# THE SYNTHESIS OF THE NAPHTHALENE ANALOGS OF STILBESTROL AND HEXESTROL, THEIR METHYL HOMOLOGS, AND THEIR DIMETHYL ETHERS

# THE SYNTHESIS OF THE NAPHTHALENE ANALOGS OF STILBESTROL AND HEXESTROL, THEIR METHYL HOMOLOGS, AND THEIR DIMETHYL ETHERS

By

MANFRED KATZ

Bachelor of Science
Oklahoma Agricultural and Mechanical College
Stillwater, Oklahoma
1950

Submitted to the Department of Chemistry
Oklahoma Agricultural and Mechanical College
In Partial Fulfillment of the Requirements
for the Degree of
MASTER OF SCIENCE
1951

# THE SYNTHESIS OF THE NAPHTHALENE ANALOGS OF STILBESTROL AND HEXESTROL, THEIR METHYL HOMOLOGS, AND THEIR DIMETHYL ETHERS

MANFRED KATZ

MASTER OF SCIENCE

1951

THESIS AND ABSTRACT APPROVED:

Ernest M. Hodnett
Thesis Adviser

O C Dermer
Faculty Representative

D. C. McIntosh
Dean of the Graduate School

# ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. E. M. Hodnett under whose direction and guidance this work has been done.

At the same time he acknowledges the financial aid rendered by the Oklahoma A. and M. College in the form of a graduate fellowship in the Department of Chemistry.

TABLE OF CONTENTS

Chapter Page

# INTRODUCTION

In 1933 Cook, Dodds, and Hewett (2) predicted that "a whole group of substances of related chemical constitution will be found to have estrus-exciting properties and the synthetic production of such substances would probably be of considerable clinical value". Since that time different workers have prepared several hundred substances which have been shown to possess some estrogenic activity.

The discovery of the estrogenic activity of stilbestrol and hexestrol in 1938 by Dodds, Goldberg, Lawson, and Robinson (3) constitutes by far the most important single advance of this research. Since that time research on synthetic estrogens has clearly shown a trend of elaborating and improving over these known structures rather than venturing into entirely new fields. Representative of the few estrogenic compounds of entirely different structure are 3-(6'-methoxy-2'-naphthyl)-2,2-dimethylpentanoic acid and the corresponding 6-hydroxy derivative (5), and the doisynolic acids which are really included in the class of the steroids. Most of the other compounds with estrogenic activity have structures which, strictly speaking, are neither stilbene nor dihydrostilbene derivatives, but are nevertheless closely related. Among these are derivatives of diphenylmethane, 1,3-diphenylpropane, triphenylethylene, and certain closedring analogs. Much research has also been done on devising shorter and better methods of synthesizing stilbestrol, hexestrol, and their derivatives. One of the better methods for synthesizing stilbestrol (12) and hexestrol (13) is due to Kharasch and Kleiman. These two syntheses are completely different from those used by Dodds and co-workers.

The great amount of painstaking detailed research done in this field is the result of the importance of synthetic estrogens as therapeutic agents, an importance which is mainly due to their greater availability and to their efficacy on oral administration. Estrogens can often improve cases of ovarian inadequacy not due to pituitary failure. Thus a cyclic estrone-progesterone program sometimes initiates or restores normal ovarian function in young women with an ovulatory failure. Various types of hypoestrogenism are known; if ovarian failure alone is the cause, estrogen therapy is justified even though it must be continued indefinitely. In certain pituitary diseases estrogens are used to depress pituitary activity. Inhibition of the pituitary lactogenic hormone provides the basis for use of estrogens to suppress lactation, although testosterone is more effective in this respect. Other clinical uses of estrogens depend upon their ability to stimulate growth of epithelial tissues; they are used in senile vaginitis, in bacterial infection of the vaginal mucosa of children, in atrophic rhinitis, and hypomastia. The rather widespread use of estrogens for treatment of climacteric symptoms probably is not always justified.

Estrogens should not be used indefinitely for this purpose, for they merely postpone a natural process. The above survey is not intended to be complete, but merely presents a few of the more firmly established uses.

In 1923 Allen and Doisy devised a convenient test for the estrogens which depends upon their ability to produce the typical estrous reaction when injected into castrated mice or rats. A positive reaction is easily recognized, for the reproductive cycle in the normal animal is characterized by distinct changes in the cell structure of the lining of the vagina. At the height of estrus the lining acquires a unique cornified character easily distinguished from that typical of the resting period or of the permanent condition of castrated animals. Microscopic examination of vaginal smears gives a reliable indication of the estrous condition of the living animal (6).

Another convenient test for estrogenic activity consists of determining the increase in oviduct weight of baby chicks by the seventeenth day after hatching. However, the effect of different synthetic estrogens on domestic fowl is in many cases different from that noted on rats and mice (10). It is obvious from the preceding statement that animal experiments serve only for the purpose of screening compounds for therapeutic trial.

The purpose of this investigation was the synthesis of the naphthalene analogs of stilbestrol and hexestrol, their dimethyl ethers, and their methyl homologs for the purpose of determining their estrogenic potency by both oral and subcutaneous administration on baby chicks and on rats or mice.

# HISTORICAL

Even before the structure of the natural female sex hormones had been fully elucidated, Cook and Dodds with their collaborators undertook to synthesize more readily accessible estrogenic substances of simpler structure. The first compounds of non-steroid structure reported in 1933 by these authors to possess estrogenic activity were 1-keto-1,2,3,4-tetrahydrophenanthrene and the corresponding 4-keto derivative. Their activity is low compared with that of estrone, and it was later recognized that activities of such low order are common to a very large number of compounds; however, there exist practically no qualitative differences between natural and synthetic estrogens. Between 1933 and 1938 Dodds and his collaborators, as well as others, synthesized a large number of compounds, many of which were found to possess weak activity. During this period there was a development away from structures containing the phenanthrene skeleton and towards the simpler, yet much more potent, stilbene derivatives (17).

The first synthesis of stilbestrol was published in 1938 by Dodds, Goldberg, Lawson, and Robinson (3) and is outlined below:

$$p\text{-}CH_3OC_6H_4CHO \xrightarrow{KCN} p\text{-}CH_3OC_6H_4CH(OH)COC_6H_4OCH_3\text{-}p$$

$$\xrightarrow[100^\circ \text{ for 24 hrs.}]{\text{Zn dust, HOAc}} p\text{-}CH_3OC_6H_4CH_2COC_6H_4OCH_3\text{-}p \xrightarrow[EtI]{EtONa}$$

$$p\text{-}CH_3OC_6H_4CH(C_2H_5)COC_6H_4OCH_3\text{-}p \xrightarrow{EtMgBr}$$

$$p\text{-}CH_3OC_6H_4CH(C_2H_5)C(OH)(C_2H_5)C_6H_4OCH_3\text{-}p \xrightarrow[KHSO_4]{PBr_3 \text{ or}}$$

$$p\text{-}CH_3OC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4OCH_3\text{-}p \xrightarrow[205^\circ]{KOH\text{-}EtOH}$$

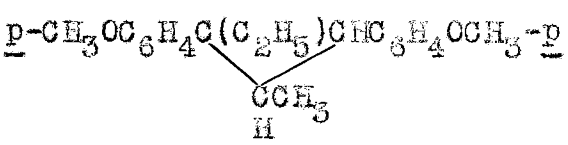
$$p\text{-}HOC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4OH\text{-}p$$

The relatively poor yield and the increasing demands for therapeutic use were incentives for many workers to develop new syntheses. Many modifications of Dodds' original method have been made as well as some entirely different ones. One of the shortest syntheses of stilbestrol, starting with anethole (I), was devised by Kharasch and Kleiman (12):

$$\underset{I}{p\text{-}CH_3OC_6H_4CH=CHCH_3} \xrightarrow[-80^\circ]{HBr} \underset{II}{p\text{-}CH_3OC_6H_4CHBrCH_2CH_3}$$

$$\text{II} \xrightarrow{NaNH_2 \text{ in liq. } NH_3} \underline{p}\text{-}CH_3OC_6H_4CH(CH{=}CH_2)CH(C_2H_5)C_6H_4OCH_3\text{-}\underline{p}$$

III

or 

$$\underline{p}\text{-}CH_3OC_6H_4C(C_2H_5)CHC_6H_4OCH_3\text{-}\underline{p} \xrightarrow[224^\circ]{KOH,\ (CH_2OH)_2}$$

IV

$$\underline{p}\text{-}HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OH\text{-}\underline{p}$$

V

Since the reaction product from the anethole hydrobromide (II) and sodium amide in liquid ammonia was not the dimethyl ether of stilbestrol, Kharasch postulated the structures III and IV which yielded stilbestrol (V) on demethylation.

Hexestrol was first obtained by Dodds in very small yields from the demethylation products of anethole. Peak and Short (15) synthesized hexestrol starting from anethole hydrobromide by means of a Wurtz-type reaction using sodium, magnesium, aluminum, zinc, or the liquid alloy of potassium and sodium. Kharasch and Kleiman (13) devised an even better synthesis. By means of cobaltous chloride as a catalyst in the presence of a Grignard reagent the anethole hydrobromide (II) is reduced to yield a free radical, which dimerizes to hexestrol dimethyl ether (VI). The reactions are as follows:

$$\underline{p}\text{-}CH_3OC_6H_4CHBrCH_2CH_3 \xrightarrow[\text{ether-toluene}]{C_6H_5MgBr,\ 0.05\ \text{equiv.}\ CoCl_2}$$

II

$$\underline{p}\text{-}CH_3OC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OCH_3\text{-}\underline{p} \xrightarrow{HI}$$

VI

$$\underline{p}\text{-}HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OH\text{-}\underline{p}$$

VII

Kharasch proposes the following mechanism:

$$C_6H_5MgBr + CoCl_2 \longrightarrow C_6H_5CoCl + MgBrCl$$

$$2\ C_6H_5CoCl \longrightarrow C_6H_5\text{-}C_6H_5 + 2\ {}^{\bullet}CoCl$$

$$\underline{p}\text{-}CH_3OC_6H_4CHBrCH_2CH_3 + {}^{\bullet}CoCl \longrightarrow \underline{p}\text{-}CH_3OC_6H_4\dot{C}HCH_2CH_3 + CoClBr$$

$$2\ \underline{p}\text{-}CH_3OC_6H_4\dot{C}HCH_2CH_3 \longrightarrow \underline{p}\text{-}CH_3OC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OCH_3\text{-}\underline{p}$$

Wilds (21) who used the ethyl Grignard reagent instead of the phenyl Grigard reagent proposes the following mechanism:

$$2\ C_2H_5MgBr + CoCl_2 \longrightarrow MgBr_2 + MgCl_2 + (C_2H_5)_2Co$$

$$(C_2H_5)_2Co \longrightarrow C_2H_6 + C_2H_4 + Co$$

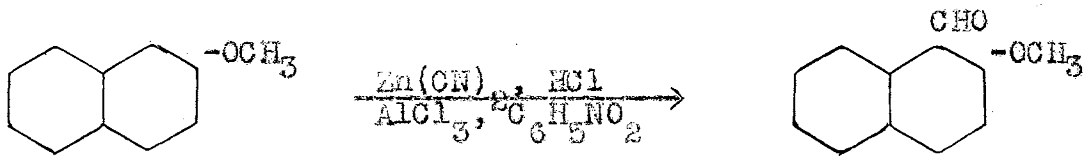
$$2\ \underline{p}\text{-}CH_3OC_6H_4CHBrCH_2CH_3 + Co \longrightarrow 2\ \underline{p}\text{-}CH_3OC_6H_4\dot{C}HCH_2CH_3 + CoBr_2$$

$$2\ \underline{p}\text{-}CH_3OC_6H_4CHCH_2CH_3 \longrightarrow \underline{p}\text{-}CH_3OC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OCH_3\text{-}\underline{p}$$

A review on synthetic estrogens covering the literature up to January, 1946 by Ulrich V. Solmssen (17) has been an invaluable aid in the literature search.

## PRELIMINARY DISCUSSION

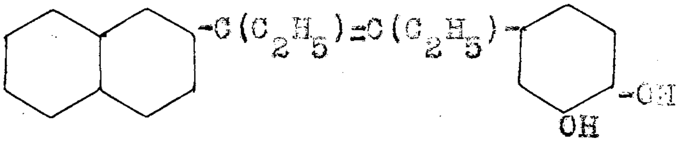
The original plan for this research was to prepare 6-methoxy-2-naphthaldehyde, to run a benzoin condensation on it, and to continue from there with essentially the same procedure used by Dodds to prepare stilbestrol. 6-Methoxy-2-propionylnaphthalene and 6-methoxy-2-acetyl-naphthalene had been prepared by Friedel-Crafts reactions between 2-methoxynaphthalene (VIII) and propionyl chloride and acetyl chloride, respectively, using nitrobenzene as solvent, whereas the 2-methoxy-1-acetylnaphthalene and 2-methoxy-1-propionylnaphthalene were obtained with benzene or carbon disulfide as the solvent (7,9). It seemed logical that 6-methoxy-2-naphthaldehyde could be obtained by a modified Gattermann reaction using nitrobenzene as the solvent. However, when this synthesis was attempted, 2-methoxy-1-naphthaldehyde (IX) was obtained instead in 64% of the theoretical yield.



VIII

IX

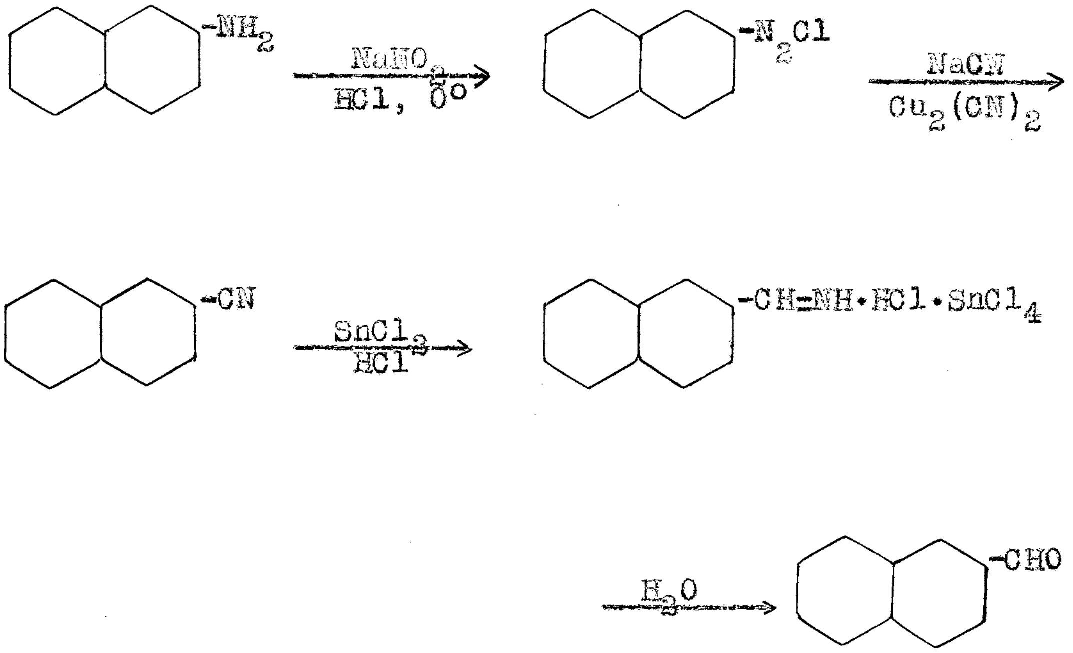
Since the author had done some previous work on the preparation of 2-naphthaldehyde and its benzoin condensation with piperonal, it was proposed that the 3,4-methylenedioxy-2-naphthoin be prepared and then taken through the same steps as in Dodds' procedure except for the last step, which would have been the splitting of the methylenedioxy group by means of phosphorus pentachloride and hot water (8) to give the following compound (X).



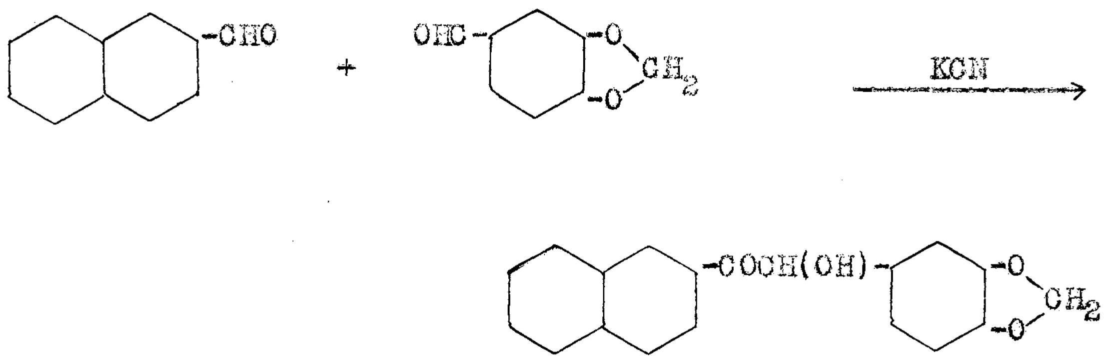
X

However, the yield of 2-naphthaldehyde by the following series of reactions (A.) as well as the yield from the crossed benzoin condensation (B.) was too low for the method to be practical.

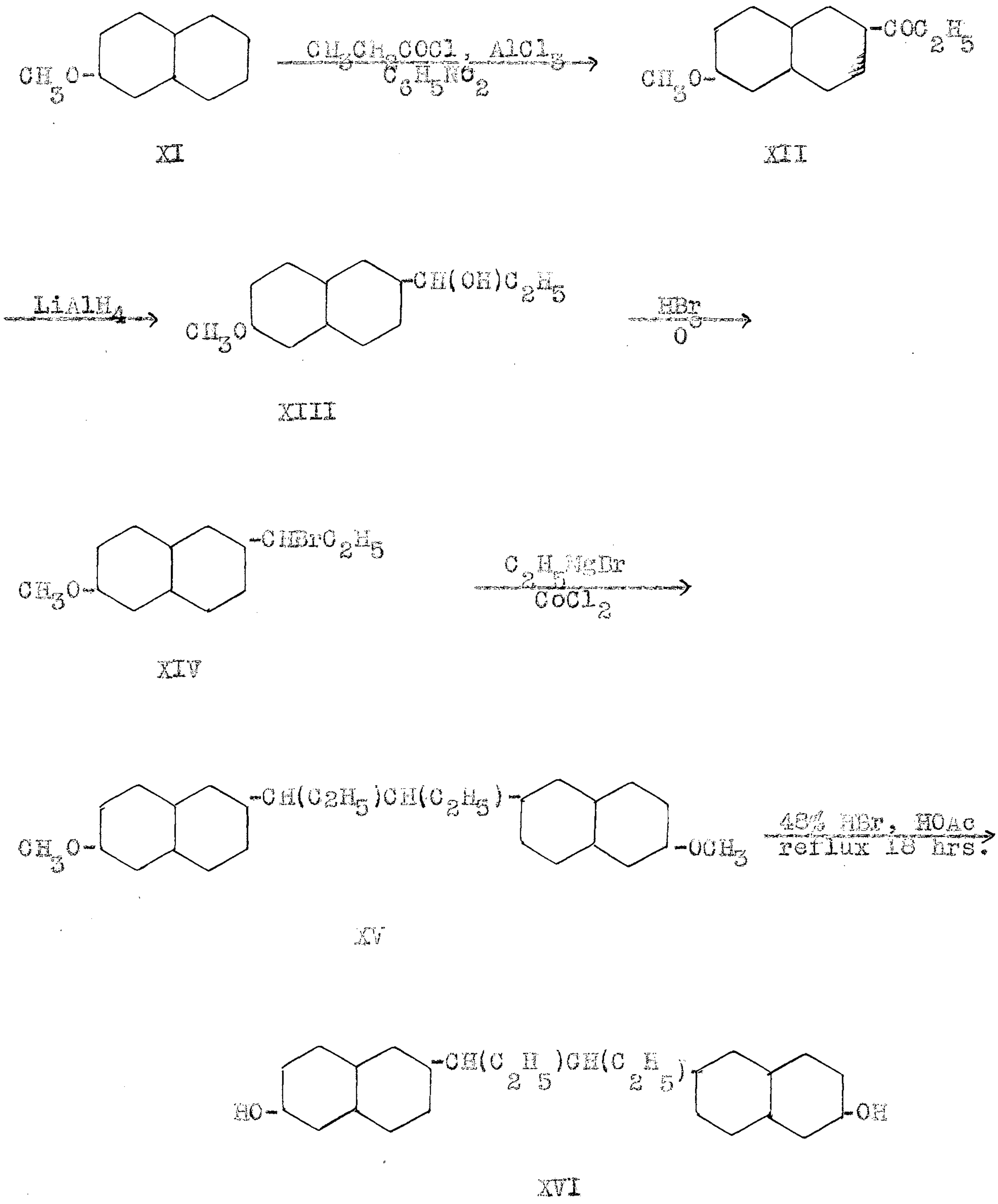
A.



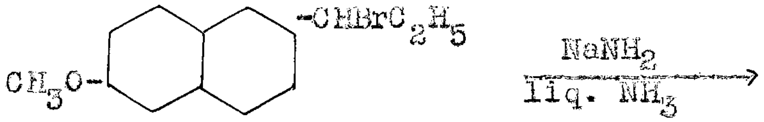
B.



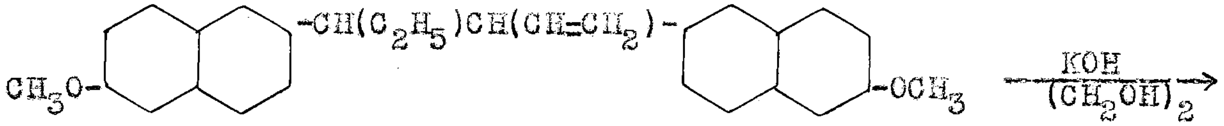
It was therefore decided to use the syntheses developed by Kharasch and Kleiman (12, 13) to obtain the naphthalene analogs of stilbestrol and hexestrol and their methyl homologs. 1-(6'-Methoxy-2'-naphthyl)-1-propanone (XII) was prepared in 55% yield by the Friedel-Crafts reaction of 2-methoxynaphthalene (XI) and propionyl chloride using nitrobenzene as the solvent (9). This ketone was reduced to 1-(6'-methoxy-2'-naphthyl)-1-propanol (XIII) by means of lithium aluminum hydride (14). 1-(6'-Methoxy-2'-naphthyl)-1-bromopropane (XIV) was prepared by dissolving the 1-(6'-methoxy-2'-naphthyl)-1-propanol in enough toluene to effect solution, and then saturating the solution, cooled to $0^{o}$ in an ice bath, with hydrogen bromide (1). The meso form of 3,4-bis(6'-methoxy-2'-naphthyl)hexane (XV) was obtained by adding 1-(6'-methoxy-2'-naphthyl)-1-bromopropane to a mixture of ethylmagnesium bromide and a catalytic amount of anhydrous cobaltous chloride (21). The racemic form of 3,4-bis(6'-methoxy-2'-naphthyl)hexane was obtained from the same reaction. On demethylation of XV by means of refluxing with a mixture of 48% hydrobromic acid and glacial acetic acid (21) the 3,4-bis(6'-hydroxy-2'-naphthyl)-hexane (XVI) was obtained.



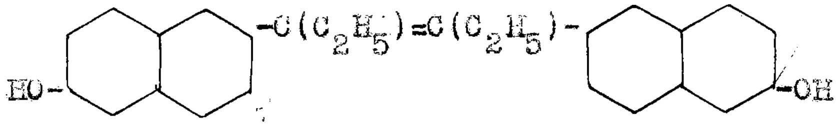
The product obtained by adding 1-(6'-methoxy-2'-naphthyl)-1-bromopropane (XIV) to a suspension of sodium amide in liquid ammonia (12) was separated into a brown oil and a white solid which is believed to be the trans isomer of 3,4-bis(6'-methoxy-2'-naphthyl)-2-hexene (XVII). On demethylation of this compound by means of refluxing with potassium hydroxide and diethylene glycol, trans-3,4-bis(6'-hydroxy-2'-naphthyl)-3-hexene (XVIII) was obtained.



XIV



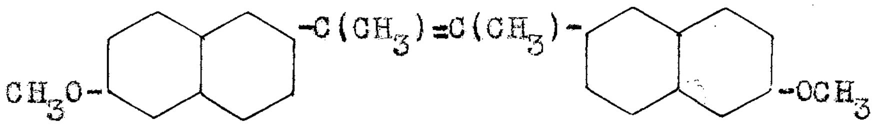
XVII



XVIII

The methyl homologs of the above compounds were prepared in the same manner as the ethyl derivatives. 6-Methoxy-2-acetylnaphthalene was obtained in only 34% of the theoretical yield from the Friedel-Crafts reaction owing to a side reaction which yielded 2,2'-dimethoxy-1,1'-binaphthyl. Scholl and Seer (16) have reported the preparation of 2,2'-dimethoxy-1,1'-binaphthyl by the self-condensation of 2-methoxynaphthalene in the presence of aluminum chloride and nitrobenzene. A 93% yield of the alcohol was obtained in the reduction of the ketone with lithium aluminum hydride. The meso isomer of 2,3-bis(6'-methoxy-2'-naphthyl)butane was obtained from the dimerization of the bromide in the presence of ethylmagnesium bromide and cobaltous chloride. On demethylation 2,3-bis-(6'-methoxy-2'-naphthyl)butane was obtained in 90% of the theoretical yield from the dimethyl ether.

The trans isomer of 2,3-bis(6'-methoxy-2'-naphthyl)-2-butene was obtained in 17% of the theoretical yield, calculated from the alcohol, and demethylated to 2,3-bis(6'-hydroxy-2'-naphthyl)-2-butene. The cis isomer of 2,3-bis-(6'-methoxy-2'-naphthyl)-2-butene was isolated from the same reaction mixture in 29% of the theoretical yield, also calculated from the alcohol, and demethylated to 2,3-bis(6'-hydroxy-2'-naphthyl)-2-butene. It is to be noted here that the ease with which the cis and trans isomers were separated was no doubt due to the fact that they cannot form the type of compounds (III and IV) with the double bonds in the position postulated by Kharasch, but must have the double bond in the 2 position as in XIX.



XIX

## EXPERIMENTAL

### Attempted Preparation of 6-methoxy-2-naphthaldehyde

In a one-liter three-neck flask, fitted with an efficient stirrer, a reflux condenser, an inlet tube, and a thermometer, were placed 100 g. of 2-methoxynaphthalene, 110.5 g. of zinc cyanide and 400 cc. of nitrobenzene. The inlet tube was connected to a source of dry hydrogen chloride, and the mixture, maintained at room temperature, was stirred while a rapid stream of hydrogen chloride was passed into it. After hydrogen chloride had been passed into the mixture for about one-half hour, the mixture became green in color and began to thicken until it was necessary to add an additional 200 cc. of nitrobenzene. Hydrogen chloride was passed into the mixture until it was saturated (about three hours). The flask was then immersed in an ice bath, and 189 g. of finely ground anhydrous aluminum chloride was added in small portions over a period of one hour. The ice bath was then removed, and the passage of hydrogen chloride was continued for an additional two and one-half hours. The mixture, which had turned black in color upon the addition of aluminum chloride, was hydrolyzed by pouring it onto a well-agitated mixture of two liters of ice slush and 100 cc. of concentrated hydrochloric acid. After the mixture had stood overnight, it was transferred into a five-liter round-bottom flask, and refluxed for three hours.

The flask was then fitted for steam distillation, and superheated steam was passed into it for eight hours in which time ten liters of distillate, containing all of the nitrobenzene, had distilled over. Upon cooling there formed a black solid on top of the water in the distilling flask. This solid was isolated by filtration, dissolved in hot alcohol, and refluxed with decolorizing carbon, and the solution was filtered. When the filtrate was cooled, 75 g. of brown crystals precipitated. These crystals were vacuum-distilled at 160-70° at a pressure of 6 mm. upon which they crystallized in beautiful yellow needles having a melting point of 84°. This melting point indicated that 2-methoxy-1-naphthaldehyde, recorded melting point 84°, had been obtained instead of the desired 6-methoxy-2-naphthaldehyde, which was further verified by oxidizing the aldehyde to the acid with alkaline potassium permanganate. When recrystalized from alcohol, the acid had a melting point of 176° as compared to 176-7° reported by Warren (20). The percentage yield of 2-methoxy-1-naphthaldehyde was 64%.

## Attempted benzoin condensation of 2-methoxy-1-naphthaldehyde and piperonal

Ten and fifty-four hundredths grams of 2-methoxy-1-naphthaldehyde and 8.45 g. of piperonal were placed in a 250-cc. three-neck flask and dissolved in 40 cc. of alcohol. The solution was brought to reflux, and then 10 g. of potassium cyanide dissolved in 20 cc. of water was added during a forty-five-minute interval through a dropping funnel. The solution was refluxed for an additional thirty minutes, and agitated for two more hours. Upon standing overnight it deposited some nice large crystals. When recrystallized from alcohol, they melted at 84°, indicating that they were unreacted 2-methoxy-1-naphthaldehyde.

### Attempted benzoin condensation of 2-methoxy-1-naphthaldehyde with itself

Nine and five tenths grams of 2-methoxy-1-naphthaldehyde dissolved in 20 cc. of alcohol, and 5 g. of potassium cyanide dissolved in 10 cc. of water were placed in a 200-cc. round-bottom flask to which a reflux condenser was attached, and refluxed for two and one-half hours. When the mixture was cooled, a mass of crystals formed, but it was found that they melted at 84°, indicating that they were unreacted aldehyde. Therefore an additional 5 g. of potassium cyanide dissolved in 5 cc. of water was added, and the solution refluxed for two more hours. Again on cooling of the mixture a mass of crystals formed which had a melting point of 84°. It was therefore concluded that 2-methoxy-1-naphthaldehyde will not form a symmetrical benzoin under these conditions.

### Preparation of cuprous cyanide (18)

Two hundred grams of copper sulfate (pentahydrate) was dissolved in 640 cc. of water, heated to 60°, and acidified with dilute sulfuric acid until the solution was acid to congo red. Then a solution of 56 g. of sodium bisulfite dissolved in 160 cc. of water which had also been heated to 60° was quickly added to the cupric sulfate solution with vigorous agitation. Then a solution of 56 g. of potassium cyanide dissolved in 160 cc. of water was immediately added in five portions to the above solution with vigorous agitation. After approximately fifteen minutes, the precipitate of cuprous cyanide which had formed was filtered onto a Buchner funnel and washed three times with 50-cc. portions of hot water.

Preparation of 2-naphthonitrile (18)

Ninety-six grams of 2-naphthylamine was diazotized by dissolving it in 170 cc. of concentrated hydrochloric acid and 170 cc. water, and cooling it to 0° in an ice bath while a solution of 48 g. of sodium nitrite dissolved in 100 cc. of water was slowly added. The mixture was mechanically stirred to assure proper mixing. The cuprous cyanide previously prepared was transferred to a two-liter round-bottom flask and dissolved in a solution of 104 g. of potassium cyanide dissolved in 250 cc. of water. This cuprous cyanide solution was slowly heated to 60°, and the cold diazonium salt solution was slowly added while the mixture was vigorously agitated. This addition took about two hours since there was violent frothing after each addition of the diazonium salt solution due to the nitrogen coming off. When all of the diazonium salt had been added, a reflux condenser was attached, and the mixture was heated on a boiling water bath for thirty minutes to complete the reaction. The flask was then fitted for steam distillation, and steam was passed into the mixture for nine hours. As the distillate cooled, a white precipitate of 2-naphthonitrile settled out and was collected on a Buchner funnel. This crude product was transferred to a 125-cc. Claisen flask and vacuum-distilled. The yield was 15.5 g. of material having a melting point of 65.5°, which compares favorably with the recorded value of 66°.

### Stephen reduction of 2-naphthonitrile to the aldehyde (19)

Anhydrous stannous chloride was prepared by placing 86 g. of acetic anhydride in a 400-cc. beaker and slowly adding to it 115 g. of stannous chloride dihydrate with stirring. After about one hour the now anhydrous stannous chloride was collected on a Buchner funnel, washed with anhydrous ether, and allowed to dry overnight in a vacuum desiccator. A one-liter three-neck flask was equipped with a wide inlet tube reaching nearly to the bottom, a mechanical stirrer, and a reflux condenser carrying a drying tube. Thirty-eight grams of anhydrous stannous chloride and 200 cc. of anhydrous ether were placed in the flask and saturated with dry hydrogen chloride. After about two hours, the mixture had become saturated with hydrogen chloride, and the stannous chloride had formed a viscous layer on the bottom of the flask. The gas inlet tube was now replaced by a dropping funnel by means of which a solution of 15.5 g. of 2-naphthonitrile dissolved in 100 cc. of anhydrous ether was quickly added.

The dropping funnel was replaced by the gas inlet tube, and dry hydrogen chloride was once more passed into the mixture until it was saturated. The mixture was agitated for another hour in which time the yellow aldimine stannichloride settled to the bottom. The ether was decanted from the aldimine stannichloride and washed twice with 50-cc. portions of ether. The flask was fitted for steam distillation, and superheated steam was passed through the mixture for eight hours. As the distillate cooled, a white precipitate of 2-naphthaldehyde formed. Twelve grams of this crude product was obtained which was further purified by vacuum distillation. The yield of this pure product was 10 g. of material with a melting point of 59-60°; 2-naphthaldehyde has a recorded melting point of 60.5-1°.

### Benzoin condensation of 2-naphthaldehyde and piperonal

Three and forty-four hundredths grams of 2-naphthaldehyde and 3.31 g. of piperonal dissolved in 10 cc. of alcohol were placed in a 200-cc. round-bottom three-neck flask which was equipped with a dropping funnel, a condenser, and a mechanical stirrer. The solution was brought to reflux, and a solution of 2.5 g. of potassium cyanide dissolved in 10 cc. of water was added during a fifteen-minute interval. During this addition the solution turned from colorless to a dark orange. The solution was refluxed an additional thirty minutes and allowed to stand overnight. In this time the solution had separated into an orange oil on the bottom and a light yellow top layer, and a few crystals had formed in the oil.

The mixture was allowed to stand for three days in which time more crystals formed. The crystals were filtered off and washed once with alcohol. The yield was 0.2 g. and the compound had a melting point of 120-22°. No further analysis of this compound was made. However, since the symmetrical benzoins of the two organic reactants have different melting points from that observed, it seems probable that the compound obtained is an isomer of 3,4-methylenedioxy-2'-naphthoin.

Preparation of (6'-methoxy-2'-naphthyl)-1-propanone (9)

In a one-liter three-neck round-bottom flask equipped with a mechanical stirrer and a thermometer were placed 94.8 g. of 2-methoxynaphthalene, 450 cc. of nitrobenzene, and 55.5 g. of propionyl chloride. The flask was immersed in a salt-ice slush and kept between 0-4° throughout the reaction period. One hundred fifty-eight grams of anhydrous powdered aluminum chloride was placed in a 250-cc. Erlenmeyer flask which was attached by means of a short piece of rubber tubing to the third neck of the flask. The aluminum chloride was added in small portions over a three-hour period. The reaction mixture turned dark green in color after the first addition of aluminum chloride and turned black as the reaction progressed. The reaction mixture was allowed to stand for thirty-six hours and was then hydrolyzed by pouring it into a mixture of ice, water, and 100 cc. of concentrated hydrochloric acid with thorough stirring. As much of the water as possible was decanted, and the product was transferred to a three-liter round-bottom flask fitted for steam distillation. After all the nitrobenzene had been steam distilled off, the black, somewhat oily residue was filtered by means of a Buchner funnel. Half of the solid so obtained was transferred to a Claisen flask and vacuum-distilled. The product from the vacuum distillation was recrystallized from alcohol. The other half of the crude product was extracted several times with hot alcohol, refluxed with decolorizing carbon, filtered, and recrystallized three times from alcohol. The combined products weighed 55 g., and had a melting point of 105-8°; Haworth and Sheldrick reported a melting point of 109°. The yield was 43% of the theoretical.

## Preparation of 1-(6'-methoxy-2'-naphthyl)-1-propanol (14)

A one-liter three-neck round-bottom flask was fitted with a dropping funnel, a mechanical stirrer, and a reflux condenser. Two grams of lithium aluminum hydride and 250 cc. of absolute ether were placed in the flask, and then 10 g. of (6'-methoxy-2'-naphthyl)-1-propanone dissolved in 200 cc. of absolute ether was added slowly through the dropping funnel. It was at times necessary to cool the flask to keep the ether from boiling too much. The stirring was continued for thirty minutes after the last of the ketone had been added. A few drops of water were then carefully added to decompose any excess of lithium aluminum hydride; this was accompanied by a vigorous evolution of hydrogen. The mixture was poured onto about 200 cc. of ice slush, and acidified by the addition of 200 cc. of 10% sulfuric acid with stirring, whereby the alcohol was liberated from the white aluminum-lithium complex.

The ether layer was separated from the water, dried over anhydrous potassium carbonate, and transferred to a 500-cc. distilling flask where the ether was distilled off. The oily residue was poured into a beaker where it slowly crystallized. Eight grams of the alcohol was obtained having a melting point of 48-50°; Campbell and Chattaway reported a melting point of 50°. The yield was 80% of the theoretical; however, a yield of 90% was obtained in a subsequent run.

## Preparation of 1-(6'-methoxy-2'-naphthyl)-1-bromopropane (1)

Four grams of 1-(6'-methoxy-2'-naphthyl)-1-propanol dissolved in 50 cc. of toluene was placed in a 250-cc. Erlenmeyer flask and immersed in a freezing mixture so as to keep the temperature below 0°. Hydrogen bromide gas, generated by allowing bromine to react with tetralin, was then passed into the toluene solution until it was saturated. The toluene solution was then washed once with ice-cold, very dilute potassium carbonate solution and once with ice-cold water to take out any excess hydrogen bromide and hydrobromic acid. The solution was dried over anhydrous calcium chloride and used thus.

## Preparation of 3,4-bis(6'-methoxy-2'-naphthyl)hexane (13)

Ethylmagnesium bromide was prepared in a 250-cc. three-neck flask fitted with a reflux condenser, a mechanical stirrer, and a dropping funnel using 0.9 g. of magnesium turnings, 3.5 g. of ethyl bromide, and 60 cc. of absolute ether. To the stirred Grignard solution at room temperature was added

0.187 g. of anhydrous cobaltous chloride, prepared by heating the hexahydrate in an oven at 150° for 36 hours. The 1-(6'-methoxy-2'-naphthyl)-1-bromopropane dissolved in 50 cc. of toluene and prepared from 4 g. of the corresponding alcohol was added over a period of thirty minutes. The mixture was allowed to stand overnight and then poured into a mixture of ice and 10 cc. of concentrated hydrochloric acid. A three-phase system was observed: the water layer, a thin layer composed of a white solid, and the ether-toluene layer. The solid was filtered out, and after recrystallization from benzene-ligroin, it had a melting point of 257-9°. Fifty-two hundredths of a gram of the desired meso isomer of 3,4-bis(6'-methoxy-2'-naphthyl)hexane was isolated which is 15% of the theoretical yield, calculated from the alcohol; however a 28% yield was obtained in a subsequent run. Campbell and Chattaway (1) reported a melting point of 255° for this compound. Carbon and hydrogen analysis yielded the following results: Calculated for $C_{28}H_{30}O_2$: C, 84.38%; H, 7.59%. Found: C, 84.29%; H, 7.84%.

The ether-toluene was separated from the water, the water was extracted once with 15 cc. of ether which was combined with the ether-toluene solution. The ether-toluene was evaporated off, and the oily residue was taken up in alcohol. After remaining in the icebox for a week, the crop of crystals which had formed was filtered out. Forty-two hundredths of a gram of product was obtained which is believed to be a mixture of the meso and racemic forms, with the former predominating, since the product melted in the range 206-29°.

The filtrate was again set in the icebox where another crop of crystals formed. Fifty-two hundredths of a gram of product was obtained this time having a melting point of 125-7°. Overall yield of the meso and racemic forms of 3,4-bis(6'-methoxy-2'-naphthyl)hexane was 53% of the theoretical yield, calculated from the alcohol.

### Preparation of 3,4-bis(6'-hydroxy-2'-naphthyl)hexane (21)

Seventy-eight hundredths gram of 3,4-bis(6'-methoxy-2'-naphthyl)hexane, 12 cc. of glacial acetic acid, and 5.5 cc. of 48% hydrobromic acid were refluxed for sixteen hours and then poured into 250 cc. of water. The product which precipitated was isolated by filtration, washed twice with water, and dried in an oven at 105° for one hour. Six hundred fifty-four thousandths of a gram of the desired product melting at 240-4° was obtained. Campbell and Chattaway (1) reported a melting point of 253°.

### Preparation of 3,4-bis(6'-methoxy-2'-naphthyl)-3-hexene (12)

A toluene solution of 1-(6'-methoxy-2'-naphthyl)-1-bromopropane prepared from 5 g. of 1-(6'-methoxy-2'-naphthyl)-1-propanol, as described previously, was added in small portions to a suspension of 4.5 g. of sodium amide in about 200 cc. of liquid ammonia contained in an unsilvered Dewar flask. The mixture was stirred vigorously, and the following color changes were observed. The mixture was yellowish-green after the first addition, but became a greenish-brown in a few minutes; each subsequent addition discharged the color, and the same sequence of color changes again took place except that the color changed to a deeper brown. After all the organic reactant had been added and the reaction mixture had stood for thirty minutes, the mixture was poured into a beaker and the ammonia allowed to evaporate. The residue was taken up in water, and the well-cooled solution was acidified with dilute sulfuric acid. The solid phase, which formed between the water and small toluene layers, was filtered off and washed with hot petroleum ether and then with alcohol. The product obtained weighed 1.60 g. and had a melting point of 233-6° when recrystallized from benzene. This is 35% of the theoretical yield, calculated from the alcohol. Carbon and hydrogen analysis yielded the following results: Calculated for $C_{28}H_{27}O_2$: C, 85.02%; H, 6.88%. Found: C, 84.48%; H, 6.96%.

The aqueous and toluene layers were separated, and the aqueous layer was extracted once with 15 cc. of benzene which was added to the toluene. The toluene was evaporated off under reduced pressure, and the residual oil was dissolved in the alcohol from the previous washings. However, it was impossible to crystallize this oil.

### Preparation of 3,4-bis(6'-hydroxy-2'-naphthyl)-3-hexene

Seven hundred seventeen thousandths of a gram of the dimethyl ether, 20 cc. of diethylene glycol, and 3.5 g. of potassium hydroxide were placed in a 100-cc. round-bottom flask which was connected to a reflux condenser with ground glass connections. The condenser was connected to a trap containing diethylene glycol so as to prevent more oxygen from entering the flask. This mixture was refluxed for twenty-four hours, and the hot solution was then poured into 300 cc. of water and filtered. The filtrate was acidified with 6N hydrochloric acid, whereupon a precipitate formed. The precipitate was filtered off, washed thoroughly with water, and dried in a vacuum desiccator overnight. The product obtained weighed 0.318 g. which is 48% of the theoretical yield. This product probably consists of two isomeric compounds since it melted in the range of 190-230°. Attempts to separate these isomers by crystallization were unsuccessful.

## Preparation of 6-methoxy-2-acetylnaphthalene

This ketone was prepared by the same procedure as for the (6'-methoxy-2'-naphthyl)-1-propanone, previously described, with the exceptions as noted. The same molar quantities of reactants were used. It was observed that the yield of the desired ketone was quite low if the product from the hydrolysis was steam-distilled directly. Therefore, the product from the hydrolysis was extracted three times with ether, the ether distilled off, and the residue, composed of nitrobenzene and the ketone, was steam-distilled until all the nitrobenzene had passed over. A light-brown crystalline mass formed in the bottom of the flask. This mass was filtered off, taken up in alcohol, refluxed with decolorizing carbon, filtered to remove the carbon, and allowed to crystallize. However, the material obtained was still rather dark and gummy. It was therefore taken up in ether, stirred thoroughly with decolorizing carbon, and filtered. The ether was allowed to evaporate to one-fifth of its original volume whereupon 40 g. of light-brown crystals formed. This material was recrystallized two more times from alcohol; whereupon it had a melting point of 105-6° as compared to 105° and 107° recorded in the literature (4). The yield of the ketone was 34% of the theoretical.

On distillation of the carbonaceous residue from the ether extraction, an orange oil which crystallized on cooling was obtained. This compound after being recrystallized from methanol-benzene was found to have a melting point of 189-90°. It was therefore concluded that this compound was 2,2'-dimethoxy-1,1'-binaphthyl which has a recorded melting point of 190-1°. This was further verified by demethylating the compound with 48% hydrobromic acid and acetic acid. The di-hydroxy derivative had a melting point of 214-6° as compared with the literature value of 216° (16).

## Preparation of 1-(6'-methoxy-2'-naphthyl)-1-ethanol

The reduction of the ketone to the alcohol was done in the same manner as described under the preparation of 1-(6'-methoxy-2'-naphthyl)-1-propanol using 4 g. of lithium aluminum hydride and 28 g. of 6-methoxy-2-acetylnaphthalene. Twenty-six grams of the alcohol was obtained which was 93% of the theoretical yield. Recrystallized from alcohol it had a melting point of 110-111°, but it was found to have a melting point of 97° when recrystallized from ether or toluene.

### Preparation of 1-(6'-methoxy-2'-naphthyl)-1-bromoethane

The preparation of the bromo compound was carried out in the same manner as 1-(6'-methoxy-2'-naphthyl)-1-bromopropane using 12 g. of the alcohol dissolved in 175 cc. of toluene.

### Preparation of 2,3-bis(6'-methoxy-2'-naphthyl)butane

This compound was prepared in the same manner as 3,4-bis-(6'-methoxy-2'-naphthyl)hexane from 2.9 g. of magnesium turnings, 12 g. of ethyl bromide, 0.68 g. of anhydrous cobaltous chloride, and the toluene solution of 1-(6'-methoxy-2'-naphthyl)-1-bromoethane prepared from 12 g. of the corresponding alcohol. Five and four tenths grams of crude product was obtained from the solid that formed on hydrolysis, and an additional 0.65 g. of product was obtained when the ether-toluene solution was evaporated to one-third its original volume and allowed to remain in the icebox overnight. The two products were combined and recrystallized from benzene. Three and five tenths grams of pure white crystals melting at 228-32° was obtained, this being 37.3% of the theoretical yield, calculated from the alcohol. Carbon and hydrogen analysis yielded the following results: Calculated for $C_{26}H_{26}O_2$: C, 84.29%; H, 7.08%. Found: C, 83.94%; H, 7.41%.

### Preparation of 2,3-bis(6'-hydroxy-2'-naphthyl)butane

One and eighteen hundredths grams of the dimethyl ether, 16 cc. of glacial acetic acid, and 7 cc. of 48% hydrobromic acid were placed in a 100-cc. round-bottom flask and refluxed for twenty hours. The solution was then poured into 250 cc. of water, whereupon a precipitate formed. This product upon isolation weighed 0.98 g. which is 90% of the theoretical yield. This compound formed an insoluble sodium salt when placed in 6N sodium hydroxide, but it did dissolve when a large quantity of water was added. Upon recrystallization from benzene, the dihydroxy compound shrank and softened somewhat at 211° but did not melt until 235-7°.

## Preparation of 2,3-bis(6'-methoxy-2'-naphthyl)-2-butene

This compound was prepared in the same manner as 3,4-bis(6'-methoxy-2'-naphthyl)-3-hexene from 8 g. of sodium amide suspended in 200 cc. of liquid ammonia and the toluene solution of 1-(6'-methoxy-2'-naphthyl)-1-bromoethane prepared from 12 g. of the corresponding alcohol. The same sequence of color changes was observed as before. The toluene solution obtained after the hydrolysis of the excess sodium amide was evaporated under reduced pressure to one-fifth of its original volume. Upon cooling, a somewhat gummy precipitate formed which was filtered out and washed thoroughly with hot alcohol; whereupon 1.8 g. of slightly yellow crystals were obtained which is 17% of the theoretical yield, calculated from the alcohol. When recrystallized from benzene-ligroin, these crystals had a melting point of 241-6°. Carbon and hydrogen analysis yielded the following results: Calculated for $C_{26}H_{24}O_2$: C, 84.75%; H, 6.57%. Found: C, 84.65%; H, 6.83%.

The remaining toluene solution was again evaporated under reduced pressure until most of the toluene was removed. The oil that remained was set in the icebox overnight where it solidified. This oily solid was placed on a Buchner funnel, and as much of the oil was pulled off as possible. The still oily solid was recrystallized from alcohol, wherefrom 3.17 g. of light yellow crystals were obtained having a melting point of 151-2°. This is 29% of the theoretical yield. The combined yield of the cis and trans isomers was 46% of the theoretical, calculated from the alcohol.

### Preparation of trans-2,3-bis(6'-hydroxy-2'-naphthyl)-2-butene

Three grams of potassium hydroxide, 20 cc. of diethylene glycol, and 0.87 g. of the dimethyl ether were refluxed for twenty-five hours and then poured into 250 cc. of water. This solution was acidified with 6N hydrochloric acid, whereupon a white precipitate formed. This precipitate was filtered out, washed thoroughly with hot water, and placed in a vacuum desiccator for a day. The yield was 0.79 g. which is 97% of the theoretical. When recrystallized from benzene-ligroin, it darkened at 195° but did not melt until 232-5°.

### Preparation of cis-2,3-bis(6'-hydroxy-2'-naphthyl)-2-butene

One gram of the dimethyl ether was demethylated in the same manner as described above. The yield was 0.84 g. which is 91% of the theoretical. When recrystallized from benzene-ligroin, it darkened at 135° but did not melt until 205-9°.

## SUMMARY

The preparation of 6-methoxy-2-naphthaldehyde by a modified Gattermann reaction was attempted; 2-methoxy-1-naphthaldehyde was obtained instead. It was found that the benzoin condensation of 2-methoxy-1-naphthaldehyde with itself and with piperonal would not take place under the experimental conditions used.

2-Naphthaldehyde was prepared, and a benzoin condensation of it with piperonal was run. The 3,4-methylenedioxy-2'-naphthoin was obtained in very small yield.

(6'-Methoxy-2'-naphthyl)-1-propanone was synthesized by a Friedel-Crafts reaction of 2-methoxynaphthalene and propionyl chloride using nitrobenzene as the solvent. The corresponding alcohol was obtained from this ketone by reducing it with lithium aluminum hydride. 1-(6'-Methoxy-2'-naphthyl)-1-bromopropane was prepared by treating the alcohol with hydrogen bromide.

The naphthalene analog of the dimethyl ether of hexestrol (3,4-bis(6'-methoxy-2'-naphthyl)hexane) was prepared by reacting the bromo derivative in the presence of ethylmagnesium bromide and anhydrous cobaltous chloride. On demethylation the naphthalene analog of hexestrol was obtained.

The naphthalene analog of the dimethyl ether of stilbestrol (3,4-bis(6'-methoxy-2'-naphthyl)-3-hexene) was obtained by

reacting the bromo derivative in liquid ammonia and sodium amide. On demethylation the naphthalene analog of stilbestrol was obtained.

The methyl homologs of the naphthalene analogs of hexestrol and stilbestrol were prepared by the same series of reactions as the ethyl homologs mentioned above.

Melting points of all the compounds synthesized were recorded. Carbon and hydrogen analyses were run on the dimethyl ethers and methyl homologs of the naphthalene analogs of stilbestrol and hexestrol.

The naphthalene analogs of stilbestrol and hexestrol, their dimethyl ethers, and their methyl homologs will be tested for estrogenic activity in the near future.

## BIBLIOGRAPHY

1. Campbell and Chattaway, Proc. Roy. Soc. London, 130-B 435 (Aug. 1941-May 1942).

2. Cook, Dodds, and Hewett, Nature, 131, 56 (1933).

3. Dodds, Goldberg, Lawson, and Robinson, Nature, 141, 247 (1938).

4. Radt, "Elsevier's Encyclopedia of Organic Chemistry," Elsevier Publishing Company, Inc., New York, N. Y., 1950, Vol. 13-B, pp. 2396 and 2400.

5. Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, 3rd ed., p. 403.

6. *Ibid.* p. 356.

7. Fieser and Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1950, 2nd ed., pp. 718 and 795.

8. *Ibid.* p. 725.

9. Haworth and Sheldrick, J. Chem. Soc., 1934, 864.

10. Jaap, Endocrinology, 37, 369 (1945).

11. Jacques and Horeau, Bull. soc. chim., 1948, 714.

12. Kharasch and Kleiman, J. Am. Chem. Soc., 65, 11 (1943).

13. *Ibid.* p. 491.

14. Nystrom and Brown, J. Am. Chem. Soc., 69, 1197, 2548 (1947).

15. Peak and Short, J. Chem. Soc., 1943, 232.

16. Scholl and Seer, Ber., 55, 334 (1922).

17. Solmssen, Chem. Revs., 37, 481 (1945).

18. Vogel, "A Text-book of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1948, p. 576.

19. *Ibid.* p. 668.

20. Warren, J. Chem. Soc., 1941, 687.

21. Wilds and McCormack, J. Org. Chem., 14, 45 (1949).

# AUTOBIOGRAPHY

Manfred Katz was born February 16, 1929, at Giessen, Germany. In 1938 he immigrated with his parents to the United States where they made their new home in Stillwater, Oklahoma. He attended part of the third, fourth, and sixth grades of grade school and graduated from high school in 1947 where he took an active interest in sports and was elected a member of the National Honor Society. He attended Oklahoma A. and M. College where he majored in chemistry and minored in mathematics and received the Bachelor of Science Degree in July 1950. He received various scholastic honors, being elected to Pi Mu Epsilon, Phi Lambda Upsilon, and Phi Kappa Phi. He began graduate work in chemistry at Oklahoma A. and M. College in the fall of 1950 where he had been granted a graduate fellowship. He is a member of the American Chemical Society, and he will be employed by the Du Pont Company upon completion of the requirements for the Degree of Master of Science.

THESIS TITLE: THE SYNTHESIS OF THE NAPHTHALENE ANALOGS OF
STILBESTROL AND HEXESTROL, THEIR METHYL
HOMOLOGS, AND THEIR DIMETHYL ETHERS

NAME OF AUTHOR: MANFRED KATZ

THESIS ADVISER: DR. E. M. HODNETT

The content and form have been checked and approved by the author and thesis adviser. "Instructions for Typing and Arranging the Thesis" are available in the Graduate School office. Changes or corrections in the thesis are not made by the Graduate School office or by any committee. The copies are sent to the bindery just as they are approved by the author and faculty adviser.

NAME OF TYPIST: FRANCES IRELAND STROMBERG