 g. (0.45 mole) of 43, and a crystal of iodine 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 3 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 with 5% aqueous NH_4OH, once with H_2O, and once with saturated aqueous NaCl, and the resulting solution was dried ($MgSO_4$). After being filtered, the solution was evaporated on an aspirator, and the residual oil was distilled in vacuo.

A forerun, consisting primarily of unreacted 46, distilled at 110-150°/0.06 mm. The product amounted to 145 g. (35.6% based on 46) of crude methyl 4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)tiglate (15a) (b.p. 180-200°/0.25 mm.). This material is a viscous yellow oil which partially solidifies upon standing overnight.

The 145 g. of 15a was heated to 250° with 23 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 50 g. of KOH in 500 ml. of 50/50 ethanol/H_2O.

The resulting hydrolyzate was diluted (H_2O), extracted 3 times with ether, and acidified (dil. HCl). The precipitate was filtered, washed well (H_2O), and vacuum dried to yield 120 g. of dark solid. This solid was extracted with three 1.5-liter portions of boiling hexane, leaving behind a black undefined tar. On cooling, the hexane solution deposited 60 g. of yellow-white crystals 12a (m.p. 77-82°) suitable for use in the next step. Evaporation of the mother liquor yielded an additional 30 g. of very crude 12a.

Total yield of 12a was 90 g. (24% based on 46). An analytical

sample of 12a was crystallized from hexane (m.p. 85-86°, s.t., vac.) (lit.[21] m.p. 86-87°).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02.

Found: C, 74.33; H, 7.07.

IR and NMR spectra (Plates I and XVI) support the reported structure for 12a.

Preparation of 3,4-Dihydro-7-methoxy-2-methyl-1(2H)-phenanthrone (13a).[46] Polyphosphoric acid (250 g. of 115% PPA) was heated to 90° in a 600-ml. beaker. Compound 12a (60 g., 0.23 mole) was added and the mixture was stirred for 15 min. An additional 250 g. of PPA was added and the mixture was reheated to 100° and then allowed to cool with stirring to 60°.

The resulting dark-brown syrup was poured into ice water and the yellowish solid which separated was filtered, washed well with distilled H_2O, and air-dried to yield 50.5 g. of crude 13a. This crude phenanthrone was dissolved in 350 ml. of benzene, and the resulting solution was passed through a 50-g., 15-cm. by 1-cm. column of alumina (Merck active aluminum oxide, neutral). The column was washed with additional benzene until no further material was eluted. Evaporation of the benzene in vacuo yielded 47.7 g. (86%) of 13a as a light yellow powder (m.p. 104.5-107.5°) suitable for use in the next step.

A 6-g. sample of the above material was recrystallized 3 times from 50-ml. portions of 1-butanol to yield an almost white, analytical sample (2.6 g.) of 13a (m.p. 107-108.5°, s.t., vac.; lit.[54] m.p. 109-110°).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71.

Found: C, 79.83; H, 6.60.

IR and NMR spectra (Plates II and XVII) support the proposed structure for 13a.

Preparation of 1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-oxo-2-phenanthrenepropionic Acid (23).[18,41] The phenanthrone (13a) (2.80 g., 0.0182 mole) was placed in a 250-ml. r.b. flask, fitted with an addition funnel and a N_2 inlet, and was dissolved in 100 ml. of warm (60°) t-butyl alcohol containing 0.2 g. of 40% aqueous KOH. The ketone was only sparingly soluble in the alcohol and the reaction mixture had to be maintained at around 60° to effect solution, even though the literature[18] recommends that the temperature be kept below 40°.

Acrylonitrile [0.62 g., 0.0182 mole (Mathieson, pract., b.p. 75-78°)] dissolved in 10 ml. of t-butyl alcohol was added dropwise over a 30-min. period. The reaction mixture was stirred overnight at 60° under N_2. The solvent was then removed by aspirator, and the residue was boiled 36 hr. with 50 ml. of aqueous 20% KOH.

The reaction mixture was then diluted (H_2O), extracted 2 times (ether), and neutralized (dilute HCl). The resulting precipitate was washed with H_2O and air dried to yield 3.3 g. of dark brown solid. This material was washed through a 35 g., 10-cm. x 1-cm. silica gel column with hot benzene and recrystallized twice from 150 ml. of benzene to yield 2.0 g. (56.5%) of white, crystalline 23 (m.p. 157.5-159°).

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45.

Found: C, 73.20; H, 6.31.

IR and NMR spectra (Plates III and XVIII) support the proposed structure.

Preparation of 1,10,11,11a-Tetrahydro-7-methoxy-11a-methyl-2H-naphth[1,2-g]indole (36) and 1,10,11,11a-Tetrahydro-11a-methyl-2H-naphth[1,2-g]

indol-7-ol (35).[17,53] The phenanthryl acid 23 (23 g., 0.076 mole, m.p. 155-157.5°) was dissolved in 500 ml. of anhydrous, reagent grade acetone in a 1-liter, 3-necked, r.b. flask equipped with a thermometer, N_2 inlet, and addition funnel with $CaSO_4$ drying tube. The mixture was cooled to -5° in a salt-ice bath, and 12.2 g. (0.122 mole) of triethylamine was added dropwise, the temperature being kept below 0°. Ethyl chloroformate [4.7 g., 0.122 mole (Eastman)] was then added, with the temperature at 0°.

The mixture was stirred in the cold for 30 min. and 10.3 g. (0.16 mole) of NaN_3 in 40 ml. of H_2O was added dropwise, again at 0°. The mixture was stirred at 0° for 1 hr. and poured into ice water.

The crystalline azide 23a that separated amounted to 18.0 g. and decomposed with partial melting at 90-100° (s.t., vac.). The azide was dissolved in 500 ml. of toluene and heated on a steam bath until gas evolution ceased (1-2 hr.). The toluene was removed in vacuo; the residue amounted to 16.0 g. of crude isocyanate 55. Crude 55 was boiled for 24 hr. with 300 ml. of 1:1:1 H_2O:glacial acetic acid:conc. HCl. The mixture was cooled, diluted (H_2O), extracted 3 times (ether), filtered and then neutralized (aqueous 10% $NaHCO_3$).

The resulting yellow solid (9.0 g.) which had a very broad melting range (120-220°), was warmed (50-60°) with 150 ml. of benzene and the mixture filtered. The residue was again extracted with an additional 150 ml. of benzene. The filtrates were combined and reduced to 150 ml. total volume by boiling on a hot plate. Cooling the solution to room temperature caused it to deposit a small additional quantity of material. This solution was then filtered and the benzene-insoluble residues (crude 35) were combined and set aside.

The yellow benzene solution was passed over a 15-cm. by 1-cm. column of neutral alumina and the column was washed with additional benzene until no further material was eluted. The colorless benzene eluate was evaporated to dryness under aspirator vacuum. The white, amorphous residue was crystallized from acetone and then sublimed at 150°/0.04 mm. to yield 5.0 g. (25% based on 23) of 36 (m.p. 180-181°, s.t., vac.). Molecular weight by mass spectral analysis is 265 (calcd. for $C_{18}H_{19}NO$: 265.34).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28.
Found: C, 81.70; H, 7.30; N, 5.29.

IR and NMR spectra (Plates IV and XIV) support the proposed structure for 36.

The insoluble residue from the benzene extraction was dissolved in 800 ml. of warm (50-60°) aqueous 2.5% NaOH. The NaOH solution was cooled and filtered to remove a very small quantity of insoluble residue. The solution was then made acid with dilute HCl, the acidified solution being held 40° to prevent crystallization of what was apparently a sparingly soluble hydrochloride. The warm, acid solution was neutralized with 10% aqueous $NaHCO_3$, and the precipitated solid was sublimed at 250°/0.04 mm. to yield 2.5 g. (13% based on 23) of light yellow crystalline 35 (m.p. 287-290°, with apparent decomposition, s.t., vac.).

Anal. Calcd. for $C_{17}H_{15}NO$: N, 5.62.
Found: N, 5.76.

IR and NMR spectra (Plates V and XX) support the proposed structure for 35. Molecular weight by mass spectral analysis is 251 (calcd. for $C_{17}H_{17}NO$: 251.32).

Preparation of cis-1,2,3a,10,11,11a-Hexahydro-7-methoxy-11a-methyl-3H-naphth[1,2-g]indole (34a) and trans-1,2,3a,10,11,11a-Hexahydro-7-methoxy-11a-methyl-3H-naphth[1,2-g]indole (34b).[43] The solid 36 (10.0 g.) 0.0402 mole) was dissolved in 500 ml. of boiling ethanol in a 1-liter, 1-necked, r.b. flask, and allowed to cool to room temperature. $NaBH_4$ (Alfa Inorganics, 10.0 g., 0.272 mole) was added, the flask was stoppered with a $CaSO_4$ drying tube, and the mixture was stirred for 8 hr. At the end of the stirring period, the ethanol solution was heated to boiling and allowed to cool with continued stirring. The $NaBH_4$ addition, the stirring period, and the heating were repeated twice more.

The ethanol was then largely removed by aspirator, 500 ml. of distilled H_2O was added to the residue, and the mixture was boiled under aspirator vacuum to remove the remainder of the ethanol. This mixture was then filtered; the ppt. was washed (H_2O) and vacuum-dried. The product, as isolated, was an amorphous, white solid (10.1 g., 100%) which melted at 90-100° (s.t., vac.). Conspicuous effervescence of the aqueous filtrate indicated the presence of considerable unreacted $NaBH_4$.

TLC analysis (on 250μ plates of Merck Silica Gel GF_{254}) indicated the presence of approximately 10% unreacted 36 [R_f(imine) = 0.86; R_f(amine) = 0.54; solvent = 5:4:1 cyclohexane:chloroform:diethylamine].[40] The developed plates were observed by short-wave u.v. light, or they were sprayed with 50/50 methanol/H_2SO_4 and heated at 110° for 15 min.

The NMR spectrum (Plate XXI) of the crude product shows the presence of the expected two diastereoisomers 34a and 34b in an approximately 9:1 ratio (by integration of methyl singlets at 1.09 and 0.62, respectively). No TLC system was found which separated 34a and 34b. Partial resolution of the isomers was observed by GLC.

An analytical sample of the diastereomeric amine mixture 34 was obtained by preparative thin layer chromatography of 480 mg. of the crude amine mixture. Portions of the crude amine (60 mg. each) were applied as 10% solutions in benzene to eight 0.25-mm. layers of Merck Silica Gel PF_{254} on glass plates. A double pass of solvent (9:1 cyclohexane:diethylamine) was made through the plates. The amine bands were scraped off the plates and the product was eluted in a Soxhlet extractor using 9:1 methanol:diethylamine. Solvents were removed in vacuo and the residue was recrystallized from hexane to yield 250 mg. of 34, m.p. 103-106° (s.t., vac.).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24

Found: C, 80.96; H, 8.03; N, 5.27.

Preparation of 1,2,3a,10,11,11a-Hexahydro-11a-methyl-3H-naphth[1,2-g]indol-7-ol (37). Crude 34 (6.0 g., 0.024 mole) was boiled under N_2 for 12 hr. with 100 ml. of aqueous 48% HBr. The mixture was diluted to approximately 1 liter with distilled H_2O, and aqueous 20% NaOH was added dropwise until the initially precipitated solid had redissolved. The alkaline solution was filtered and neutralized with aqueous 10% $NaHCO_3$. The precipitate was filtered out, washed (H_2O), and vacuum-dried to yield 4.1 g. (72%) of yellow powder (m.p. 235-265°).

This crude 37 gave an NMR spectrum (Plate XXII) consistent with the proposed structures. Initial attempts at TLC analysis similar to that for 34 proved unsatisfactory.

Preparation of 2-Hydroxymethylene-1-tetralone (50).[2,29] Commercial $NaOCH_3$ [Fisher Scientific Co., "Purified" grade, 18.1 g. (0.336 mole)] and 25.0 g. (0.336 mole) of ethyl formate (Matheson Coleman and Bell) were stirred magnetically under N_2 purge with 170 ml. of anhydrous,

reagent grade, benzene in a 500-ml., 3-necked, r.b. flask.

1-Tetralone (20) [Columbia Organic Chemicals Co., pract., redistilled, b.p. 91°/0.7 mm. (lit.,[13] b.p. 129°/12 mm.), 24.5 g., 0.168 mole] in 200 ml. of anhydrous benzene was added dropwise to the reaction mixture (the temperature being kept at 10-15° by means of an ice bath). After the addition was completed, the reaction mixture was allowed to warm to room temperature overnight. The mixture became a semi-solid yellow mass and stirring ceased.

The reaction mixture was hydrolyzed with 200 ml. of ice-cold distilled H_2O and the resulting organic layer was washed successively with H_2O and aqueous 5% NaOH. The combined aqueous extracts were washed with ether and acidified with dil. HCl. The precipitated oil was extracted from the H_2O by 2 ether washes. The combined ether extracts were dried (saturated NaCl solution followed by anhydrous $MgSO_4$). Evaporation of the ether yielded 27.3 g. (92%) of 50 as a crude red oil, which was used in the following procedure without further purification or characterization.

Preparation of 2-(n-Butylthiomethylene)-1-tetralone (51).[28] Crude 50 (27.3 g., 0.156 mole), 16 g. (0.178 mole) of 1-butanethiol (Aldrich Chemical Co.), 200 ml. of anhydrous benzene, and 50 mg. of p-toluenesulfonic acid were boiled in an N_2 atmosphere under a Dean-Stark water separator for 6 hr. The reaction mixture was cooled, washed with 50 ml. of aqueous 10% $KHCO_3$ and dried (Na_2SO_4). The solvent was removed at reduced pressure. The residual yellow oil weighed 41 g. (106%) and smelled of unreacted 1-butanethiol. The crude 51 was used in the following procedure without further processing.

Preparation of 2-Methyl-1-tetralone (21).[16] Raney nickel alloy

powder [W. R. Grace and Co., No. 2813, 150 g. (50% Ni by weight)] was added over a 30-min. period to a stirred solution of 195 g. of NaOH dissolved in 750 ml. of H_2O maintained at 75° in an open beaker. Stirring and digestion of the reaction mixture was allowed to continue for an additional 30 min. while the reaction mixture temperature was allowed to fall of its own accord.

The catalyst was transferred to a 2-liter graduated cylinder. An 8-mm. glass tube connected to a distilled water tap was inserted to the bottom of the cylinder, and the flow of water was adjusted so that the metal rose to within 2-3 in. of the top of the cylinder. The washing was continued for 10-15 min. The H_2O was then replaced with ethanol in three successive washes.

Crude 51 (21.6 g., 0.088 mole) was dissolved in 50 ml. of ethanol and added to the approx. 75 g. of especially prepared Raney nickel, suspended in 250 ml. of ethanol. After the initial exothermic reaction, the mixture was boiled for 1 hr. The catalyst was removed by filtration (caution: extreme fire hazard) and the ethanol evaporated by aspirator. The residual oil was vacuum distilled through a short-path condenser (b.p. 82-84°/0.6 mm., lit.[1] b.p. 136-138°/16 mm.). The yield of 21 was 17 g. (94%), identical with authentic 2-methyl-1-tetralone by comparative GLC analysis. (Appreciation is extended to Dr. James M. Springer for providing the author with a sample of authentic 2-methyl-1-tetralone.

Preparation of 1,2,3,4-Tetrahydro-2-methyl-1-oxo-2-naphthalenepropionic Acid (53).[18] Ketone 21 (5.0 g., 0.0312 mole) was dissolved in 50 ml. of t-butyl alcohol containing 0.2 g. of aqueous 40% KOH. Acrylonitrile [1.7 g., 0.032 mole (Matheson, pract., b.p. 75-78°)], dissolved in 10 ml. of t-butyl alcohol was added dropwise at such a rate

that the temperature of the water-cooled reaction mixture stayed below 40°.

The reaction mixture was stirred overnight under N_2 purge. The solvent was then removed by aspirator and the residue boiled 36 hr. with 50 ml. of aqueous 20% KOH. The mixture was diluted with H_2O, extracted with ether, neutralized with aqueous dil. HCl, and extracted again with ether. This latter ether extract was dried (sat. NaCl solution, followed by $MgSO_4$) and the ether evaporated to yield 7.15 g. (98%) of crude 53 as a yellow oil. NMR (Plate XXIX) analysis was satisfactory for the structure proposed and crude 53 was used in the following procedure without further purification or characterization.

Preparation of 3,3a,4,5-Tetrahydro-3a-methyl-2H-benz[g]indole (40).[15,53] Crude 53 (7.15 g., 0.031 mole) dissolved in 25 ml. of anhydrous, reagent grade acetone was cooled to 0° in a salt-ice bath. Triethylamine (5 g., 0.05 mole) was added dropwise, the temperature of the reaction mixture being kept at 0°. Ethyl chloroformate [6 g., 0.05 mole (Eastman)] was added dropwise, again at 0°. The mixture was magnetically stirred in the cold for 30 min. and then 4.3 g. (0.065 mole) of NaN_3 in 15 ml. H_2O was added dropwise (still near 0°).

The mixture was stirred for 1 hr. in the cold and then poured into ice water and extracted with toluene. The toluene extract was dried ($MgSO_4$) and heated on a steam bath until N_2 evolution ceased. The toluene was removed *in vacuo* and the resulting yellow oil was boiled overnight with 150 ml. of a 1:1:1 mixture of conc. HCl, H_2O, and glacial acetic acid. Solvents were removed *in vacuo*, the residue was taken up in 50 ml. of H_2O, and the solution was extracted with ether.

The aqueous phase was made strongly alkaline (aqueous NaOH) and the

resulting oily precipitate was extracted into ether and dried ($MgSO_4$). The yellow residue remaining after removal of the solvent amounted to 3.1 g. of crude 40. This material was distilled through a short-path condenser yielding 2.6 g. (45%) of water-white liquid (b.p. 84-87°/0.04 mm.)

Anal. Calcd. for $C_{13}H_{15}N$: N, 7.56.
Found: N, 7.73.

IR and NMR spectra (Plates XI and XXX) support the proposed structure for 40.

Preparation of cis-2,3,3a,4,5,10-Hexahydro-3a-methyl-1H-benz[g]indole (41a) and trans-2,3,3a,4,5,10-Hexahydro-3a-methyl-1H-benz[g]indole (41b). Imine 40 (3.0 g, 0.016 mole) was dissolved in 100 ml. of methanol in a 250-ml., 1-necked flask equipped with a $CaSO_4$ drying tube, and 4.0 g. (0.11 mole) of $NaBH_4$ (Alfa Inorganics) was added. The mixture was stirred at room temperature for 8 hr. and then the $NaBH_4$ addition process and 8-hr. stirring period were repeated. An aliquot of the reaction mixture was diluted with H_2O, extracted with ether and analyzed by GLC. Two peaks were observed, one with a retention time identical, by mixed injection, with 40, the starting material. Repeated treatment of the reaction mixture with $NaBH_4$ in both methanol and ethanol ($NaBH_4$ reacts significantly with methanol but only very slowly with ethanol) resulted in reduction of the so-called "starting material" peak but did not eliminate it. The product was isolated by aspirator evaporation of the solvent, dilution of the residue with H_2O, and ether extraction. The ether layer was dried ($MgSO_4$) and evaporated. The residue was vacuum distilled (b.p. 80-85°/0.06 mm.) to yield 1.5 g. (50%) of a mixture of the diastereomeric amines (41a and 41b). NMR and IR analysis of

the product (Plates XII and XXXI) indicate the absence of any starting material (Imine 40 apparently has a GLC retention time identical with amine isomer 41b). The diastereoisomers are present (by NMR integration of the methyl singlets at δ 0.90 and δ 0.45 respectively) in an 81:19 ratio, the cis configuration being tentatively assigned to the major isomer.

Anal. Calcd. for $C_{13}H_{17}N$: N, 7.48.

Found: N, 7.65.

Preparation of 2-Hydroxymethylene-6-methoxy-1-tetralone (57).[2,30,49] Sodium methoxide [Fisher Scientific Co., "Purified" grade, 37.2 g. (0.672 mole)] was suspended in 350 ml. of anhydrous, reagent grade benzene in a dry, 2-liter, 3-necked, r.b. flask, fitted with a thermometer, N_2 inlet, and $CaSO_4$ drying tube. Ethyl formate [Matheson, Coleman, and Bell, 51.0 g. (0.672 mole)] was added and the mixture was cooled to 10°.

6-Methoxy-1-tetralone (46) [Aldrich Chemical Co., m.p. 76-78° (lit.,[47] m.p. 78.4-79°), 60.0 g., 0.342 mole] in 400 ml. anhydrous benzene was poured into the magnetically stirred mixture, which turned blue and warmed to approx. 20°. After 30 min., a yellow solid formed and stirring was stopped. The solid was broken up with a stirring rod, the flask openings were stoppered, and the mixture was shaken vigorously and allowed to stand at room temperature for 6 hr.

The mixture was then hydrolyzed with 800 ml. of ice water and the resulting organic layer was washed successively with distilled H_2O and with aqueous 5% NaOH. The combined aqueous extracts were washed (ether) and acidified (dilute aqueous HCl). The product was a brown, crystalline, sandy solid which, when air dried, amounted to 43.3 g. (61.5%) of

crude 47 (m.p. 64-68°). Crystallization from hexane with the use of decolorizing carbon yielded 34 g. of yellow crystals (m.p. 67.5-71°).

Preparation of 4,5-Dihydro-7-methoxy-1H-benz[g]indazole (58).[2,49] Crude 57 (40.0 g., 0.196 mole) was dissolved in 400 ml. of methanol and 30 ml. of 95% hydrazine was added. An exothermic reaction ensued with further darkening of the already dark-brown methanol solution. After 3 hr. of stirring, the reaction mixture had returned to room temperature and lightened somewhat in color.

Distilled H_2O (500 ml) was added to the reaction mixture and the resulting suspension of yellow solid in brown mother liquor was cooled in an ice bath, filtered, and the solid washed with 100 ml. of 5:4 H_2O: methanol. The air-dried yellow powder amounted to 25.0 g. (64%). After 3 recrystallizations from 400-ml. portions of benzene, the yield was 20.5 g. of yellow, crystalline powder, m.p. 162-163.5° (s.t., vac.) (lit.[49] m.p. 164-166°). IR and NMR spectra (Plates XIV and XXXIV) are consistent with the reported structure for 58.

Preparation of 4,5-Dihydro-1H-benz[g]indazol-7-ol (42). Compound 58 (10.0 g., 0.0500 mole, m.p. 162-163.5°) was boiled with 250 ml. of aqueous 48% HBr for 12 hr. under N_2 purge. The mixture was cooled and filtered and the resulting pink solid was dissolved in 200 ml. of aqueous 6% NaOH. The alkaline solution was filtered and neutralized with 10% $NaHCO_3$ solution to yield 6.8 g. (73%) of off-white powder (42), m.p. 198-203°, s.t., vac.).

An analytical sample of 42 was recrystallized from acetonitrile and sublimed (180°/0.03 mm.) to yield a white, hard, microcrystalline solid (m.p. 206.5-208°, s.t., vac.)

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05.

Found: C, 70.85; H, 5.37; N, 14.81.

IR and NMR spectra (Plates XV and XXXV) support the proposed structure for 42.

Preparation of 6-Methoxy-1-naphthalenebutyric Acid (12).[47] Zinc pieces (approx. 0.25 in. by 0.5 in. by 1/100 in., 23 g., 0.35 mole) were washed consecutively with dilute HCl, distilled H_2O, acetone, and anhydrous ether. The zinc was dried at 100° for about 0.5 hr. before use.

The zinc, 55 ml. of anhydrous benzene, and 1.5 g. of anhydrous $HgCl_2$ were stirred for 0.5 hr. under N_2 purge in a 250 ml., r.b. flask fitted with a reflux condenser. Ethyl 4-bromo-2-butenoate (Aldrich Chemical Co., technical grade, 21.5 g., 0.112 mole) and 21.0 g. (0.119 mole) of 6-methoxy-1-tetralone (46) (Aldrich) dissolved in 55 ml. of anhydrous ether and 15 ml. of dry benzene were added to the flask, along with a crystal of iodine. After the initial exothermic reaction subsided, the mixture was heated to boiling, and, at 1.5-hr. intervals, 11 g. (0.17 g. at.) of zinc, 6.75 g. (0.0344 mole) of the butenoate, and a crystal of iodine were added. This procedure was repeated 3 times.

After the final addition, the reaction mixture was boiled for 3 hr. The mixture was then cooled, poured into ice water, acidified with acetic acid and extracted with ether. The organic phase was extracted 3 times with aqueous 5% NH_4OH, once with H_2O, and once with saturated NaCl solution, and dried ($MgSO_4$). Solvents were removed under aspirator vacuum and the residual oil distilled in vacuo.

A forerun consisting primarily of unreacted 46 distilled at 110-150°/0.06 mm. The product, a viscous yellow oil, amounted to 12.2 g. (37.8% based on 46) of crude ethyl 4-(6-methoxy-1,2,3,4-tetrahydro-1-

naphthylidene)crotonate (15) (b.p. 170-185°/0.075 mm., lit.[47] b.p. 182-188°/1.3 mm.).

Three grams of 10% Pd/C was added to the flask containing the 12.2 g. (0.045 mole) of 15, and the mixture was heated to 280° under CO_2 purge for 4 hr. The mixture was then cooled, taken up with ether, and filtered. Solvents were removed by aspirator, and the residue was hydrolyzed by boiling 3-4 hr. under N_2 with 5 g. of KOH in 100 ml. of 50:50 ethanol:H_2O.

The hydrolyzate was diluted with H_2O, extracted 3 times with ether, and acidified with HCl. The resulting precipitate was filtered out, washed (H_2O), and air-dried, to yield 10.5 g. (36% based on 46 of crude 12. Recrystallized from 200 ml. of methanol, the crude acid yielded 7.5 g. (26% based on 46 of light brown crystals, m.p. 151-152.5° (lit.[47] m.p. 151°). IR and NMR spectra (Plates VI and XXIII) are consistent with the reported structure for 12.

Preparation of 3,4-Dihydro-7-methoxy-1(2H)-phenanthrone (13).[46,47]

Acid 12 (7.5 g., 0.031 mole) was dissolved in aqueous Na_2CO_3 and precipitated with HCl to yield a finely divided powder. Polyphosphoric acid (50 g. of 115% PPA) was heated to 110° in a 400-ml. beaker. Heating of the PPA was halted, the powdered 12 was added and the mixture was stirred for 15 min. An additional 50 g. of PPA was then added and the mixture was reheated to 110° and then allowed to cool to 60° with occasional stirring.

The resulting brown syrup was poured into ice water and the solid which separated was filtered, washed with H_2O, air-dried, and dissolved in 50 ml. of benzene. The benzene solution was poured onto a 15-g., 5-cm. by 1-cm. column of alumina (Merck active aluminum oxide, neutral),

and the column was washed with additional benzene until no further material was eluted. Evaporation of the benzene in vacuo yielded 5.0 g. (71%) of 13 (m.p. 97-99°, lit.[47] m.p. 98-100°). IR and NMR spectra, (Plates VII and XXIV) are consistent with the reported structure for 13.

Preparation of 10,11-Dihydro-7-methoxy-3H-naphth[1,2-g]indazole (38).[2,30,49] Phenanthrone 13 (3.5 g., 0.0154 mole) was added to a stirred mixture of 1.7 g. (0.0315 mole) of $NaOCH_3$ (Fisher, "Purified"), 2.3 g. (0.0312 mole) of ethyl formate (Matheson), and 50 ml. of benzene under N_2 in a 100 ml. r.b. flask.

The mixture was stirred for 6 hr. and then poured into one liter of ice water; the resulting mixture was extracted with 300 ml. of ether. The organic phase was washed with 500 ml of aqueous 5% NaOH; the aqueous extracts were combined, and the combined extracts were acidified with excess conc. HCl. The precipitated solid material was filtered out and vacuum-dried to yield 2.8 g. (72%) of 3,4-dihydro-2-(hydroxymethylene)-7-methoxy-1(2H)-phenanthrone (14) as a yellow powder.

Compound 14 (2.8 g. 0.011 mole) was dissolved in 300 ml. of methanol, and 3 ml. of 95% hydrazine was added. The solution was stirred 4 hr. and then reduced to 50 ml. in volume by boiling on a hot plate. Upon cooling, 1.7 g. of 38 (43% based on 13) separated as feathery yellow needles (softened at 190°, m.p. 212-213° s.t., vac.). This material was recrystallized from 200 ml. of benzene, yielding 1.1 g. (29% based on 13) of 38 as a white powder (m.p. 212.5-214°, s.t., vac.).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64, N, 11.19.

Found: C, 76.88; H, 5.74; N, 11.02.

IR and NMR spectra (Plates VIII and XXV) support the proposed structure for 38.

Preparation of 10,11-Dihydro-3H-naphth[1,2-g]indazol-7-ol (39). The methyl ether 38 (0.50 g., 0.0020 mole) was boiled with 25 ml. of aqueous 48% HBr for 12 hr. under N_2 purge. The mixture was cooled, made strongly alkaline with aqueous 10% NaOH, and filtered. The alkaline filtrate was neutralized with aqueous 10% $NaHCO_3$ solution, and the resulting gray ppt. was filtered out and sublimed at 240°/0.03 mm. to yield 0.4 g. (85%) of 39 as a light orange crystalline solid (m.p. 258-261°, s.t., vac.). IR and NMR spectra (Plates IX and XXVI) support the proposed structure for 39. Indazolol 39 (0.2 g.) was recrystallized from 1:1:1 pyridine:benzene:cyclohexane and then sublimed again as above to yield 0.15 g. of a white, crystalline solid, m.p. unchanged. This material was submitted for analysis.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86.
Found: C, 76.52; H, 5.26; N, 12.00.

Attempted Methylation of 1-Tetralone (20).[23] In an unsuccessful attempt to prepare 2-methyl-1-tetralone (21), 20 (15 g., 0.1 mole) treated with sodium t-butoxide in t-butyl alcohol (4.5 g. of Na dissolved in 400 ml. of t-butyl alcohol) and condensed with 20 ml. of CH_3I exactly according to the method of Hattersley, Lockhart, and Wright.[23]

GLC analysis of the product indicated the presence of unreacted 20, the desired product 21, and an unidentified component, believed to be 2,2-dimethyl-1-tetralone. These components were found to be present in 21:60:19 ratio.

Preparation of 1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-oxo-2-phenanthrenepropionic Acid (23) (Alternate Method).[9] Ketone 13a (44.2 g., 0.184 mole) was dissolved in 250 ml. of 1,4-dioxane in a 500-ml. r.b. flask, fitted with thermometer, addition funnel, $CaSO_4$ drying tube, and

an N_2 inlet. Triton B (methanolic, 40%) (Aldrich, 10 g.) was added and the solution darkened. Acrylonitrile (Matheson, "practical," b.p. 75-78°, 10.0 g., 0.293 mole) was added dropwise at such a rate that the reaction temperature stayed below 40°.

After completion of the addition, the reaction mixture was stirred overnight and then poured into dilute aqueous HCl. The product separated as a yellow, semi-solid mass which did not lend itself to filtration. Ether (2 liters) was added and the mixture was shaken in a separatory funnel. Approximately 1 g. of brown, ether-insoluble solid separated and was filtered from the liquids. The ether layer was washed (H_2O) and dried (saturated NaCl solution, followed by $MgSO_4$); solvents were then removed in vacuo.

The residue (55.4 g. of brown, viscous oil) was boiled 36 hr. with 1150 ml. of aqueous 20% KOH. A soapy, yellow, foaming suspension resulted. Water (3 liters) was added and the resulting aqueous phase was extracted with two, 0.5-liter portions of ether which were set aside. The aqueous phase was acidified with HCl; a very viscous, brown oil separated and slowly crystallized. The resulting solid was filtered out and air-dried to yield 35.2 g. (65.6%) of quite crude 23 (m.p. 150-155°).

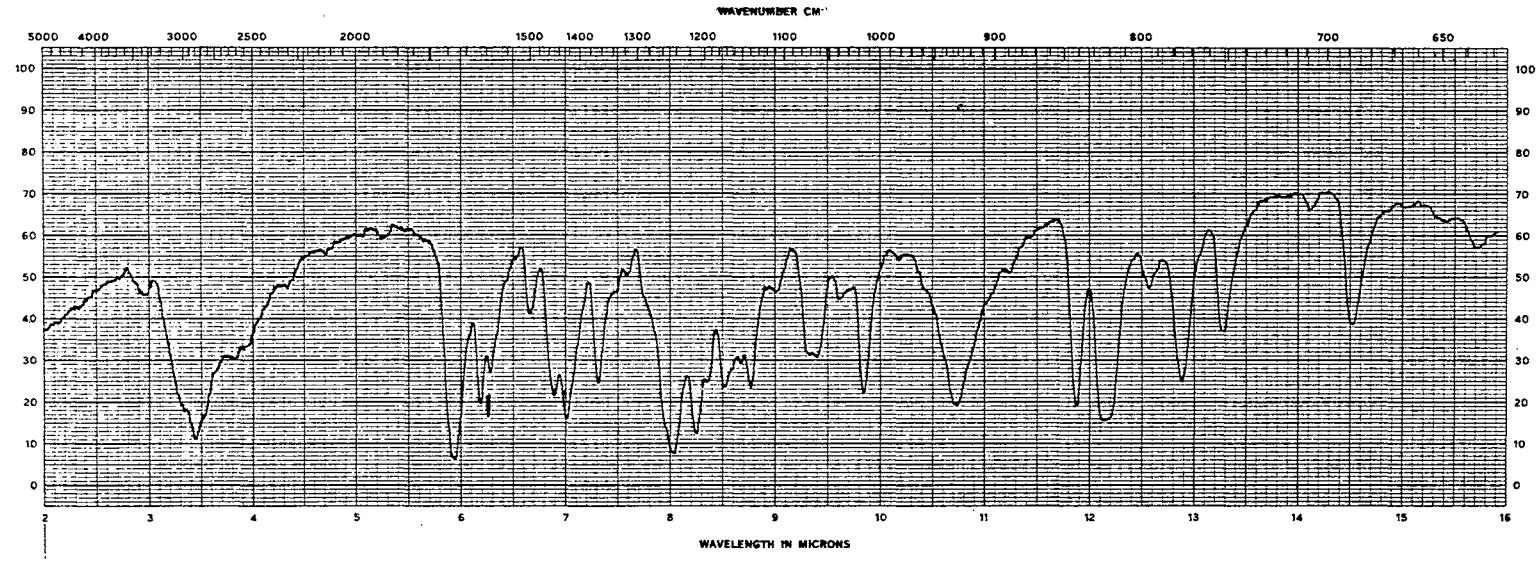
This crude 23 was dissolved in hot benzene and poured through a 15-cm. by 1-cm. column of neutral alumina (50 g.). The column was washed with additional hot benzene until nothing more was eluted (a dark layer at the top of the column remained). The eluate was concentrated to 500 ml. and, upon cooling, deposited 26.3 g. (49%) of light yellow 23 (m.p. 155-157.5°).

The ether layers previously set aside were dried ($MgSO_4$) and

evaporated to yield 14.3 g. (32.4%) of recovered ketone 13a (m.p. 104-107°C).

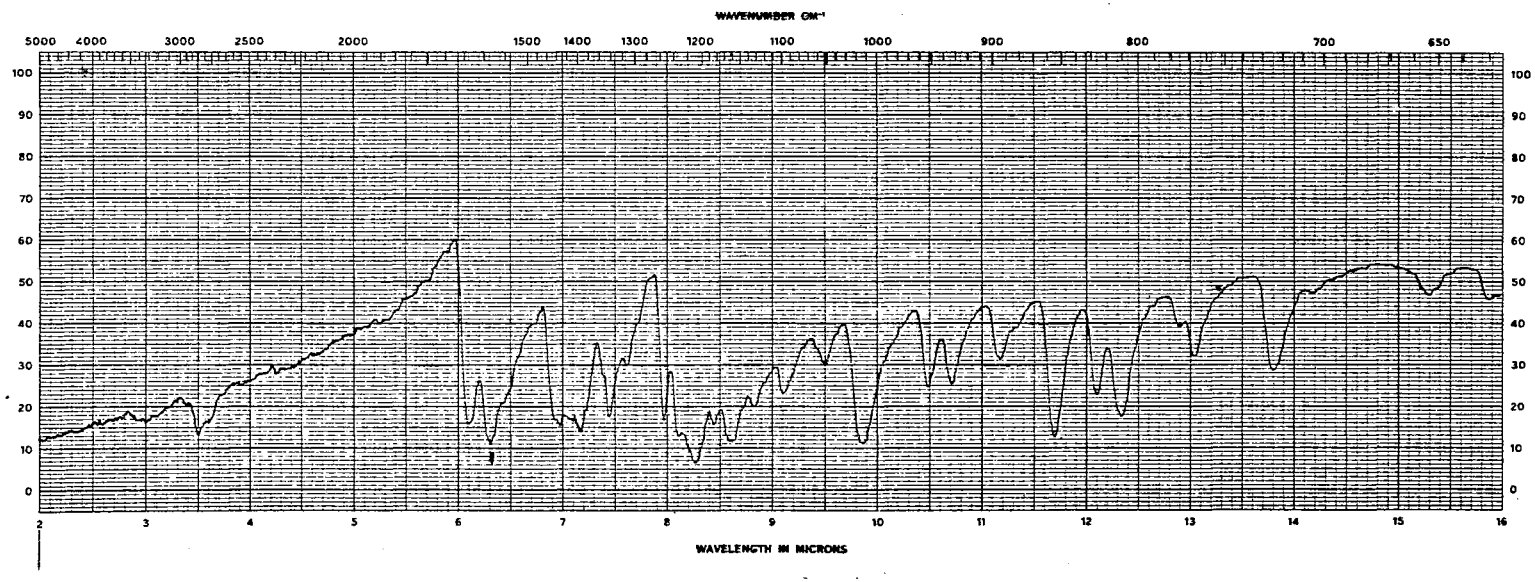
Attempted Preparation of 3,4-Dihydro-2-methyl-1(2H)-phenanthrone (54a). 3,4-Dihydro-1(2H)-phenanthrone (10 g., 0.05 mole), prepared by the method of Haworth,[24] was condensed with excess ethyl formate in the presence of sodium methoxide, to yield the hydroxymethylenephenanthrone 54b (8.2 g., 0.036 mole, 72%). Compound 54b, in turn, was converted to 10.0 g. (0.0335 mole, 93%) of the n-butylthiomethylene derivative 54 by reaction with 3.6 g. (0.040 mole) of n-butanethiol in the presence of PTSA.[28] This latter material was dissolved in 100 ml. of ethanol and added to 50 g. of especially prepared Raney nickel (previously described on page 60) suspended in 150 ml. of ethanol.[16] The mixture was boiled 1 hr., after which the work up afforded 6.2 g. (89%) of an oily semi-solid. GLC analysis of this product demonstrated the presence of several major components. Trituration of the oily product with hexane afforded 1.8 g. of an amorphous brown solid; NMR analysis indicated that this material was not the desired methylphenanthrone 54a.

Plate I



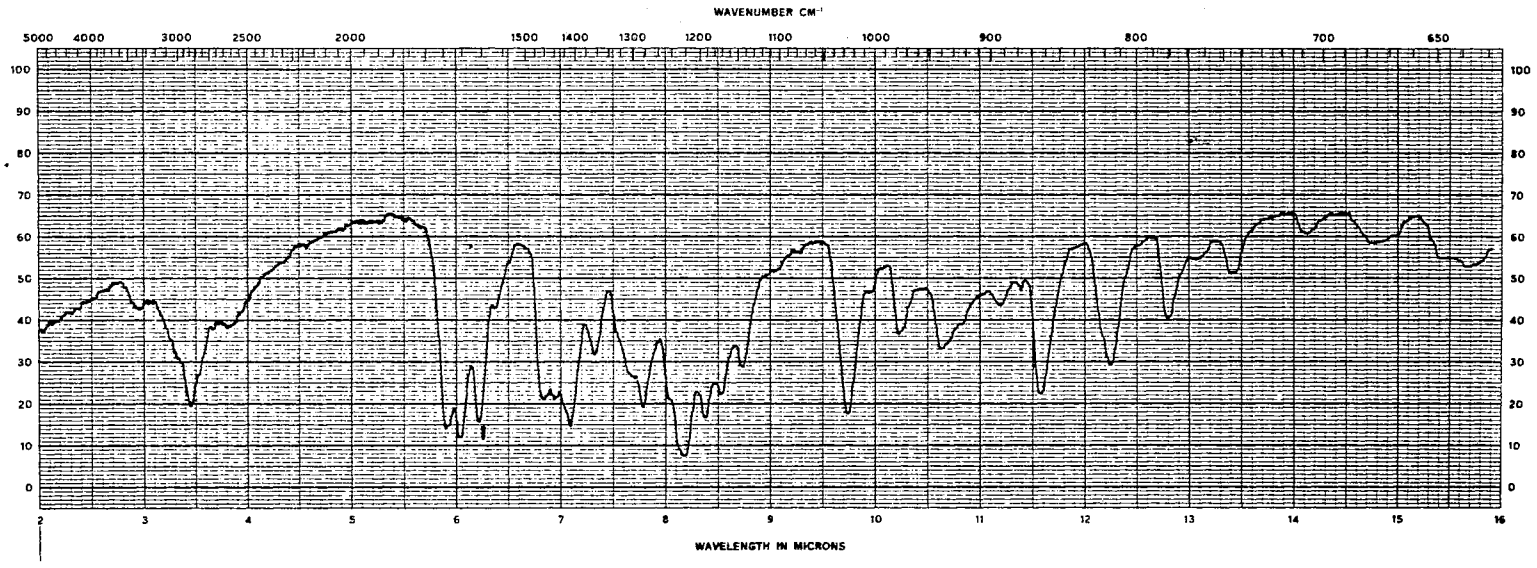
6-Methoxy-α-methyl-1-naphthalenebutyric Acid (12a), KBr Pellet

Plate II



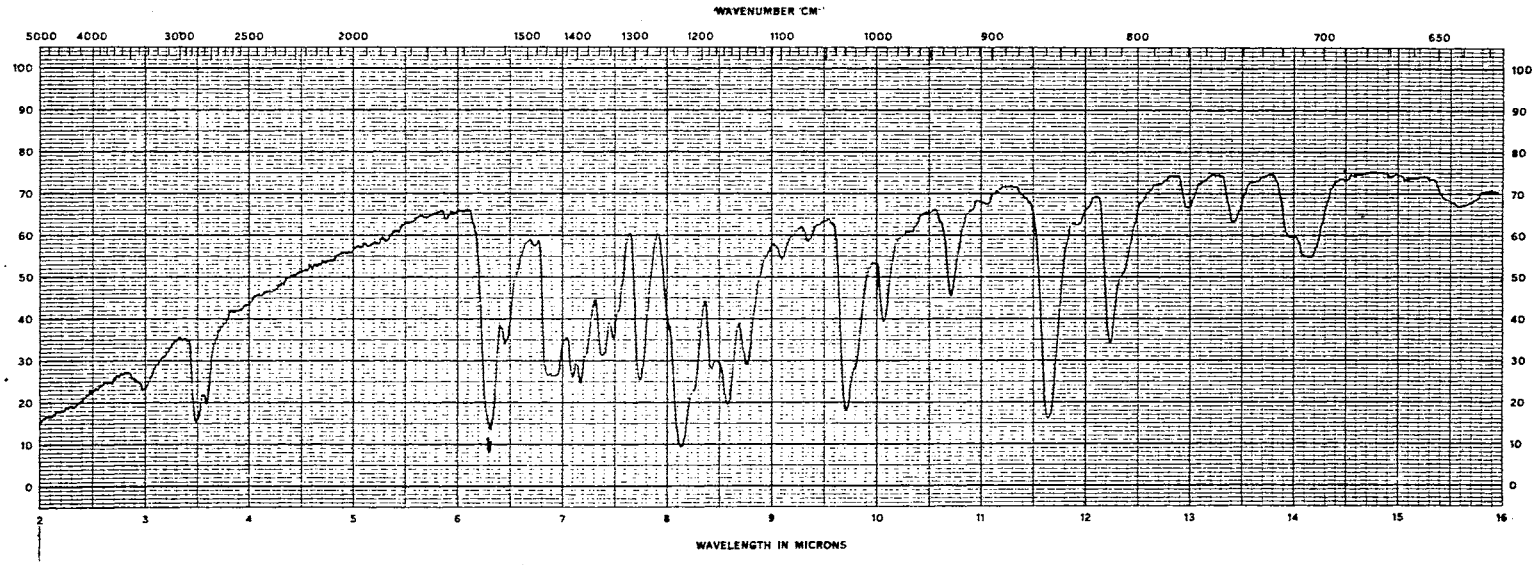
3,4-Dihydro-7-methoxy-2-methyl-1(2H)-phenanthrone (13a), KBr Pellet

Plate III



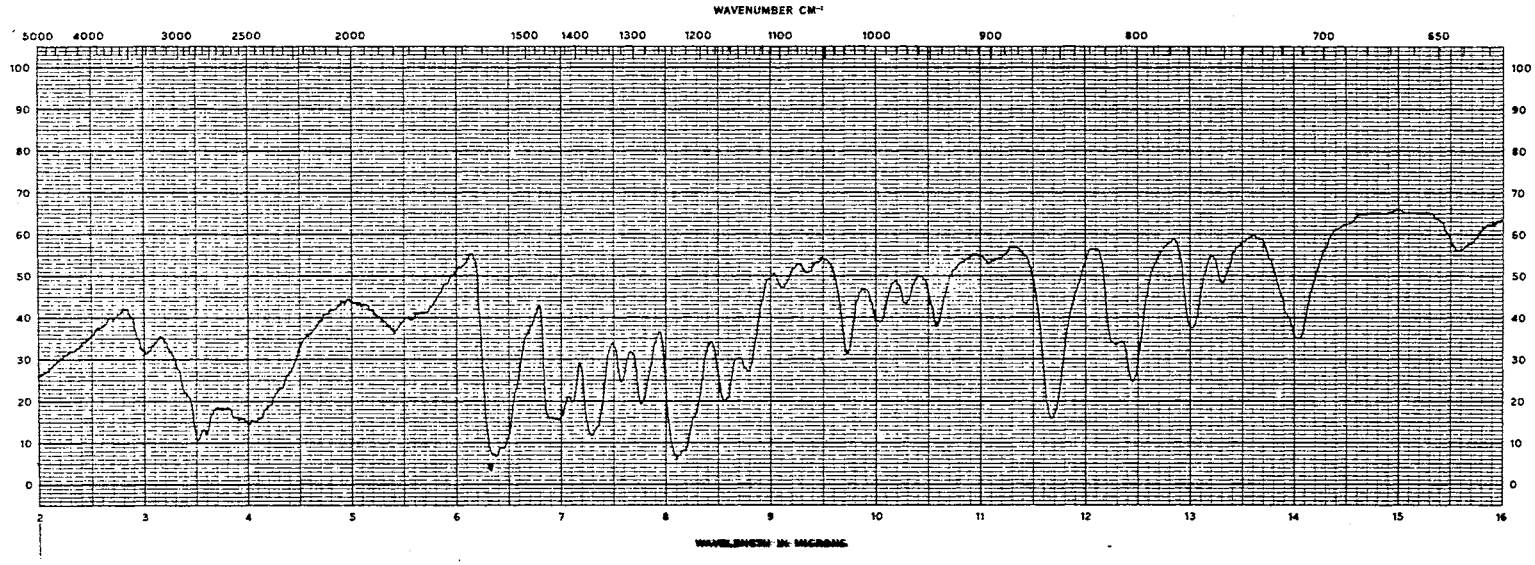
1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-oxo-2-phenanthrenepropionic Acid (23), KBr Pellet

Plate IV



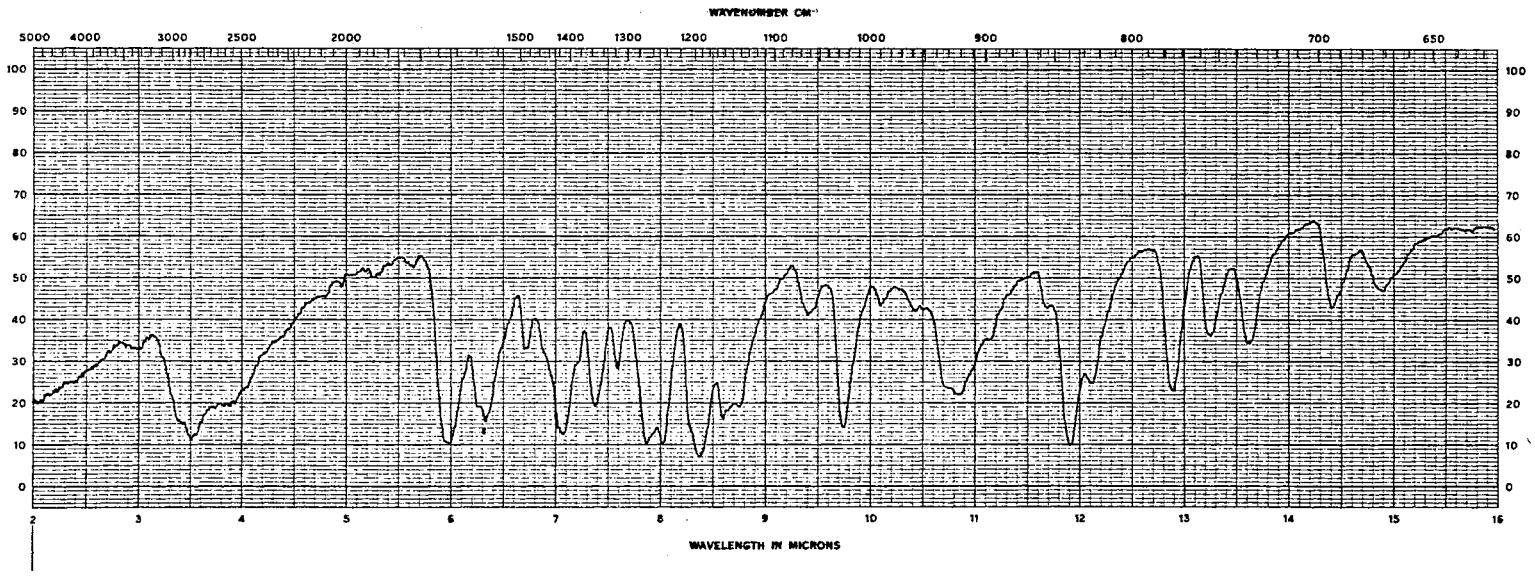
1,10,11,11a-Tetrahydro-7-methoxy-11a-methyl-naphth[1,2-g]indole (34), KBr Pellet

Plate V



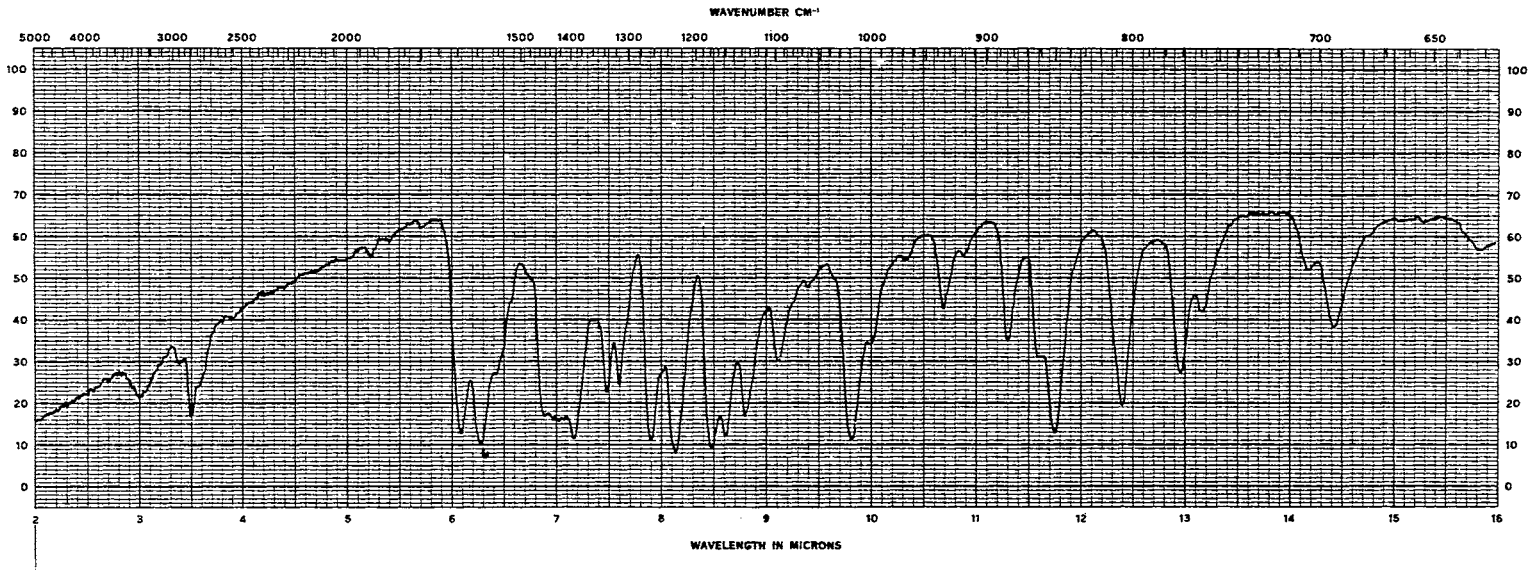
1,10,11,11a-Tetrahydro-11a-methylnaphth[1,2-g]indol-7-ol (35), KBr Pellet

Plate VI



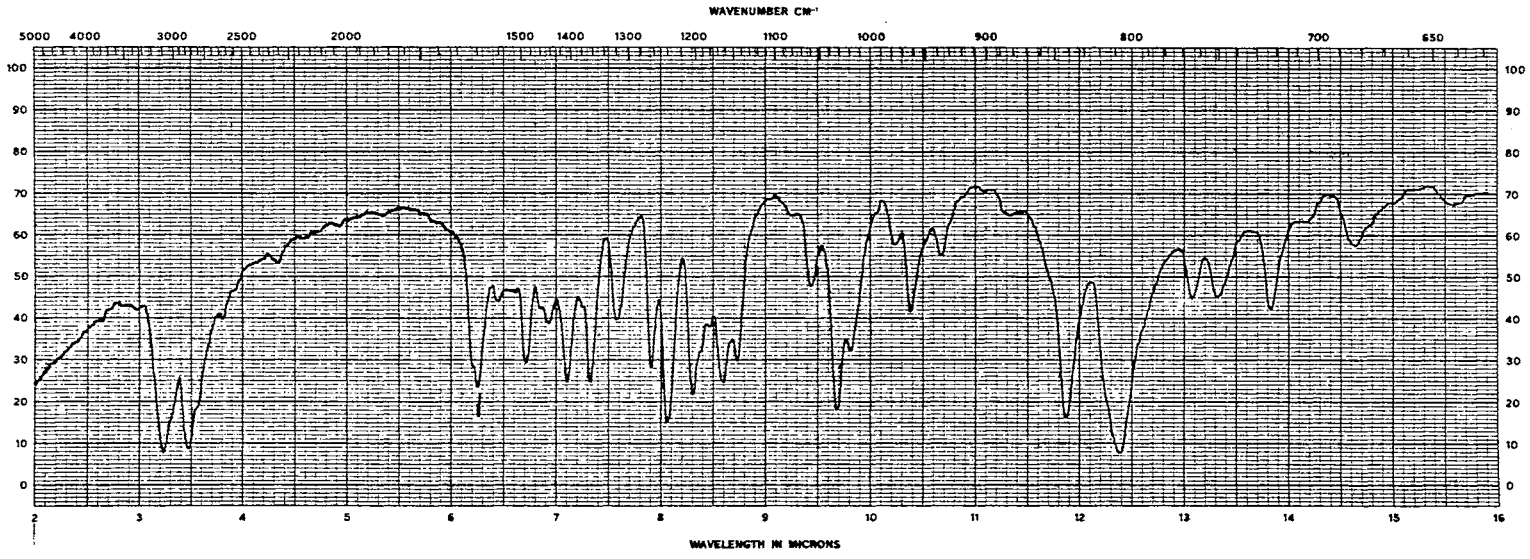
6-Methoxy-1-naphthalenebutyric Acid (12), KBr Pellet

Plate VII



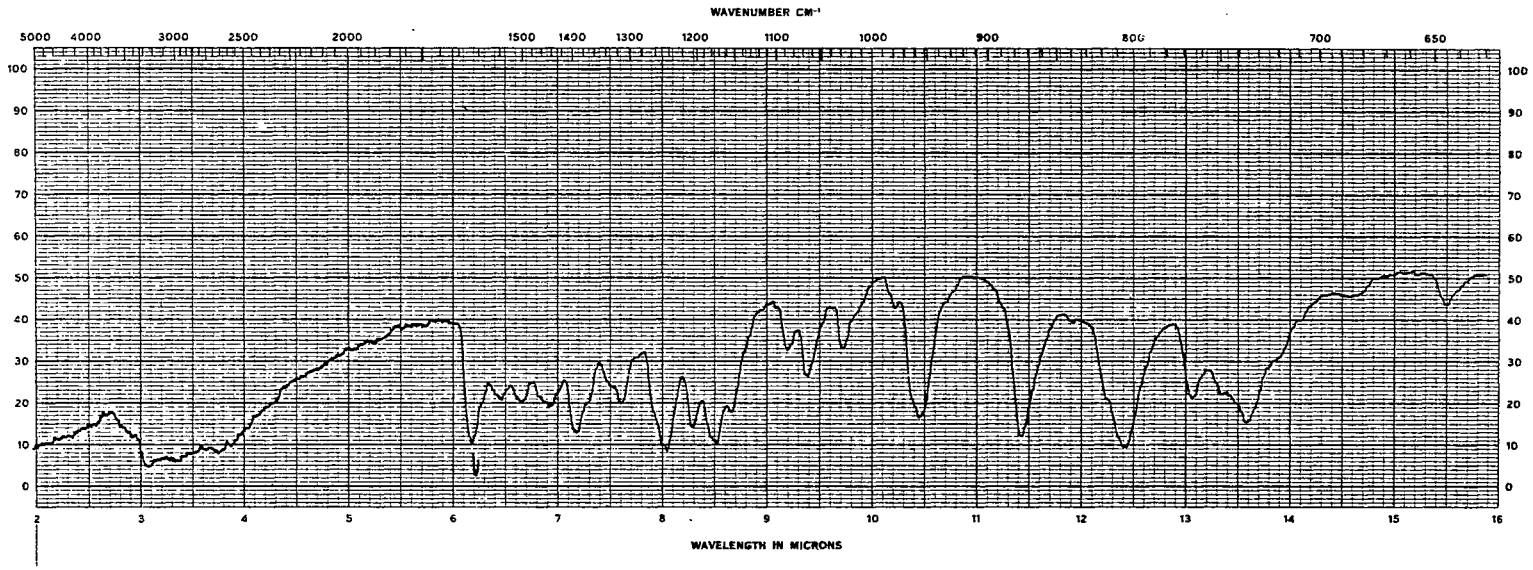
3,4-Dihydro-7-methoxy-1(2H)-phenanthrone (13), KBr Pellet

Plate VIII



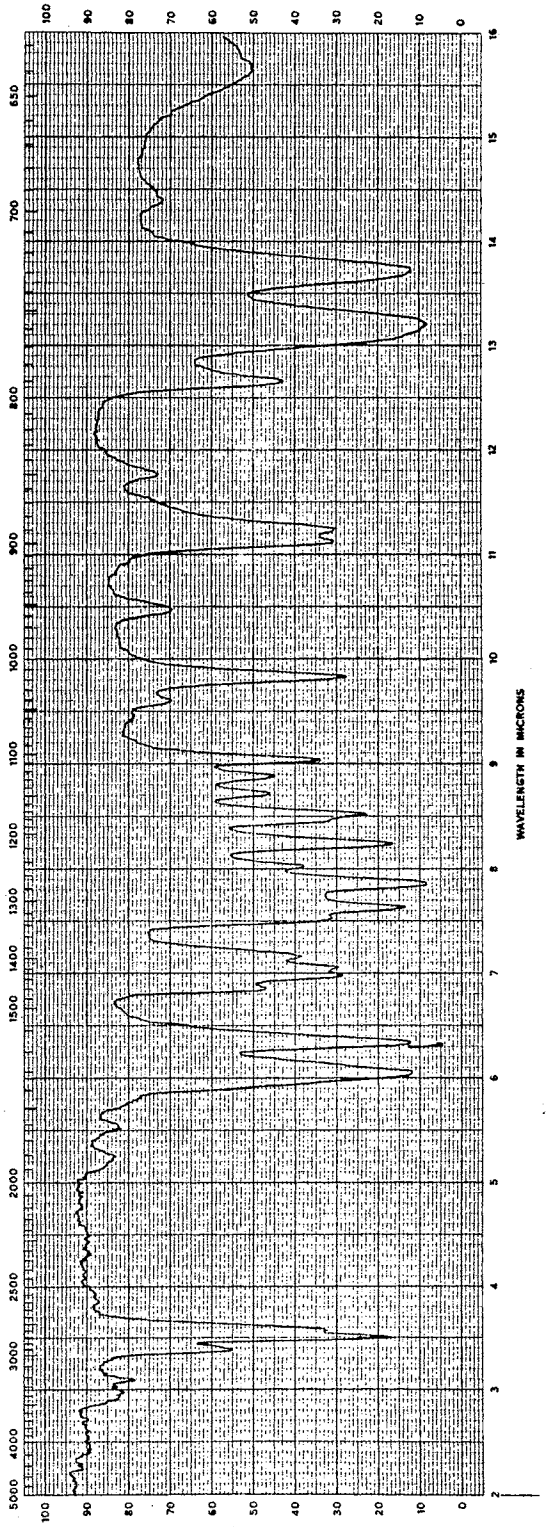
10,11-Dihydro-7-methoxy-3H-naphth[1,2-g]indazole (38), KBr Pellet

Plate IX



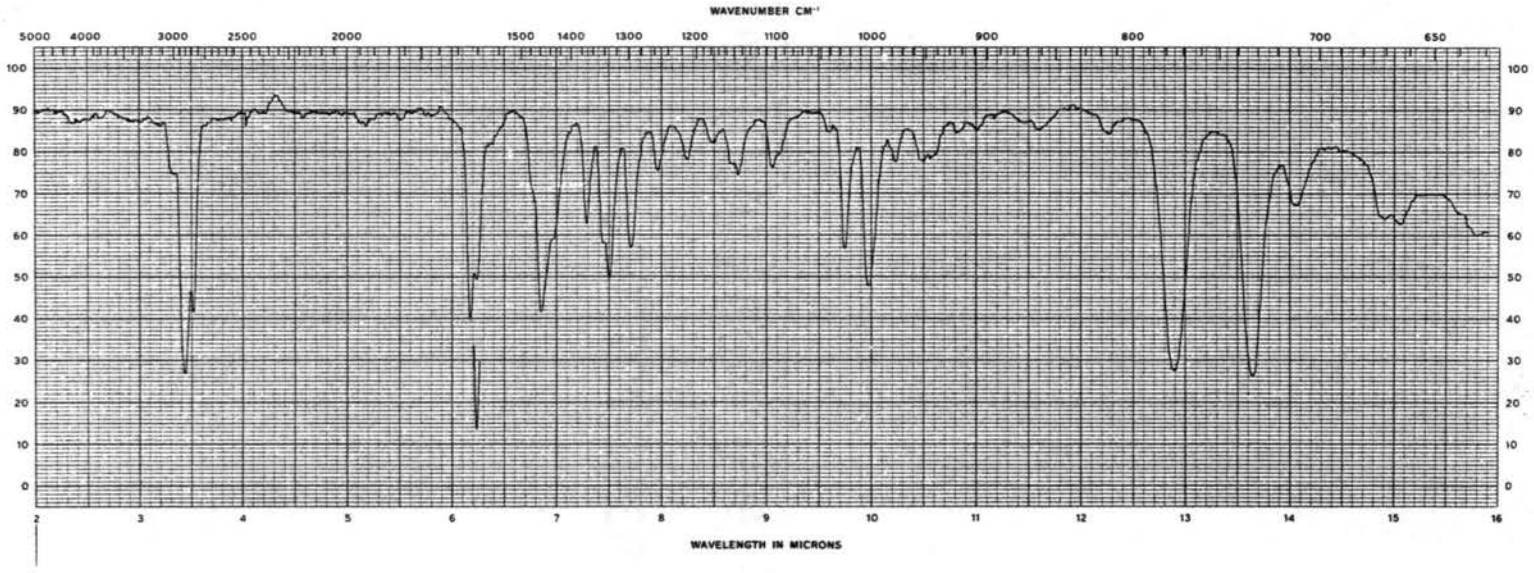
10,11-Dihydro-3H-naphth[1,2-g]indazol-7-ol (39), KBr Pellet

Plate X



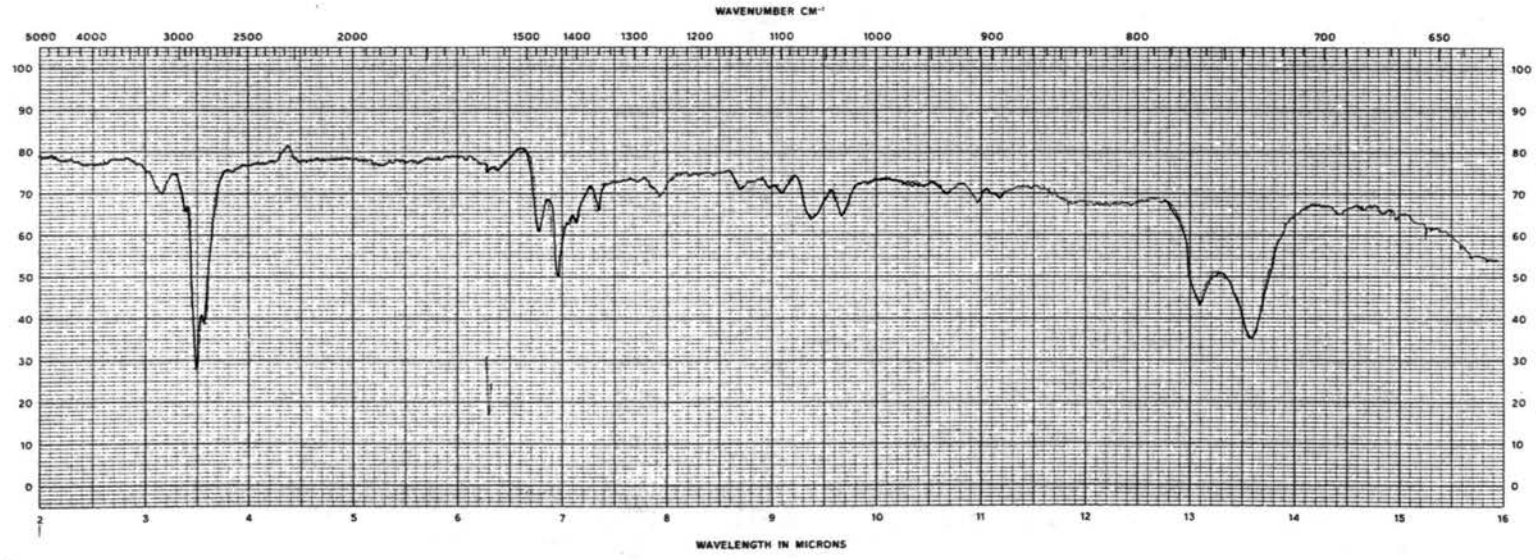
1-Tetralone (20), Film on NaCl Plates

Plate XI



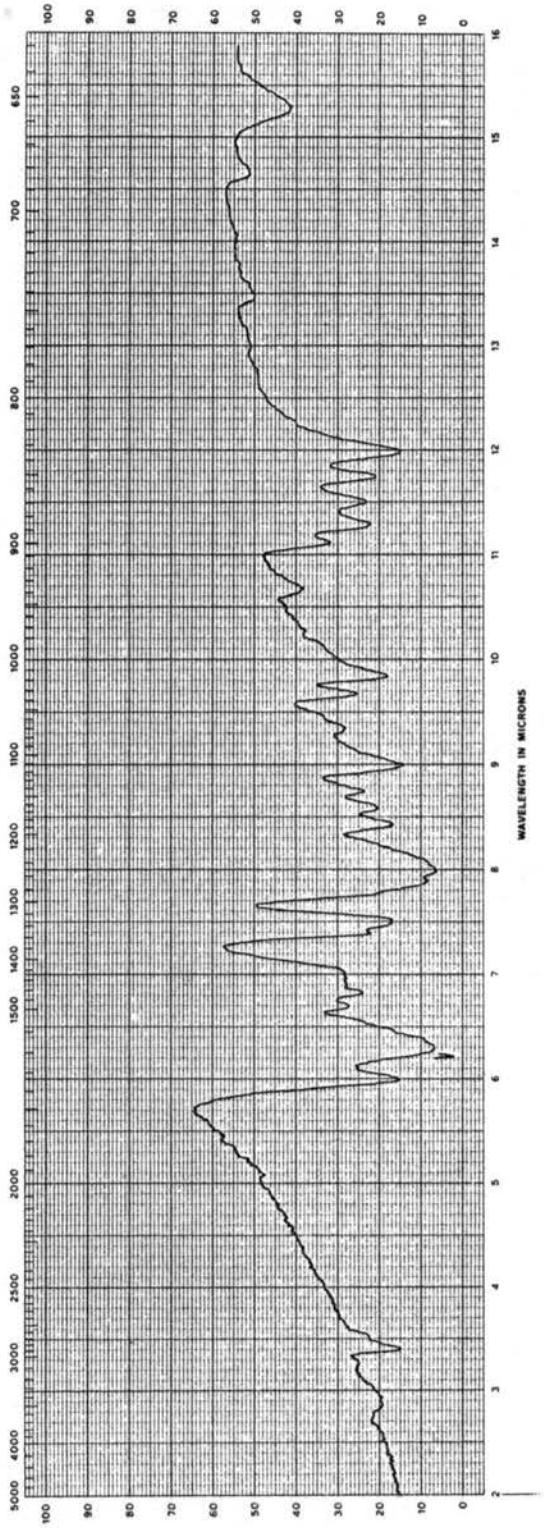
3,3a,4,5-Tetrahydro-3a-methyl-2H-benz[g]indole (40), Film on NaCl Plates

Plate XII



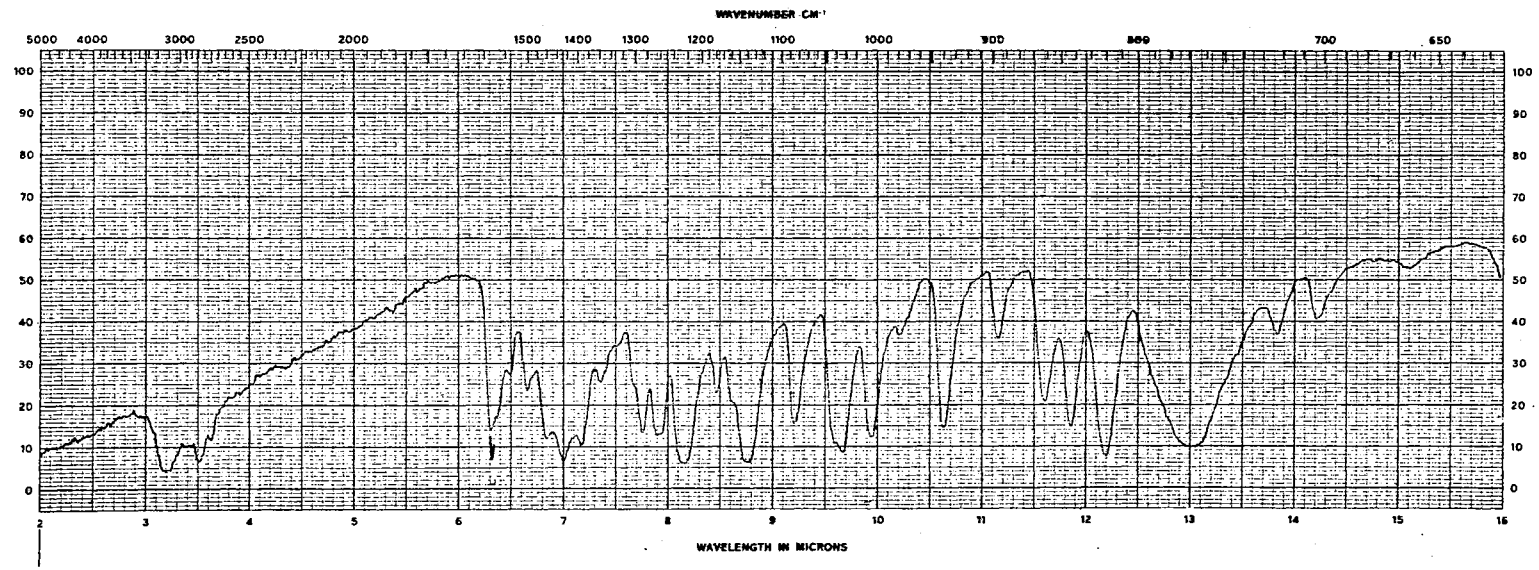
2,3,3a,4,5,10-Hexahydro-3a-methyl-1H-benz[g]indole (41), Film on NaCl Plates

Plate XIII



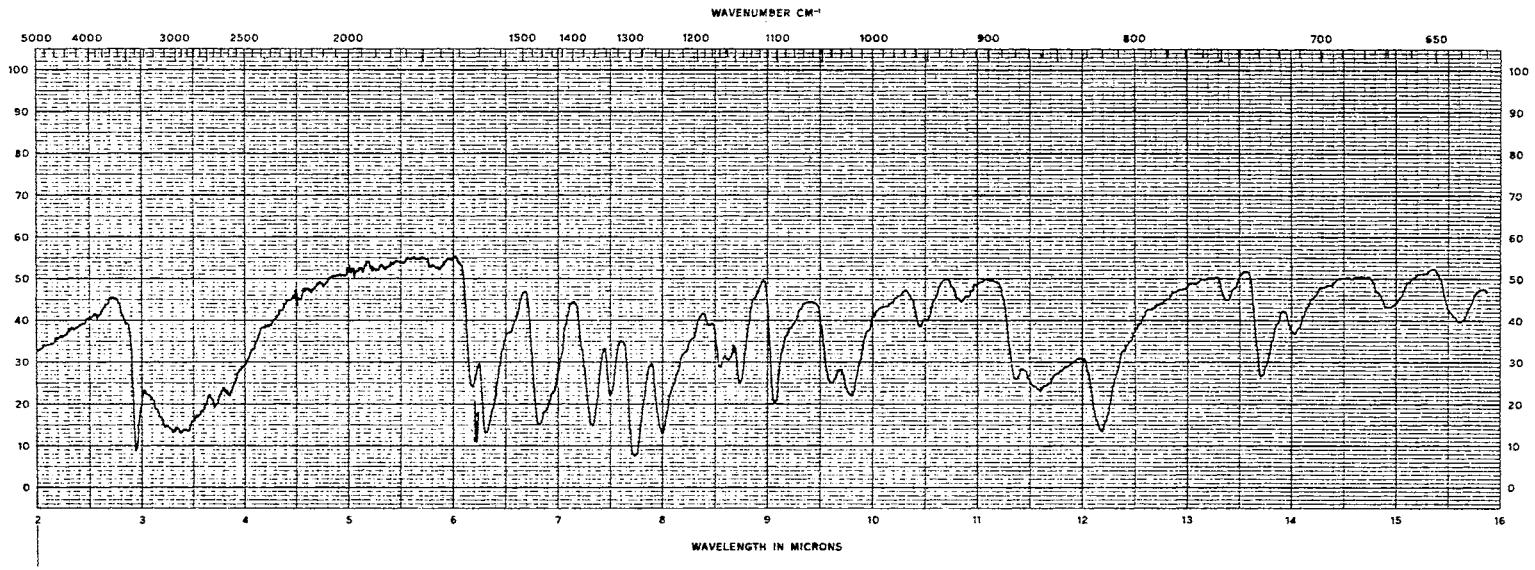
6-Methoxy-1-tetralone (46), KBr Pellet

Plate XIV



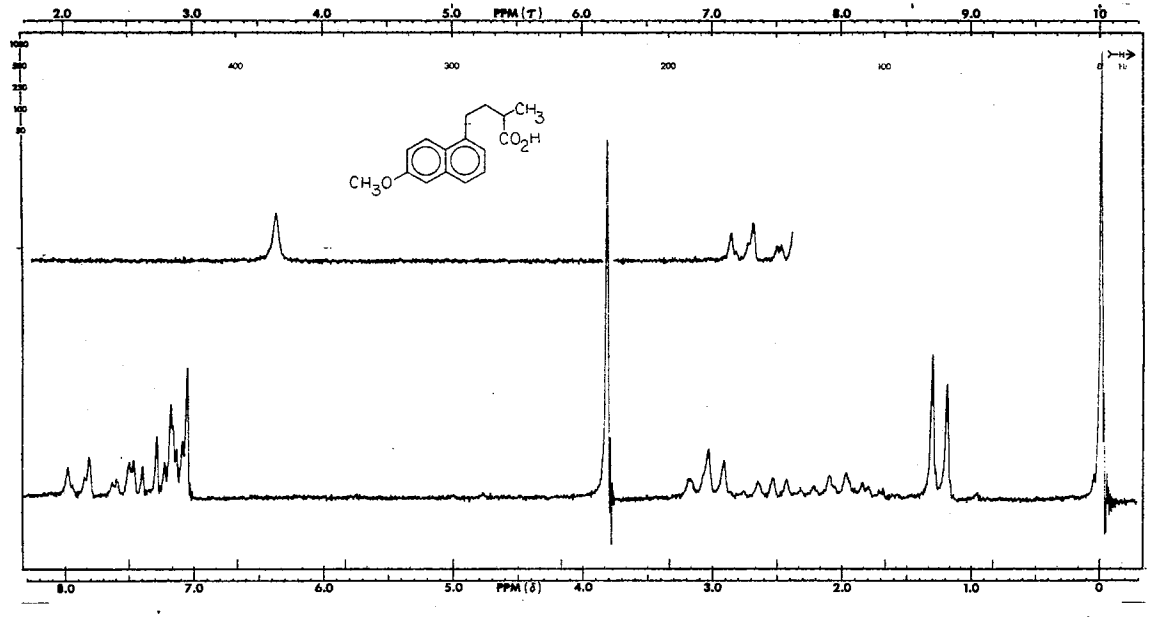
4,5-Dihydro-7-methoxy-1H-benz[g]indazole (58), KBr Pellet

Plate XV



4,5-Dihydro-1H-benz[g]indazol-7-ol (42), KBr Pellet

Plate XVI



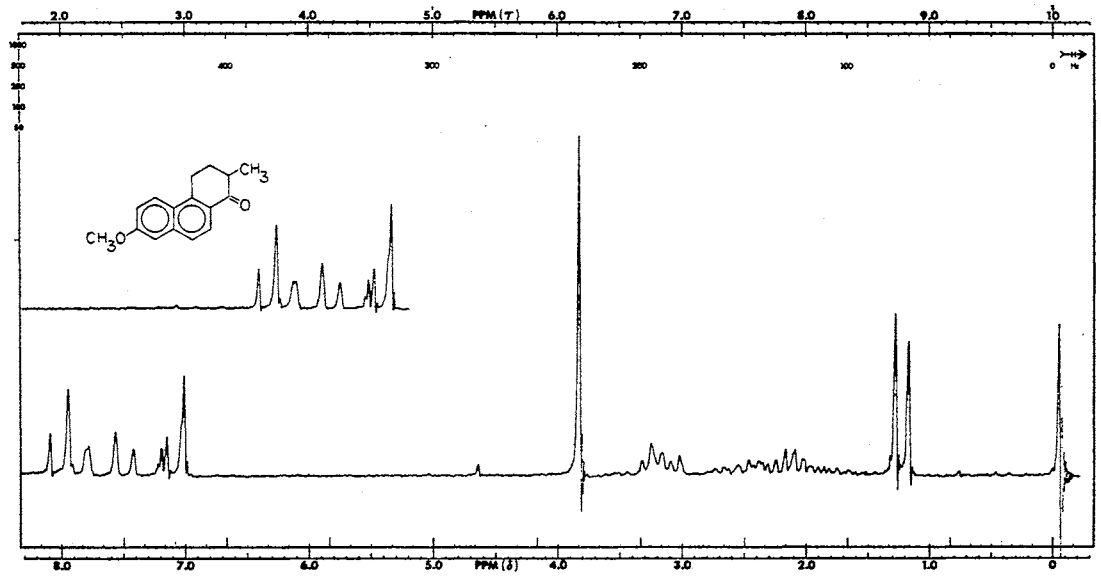
6-Methoxy-α-methyl-1-naphthalenebutyric Acid (12a)

Solvent . . . $CDCl_3$(15)[a] R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. . . . 3.2

F.B. . . . . 4.0 Hz S.T. . . . 250 sec S.O. . . 322,22 Hz I.A. 63

[a]Where possible, on this and succeeding spectra, the approximate weight per cent of solute is given in parenthesis following the solvent type designation.

Plate XVII

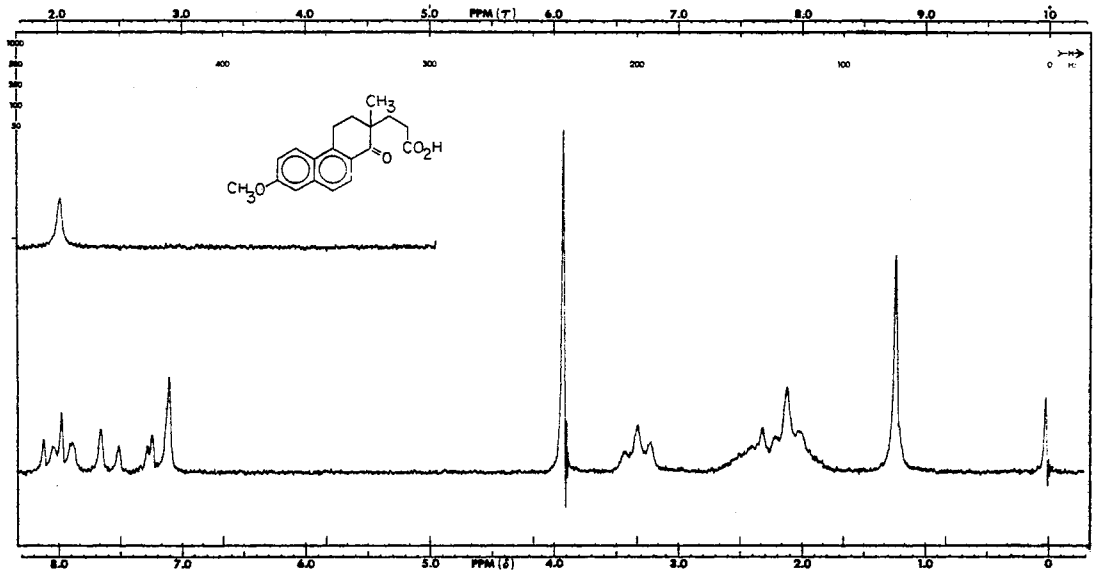


3,4-Dihydro-7-methoxy-2-methyl-1(2H)-phenanthrone (13a)

Solvent . . . $CDCl_3$(10) R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. . . . 2.5

F.B. . . . . 2.0 Hz S.T. . . . 250 sec S.O. . . .140,40 Hz I.A. 50

Plate XVIII

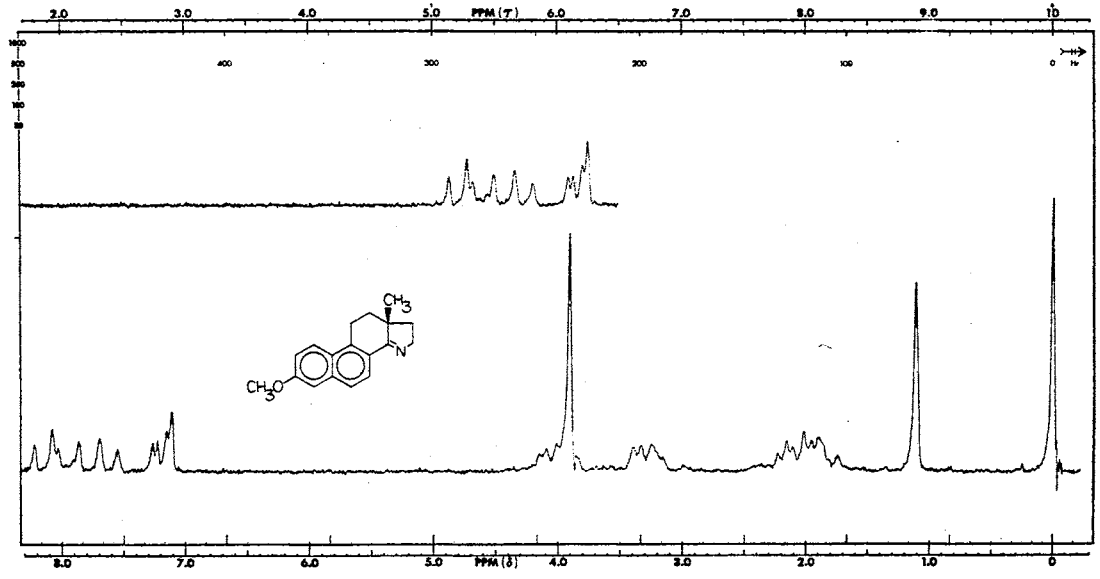


1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-oxo-2-phenanthrenepropionic Acid (23)

Solvent . . . $CDCl_3$(10) R.F. . . . 0.05 mG S.W. . . . 500 Hz S.A. . . . 6.3

F.B. . . . . .2.0 Hz S.T. . . . 250 sec S.O. . . 200,0 Hz I.A. 80

Plate XIX

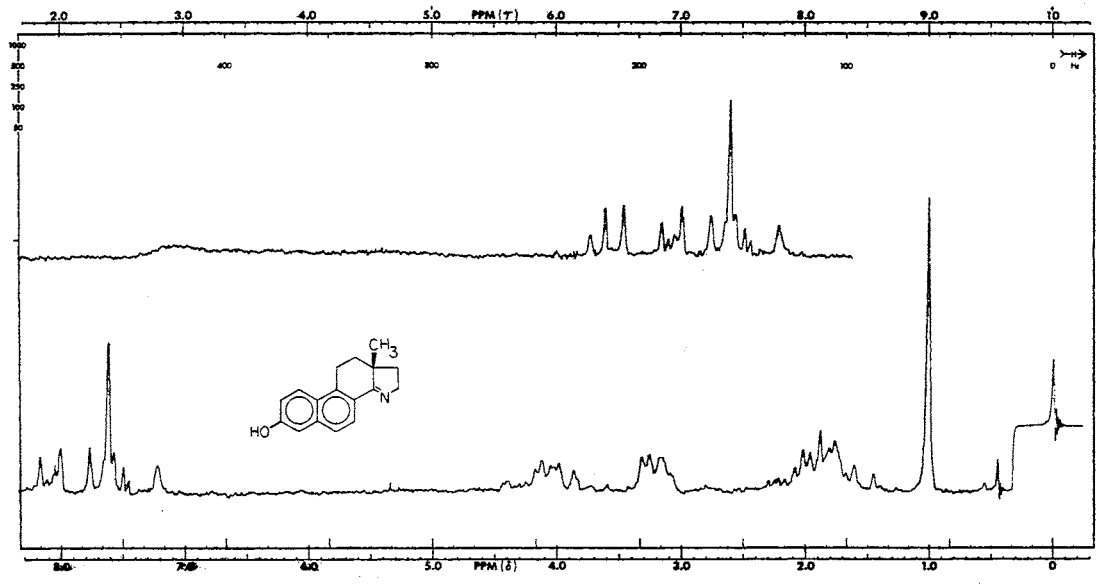


1,10,11,11a-Tetrahydro-7-methoxy-11a-methyl-2H-naphth[1,2-g]indole (36)

Solvent . . . $CDCl_3$(10) R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. . . . 5.0

F.B. . . . . 4.0 Hz S.T. . . . 250 sec S.O. . . 200,0 Hz I.A. . . . 63

Plate XX

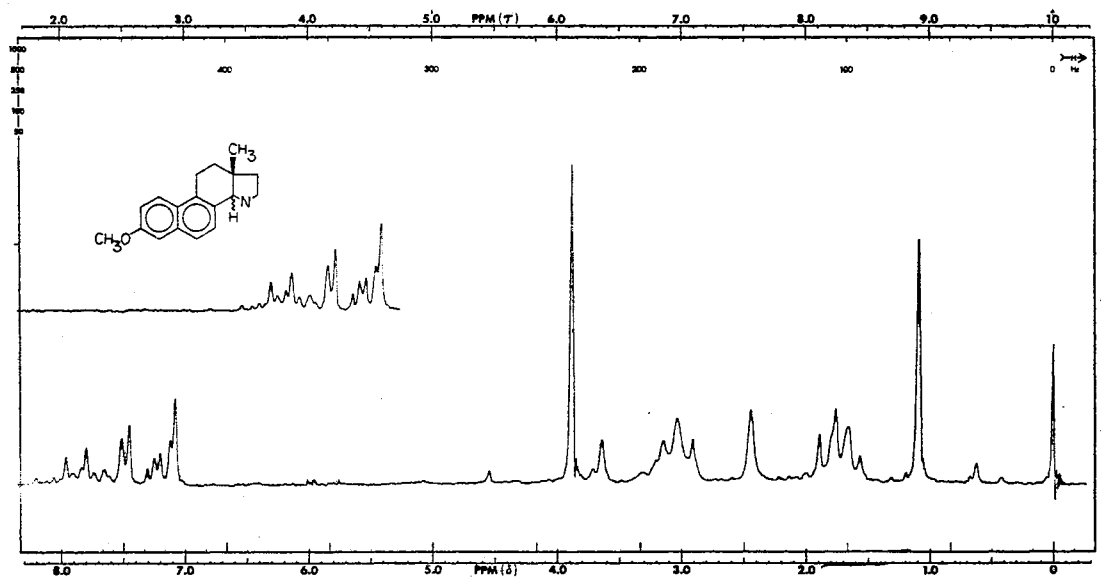


1,10,11,11a-Tetrahydro-11a-methyl-2H-naphth[1,2-g]indol-7-ol (35)

Solvent . . . C_5D_5N(5) R.F. . . . 0.1 mG S.W. . . . 500 Hz S.A. . . . 20

F.B. . . . . 1.0 Hz S.T. . . . 250 sec S.O. . . 304,4 Hz I.A. . 80(S.A. 5)

Plate XXI

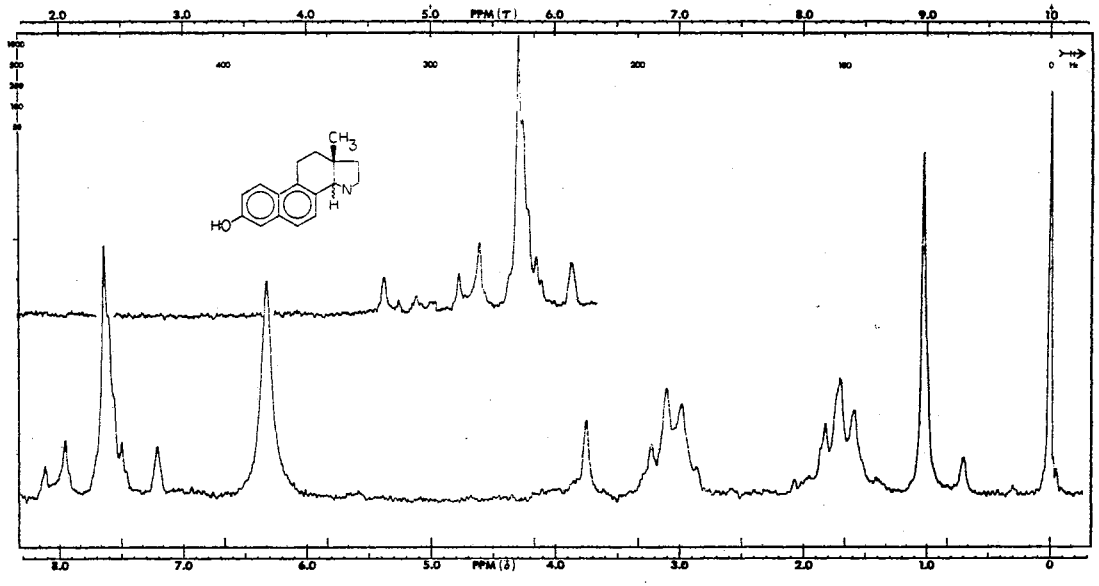


1,2,3a,10,11,11a-Hexahydro-7-methoxy-11a-methyl-3H-naphth[1,2-g]indole (34)

Solvent . . . $CDCl_3$ (10-20) R.F. . . . 0.05 mG S.W. . . . 500 Hz S.A. 5

F.B. . . . . 1.0 Hz S.T. . . . 250 sec S.O. . . 109,9 Hz I.A. . . 50 (S.A. 3.2)

Plate XXII

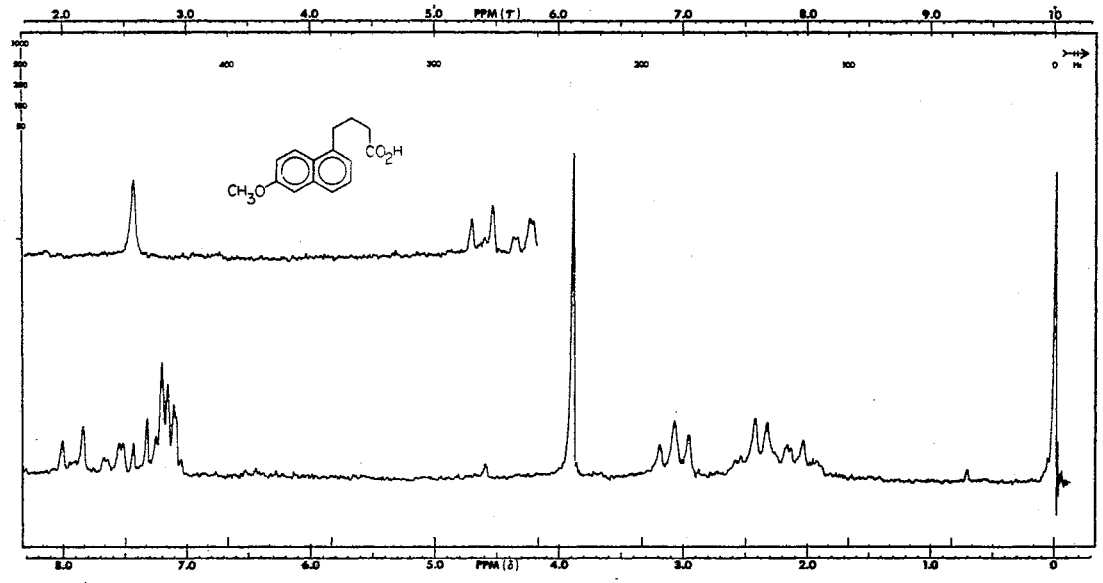


1,2,3a,10,11,11a-Hexahydro-11a-methyl-3H-naphth[1,2-g]indol-7-ol (37)

Solvent . . . C_5D_5N(10) R.F. . . . 0.05 mG S.W. . . . 500 Hz S.A. 16

F.B. . . . . 1.0 Hz S.T. . . . 250 sec S.O. . . .229,29 Hz I.A. . . 80(S.A. 3.2)

Plate XXIII

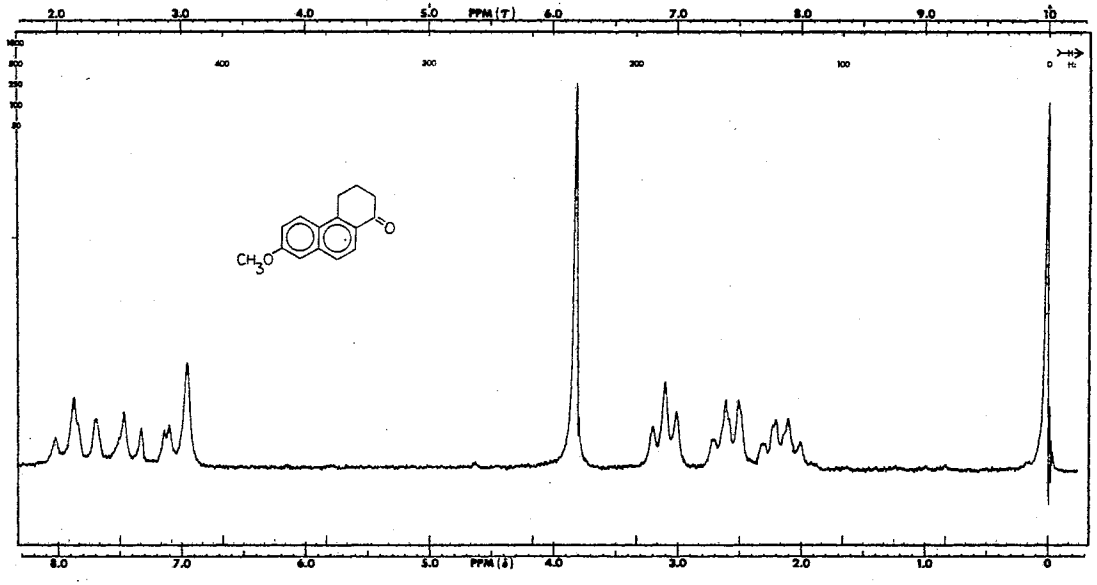


6-Methoxy-1-naphthalenebutyric Acid (12)

Solvent . . . $CDCl_3$(5) R.F. . . . 0.05 mG S.W. . . . 500 Hz S.A. 12

F.B. . . . . 1.0 Hz S.T. . . . 250 sec S.O. . . 208,8 Hz I.A. . . . 80(S.A. 3.2)

Plate XXIV

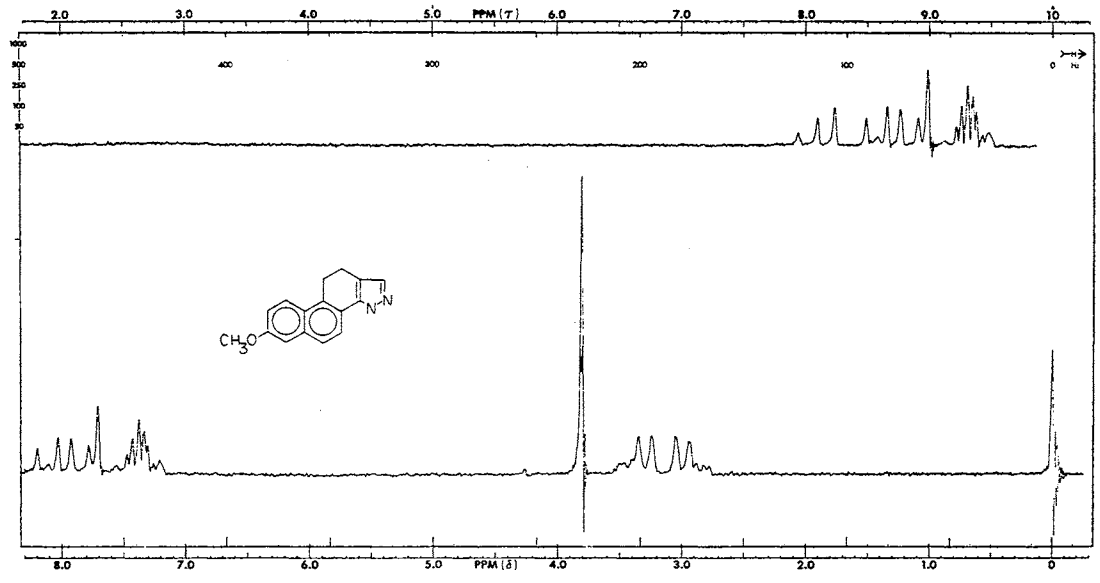


3,4-Dihydro-7-methoxy-1(2H)-phenanthrone (13)

Solvent . . . $CDCl_3$(20) R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. 4

F.B. . . . . 2.0 Hz S.T. . . . 250 sec S.O. . . . . 0 I.A. . . . . off

Plate XXV

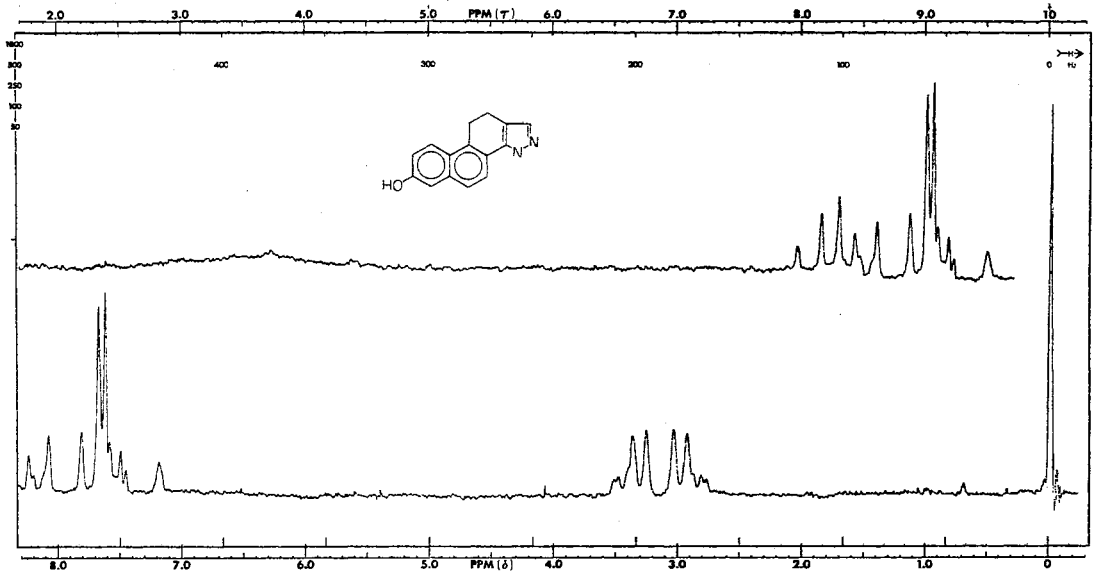


10,11-Dihydro-7-methoxy-3H-naphth[1,2-g]indazole (38)

Solvent . . . C_5D_5N(10-15) R.F. . . . 0.04 mG S.W. . . . 500 Hz S.A. 5

F.B. . . . . 2.0 Hz S.T. . . . 250 sec S.O. . . 200,2 Hz I.A. . . . 80

Plate XXVI

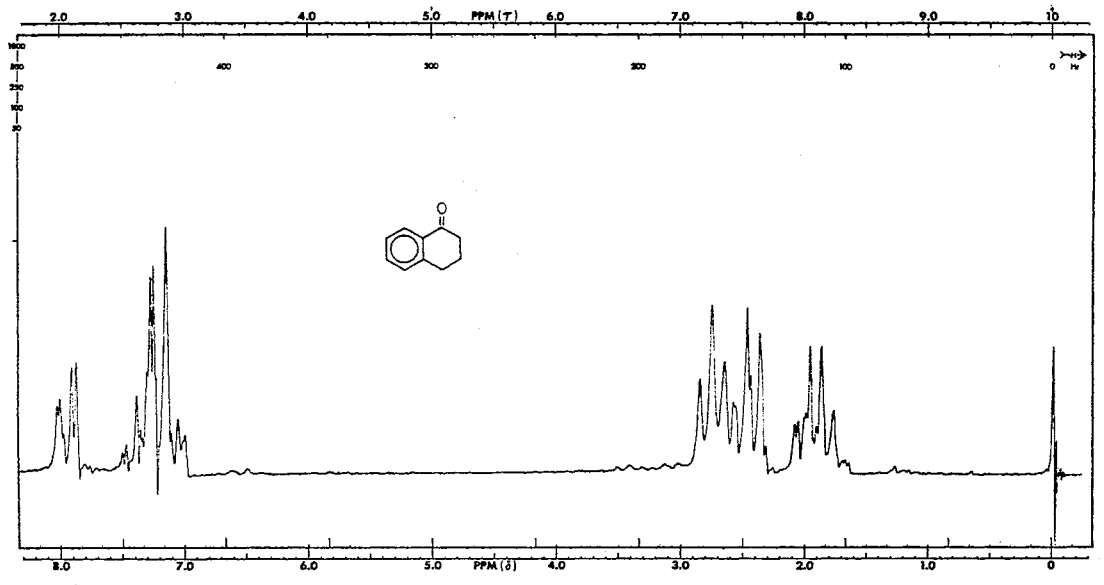


10,11-Dihydro-3H-naphth[1,2-g]indazol-7-ol (39)

Solvent . . . C_5D_5N(12) R.F. . . . 0.05 mG S.W. . . . 500 Hz S.A. 12

F.B. . . . . 1.0 Hz S.T. . . . 250 sec S.O. . . 26,426 Hz I.A. . . . 80(S.A. 3.2)

Plate XXVII

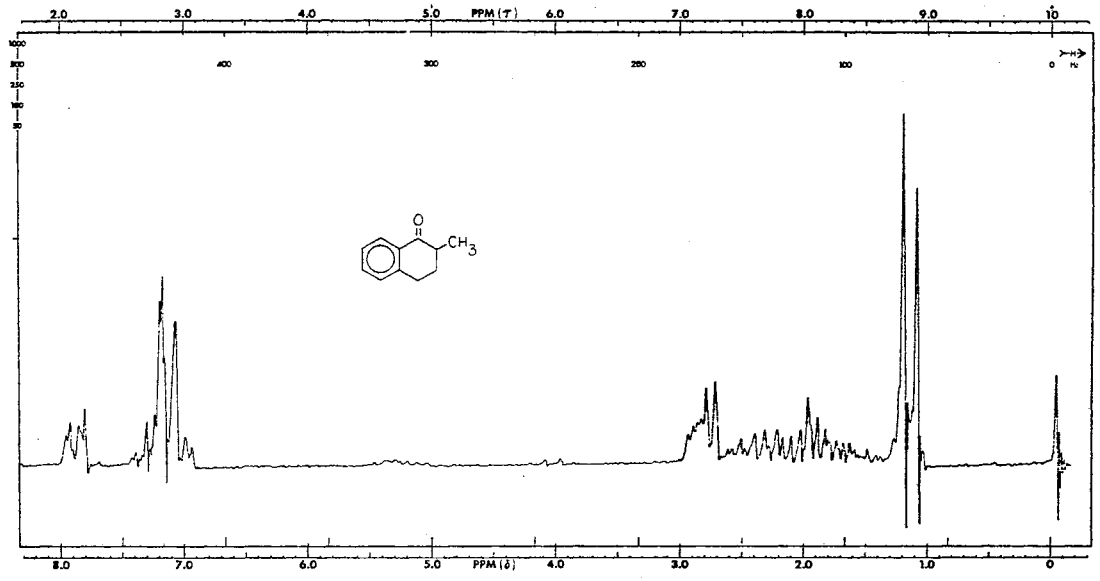


1-Tetralone (20)

Solvent . . . Neat R.F. . . . 0.015 mG S.W. . . . 500 Hz S.A. . . .1

F.B. . . . . 4.0 Hz S.T. . . . .250 sec S.O. . . . .39 Hz I.A. . . 40

Plate XXVIII

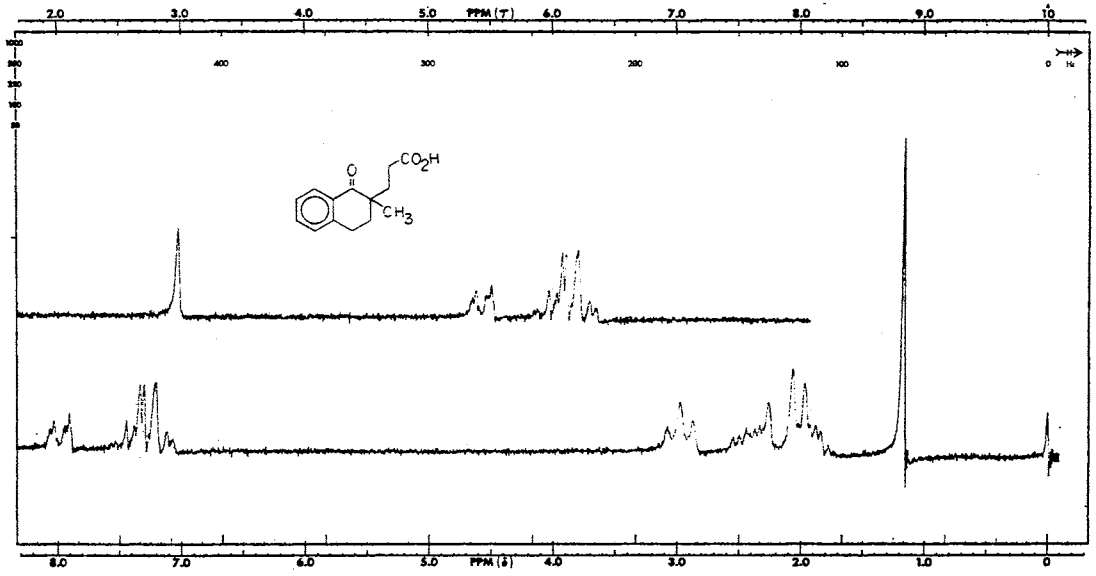


2-Methyl-1-tetralone (21)

Solvent . . . $CDCl_3$ R.F. . . . 0.02 mG S.W. . . . 500 Hz S.A. . . .1.6

F.B. . . . . .2.0 Hz S.T. . . . 250 sec S.O. . . . . .0 I.A. . . . 40

Plate XXIX

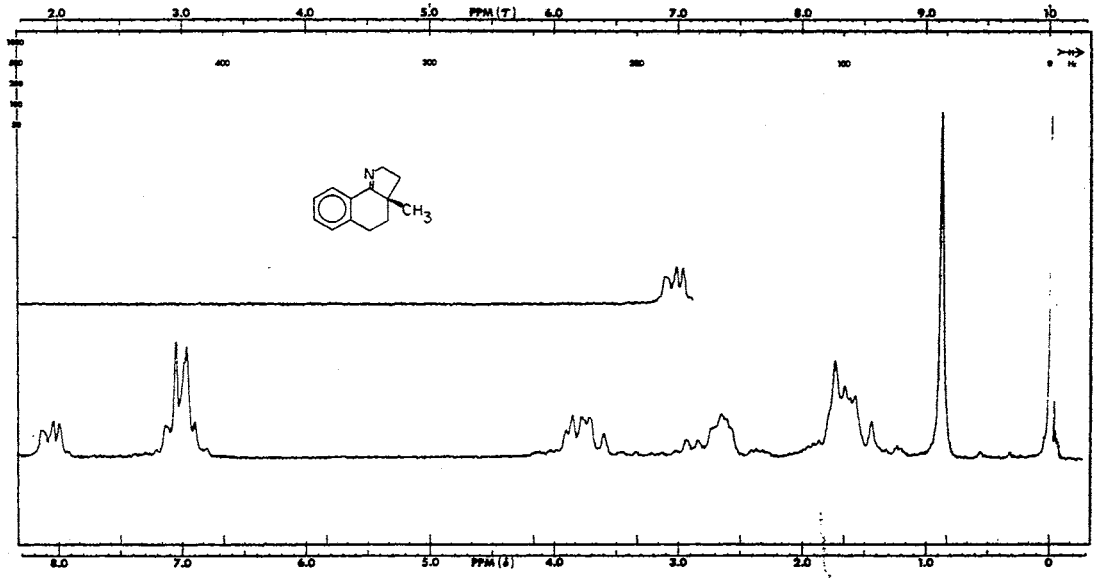


1,2,3,4-Tetrahydro-2-methyl-1-oxo-2-naphthalenepropionic Acid (53)

Solvent . . . $CDCl_3$ R.F. . . . 0.015 mG S.W. . . . 500 Hz S.A. . . . 2

F.B. . . . 4.0 Hz S.T. . . . .250 sec S.O. . .219,19 Hz I.A. . . .50

Plate XXX

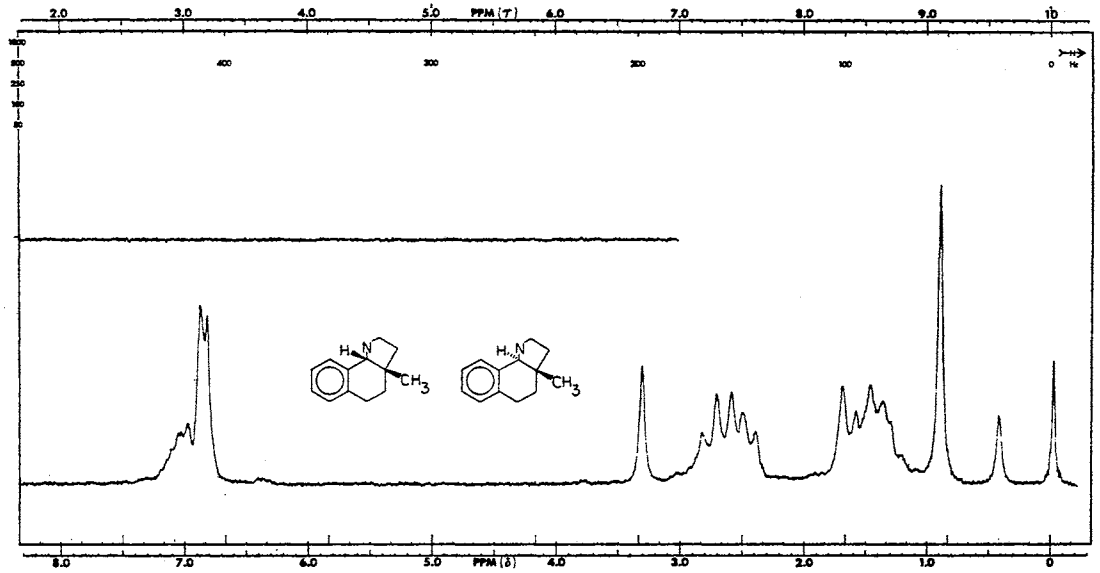


3,3a,4,5-Tetrahydro-3a-methyl-2H-benz[g]indole (40)

Solvent . . . Neat R.F. . . . 0.016 mG S.W. . . . 500 Hz S.A. . . 1.2

F.B. . . . . 4.0 Hz S.T. . . . 250 sec S.O. . 449,749 Hz I.A. . . .40

Plate XXXI

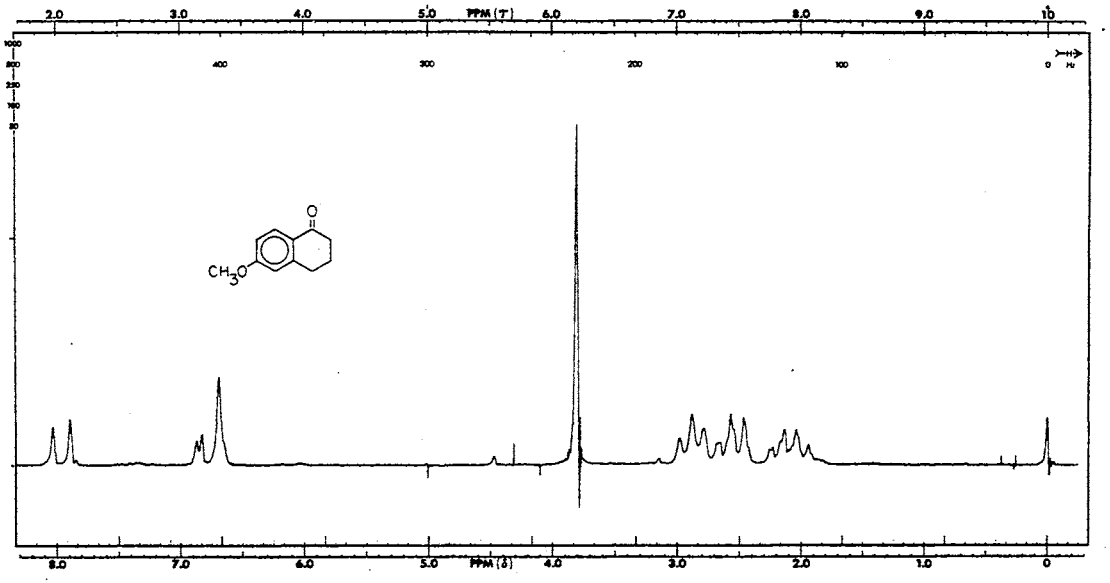


2,3,3a,4,5,10-Hexahydro-3a-methyl-1H-benz[g]indole (41)

Solvent . . . Neat R.F. . . . 0.02 mG S.W. . . . 500 Hz S.A. . . 6.3

F.B. . . . . 4.0 Hz S.T. . . . 250 sec S.O. . . 300,0 Hz I.A. . . .20

Plate XXXII

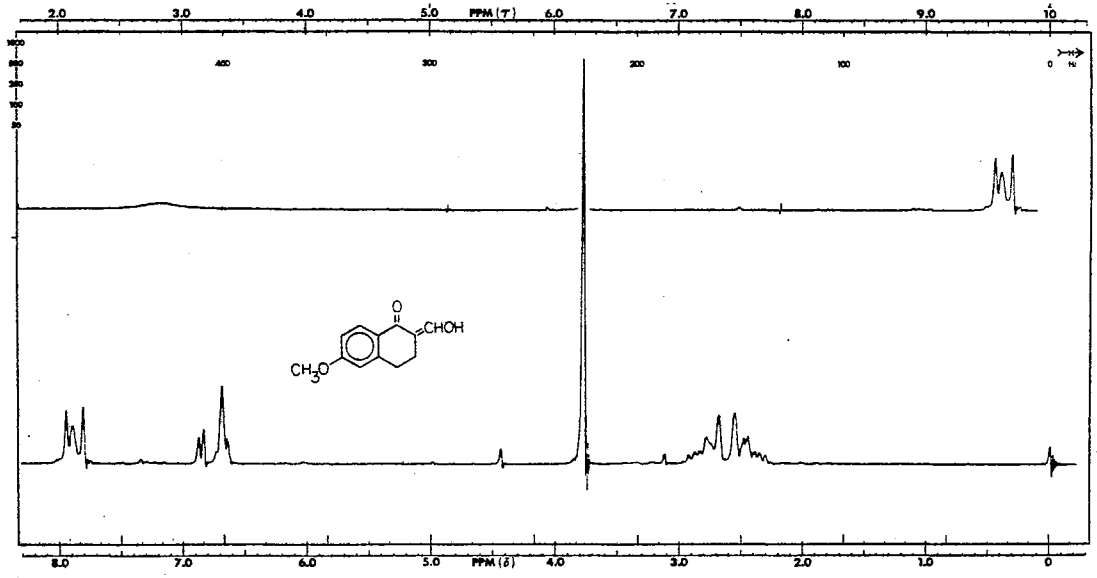


6-Methoxy-1-tetralone (46)

Solvent . . . $CDCl_3$ R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. . . . 1.2

F.B. . . . . .4.0 Hz S.T. . . . 250 sec S.O. . . . . 4 Hz I.A. 80

Plate XXXIII

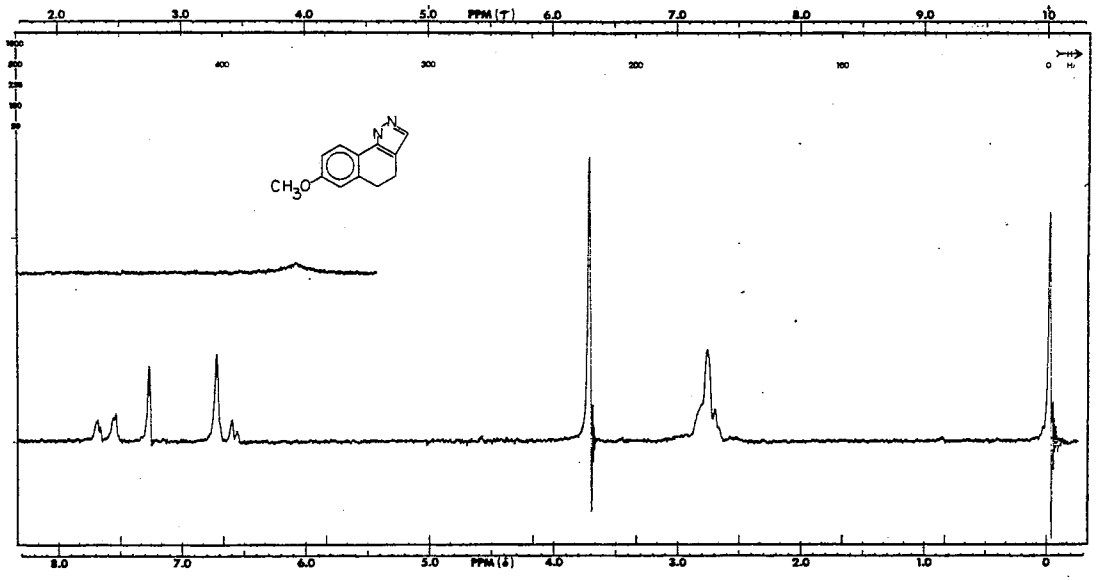


2-Hydroxymethylene-6-methoxy-1-tetralone (57)

Solvent . . . $CDCl_3$(30) R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. . . . 0.8

F.B. . . . . 4.0 Hz S.T. . . . 250 sec S.O. . . 450,0 Hz I.A. 80

Plate XXXIV

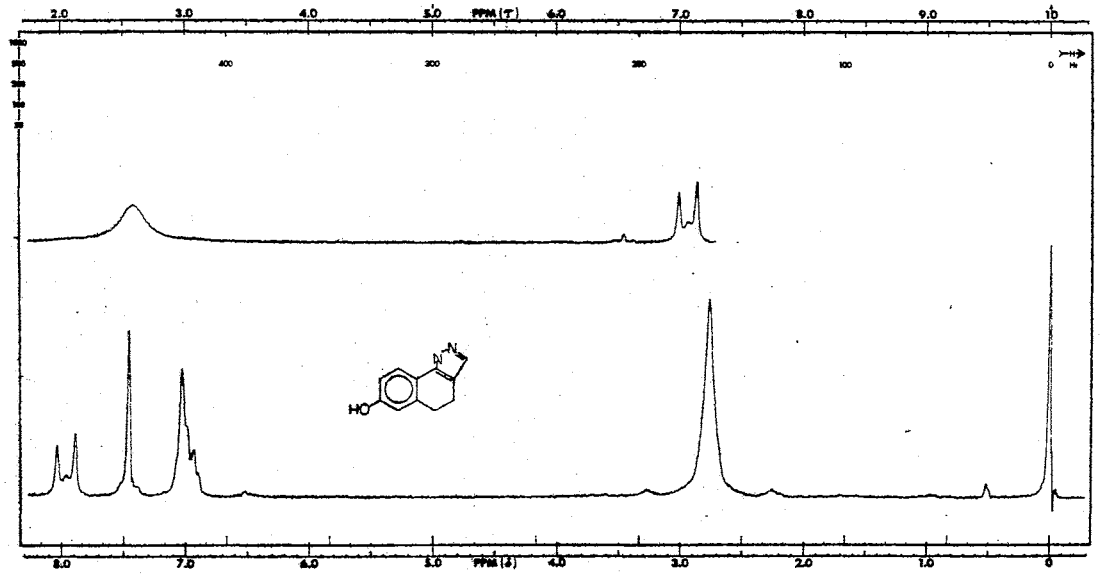


4,5-Dihydro-7-methoxy-1H-benz[g]indazole (58)

Solvent . . . $CDCl_3$ R.F. . . . 0.02 mG S.W. . . . 500 Hz S.A. . . 2.5

F.B. . . . . 2.0 Hz S.T. . . . 250 sec S.O. . . 300,0 Hz I.A. . . .80

Plate XXXV



4,5-Dihydro-1H-benz[g]indazol-7-ol (42)

Solvent . . . C_5D_5N(40) R.F. . . . 0.03 mG S.W. . . . 500 Hz S.A. . . . 2.0

F.B. . . . . .4.0 Hz S.T. . . . 250 sec S.O. . .35,335 Hz I.A. 40

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VITA

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Doctor of Philosophy

Thesis: SYNTHETIC APPROACHES TO 15-AZASTEROIDS AND 15,16-DIAZASTEROIDS--NAPHTH[1,2-g]INDOLES AND NAPHTH[1,2-g]INDAZOLES AND RELATED COMPOUNDS

Major Field: Chemistry

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