1961

Analogs of steroid hormones lacking ring C

Donald Peter Page
The University of Montana

ANALOGS OF STEROID HORMONES LACKING RING C

by

DONALD P. PAGE

B. A., University of Omaha, 1960

Presented in partial fulfillment of the requirements

for the degree of Master of Science

Montana State University

1961

Approved by:

Richard E. Fuller
Chairman, Board of Examiners

Ellis Walton
Dean, Graduate School

Date

ACKNOWLEDGMENT

Gratitude is expressed to my advisor, Professor Richard E. Juday, for his guidance throughout this project.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER I

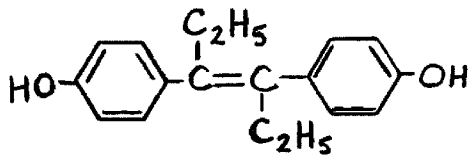
INTRODUCTION

The purpose of this problem was to synthesize a compound related in general molecular shape to steroid hormones but not having the actual steroid nucleus and have it tested for steroid hormone activity, with the hope that it might be effective in cancer therapy. One characteristic that many cancers have in common is their dependency on steroid hormones for growth. This is true for cancer of the prostate and mammary glands. These cancers may at times be inhibited by administration of hormones of the opposite sex to cause changes in the hormone balance. Although the mechanism of this action is unknown, it is thought possibly that they act in part by antagonizing the action of the opposite sex hormones. At the present time there is no satisfactory evidence that can dissociate anticancer effects from the androgenic or estrogenic activity of the steroids. A few compounds have been found that block the action of these hormones on normal tissues and it seems that similar compounds might have anticancer activity. Most of the work, thus far, has been on the synthesis of artificial estrogens. The work that has been undertaken here is the synthesis of a non-steroid androgen.

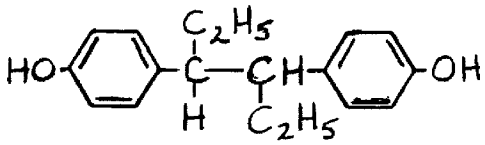
CHAPTER II

DISCUSSION A

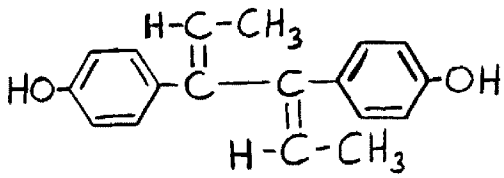
The synthesis and use of non-steroid hormones is a relatively new field. The first work was done in the early 1930's by Dodds and co-workers. They began examining the possibility of how the molecule of a natural estrogen might be changed without destroying the estrogenic activity. In 1938 they discovered three estrogenically potent compounds. (5)



Diethyl stilbestrol

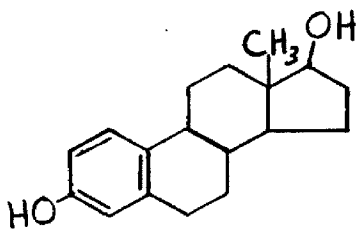


Hexestrol



Dienestrol

All three may be considered to be analogs of estradiol but are quite different in structure.



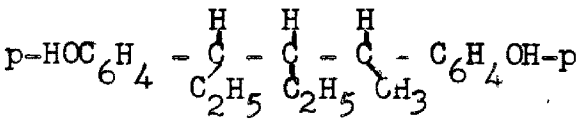
Estradiol

As was pointed out above, the study of the relationships of hormones to cancers has become an important field, and diethylstilbestrol

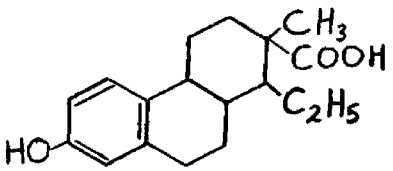
has found a place in prostate cancer therapy. These early successes led to further studies and discoveries, by this same group as well as others, of compounds closely related to the stilbene-type estrogens. Robson and co-workers prepared 1,1-bis (p-ethoxyphenyl)-2-bromo-2-phenylethylene.(5)

$(p\text{-}C_2H_5OC_6H_4)_2C{=}\underset{Br}{C}\text{-}C_6H_5$

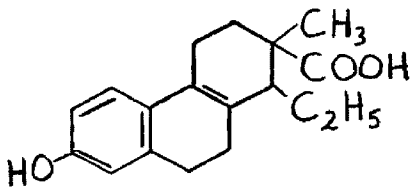
Blanchard, Stuart and Tallman prepared benzestrol. (5)



In 1944 Miescher and co-workers discovered a new type of estrogen closely related to the natural hormone. Two examples of this class of highly potent estrogens, known as the doisynolic acids, are shown below.(5)

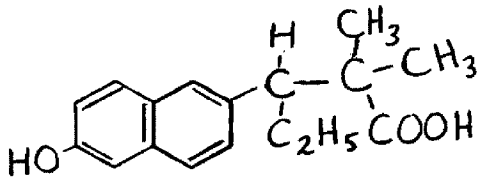


Doisynolic acid



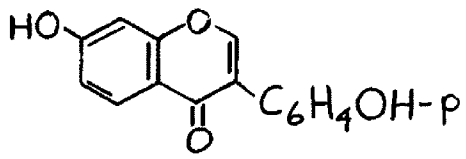
Monodehydrodoisynolic acid

In 1947 Horeau and Jacques discovered the allenolic acids. Horeau acid is an example of this class. (5)



Horeau acid

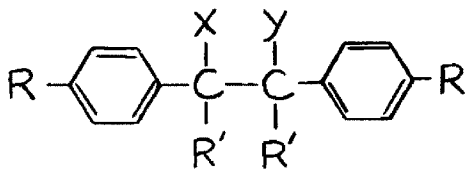
Four year later Bradbury and White discovered the estrogenic activity of isoflavones such as genistein. (5)



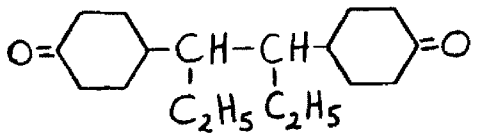
Genistein

Since the discovery of the stilbene estrogens, most of the research done on artificial estrogens has been towards improving these structures rather than expanding into other fields. In addition to the exceptions cited above, there has been work done on derivatives of diphenylmethane, diphenylpropane, and triphenylethylene. But these are nevertheless closely related to the stilbene estrogens. Today there are several hundred substances known to possess estrogenic activity. The relative structural requirements for biological activity are not as strict for estrogens as it seems to be in the case of androgens. No compounds lacking the steroid nucleus have yet been found that possess more than slight activity. Therefore, little is known regarding the simpler analogs of the androgens.

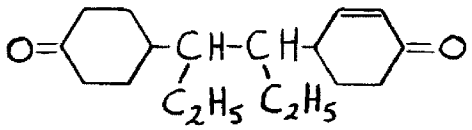
Considerable attention has been devoted to androgen analogs in the perhydrohexestrol series. Walter Schoeller and co-workers said a series of compounds existed with the general formula given below, in which R represents OH or a group convertible to hydroxyl; X and Y represent H, halogens, hydroxyl groups or groups convertible to a hydroxyl; and R' represents saturated or unsaturated alkyl groups. (12)



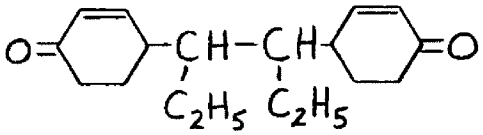
These compounds were said to possess activity as sex hormones. An example of such a compound prepared was diethylbis-(oxocyclohexenyl) ethane, which was said to possess androgenic activity. In 1949 Ungnade and Tucker, using a method similar to that of Schoeller, decided to prepare a pure sample of the compound and see if it would increase the activity. (13) They used N-bromosuccinimide for bromination of I, and debrominated to get the desired products; II, III, IV.



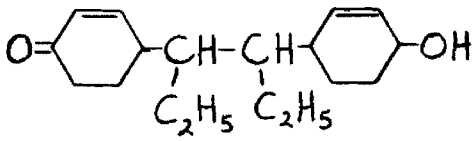
I



II

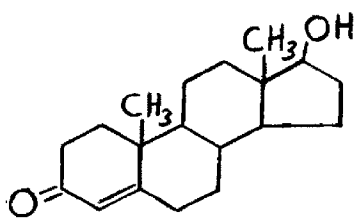


III



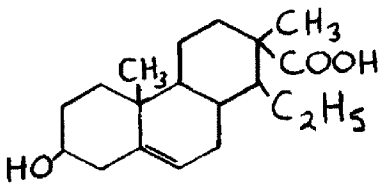
IV

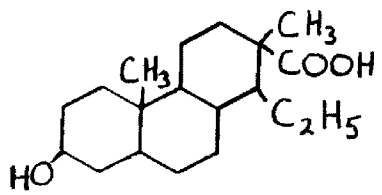
Ultraviolet absorption spectra of II and III showed relatively low extinction values at 225 mu and a weak secondary maximum at 280-285 mu. The formation of colored ketonic by-products and small extinction coefficients for II and III lend support to the assumption that II, III, and IV probably consist of mixtures of conjugated and non-conjugated unsaturated ketones. II and III were tested biologically. Both showed little or no androgenic activity, although they bear about the same structural relationship to the natural hormone testosterone, as diethylstilbestrol. does to estradiol.

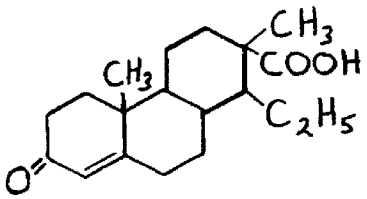


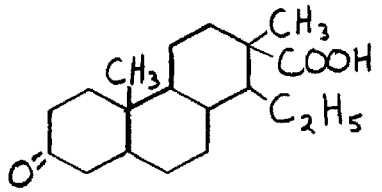
Testosterone

Miescher, who did work on the estrogenic doisynolic acids, prepared some doisynolic acids derived from androgens. (7)



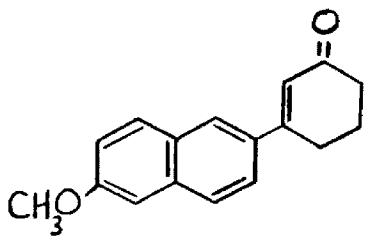




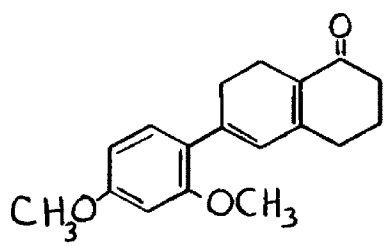


These may be considered to be analogs of dehydroandrosterone, or androstenedione, or of testosterone as well as of isoandrosterone and androstanedione. None of these showed any activity.

Nazarov prepared an analog of doisynolic acid not containing ring B, 1 methyl-4-(p-hydroxyphenyl)-4-cyclohexene-1-carboxylic acid. (8) He also prepared some steroid analogs without ring B or ring C. (9) He reacted the Grignard reagent from 2-bromo-6-methoxynaphthalene with medihydroresorcinol ether and obtained V in a small yield. VI was prepared in a similar manner.

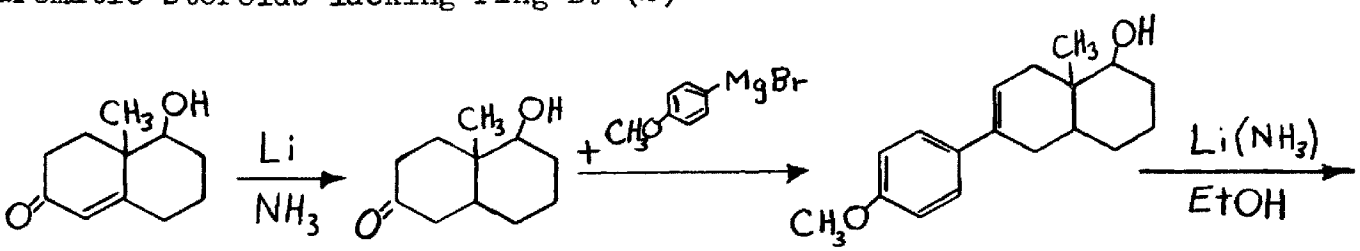


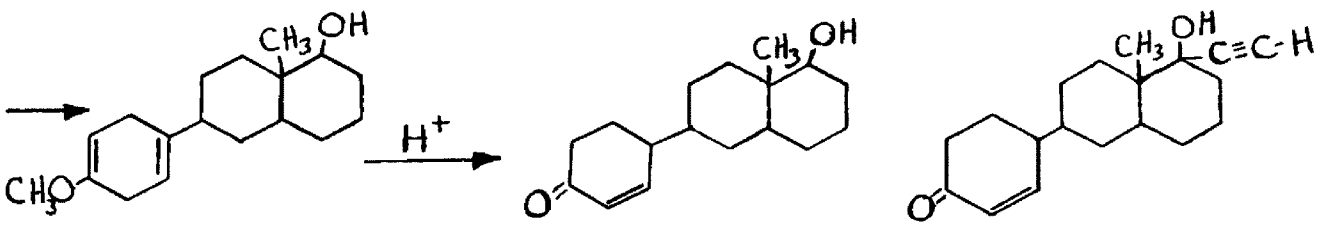
V



VI

Some recent work has been done by Birch and co-workers on hydroaromatic steroids lacking ring B. (2)

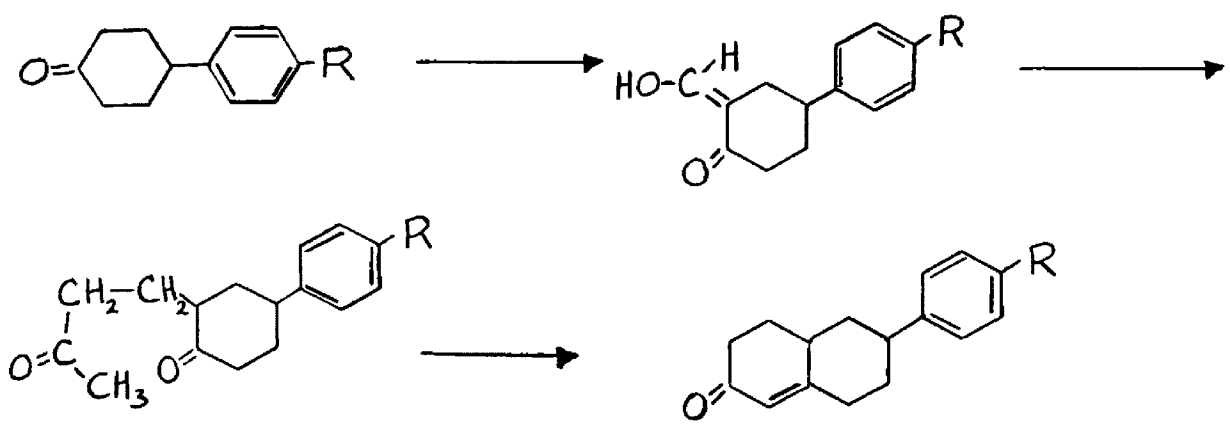




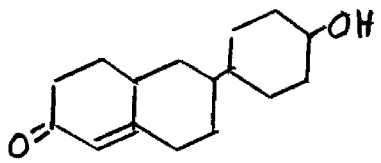
VII VIII

The final product, an analog of testosterone, was considered to be a mixture of 70% conjugated and 30% unconjugated. The mixture failed to show any androgenic activity. VIII was synthesized in a similar manner. Ultraviolet absorption data showed a maximum at 220-225 mu with the extinction coefficient equal to 7000.

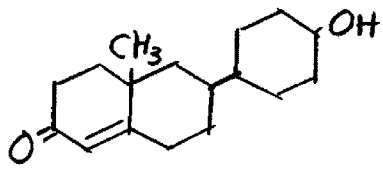
Wilds and Shunk did some work on the synthesis of steroid analogs lacking ring C. They prepared some analogs of progesterone and desoxycorticosterone by the Robinson Mannich base method. (15, 16, 17)



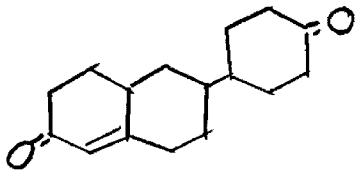
In a similar manner they also prepared analogs of testosterone and androstenedione.



IX



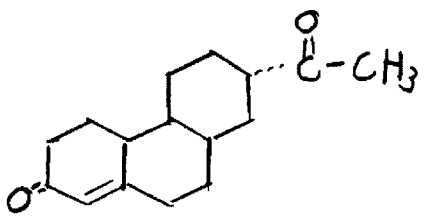
X



XI

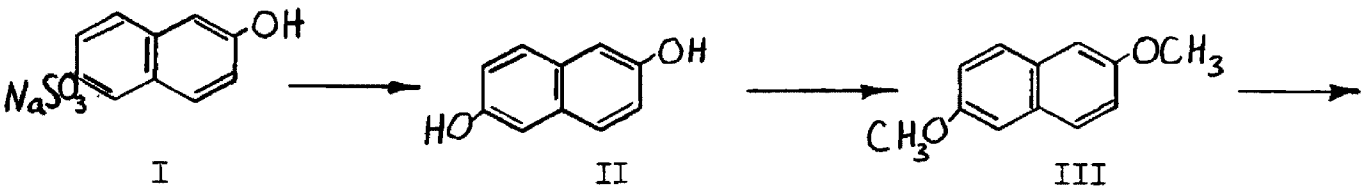
All three compounds showed ultraviolet absorption at 238 mu with extinction values respectively: 16,900, 16,450, and 6,800. The low value for XI was due to the fact that it was only about 40% conjugated. At present no consistent androgenic activity has been demonstrated in these analogs lacking ring C.

A couple of examples of recent work on hormone antagonists have been those reported by Palopoli (10) and Lauppi and Studer (6). Palopoli reported in 1958 that certain derivatives of triphenylethane possess antiestrogenic activity. Lauppi and Studer have reported on the antiandrogenic activity of a phenanthrene derivative.

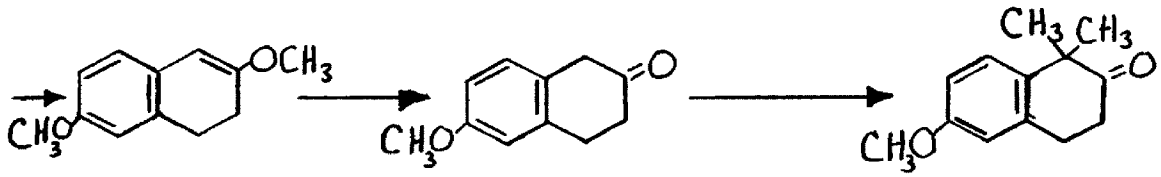


DISCUSSION B

The synthetic procedure used in this lab for the preparation of steroid analogs lacking ring C, although it is a nine step synthesis, can be looked upon as consisting of two parts. The first part would be the preparation of 6-methoxy-1,1-dimethyl-2-tetralone (VI).



I II III



VI V IV

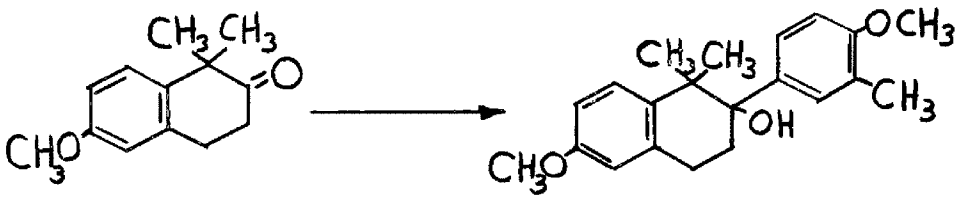
This compound is used as a general starting material for the preparation of compounds having different ring functions substituted on C-6.

The starting material is the commercially obtainable sodium 2-naphthol-6-sulfonic acid (I). It was subjected to fusion with potassium hydroxide to obtain 2,6-naphthalenediol (II). The yield of the diol is relatively small, usually from 35-40%. The dimethyl ether, 2,6-dimethoxy naphthalene (III), was prepared by reacting the disodium salt of the naphthalenediol with dimethyl sulfate. The yields here are about 60 to 65%. Reduction of the 2,6-dimethoxynaphthalene (III) to the 2,6-dimethoxy-3,4-dihydronaphthalene (IV) was effected by treatment with sodium and isoamyl alcohol. According to the method of Robinson and Weygand (11), a large excess of sodium was needed; but it was found that a much smaller

excess gave good yields in the order of 75-80%. Hydrolysis of 2,6-dimethoxy-3,4-dihydronaphthalene (IV) to 6-methoxy-2-tetralone (V) was accomplished with formic acid. Cornforth, Cornforth and Robinson used aqueous hydrochloric acid to hydrolyze the enol ether to the tetralone (4). The yield obtained with hydrochloric acid was less, about 55-60%, than the yield obtained with formic acid (about 80%). Oxalic acid has also been used for the hydroylsis . Formic acid had not previously been used in this reaction but it seemed to be a good prospect because it combined high polar and strong acid properties with good solvent properties for organic compounds. The final reaction of what may be considered to be the first part of the synthesis is the substitution of two methyl groups in position 1 of the naphthalene structure. The substitution was accomplished by treating the tetralone with sodium hydride and methyl iodide. The yield of 6-methoxy-1,1-dimethyl-2-tetralone (VI) was around 70%. This is a key point in the synthesis, in that one can increase the number of possible analogs by changing the groups substituted in position 1. Besides the dimethyl substituted compound prepared here, the monoethyl compound has been prepared in this laboratory. Other possible alkyl groups are propyl or isopropyl.

The second part of the synthesis could be considered to be the addition of the third ring, corresponding to ring D, and the reactions leading to the final compound. The third ring was added by addition of the organolithium compound prepared from 4-bromo-2-methylanisole. This was prepared by addition of the bromo compound to lithium sand at -2° to -5°C, in an argon atmosphere. The lithium sand contained about 2-5% sodium. It was found that better yields were obtained if the temperature

was kept about -5°C. 6-methoxy-1,1-dimethyl-2-tetralone (VI) was added to the organolithium compound at low temperature, in an argon atmosphere. 2-methoxy-5,5-dimethyl-6-hydroxy-6-(3-methyl-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene (VII) was obtained in about 50% yield.

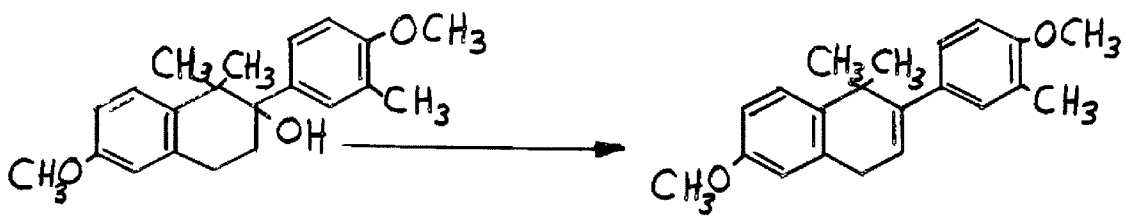


VI VII

The infrared spectra showed phenol ether peaks at 3.4 u, 6.7 u, and 8 u. These peaks were also shown by anisole. There was a small absorption peak at 2.78 u, which was due to the hydroxyl group formed.

At this point, one can see that there are more possibilities for a third ring. The analog, without a methyl group on the third ring, has been prepared in this laboratory. Another possibility is the addition of a five membered ring instead of a six membered ring.

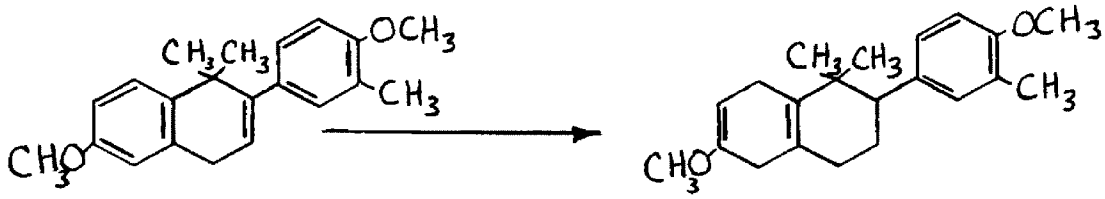
Dehydration of VII to 2-methoxy-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)-5,8-dihydronaphthalene (VIII) was accomplished with thionyl chloride in toluene.



VII VIII

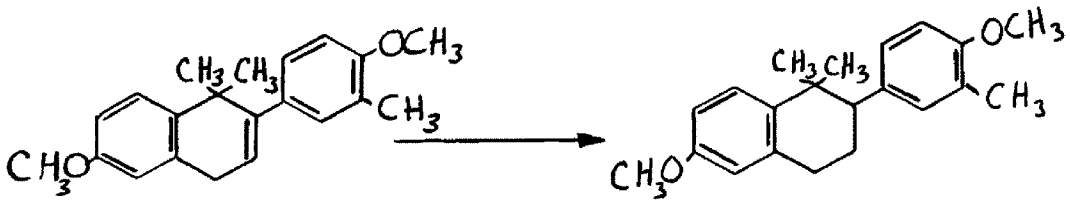
Thionyl chloride in pyridine and potassium hydrogen sulfate were also tried, but the best results were obtained with the thionyl chloride in toluene. The yield was almost quantitative.

The first work done on the reduction of a methoxy, such as in (VIII) to the enol ether form of 2-methoxy-1,4,5,6,7,8-tetrahydro-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)-naphthalene (IX) was done by Birch.(1) He used an alcohol ammonia solution with addition of sodium.



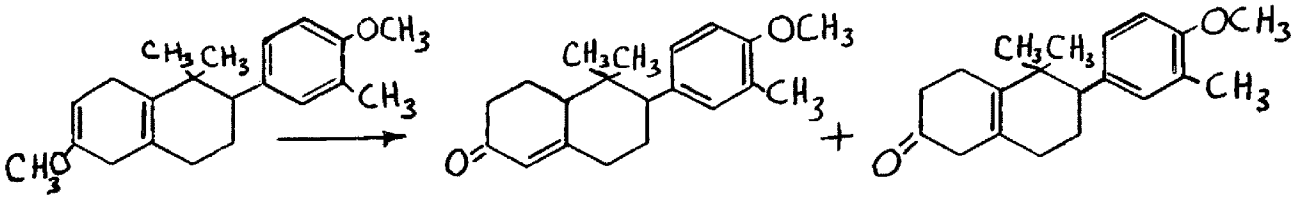
VIII IX

Wilds later improved upon Birch's method by addition of the alcohol last and using lithium instead of sodium. (14) Wilds method of reduction was used here. The reduction was intended to reduce both rings to the enol ether and the double bond in ring B, as in some previous work when the ortho methyl was not present; but apparently due to an unfavorable steric effect of the methyl, only the one ring was reduced. The infrared spectra showed phenol ether peaks for the unreduced ring at 6.7 u and 9.6 u. It showed some other peaks at 8.1 u and 8.2 u due to the enol ether. The product here contained about 10% 2-methoxy-5, 5-dimethyl-6-(3-methyl-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene.(VIIIa). Reduction of VII with a lithium-ammonia solution followed by addition of ammonium chloride gave VIIIa. It was found to be the same as the impurity in IX.



VIII VIIIa

Even after subsequent reductions, the amount of impurity was the same. The hydrolysis of IX to 2(3H)-naphthalenone-4,4a,5,6,7,8-tetrahydro-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)(X) is effected by hydrobromic acid in aqueous dioxane.



IX X XI

Formic acid was unsatisfactory because of the low solubility of the compound. The final product was a mixture of the conjugated form of X and the unconjugated 2(3H)-naphthalenone-1,4,5,6,7,8-tetrahydro-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)(XI). X can be considered to be an analog of testosterone. It differs from those compounds of Wilds in that it has alkyl substituents in the 5 position of naphthalene nucleus. Alkyl substituents in this position have been found essential for activity in the case of some estrogens.

The infrared and ultraviolet absorption data points to the fact that the desired conjugation was obtained to a great extent. The ultraviolet absorption showed a peak at 230 mu (Fig. 1) with an extinction coefficient of about 10,400. The usual value for the extinction

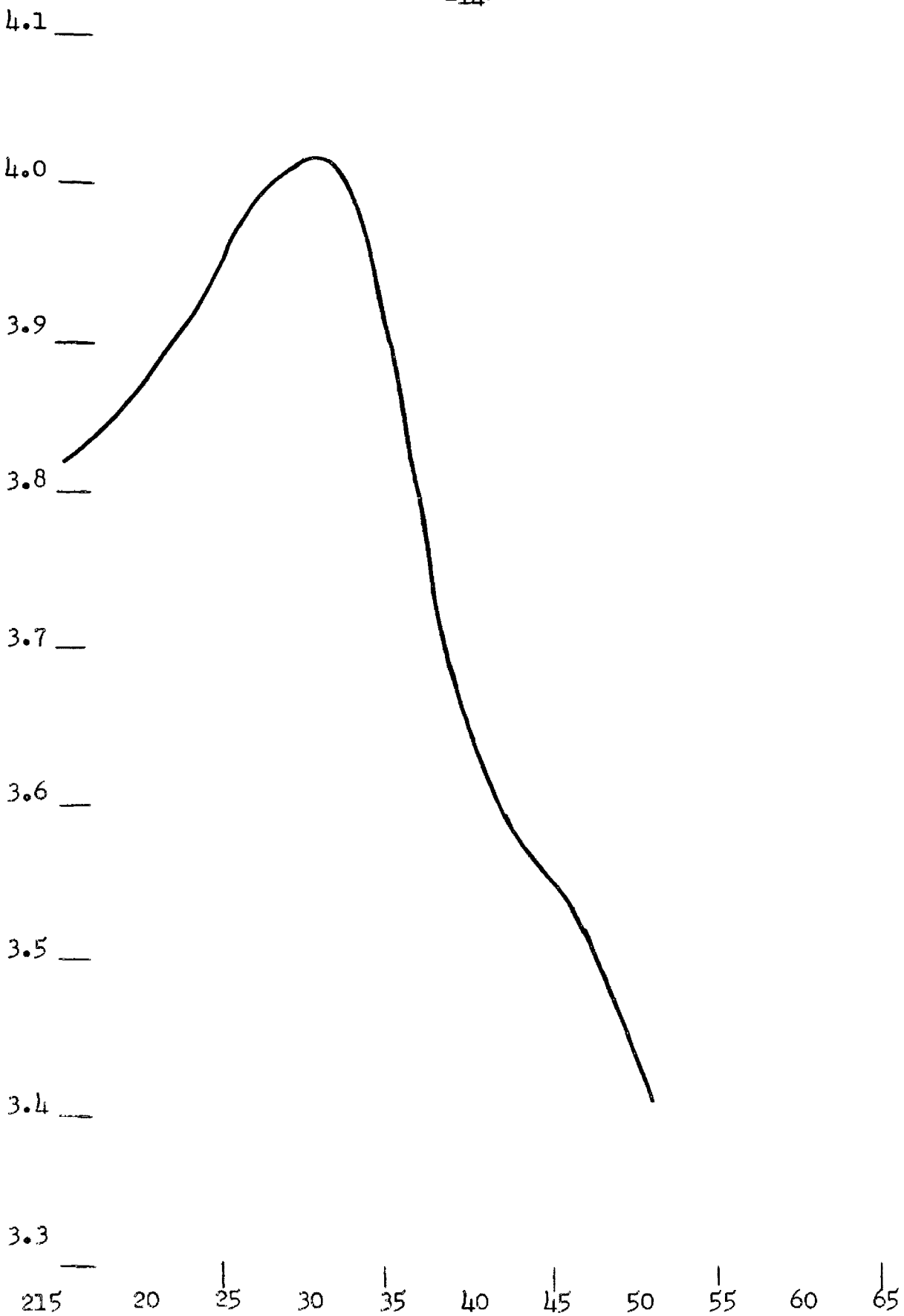


Figure. 1 Ultraviolet Absorption Curve for X

coefficient of this type of compound is around 16,000. This indicates that the product is probably over 60% conjugated. The infrared spectrum showed a carbonyl peak at 5.8 u with another peak close at 5.95 u. It also showed a phenol ether peak at 7.9 u, due to the unreduced ring. In comparing this I.R. with the one for cyclohexanone, which is characteristic for a saturated ketone, it was found that it had a peak of 5.8 u. The peak at 5.95 u is accounted for by the fact that a double bond in the alpha, beta position shifts the peak about .2 u.

CHAPTER III

EXPERIMENTAL

4-Bromo-2-methylanisole .-A solution of 9.5 ml. of bromine in 20 ml. of carbon tetrachloride was added, with stirring, to 20 g. of o-methyl anisole in 15 ml. of carbon tetrachloride. The reaction vessel, a 300 ml. three-necked flask, was immersed in a salt-ice water bath. The addition of the bromine took about 50 min. to an hour. After the addition, the mixture was washed with 20% sodium hydroxide and water. It was dried over calcium chloride. The solvent was evaporated off; and the product, a white crystalline solid, was recrystallized from methanol. The yield was 28.5 g. (85%), m.p. 65.5°-66.5°C Lit (3): 67.5°-68-5°.

2,6-Naphthalenediol (II).-Using a 500 ml. three-necked steel flask, fitted with a stirrer and thermocouple, 250 g. of potassium hydroxide and 50 g. of sodium hydroxide were heated to 275°; then, 110 g. of sodium 2-naphthol-6-sulfonic acid (I) was added with stirring. The heating was continued until the temperature reached about 320°C. The heating was discontinued and the mixture was cooled to about 100°C. Water was added cautiously until the flask was about one-half full. The contents were poured over 500 ml. of hydrochloric acid and ice with stirring. The product was filtered and dissolved in 1200 ml. of boiling water. 10 g. of Norit was added and the hot solution filtered. The yield was 27 g. (38%), m.p 218°.

2,6-Dimethoxynaphthalene (III).-To a solution of 17 g. of sodium dissolved in 300 ml. of methanol, in a 1 l. three-necked flask, was

added 55 g. of 2,6-naphthalenediol with stirring. The bulk of the methanol was removed by vaccum evaporation and 350 ml. of benzene was added. The benzene was distilled until the temperature reached 75°C. The mixture was cooled and 83 ml. of dimethyl sulfate was added. The mixture was refluxed about one-half hour. The mixture was diluted with water and the rest of the benzene distilled off. It was acidified and filtered. The product was treated with ethanol to dissolve out the gum. The yield of crude product was 50 g.(84%), m.p. 150° (11).

3,4-Dihydro-2,6-dimethoxynaphthalene (IV).-A solution of 45 g. of 2,6-dimethoxynaphthalene (III) in 550 ml. of isoamyl alcohol was heated to boiling in a three-necked flask, fitted with stirrer and reflux condenser; 45 g. of sodium was then added in small pieces. The mixture was stirred and refluxed until the sodium was dissolved. The solution was cooled and water added to decompose the alcoholate. Benzene was added and the organic layer separated. The organic solvent was distilled off in vacuo, until the product solidified. Ethanol was used for recrystallization. The yield was 34.5 g. (77%), m.p. 83°-4° (11).

6-Methoxy-2-tetralone (V).-A mixture of 25g.of 3,4-dihydro-2,6-dimethoxynaphthalene (IV) and 50 ml. of 88% formic acid was shaken in a separatory funnel to dissolve the reactant. A few drops of water were added, and the mixture was allowed to stand for about 10 minutes. It was diluted with water and extracted twice with benzene. The benzene layers were washed with water and then sodium bicarbonate. After drying over magnesium sulfate, the benzene was removed by vacuum evaporation and the product was distilled at 120°-122°/1mm. The yield was 19.5 g. (81%).

1,1-Dimethyl-6-methoxy-2-tetralone (VI).-To a solution of 33.5 g. of 6-methoxy-2-tetralone (V) in 150 ml. of dry ether; using a three-necked

flask fitted with stirrer, dropping funnel, and reflux condenser, 10.2 g. of sodium hydride was added. An argon atmosphere was used. After the evolution of hydrogen had subsided, 26.3 ml. of methyl iodide, in ether, was added. The reaction flask was cooled in a pan of cold water during the reaction. After the addition was complete, the mixture was refluxed for about an hour and five more ml. of methyl iodide was added. The reflux was continued for about an hour, after which time the mixture was cooled and hydrolyzed with water and dilute hydrochloric acid. After washing with water and sodium hydroxide, the water layers were extracted with benzene which was combined with the ether layer and dried over magnesium sulfate. The solvent was removed by vacuum evaporating and the product distilled at 116°-118°/1mm. The yield was 27 g. (70%). n_D^{21} = 1.5448 compared with the accepted value of 1.5440.

2-Methoxy-5,5-dimethyl-6-hydroxy-6-(3-methyl-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene (VII).-Using a 300 ml. three-necked flask fitted with stirrer, thermometer, and dropping funnel, 12 g. of 4-bromo-2-methylanisole in 25 ml. of dry ether and 25 ml. of dry toluene was added dropwise to 2 g. of lithium sand containing 0.2 g. of sodium in dry ether. An atmosphere of argon was maintained in the reaction vessel at a temperature between -2° and -5°C. After the addition was complete, the reaction mixture was decanted into another flask through a plug of glass wool. With the temperature at about 0°C, 8 g. of 1,1-dimethyl-6-methoxy-2-tetralone (VI) was added dropwise with stirring in an argon atmosphere. After addition of the tetralone, the mixture was hydrolyzed with water. The ether layer was washed with water and the solvent removed by vacuum evaporation. A small amount of petroleum ether was added to the residue and the

container refrigerated. The product was filtered and recrystallized from methanol. A yield of 6 g. (47%) of product was obtained, m.p. 143°-145°. Infrared spectrum (CCl_4): 6.65 u, 7.98 u, 9.6 u.

Anal. Calcd, for $C_{21}H_{26})_3$: C, 77.3; H, 7.9. Found C, 77.13; H, 7.98.

2-Methoxy-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)-5,8-dihydronaphthalene (VIII).- To a solution of 3 g. of 2-methoxy-5,5-dimethyl-6-hydroxy-6-(3-methyl-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene (VII) dissolved in a minimum of hot toluene in a 50 ml. suction flask was added 1.2 ml. of thionyl chloride (50% excess). The mixture was heated to boiling for a few minutes and the excess thionyl chloride and toluene removed by vacuum evaporation. The product, which crystallized on cooling, was recovered by suction filtration and recrystallized from ethanol. A yield of 2.3 g. (82%) was obtained, m.p. 108°-110°C. The infrared spectrum was similar to that of VII except that it did not have a small peak at 2.75 u.

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.8; H, 7.8. Found: C, 81.82; H, 7.62.

2-Methoxy-1,4,5,6,7,8-tetrahydro-5,5-dimethyl-6-(3-metnyl-4-methoxyphenyl)-naphthalene (IX).- A 500 ml. three-necked flask containing 100 ml. of liquid ammonia was kept at -35°C in a dry ice-ethanol bath. To this was added a solution of 3 g. of 2-methoxy-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)-5,8-dihydronaphthalene (VIII) in 50 ml. of morpholine. Small pieces of lithium, totaling 3 g., were added with stirring. After all the lithium had dissolved and a bronze-colored layer had formed, absolute alcohol was added until the layer broke up and the blue color of the

lithium was discharged. Water was added and the product, which separated out, was recovered by suction filtration. The crude product, weighing about 3 g., was recrystallized from acetone. Even after several recrystallizations the melting point of 122°-130°C was not improved. A derivative with 2,4-dinitrophenylhydrazine was prepared. It melted at 178°-182°C. This indicated that some of the desired product was obtained. In an attempt to prepare a pure sample for analysis, 1 g. of the product was chromatographed on 20 g. of alumina using a benzene-cyclohexane solvent system. A good separation was not obtained, so a column of charcoal was used. The only fraction that was obtained with a good melting point (127°-129°C) showed phenol ether peaks on its infrared spectrum at 6.7 u and 8.1 u.

2(3H)-Naphthalenone-4,4a,5,6,7,8-tetrahydro-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl) (X).- To a solution of 3 g. of 2-methoxy-1,4,5,6,7,8-tetrahydro-5,5-dimethyl-6-(3-methyl-4-methoxyphenyl)-naphthalene (IX) in 20 ml. of dioxane with a little water was added 1.2 ml. of hydrobromic acid. After standing for 10 minutes the reaction mixture was diluted with water and extracted twice with benzene. The benzene was removed by vacuum evaporation, and the viscous oil was dissolved in about 3 ml. of methanol and seeded. The crystals that were obtained proved to be impurities. The semicarbazone was prepared and treated with benzene to dissolve out any impurities. The semicarbazone melted at 205°-208°C. The benzene-soluble residue melted at 123°-127°C. It amounted to about 10% of the product. It was thought that this was VIII with the non-aromatic double bond reduced. The final product, obtained by vacuum distillation at 148°-150°C, was a very viscous liquid. Infrared spectrum (CCl_4): 5.8 u, 5.95 u. 6.7 u, and 7.9 u.

Anal. Calcd. for $C_{20}H_{26})_2$: C, 80.5; H, 8.7. Found: c, 80.29; H, 8.63.

2-Methoxy-4-dimethyl-6-(3-methyl-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene (VIIIa).- A 300 ml. three-necked flask containing 10 ml. of liquid ammonia was kept at -35°C in a dry ice-ethanol bath. To this was added a solution of 1 g. of VIII in morpholine. Ammonium chloride was added until the blue color was discharged. Water was added, and the product was removed by suction filtration. After crystallizing from ethanol, the melting point was 124.5°-127.5°C. A mixed melting point with the impurity from X showed no depression.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39. Found: C, 81.51; H, 8.41.

CHAPTER IV

SUMMARY

The purpose of this problem was to synthesize a compound related in general molecular shape to steroid hormones, but not having the actual steroid nucleus, and to have it tested for steroid hormone activity and hormone antagonist activity with the hope that it might be effective in cancer therapy.

The starting material was the commercially obtainable sodium-2-naphthol-6-sulfonic acid (I). Fusion with potassium hydroxide followed by methylation gave 2-6-dimethoxynaphthalene (III). Treating this with iso amyl alcohol and sodium followed by hydrolysis with formic acid gave 6-methoxy-2-tetralone (V). Two methyls were substituted in position 1 by treating V with sodium hydride and methyl iodide to obtain 1,1-dimethyl-6-methoxy-2-tetralone (VI). The third ring was added by means of addition of the organolithium compound of 4-bromo-2-methylanisole. This was prepared by addition of the bromo compound to lithium sand at -2 to -5, in an argon atmosphere. The product (VII) was dehydrated by using thionyl chloride to obtain (VIII). The first work done on reduction of a methoxy, such as VIII to the enol ether form of IX was done by Birch. He used an alcohol ammonia solution with addition of sodium. Wilds later improved upon Birch's method by addition of the alcohol last and using lithium. Wilds' method was used here. The hydrolysis of IX to the conjugated unsaturated ketone X was effected by hydrobromic acid. The final product could be considered to an analog of testosterone. Ultraviolet and infrared

absorption data showed the desired conjugation to be in the order about 60%.

LITERATURE CITED

1. Birch, A. D., J. Chem. Soc., 430 (1944).
2. Birch, A. D., J. Chem. Soc., 4688 (1958).
3. Carpenter, M. S. and Easter, J. Org. Chem. 20, 401-411 (1955).
4. Cornforth, Cornforth, and Robinson, J. Chem. Soc., 689-91 (1942).
5. Grundy, Jessee, Chem. Rev., 57, 281-416 (1957).
6. Lauppi and Studer, Experinetia, 15, 264 (1959).
7. Miescher, K., Helv. Chim. Acta. 30, 786 (1947).
8. Nazarov, I. N., C. A. 51, 8663 (1957).
9. Nazarov, I. N., C. A. 53, 4242f (1959).
10. Palopoli, Abstracts of Paper, 134th meeting, Amer. Chem. Soc., Chicago Ill. (1958).
11. Robinson and Weygand, J. Chem. Soc., 386-91 (1941).
12. Schoeller, U. S. Patent 2,392,864, (1946).
13. Ungnade and Tucker, J. Amer. Chem. Soc. 71, 1381 (1949).
14. Wilds and Nelson, J. Amer. Chem. Soc. 75, 5360 (1953).
15. Wilds and Shunk, J. Amer. Chem. Soc. 72, 2388 (1950).
16. Wilds and Shunk, J. Amer. Chem. Soc. 76, 1733-6 (1954).
17. Wilds and Shunk, J. Amer. Chem. Soc. 77, 647-51 (1955).