

THE DIELS-ALDER REACTION OF 1-VINYL-6-METHOXY-3,4-DIHYDRONAPHTHALENE WITH MALEIC ANHYDRIDE, MESACONIC ACID AND CITRACONIC ANHYDRIDE. THE CONFIGURATION OF THE C/D RING JUNCTURE OF THE ESTROGENIC HORMONES.

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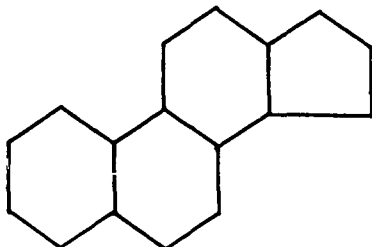
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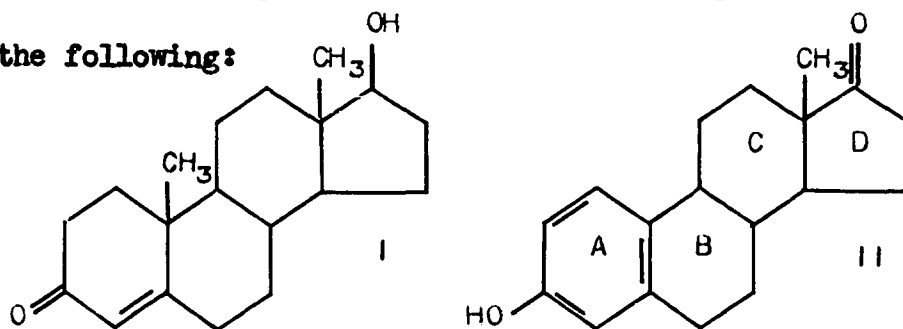
INTRODUCTION

Nature of the Problem

Only a few decades ago it was found that a certain group of physiologically active substances possessed a common basic unit of structure known as the perhydrocyclopentanophenanthrene skeleton:



The members of the group, which are called steroids, embrace a wide variety of organic compounds having a specific activity in connection with body metabolism. Chief among these particular chemical substances are the sexual hormones. From the elaboration of the structures of the latter, it was found that slight variations in chemical constitution caused pronounced changes in physiological activity. Testosterone (I) and estrone (II), examples of male and female sex hormones respectively, differ fundamentally in the degree of unsaturation of one of the rings and in the number of angular methyl groups attached to the ring structure as indicated by the following:

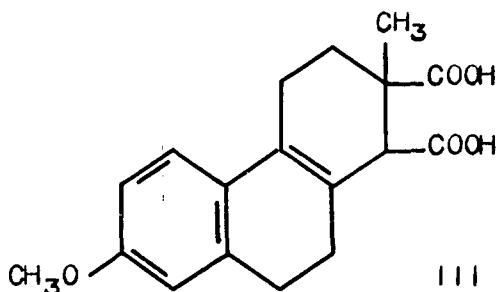


Developments in the field of organic chemistry, which led to the elucidation of the above structures and to partial syntheses of these hormones, culminated in the well-known advances in modern hormonal therapy of sexual disorders. In addition, there is the

current dramatic interest in steroids as valuable agents in the treatment of arthritis. The discovery that cortisone, a steroidal hormone found in the adrenal cortex, and several related compounds might be successful in treating this stubborn affliction of mankind has focused renewed attention on the chemistry of the steroids.

Because hormones are found in the body of both animal and man in such small quantities, an obvious contribution of organic chemistry to medicine is the synthetic preparation of these hormonal substances on a large scale. To date, only a few hormones of the steroidal type have been synthesized totally and these have been obtained on a relatively small scale.

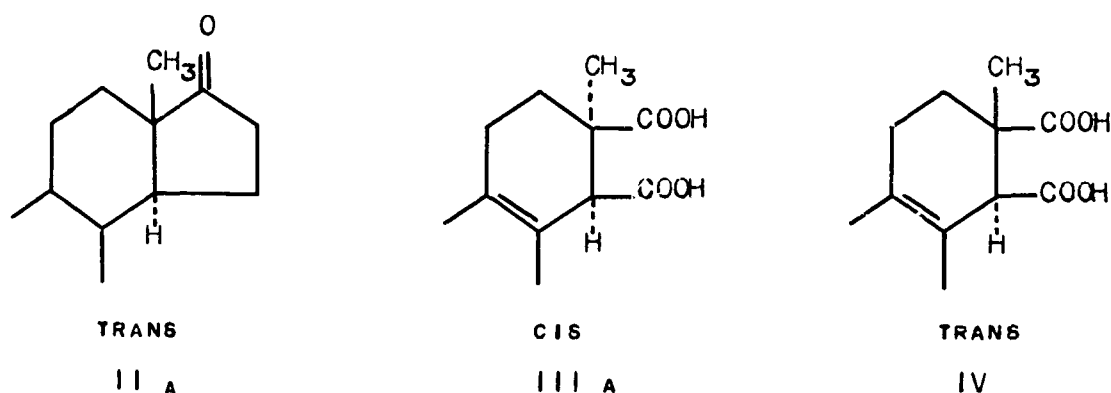
Several synthetic approaches to the simpler steroids are suggested by a consideration of certain chemical reactions. Among the latter is the Diels-Alder reaction which is defined as the condensation of a "diene" with a "dienophile" to yield an "adduct(s)". Dane and co-workers (1) were the first to use 1-vinyl-6-methoxy-3,4-dihydronaphthalene in the Diels-Alder reaction in attempts to prepare estrone. Bachmann and Chemerda (2) and Breitner (3) in 1941-1942 condensed the same diene with citraconic anhydride and obtained III.



3.

Although a structural isomer or stereoisomer of estrone was obtained from the intermediates by both groups of workers by constructing the five-membered D ring, the natural hormone was not obtained. More recently the same reaction has been studied by Heer and Miescher (4).

A possible explanation of the failure to obtain estrone via the above synthetic route lies in the stereochemical considerations of the above Diels-Alder reaction and of estrone itself. The exact structures of estrone, equilenin and equilin were well-known except for one point not yet conclusively proven. The stereochemical configuration of the bonds involved in the C/D ring fusion is not established unequivocally. Certain tentative data (5) indicate that the configuration at the C/D ring juncture is trans (IIa), but additional experimental evidence must be adduced before all doubt is removed. Regarding the Diels-Alder reaction, it has been found



repeatedly that this reaction is highly selective in the stereochemical sense. For instance, citraconic anhydride is derived from a cis-dicarboxylic acid and thus the adducts from the above Diels-Alder reaction have a cis configuration (IIIa) with respect to the

two carboxylic acid groups in the resultant phenanthrene molecule. If mesaconic acid, the trans-diacid corresponding to the cis-diacid citraconic acid, were used in the same Diels-Alder reaction then the adduct should have the trans configuration (IV) and a synthesis of estrone might well be possible. In addition, the question of the one remaining aspect of the stereochemical structure of estrone and related hormones would be cleared up beyond doubt.

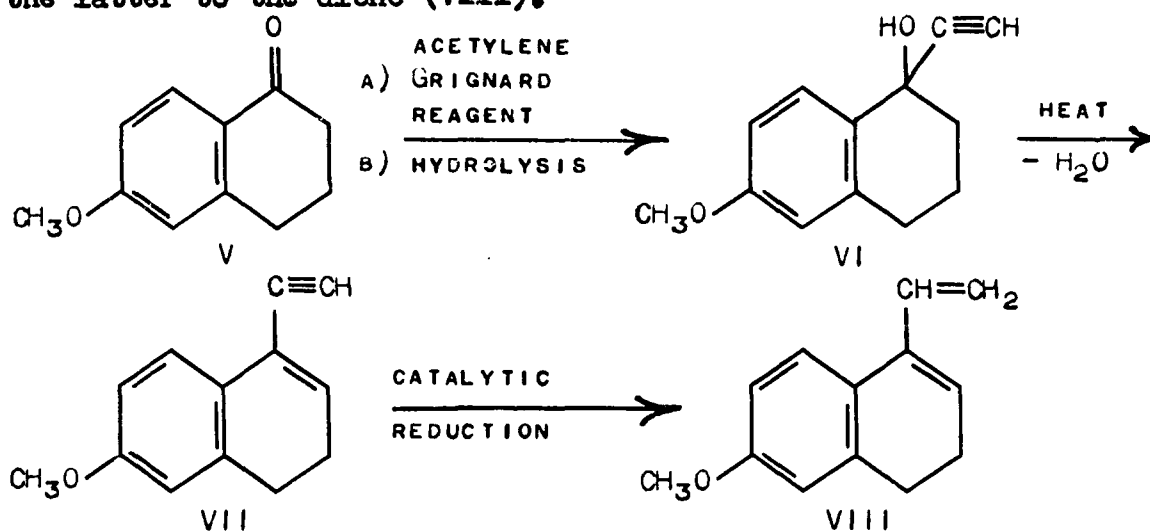
Statement of the Problem

The purpose of the present investigation was:

- 1) To study the Diels-Alder reaction of 1-vinyl-6-methoxy-3,4-dihydronaphthalene with mesaconic acid.
- 2) To study further the known reactions of the same vinyl-dihydronaphthalene with maleic anhydride and citraconic anhydride.
- 3) To utilize the products of the Diels-Alder reactions to elucidate the configuration of the C/D ring juncture in the estrogenic hormones, equilinenin, estrone and estradiol.
- 4) To employ the products of the Diels-Alder reactions in the synthesis of various steroid structures.

RESULTS OF THE INVESTIGATION

For our study it was necessary to have 1-vinyl-6-methoxy-3,4-dihydronaphthalene (VIII). This can be prepared from the reaction of 6-methoxy-1-tetralone (V) and the acetylene Grignard reagent, followed by dehydration of the resulting acetylenic carbinol (VI) to the eneyne (VII), and catalytic reduction of the triple bond of the latter to the diene (VIII).

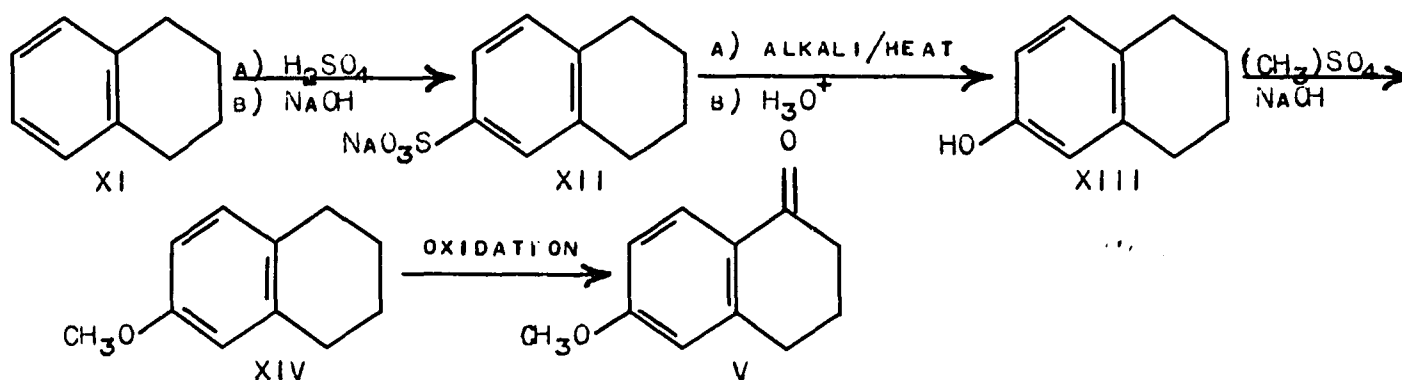


First of all, the methods of preparing the starting ketone, 6-methoxy-1-tetralone were investigated.

Preparation of 6-methoxy-1-tetralone

6-Methoxy-1-tetralone (V) has been synthesized according to three general methods. One of these starts with tetrahydronaphthalene (XI) (6). Burnop et al sulfonated tetrahydronaphthalene in the β -position of the aromatic ring. The sodium salt of the sulfonic acid (XII) obtained from this reaction is fused with a mixture of sodium and potassium hydroxides at $280\text{--}300^\circ$ to convert the sulfo-group to a phenolic group. Without isolation of the free phenol (XIII), the latter is methylated with dimethyl sulfate in the presence of sodium hydroxide giving rise to 6-methoxytetralin

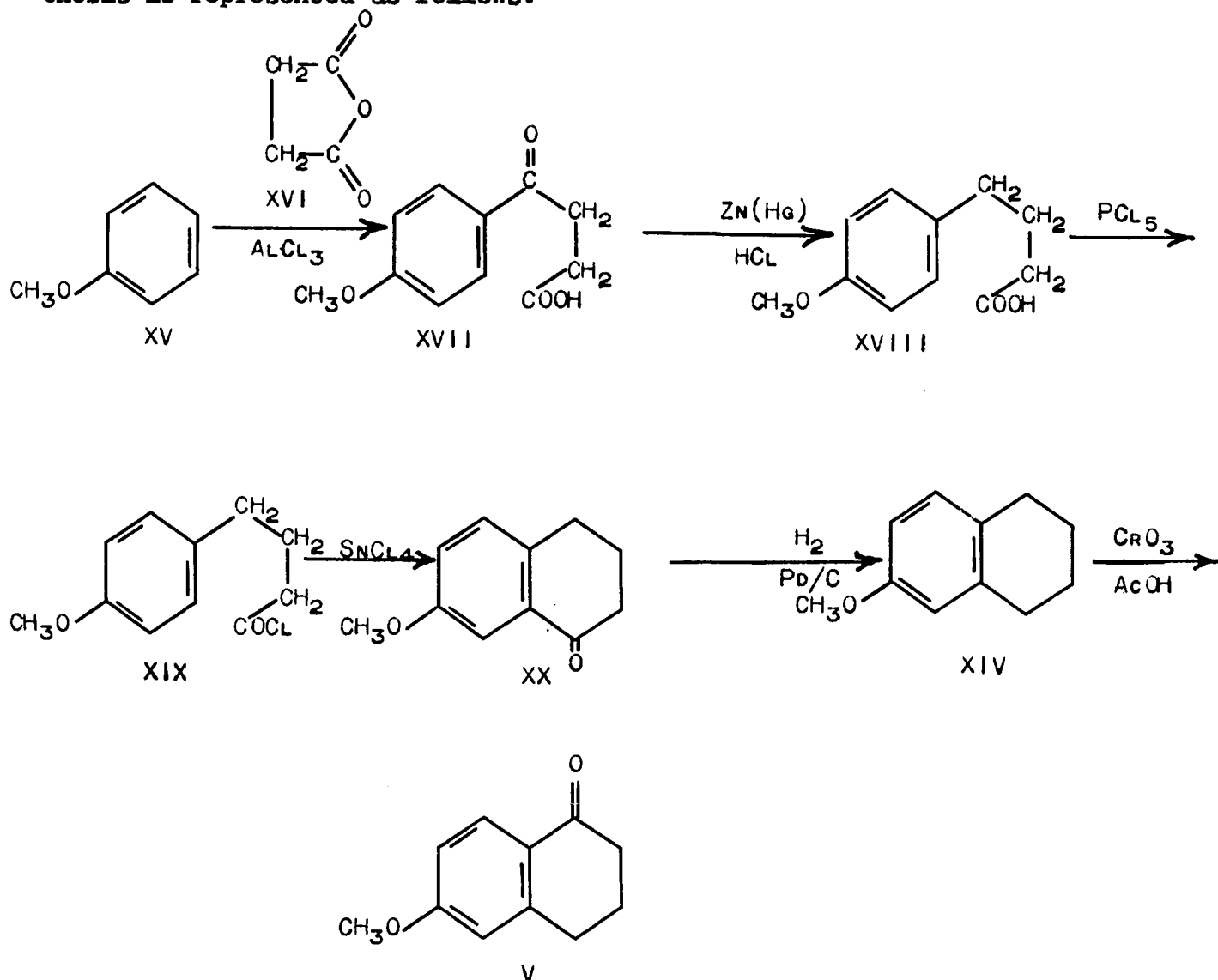
(XIV). This compound is oxidized with chromic anhydride (CrO_3) in glacial acetic acid yielding 6-methoxy-1-tetralone (V). The overall yield of ketone reported in this series of reactions is 20% based on tetrahydronaphthalene and the reactions are as follows:



When this method was used to prepare moderately large quantities of material, an unusual amount of difficulty was experienced in laboratory manipulation. This was so particularly in the case of the alkali fusion where thorough mixing of the reactants was almost impossible, causing local overheating, and where the fusion mass, when cooled, was of such a hard consistency as to resist ready dispersion in aqueous medium. A yield of 16% of 6-methoxy-1-tetralone was obtained in practice and other more facile methods were sought.

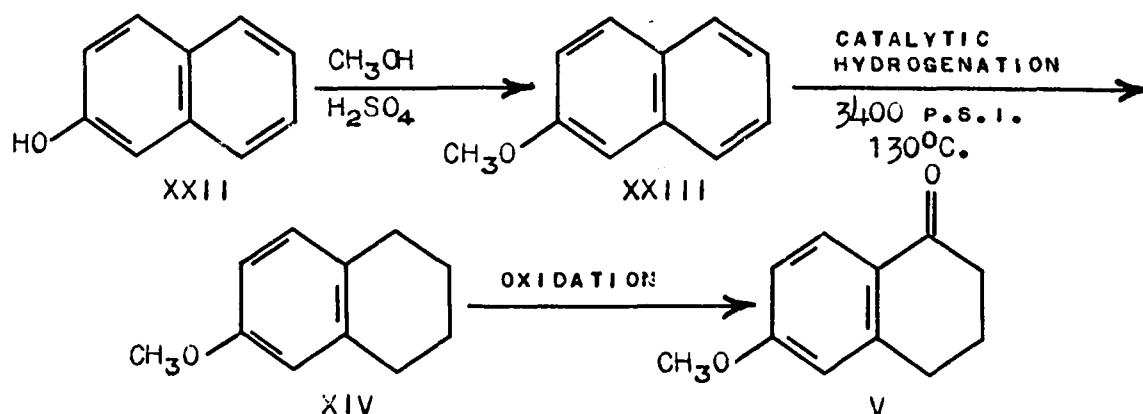
A second method as devised by Thomas and Nathan, utilizes anisole (XV) as the starting material (7). This aryl alkyl ether is condensed with succinic anhydride (XVI), aluminum chloride being used as a catalyst in this typical example of the Friedel-Crafts reaction. The β -p-anisoylpropionic acid (XVII) resulting from this condensation is reduced with amalgamated zinc and hydrochloric acid

to convert the ketonic group to a methylene group forming γ -p-anisylbutyric acid (XVIII). This acid is treated with phosphorus pentachloride to form the acid chloride (XIX) which is then cyclized with stannic chloride. The 7-methoxy-1-tetralone (XX) thus formed is hydrogenated with palladium on charcoal as the catalyst. A quantity of hydrogen just sufficient to reduce the ketone to a methylene group is absorbed. The 6-methoxytetralin (XIV) which results is oxidized as in the above method to give an overall yield of the ketone of 43% based on anisole. This synthesis is represented as follows:



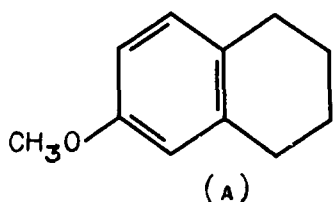
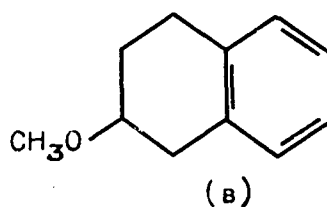
The above series of reactions was carried out with little difficulty. However, the zinc-hydrochloric acid reduction required refluxing for 48 hours accompanied by addition of more hydrochloric acid every six hours. During the purification of the γ -p-anisoylpropionic acid, steam distillation and dimethyl sulfate treatment were necessary. The overall yield of 6-methoxy-1-tetralone experienced was 31%.

The third method involves a preferential reduction of one of the rings in β -naphthyl methyl ether (XXI) (8). Formerly, reduction of substituted naphthalenes invariably led to hydrogenation of the ring carrying the substituent. In this case, however, Stork found that the unsubstituted ring was the first to be reduced and this occurred almost to the exclusion of reduction of the other ring. The conditions of the reduction are the use of Raney nickel catalyst, a pressure of 3400 p.s.i. and a temperature of 130°C . The product obtained consists chiefly of 6-methoxytetralin which is oxidized to the ketone as in the other two methods. The naphthyl methyl ether used as a starting material may be prepared readily from β -naphthol (XXII) by refluxing with methanol in the presence of sulfuric acid. The overall yield of ketone is 51% based on β -naphthol and the reactions which are employed are the following:



The hydrogenation of the methyl ether as described by Stork was relatively drastic and inconvenient with respect to laboratory manipulation. A more facile procedure was devised and consisted of the use of Adams' platinum oxide catalyst in glacial acetic acid. The reduction occurred smoothly at 70-80°C. with 10-60 pounds of hydrogen pressure. Successive runs in the Parr type hydrogenation apparatus could be performed in a few hours. The 6-methoxytetralin was oxidized with chromic anhydride as before to give an overall yield of 53% of 6-methoxy-1-tetralone.

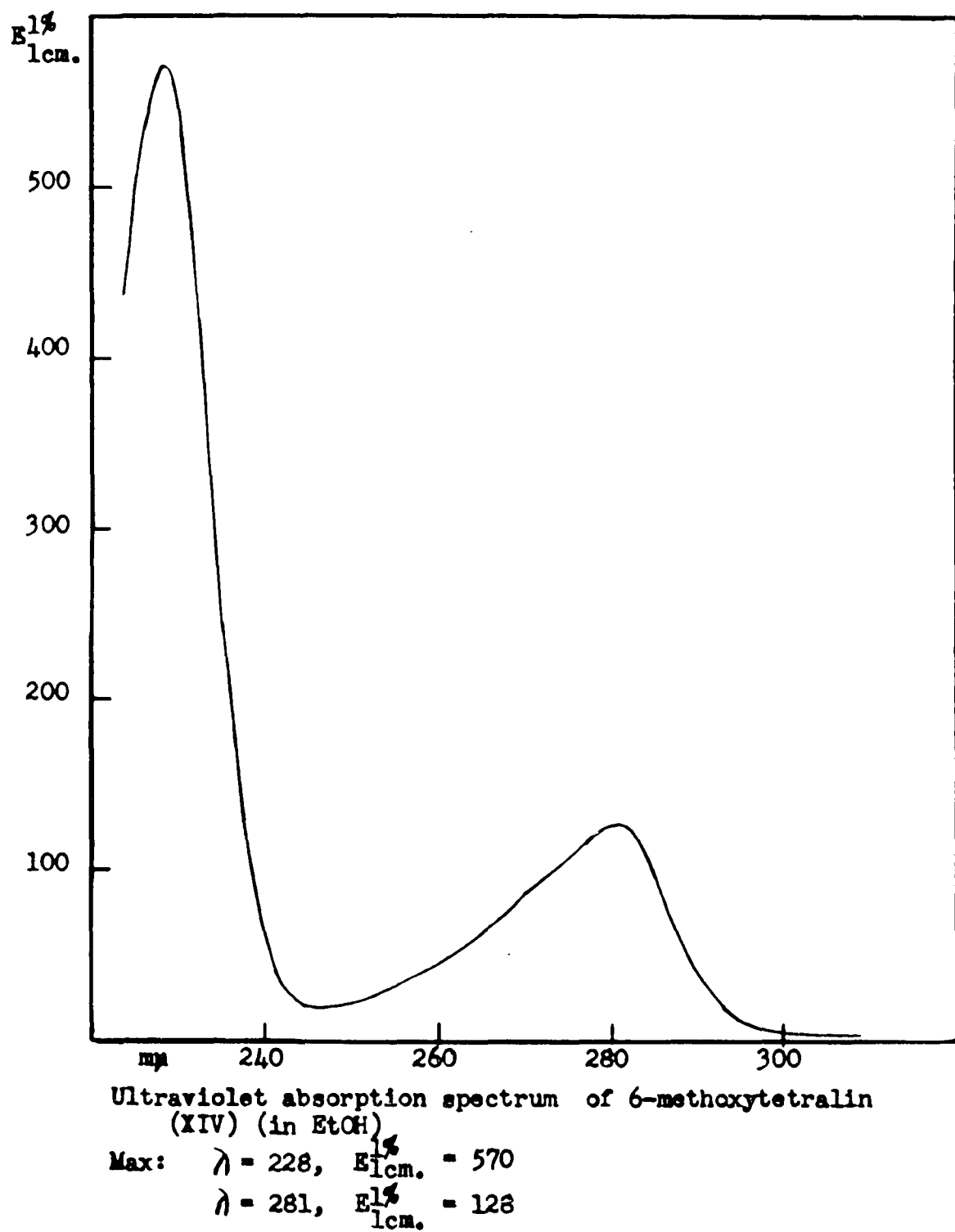
To confirm the validity of the modification of the above method an easy criterion of determining which ring of the naphthyl methyl ether was reduced had to be at hand. Much more conclusive than boiling-point data was the evidence obtained when a sample of the reduction product was submitted for an ultraviolet absorption spectrum determination. The two possible reduction products obtainable upon the absorption of two moles of hydrogen by the ether are:



One of these (a) would show large absorption in the 225-230 mμ range, characteristic of methoxy-xylene. The other (b), non-phenolic in character, should exhibit strong absorption in the region of 205-215 mμ. Plate 1, the absorption spectrum of the

9a.

PLATE 1.



reduction product actually obtained by the modified reduction process, indicates clearly that the reduction proceeded in the desired direction with formation of 6-methoxytetralin.

The oxidation of 6-methoxytetralin to the corresponding ketone mentioned above was carried out with chromic anhydride in glacial acetic acid at low temperature. The various methods that have been suggested for the isolation of the product from the reaction mixture all involve tedious procedures and/or some loss in yield. The steam distillation method of Burnop et al (6) is most time-consuming and the distillation of the ketone itself as recommended by others requires high temperatures resulting in some decomposition. In the course of this investigation it was found that extraction of the ketone from the water-digested reaction mixture with benzene, followed by chromatography of the dried benzene solution over a column containing Brockmann activated aluminum oxide and removal of the solvent from the effluent liquid, yielded the white or pale yellow 6-methoxy-1-tetralone in practically pure form. The best yield obtained in the oxidation of 6-methoxytetralin to the ketone was 62% using the chromatographic method of purification. This is to be compared with a 47% yield of the ketone when distillation was employed as the means of purification.

The method starting from tetralin is the poorest in yield: 16% overall when the published method is followed. The method starting from anisole, gives a better overall yield of the ketone, 31%, but requires a longer period of time to effect the reactions involved. The method, starting from β -naphthol, is by far the most satisfactory

from the standpoint of both time and yield (51%), but, as published the method suffers from the drastic hydrogenation conditions necessary. By the method of reduction and purification described in the present work, 6-methoxy-1-tetralone can be prepared conveniently in yields of 50-60% with a reasonable expenditure of time.

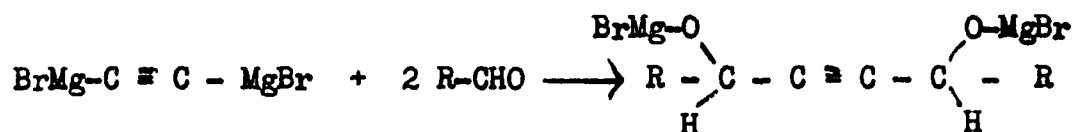
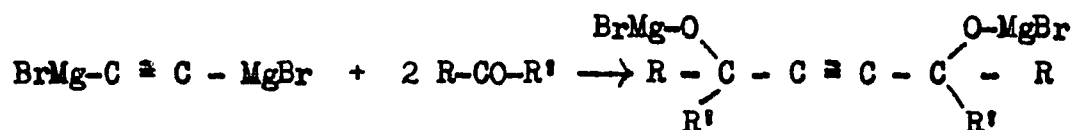
Preparation of the Acetylene Grignard Reagent

The acetylenation of 6-methoxy-1-tetralone may be effected in two general ways. One involves the direct addition of acetylene to the carbonyl group in the presence of a basic catalyst and under increased pressure. The other makes use of the acetylene Grignard reagent which adds in the usual Grignard fashion to the carbonyl group of 6-methoxy-1-tetralone. Although Breitner (3) and later Heer and Miescher (4) claimed success with the first method, it was unwise to risk the hazards of working with acetylene under pressure during the course of this investigation. Instead, the Grignard reaction as employed by Dane et al (1) and by Bachmann and Chmerda (2) was employed. However, due to continued difficulty in the preparation of the Grignard reagent, the decision was made to study in detail the formation of the acetylenic Grignard reagent as a possible source of the trouble.

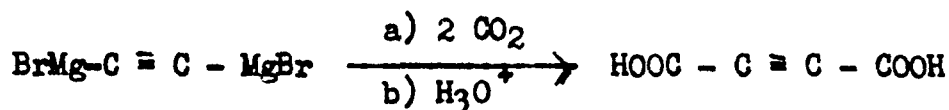
In 1902 Jotsitch (9) first described the reaction which takes place upon the introduction of acetylene gas into a solution of ethylmagnesium bromide in ether. This may be represented as follows:



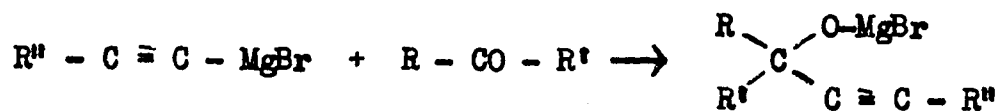
The product of this reaction, acetylene dimagnesium bromide, was found to condense with aldehydes and ketones as follows:



When the Grignard-like product was treated with carbon dioxide, acetylene dicarboxylic acid resulted:



In addition Jotsitch experimented with mono-substituted acetylenes and found the following reactions to take place:



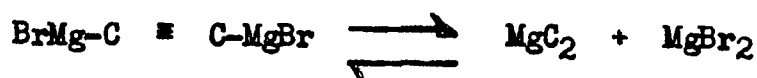
There was thus disclosed a method for the preparation of both secondary and tertiary acetylenic carbinols and acetylenic glycols from aldehydes and ketones.

The particular adaptation of these reactions as devised by Bachmann and Chemerda (2) involved the preparation of a mixture of acetylene mono- and bis-magnesium iodides. This was accomplished

by bubbling acetylene gas for twenty-four hours into an ethereal solution of ethylmagnesium iodide at 0°C. The viscous violet layer which resulted was separated from supernatant ether by decantation and was dissolved in benzene. This solution was used directly for condensation with 6-methoxy-1-tetralone.

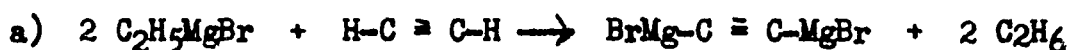
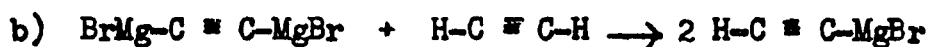
When the acetylene Grignard mixture was prepared during this investigation according to the above method, very unsatisfactory yields of the condensation product with 6-methoxy-1-tetralone were obtained. It was suspected that some ethylmagnesium iodide may have been entrapped in the viscous violet oil and consequently failed to gain reactive contact with the acetylene. To prove this point, the solution of the viscous oil in benzene would have to be analyzed. Aqueous hydrolysis of an aliquot of this solution would yield ethane in addition to acetylene if all of the ethylmagnesium iodide had not reacted with acetylene originally. Since this explanation of the unsatisfactory yields appeared most likely, a determination of the constitution of the acetylene Grignard reagent in benzene solution was attempted.

This same problem had been considered on a rather theoretical basis by Kleinfeller (10) in 1929 when he postulated an equilibrium between acetylene bis-magnesium bromide and a mixture of magnesium bromide and magnesium carbide:

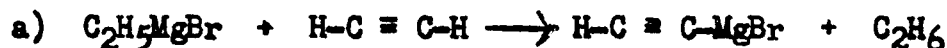


This equilibrium was used to explain the rapid decomposition of the compound when heated to 50°C. or when stored for short periods of time in solutions of various organic halides.

The most exhaustive study of the reaction leading to the formation of acetylene bis-magnesium halide was carried out by Kleinfeller and Lohmann (11). The following mechanism of reaction:

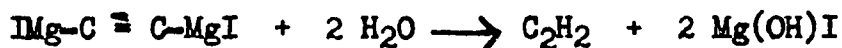


which had been proposed previously was replaced by this new scheme of reactions:



that the last sequence of reactions is probably the correct one is supported by a kinetic study of the preparation of the acetylene Grignard reagent. According to the results of this study, the reaction is clearly monomolecular with respect to ethyl magnesium bromide. It should be noted here, however, that the authors admit that the formation of the ether-insoluble acetylene magnesium bromide derivatives alters the reaction from a homogeneous to a heterogeneous type. The kinetic conclusions which they propose are based on homogeneous reaction kinetics and thereby run the risk of being invalidated through this change in the physical nature of the reaction.

We have attempted to obtain information on the composition of the acetylene Grignard reagent by a combination of hydrolysis and titration. The mono Grignard reagent on hydrolysis yields one equivalent of acetylene and one equivalent of base; the bis Grignard reagent yields one equivalent of acetylene and two of base.

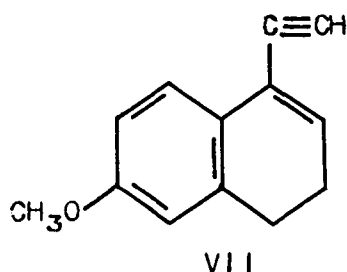
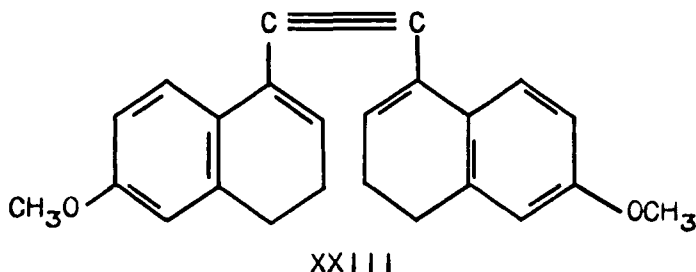


The volume of acetylene which was liberated was measured by absorption in a solution of mercuric cyanide and potassium hydroxide in an Orsat apparatus and the base was titrated with standard acid. An unaccountable blank was encountered when all the reagents except the Grignard reagent were present. Assuming that this same blank operated in the determination itself the results indicated that the acetylene Grignard reagent consisted of 85-93% of the bis compound and 7-15% of the mono compound and that no ethylmagnesium iodide (used to prepare the acetylene Grignard reagent) remained.

1-Vinyl-6-methoxy-3,4-dihydronaphthalene

Dane et al (1) and Bachmann and Chermada (2) acetylenated 6-methoxy-1-tetralone successfully with the acetylene Grignard reagent. The procedure of Dane et al involved the addition of the ketone dissolved in ether to a solution of acetylene magnesium bromide in ether at 0°C. When the temperature had reached 25°C. over a period of six to seven hours, the mixture was hydrolyzed

and, upon working up the products, two chief fractions were obtained. One, an oily distillate, possessed properties expected of a dehydrated acetylenic carbinol (VII) and the other, a solid, was identified as the dehydrated acetylenic glycol (XXIII). The structures of these compounds are:



The yields of the two products ranged between 10 and 20%. The unsubstituted ethynyl compound was characterized by its reduction with one mole of hydrogen and subsequent condensation of the reduced product with maleic anhydride.

Bachmann and Chemerda (2) were able to effect the condensation of 6-methoxy-1-tetralone with acetylene magnesium iodide leading to a yield of 52% of the dehydrated acetylenic carbinol. The ketone was added to the solution of the acetylene Grignard reagent as described earlier and, after standing at room temperature, the mixture was hydrolyzed with ammonium chloride in the cold. Concentration of the organic solvent layer led to the separation of a solid which was considered to be the acetylenic glycol. After filtering off this solid, the filtrate was distilled under high vacuum. Dehydration took place during the distillation giving rise to 1-ethynyl-6-methoxy-3,4-dihydronaphthalene (VII). Here again the product was characterized by reduction to the vinyl compound (VIII) and subsequent condensation with maleic anhydride (XXIV).

As noted in the above discussion the 1-ethynyl-6-methoxy-tetralol-1 (VI) appeared to lose water spontaneously during its distillation (1,2). Breitner (3), however, assumed that only partial cleavage of water took place during the distillation and consequently he subjected the distillate to refluxing with acetic anhydride to effect complete dehydration.

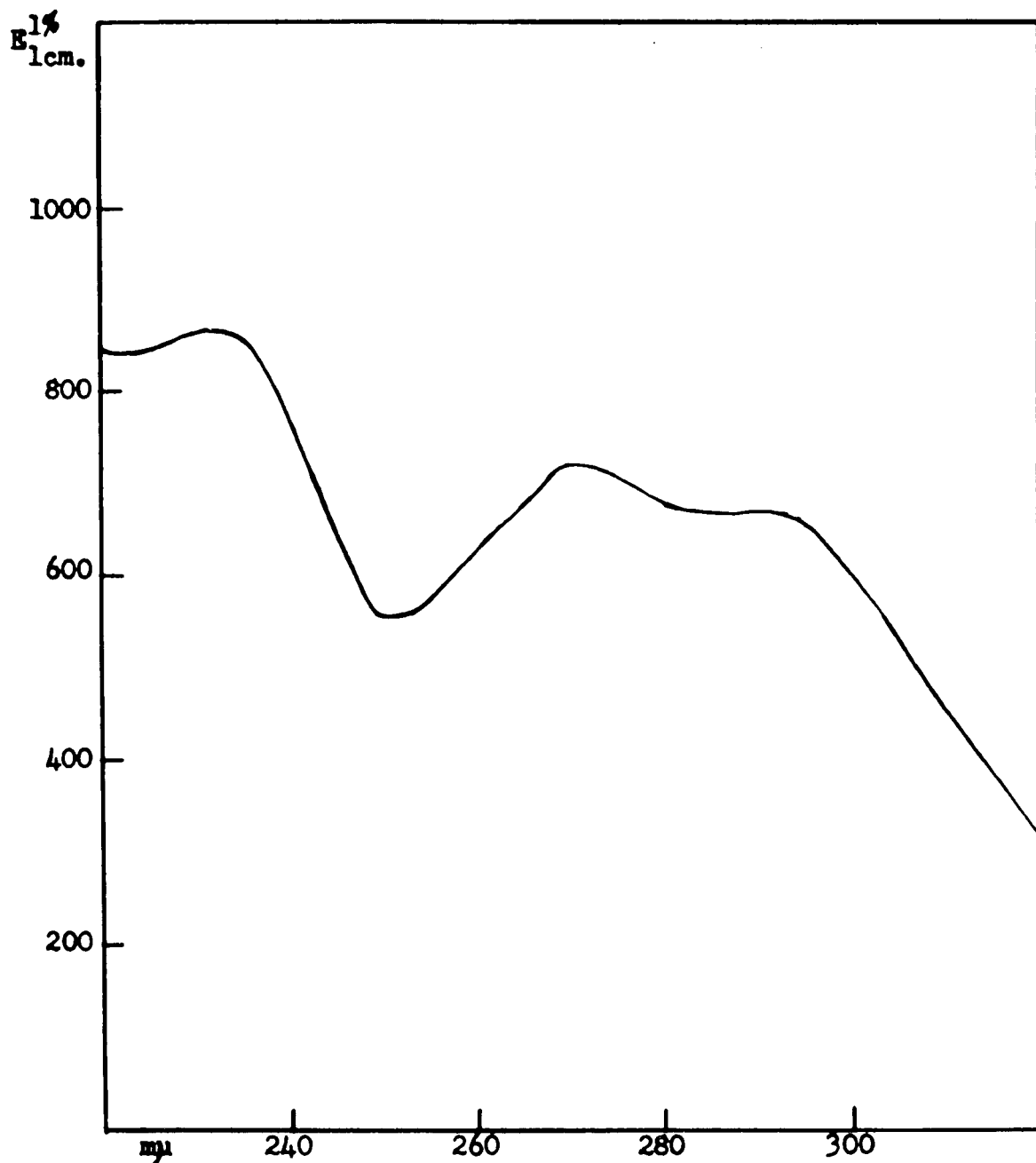
To bring about the addition of two hydrogen atoms to the eneyne for the preparation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene from the acetylenic compound, two reduction methods have been employed. Dane et al and Bachmann and Chemerda both used catalytic hydrogenation with palladium supported on either calcium carbonate or on charcoal as the catalyst. Breitner, however, made use of the zinc-copper couple, which is a specific reducing agent for hydrogenating triple bonds to double bonds, and claimed almost quantitative yields of the diene.

Once the constitution of the acetylene Grignard reagent was established as described earlier, the condensation reaction of 6-methoxy-1-tetralone with this solution was carried out according to the procedures suggested by previous investigators. The first experiment led to a very low yield of eneyne. The ketone dissolved in benzene was added to the Grignard solution at room temperature and allowed to stand for about sixteen hours. Upon hydrolysis of the reaction mixture it was found, by fractional distillation and by chromatography, that a considerable amount of starting ketone remained unchanged. This result led to heating the mixture of the

reactants at 55-60°C. for several hours after addition of the ketone. In this way reaction between the ketone and the acetylene Grignard reagent was effected so that little unchanged ketone could be isolated from the reaction.

The isolation of the product from the reaction mixture was based on a slightly modified version of the method of Bachmann and Chemerda. Hydrolysis of the mixture was effected with ammonium chloride and ice and the organic layer was separated therefrom. It was found that if this extract were dried with an inorganic drying agent such as magnesium sulfate a deep red color developed immediately and subsequent isolation of the reaction products led to much lower yields. In later and more successful runs the undried solution of the hydrolytic reaction product in benzene was concentrated in vacuo in an atmosphere of nitrogen. Because butyl ether was used as the solvent for the Grignard reagent, lower pressures were necessary to effect complete removal of solvent but an advantage was gained in that the solid "bis" compound (XXIII) (1), which was a by-product of the condensation, did not separate as readily as in ethyl ether. The structure of the "bis" compound (XXIII) proposed by Dane et al was confirmed by an ultraviolet absorption spectrum determination on the isolated and purified solid fraction (Plate 2). The curve shown in this plate exhibits strong absorption in the region of 250-300 mμ, characteristic of the system phenyl-conjugated double bond. The possibility that the solid "bis" compound might be the

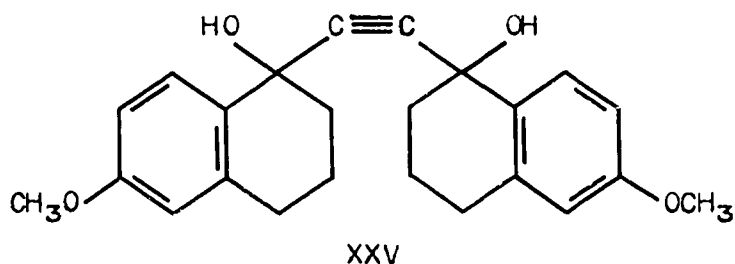
PLATE 2.



Ultraviolet absorption spectrum of bis (3,4-dihydro-6-methoxynaphthyl) acetylene (XXIII) (in H_2O)

Max: $\lambda = 232$, $E_{1\text{cm.}}^{1\%} = 864$
 $\lambda = 270$, $E_{1\text{cm.}}^{1\%} = 721$
 $\lambda = 293$, $E_{1\text{cm.}}^{1\%} = 669$

acetylenic glycol (XXV)

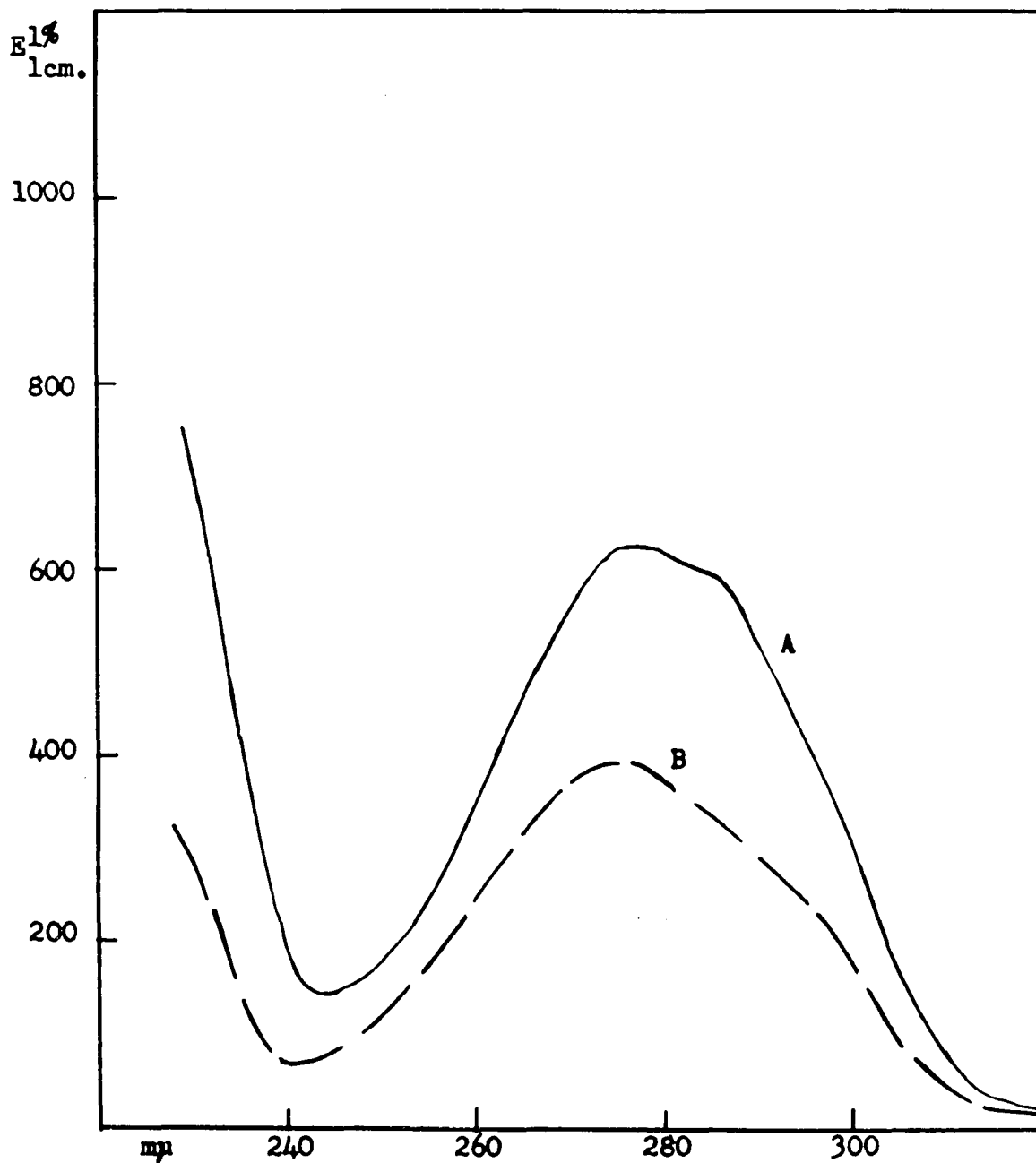


is ruled out by the fact that such a compound would exhibit strong absorption^{only} in the region of 210-230 μ , characteristic of methoxyxylene.

The residue obtained on evaporation of the benzene and butyl ether was subjected to distillation at pressures of less than 1 mm. This procedure effected dehydration of the acetylenic carbinol (VI) and partial purification of the resulting eneyne (VII).

A determination of phenylacetylene compounds based on ultraviolet absorption spectra is indicated by a comparison of the $E_{1\text{ cm.}}^{1\%}$ values of curves A and B in Plate 3. Curve A is that of an alcoholic solution of the eneyne-containing distillate while Curve B was obtained as follows: An alcoholic solution of the eneyne in one experiment was treated with a slight excess of alcoholic silver nitrate and stirred thoroughly at room temperature. The mixture was centrifuged and a sample of the supernatant liquid was subjected to an ultraviolet absorption spectrum determination. The reduction of the $E_{1\text{ cm.}}^{1\%}$ value from 629 to

PLATE 3.



A. Ultraviolet absorption spectrum of 1-ethynyl-3,4-dihydro-6-methoxynaphthalene (VII) (in EtOH)

Max: $\lambda = 276$, $E_{1\text{cm.}}^{1\%} = 614$

B. Curve of same material after treatment with AgNO_3

Max: $\lambda = 275$, $E_{1\text{cm.}}^{1\%} = 395$

395 indicated that the amount of triple-bond compound present in the sample of eneyne (precipitated by the silver nitrate) was of the order of 35-40%, assuming equivalent contribution of the eneyne and contaminants to the absorption at ca. 275 μ .

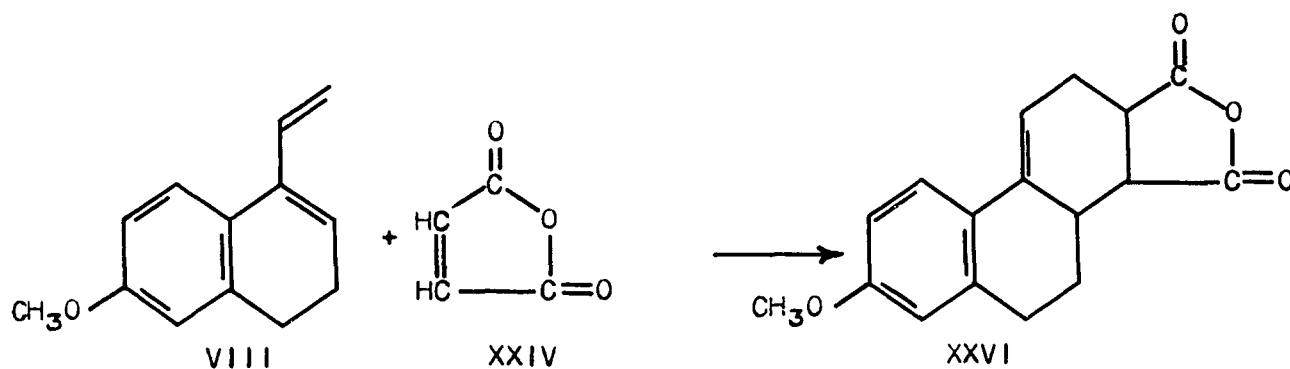
The distillate containing the eneyne was hydrogenated in ethanol in the presence of 5% palladium on charcoal. The criteria of a good preparation of the resulting diene were 1) lack of reaction with ammoniacal silver nitrate and 2) immediate formation of an insoluble adduct upon reaction with maleic anhydride in benzene.

Several reductions of the eneyne were carried out by refluxing an alcohol-water mixture of 1-ethynyl-6-methoxy-3,4-dihydronaphthalene (VII) with zinc dust previously coated with copper. This was the procedure employed by Breitner (2) who claimed almost quantitative yields of the vinyl derivative (III). Although small amounts of the diene were obtained by this procedure it was discarded in favor of the catalytic reduction method. This was due chiefly to the extremely long periods of time necessary to gain a negative ammoniacal silver nitrate test. The test was run on small samples of the refluxing mixture withdrawn at definite intervals. Perhaps the heterogeneous nature of the reduction mixture was responsible for the long time necessary to effect reduction. It was feared that polymerization of the eneyne or diene might take place more rapidly than the hydrogenation of the eneyne. In fact,

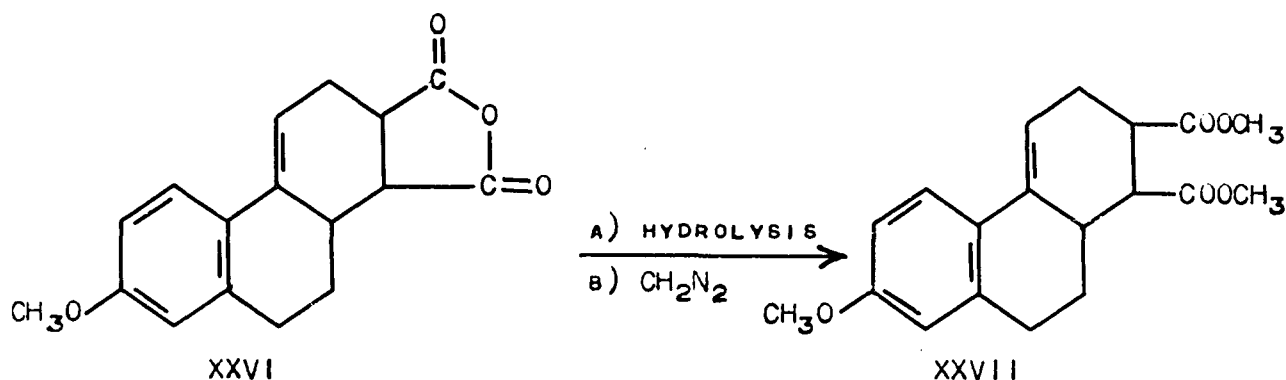
the product from one such a reduction was found to be completely non-volatile when subjected to a distillation temperature of 250°C. at a pressure of 0.5 mm., so it was concluded that polymerization did indeed take place more rapidly than did the desired reduction by the zinc-copper couple.

Diels-Alder Reactions with 1-Vinyl-6-methoxy-3,4-dihydronaphthalene

Reaction with Maleic Anhydride. Dane and co-workers (1) were the first to obtain an adduct (XXVI; m.p. 200-201°) from 1-vinyl-6-methoxy-3,4-dihydronaphthalene and maleic anhydride. Bachmann and Chemerda (2) found that the condensation took place almost



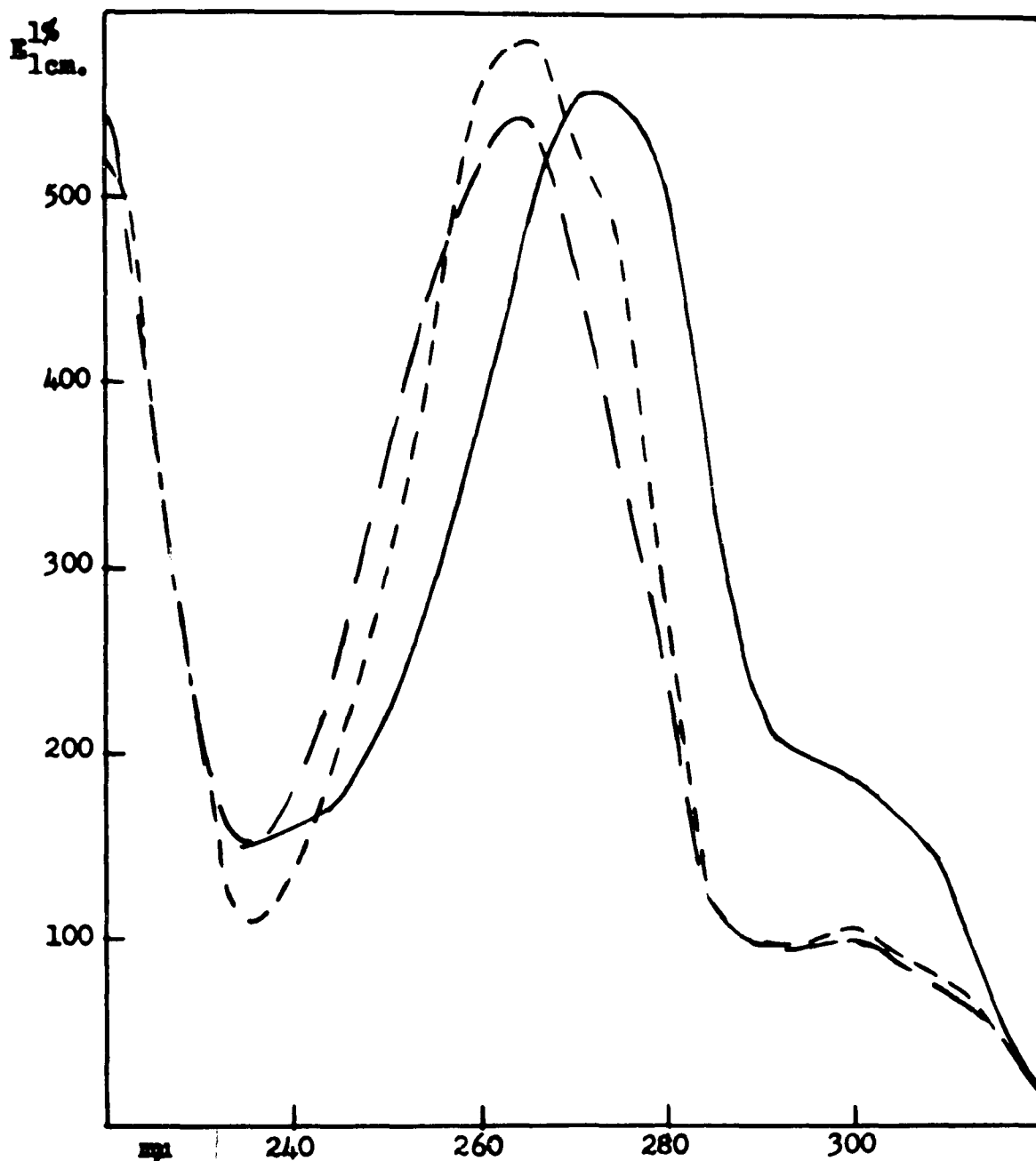
immediately in benzene. Dane also prepared the dimethyl ester (m.p. 117°) (XXVII) from the anhydride. We have confirmed the



results of Dane and of Bachmann and Chemerda and have proved that the structure XXVII, cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic anhydride (our m.p. $203-204^{\circ}$), is correct. By hydrolysis of the anhydride and of the dimethyl ester we have obtained the corresponding dicarboxylic acid (m.p. $210-215^{\circ}$), (XXVIII), which had not been reported previously.

When the diacid (m.p. $210-215^{\circ}$) was kept at its melting point a new anhydride (m.p. $123-124^{\circ}$) was produced. The ultraviolet absorption spectra (Plates 4 and 5, b and a')

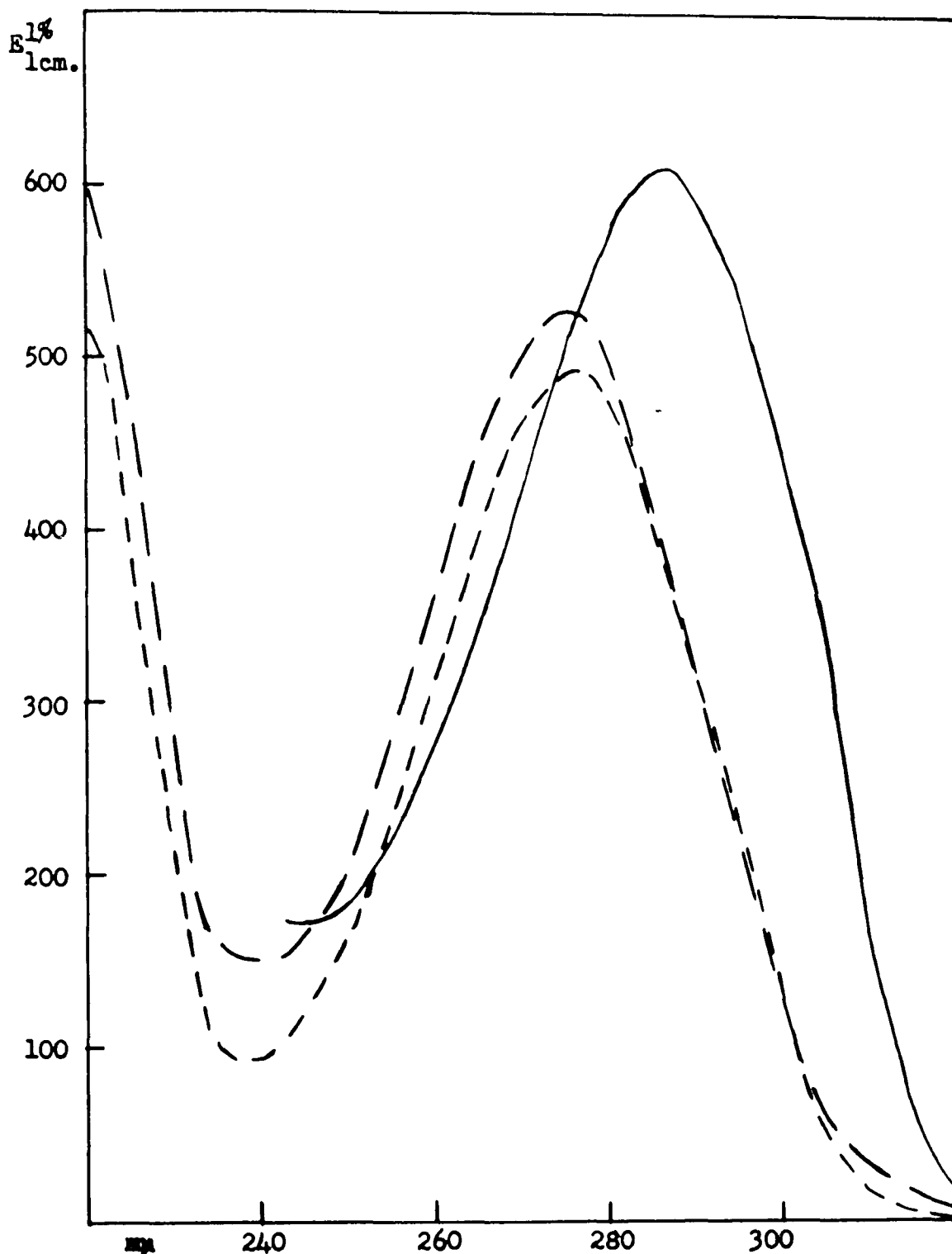
PLATE 4.



Ultraviolet absorption spectra of:

- a) ——— cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XXVI) (in CHCl_3) Max: $\lambda = 272$, $E_{1\text{cm.}}^{1\%} = 559$
 b) — — — cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid (XXVIII) (in EtOH) Max: $\lambda = 264$, $E_{1\text{cm.}}^{1\%} = 544$
 c) - - - - - dimethyl ester of cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid (XXVII) (in EtOH) Max: $\lambda = 265$, $E_{1\text{cm.}}^{1\%} = 584$

PLATE 5.



Ultraviolet absorption spectra of:

a') — cis-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XXIX) (in CHCl₃) Max: λ = 286, $E_{1\text{cm.}}^{1\%}$ = 611

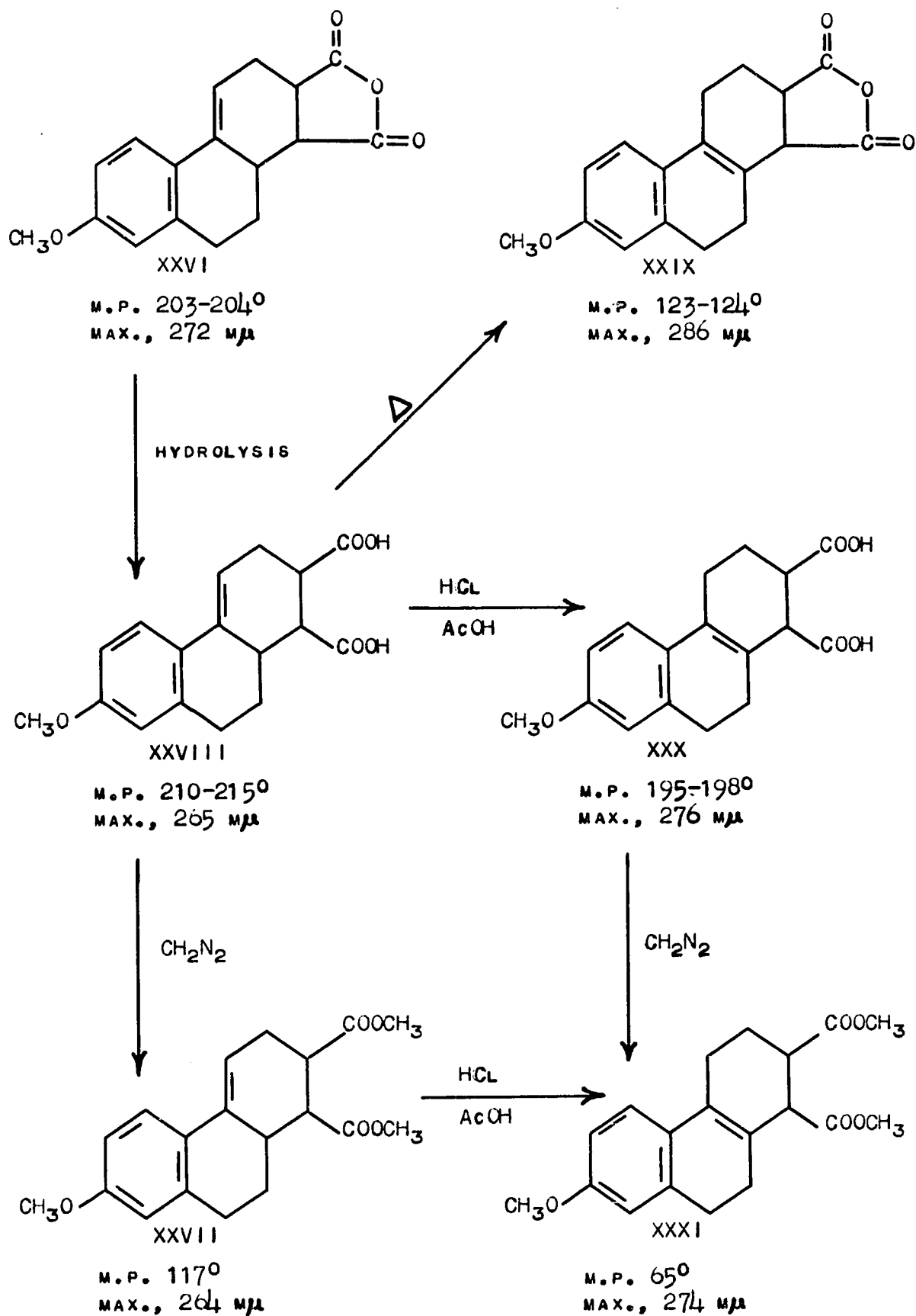
b') — cis-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXX) (in EtOH) Max: λ = 275, $E_{1\text{cm.}}^{1\%}$ = 527

c') — dimethyl ester of cis-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXI) (in EtOH) Max: λ = 276, $E_{1\text{cm.}}^{1\%}$ = 495

showed a shift in the maximum to 286 μ (from 272 μ). This could only mean that a shift of the double bond to the position between the two rings had taken place for such a shift would result in moving the absorption band to the region of greater wavelength. The new anhydride, therefore, is cis-7-methoxy-1,2,3,4,9,10-hexahydro-1,2-dicarboxylic anhydride (XXIX).

When the acid (m.p. 210-215°) (XXVIII) with the double bond in the C ring was heated with a solution of anhydrous hydrogen chloride in acetic acid, isomerization occurred with the formation of a new acid (m.p. 195-198°) (XXX) with the double bond between the B and C rings. Similarly when the ester (m.p. 117°) (XXVII) with the double bond in the C ring was heated with hydrogen chloride in acetic acid, the ester was isomerized to a new ester (m.p. 65°) (XXXI) with the double bond between the rings. The new ester was identical with that obtained by treatment of the new acid (m.p. 195-198°) with diazomethane. All of the chemical results are consistent with one another as shown in Chart I. Moreover, the maxima of all of the compounds (Plate 5) of the new series (double bond between the rings) occur at higher wave lengths and lack the extra inflection or peak present in the compounds with the double bond in the C ring.

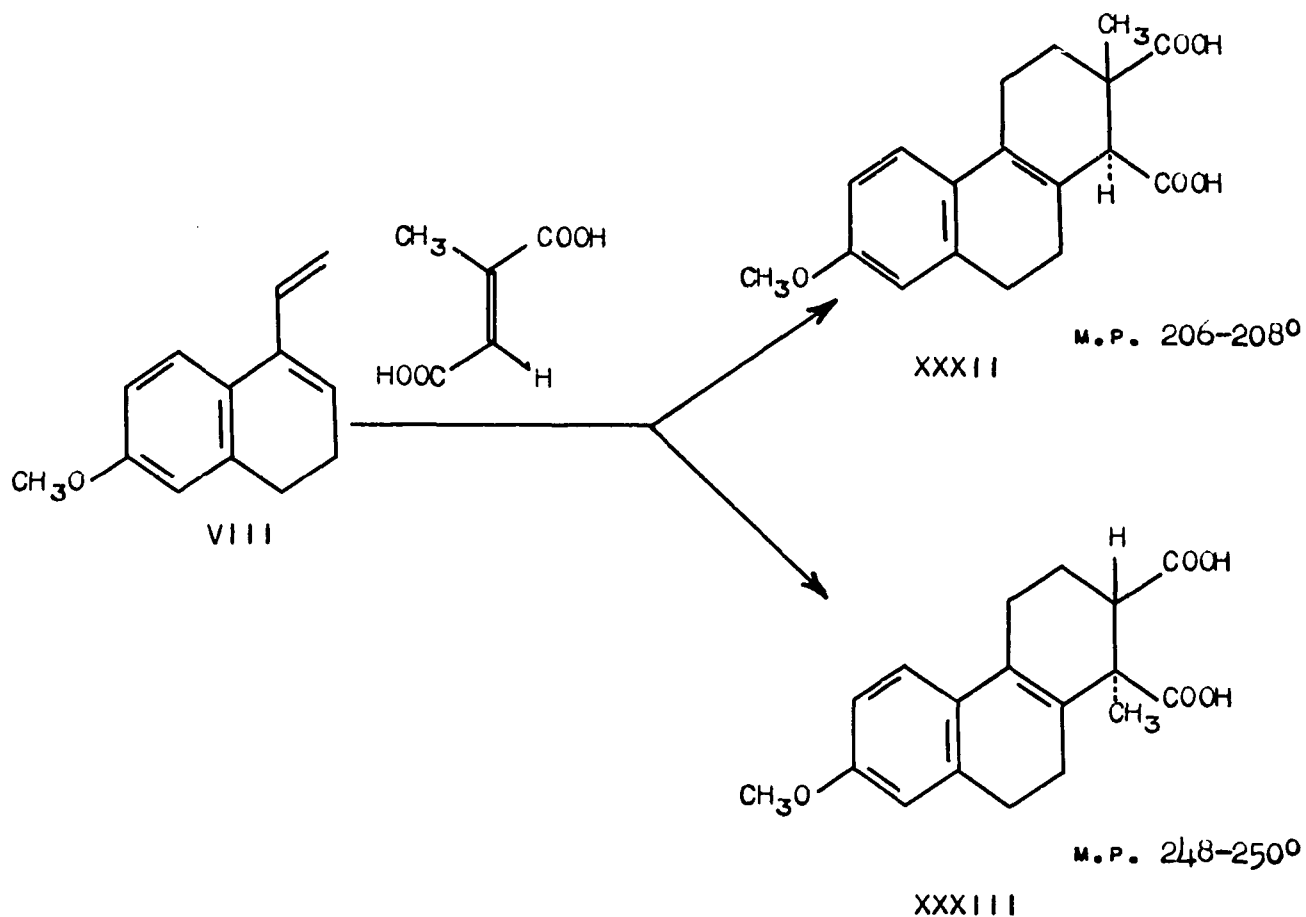
CHART I



Reaction with Mesaconic Acid. Bachmann and Scott (12)

were the first to show unequivocally that a trans acid could add to a diene. They succeeded in obtaining adducts from anthracene and fumaric acid and from anthracene and mesaconic acid (methyl fumaric acid). The adducts were stereoisomers of those obtained from anthracene and maleic acid and from anthracene and citraconic acid. They showed that the cis unsaturated acids gave adducts which had the cis configuration with respect to the carboxy groups; the trans unsaturated acids gave adducts with a trans configuration.

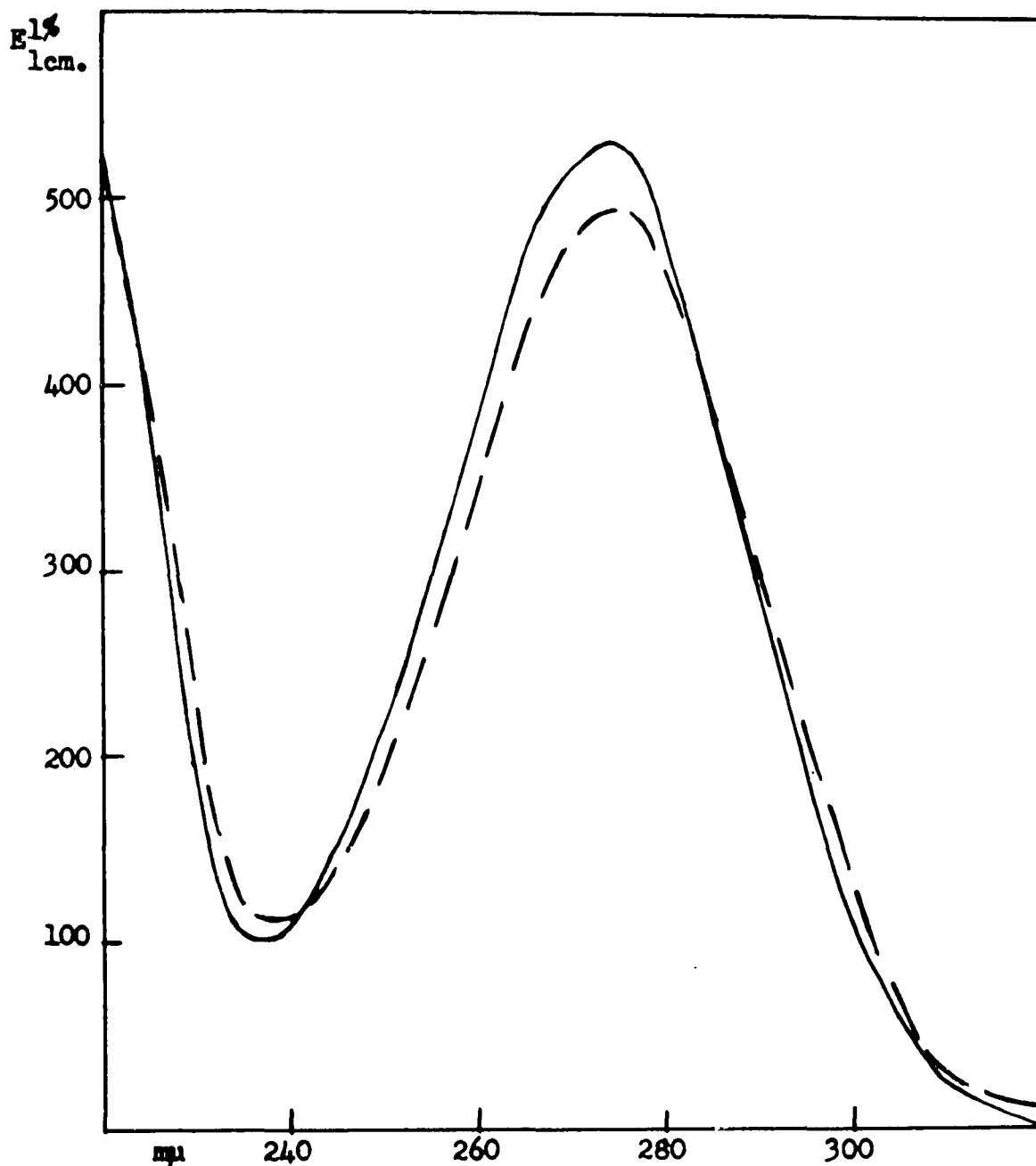
We have found that 1-vinyl-6-methoxy-3,4-dihydronaphthalene reacts with mesaconic acid in boiling propionic acid to give a mixture of isomeric adducts. The reaction is slow (four to five days being required) and the yield of product is low (presumably on account of polymerization or decomposition of the diene before it can undergo the addition reaction). The reactions which occur with the formation of the two structural isomers, trans-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXII) and trans-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXIII), are the following:



The mixture of isomers was separated by recrystallization into the two pure compounds (XXXII and XXXIII). In the acidic medium which was used for the Diels-Alder reaction, the original adducts isomerized to the compounds having the double bond between the two rings. Confirmation of this conclusion is indicated by the position of the peak (274-275 mμ) of the ultraviolet absorption curves of XXXII and XXXIII as shown in Plate 6. This observation is to be compared with the ultraviolet absorption spectra of the corresponding maleic anhydride adduct diacid XXX in Plate 5.

26a.

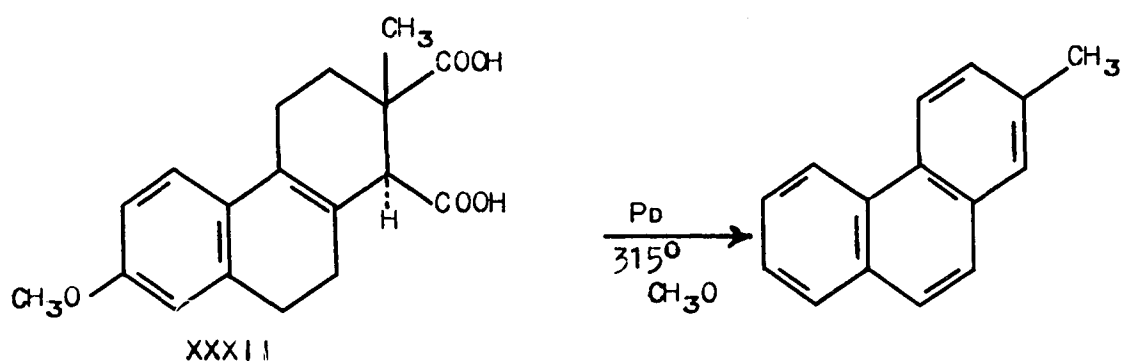
PLATE 6.



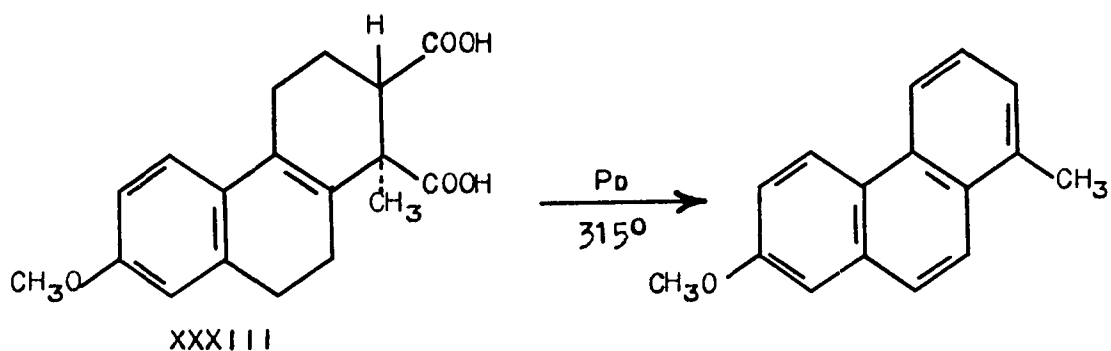
Ultraviolet absorption spectra of:

- a) ——— trans-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydro-phenanthrene-1,2-dicarboxylic acid (XXXIII) (in H_2O)
Max: $\lambda = 274$, $E_{1\%}^{1\text{cm.}} = 532$
- b) - - - trans-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydro-phenanthrene-1,2-dicarboxylic acid (XXXII) (in H_2O)
Max: $\lambda = 274$, $E_{1\%}^{1\text{cm.}} = 510$

The structure of XXXII (m.p. 206-208°) was established by treatment of the compound with palladium on charcoal at 315-320°; under these conditions decarboxylation and dehydrogenation occurred with the formation of the known 2-methyl-7-methoxyphenanthrene.

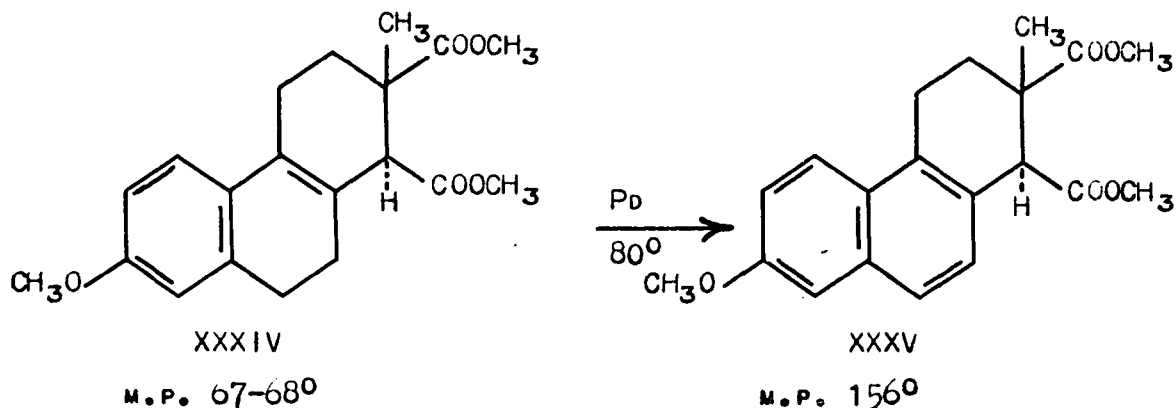


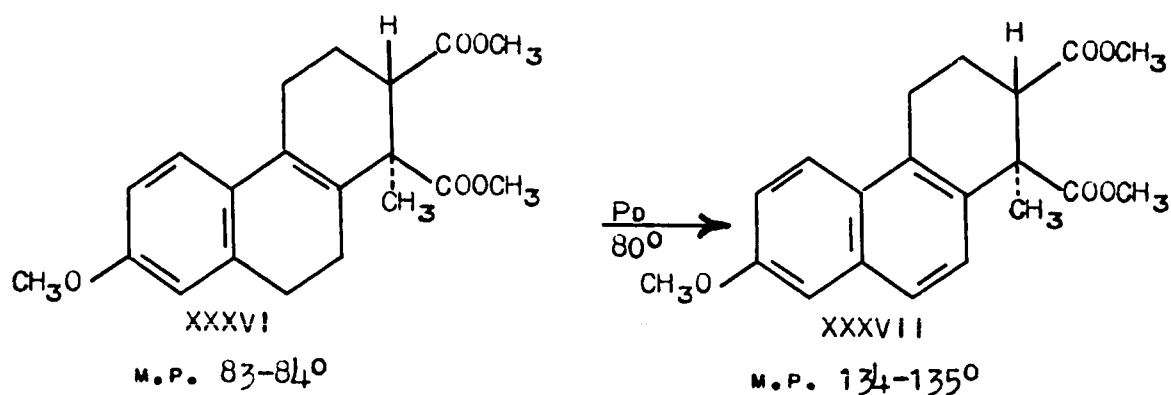
Under similar conditions XXXIII (m.p. 248-250°) yielded the known 1-methyl-7-methoxyphenanthrene.



These reactions definitely locate the position of the methyl group in the two adducts.

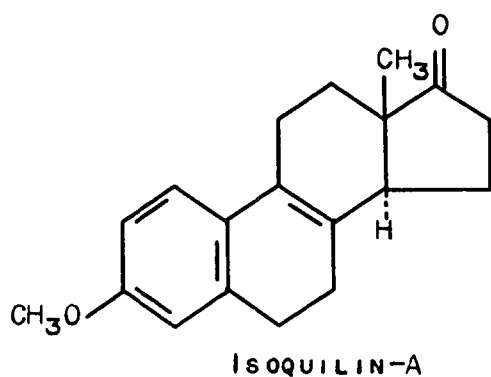
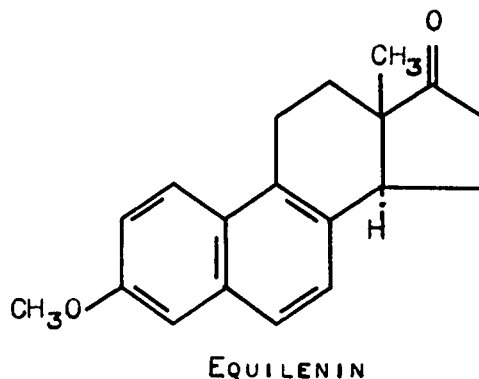
Both acids were converted into their methyl esters by means of diazomethane. When ethanolic solutions of the esters were refluxed with palladium on charcoal only dehydrogenation of the middle (B) ring took place. The 2-methyl diester (XXXIV) yielded the new dimethyl ester of trans-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XXXV); the 1-methyl diester (XXXVI) gave the known dimethyl ester of trans-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XXXVII) of Bachmann and Scott (12). This latter reaction is further evidence of the correctness of the structure assigned to the 1-methyl adduct.





Of considerable interest is the fact that the trans configuration was not affected under the conditions of the dehydrogenation.

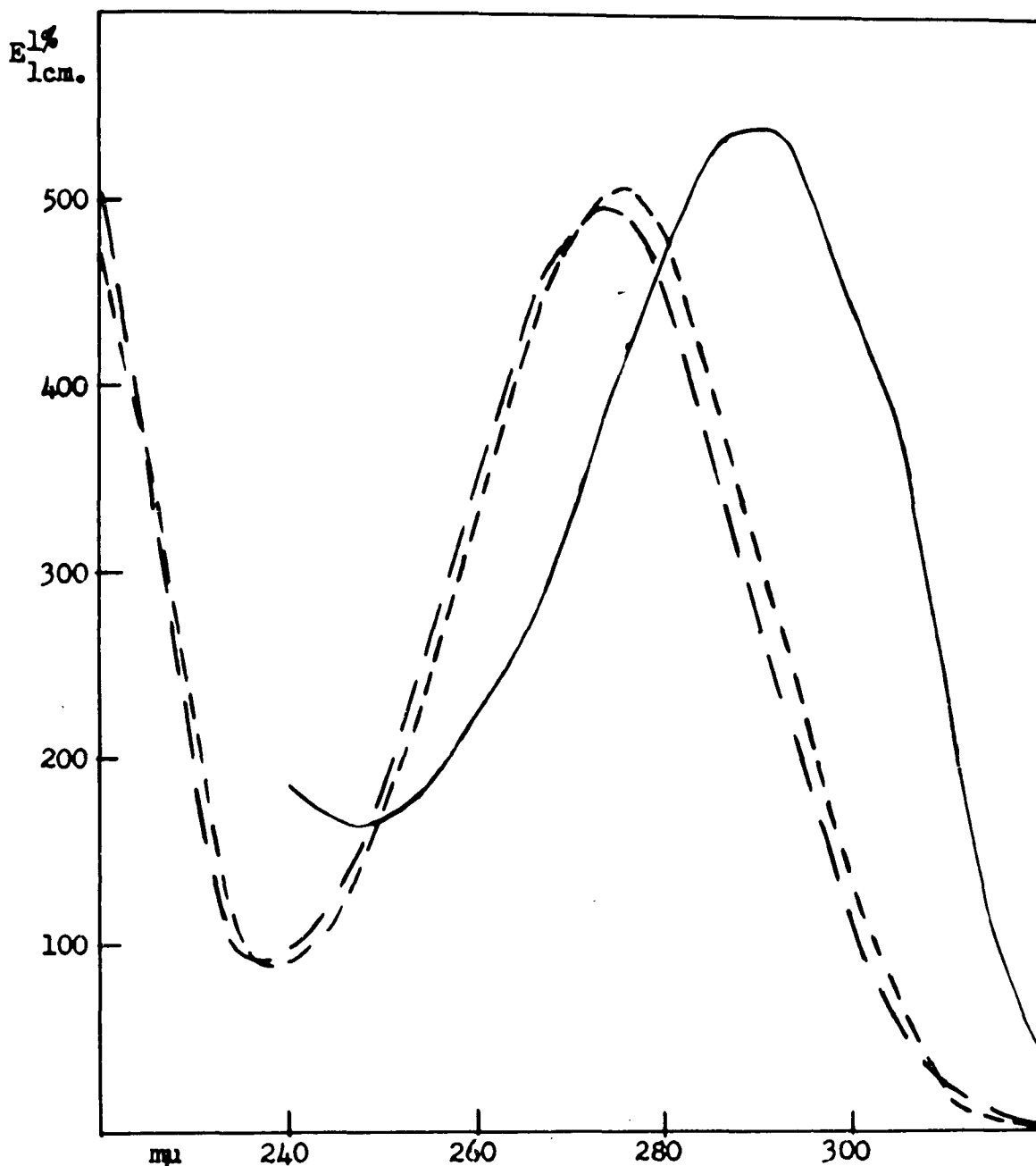
Compounds XXXIV and XXXV are valuable key intermediates for steroid syntheses. By known methods (Arndt-Eistert reaction and Dieckmann cyclization) XXXIV should yield isoequilin A and XXXV should yield equilenin.



The present research has opened the way to the preparation of steroids with known configuration at the C/D ring juncture.

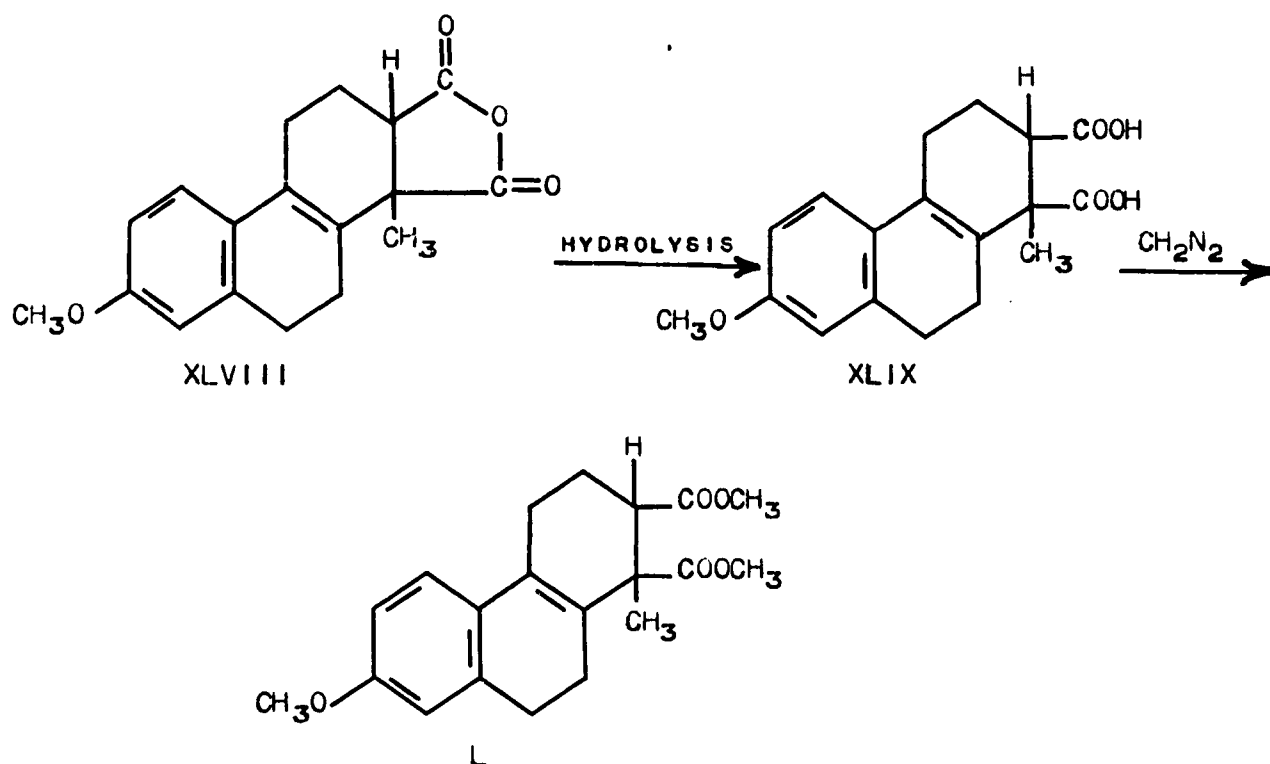
Reaction with Citraconic Anhydride. The reaction of 1-vinyl-6-methoxy-3,4-dihydronaphthalene with citraconic anhydride (methylmaleic anhydride) has been repeated in order to obtain further information on the adducts and on the compounds derived from them. Bachmann and Chemerda (2) were the first to show that two structurally isomeric adducts, the 1-methyl and 2-methyl derivatives, were produced in the reaction. Heer and Miescher (4) have shown that the double bond in the 2-methyl derivative was located between the two rings. However, the latter investigators place the double bond of the 1-methyl derivative (m.p. 174-5°) (XLVIII) in the C ring. We have isolated this compound and upon purification have found the melting point to be 126-8°. Furthermore, the ultraviolet absorption spectra of this anhydride, the corresponding new diacid (m.p. 135-7°) (XLIX) obtained upon mild alkaline hydrolysis and the known dimethyl ester (m.p. 84°) (L) of the latter diacid are shown in Plate 7. All of these curves are similar to the curves (Plate 5) of the maleic anhydride adduct derivatives which were shown to possess the double bond at the B/C ring juncture and not in ring C alone. The structures and relationships of these three compounds are as follows:

PLATE 7.

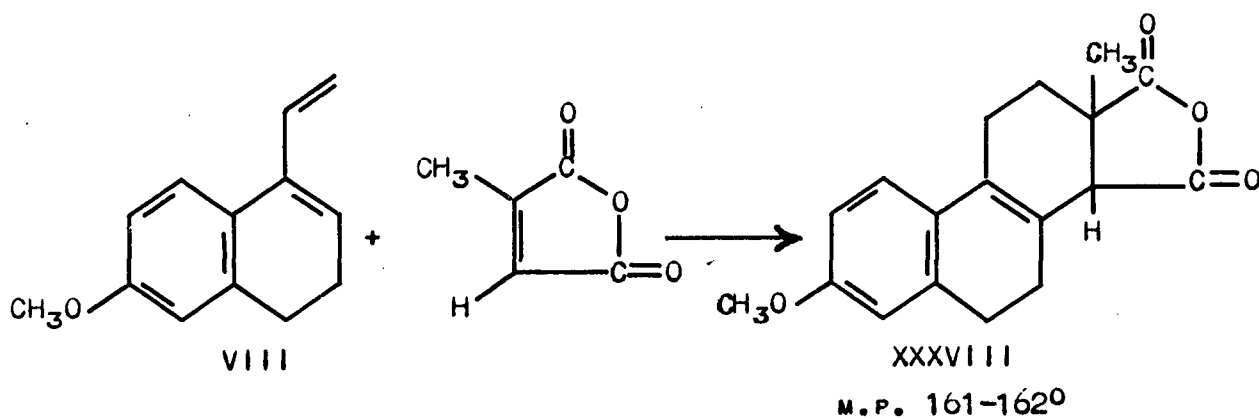


Ultraviolet absorption spectra of:

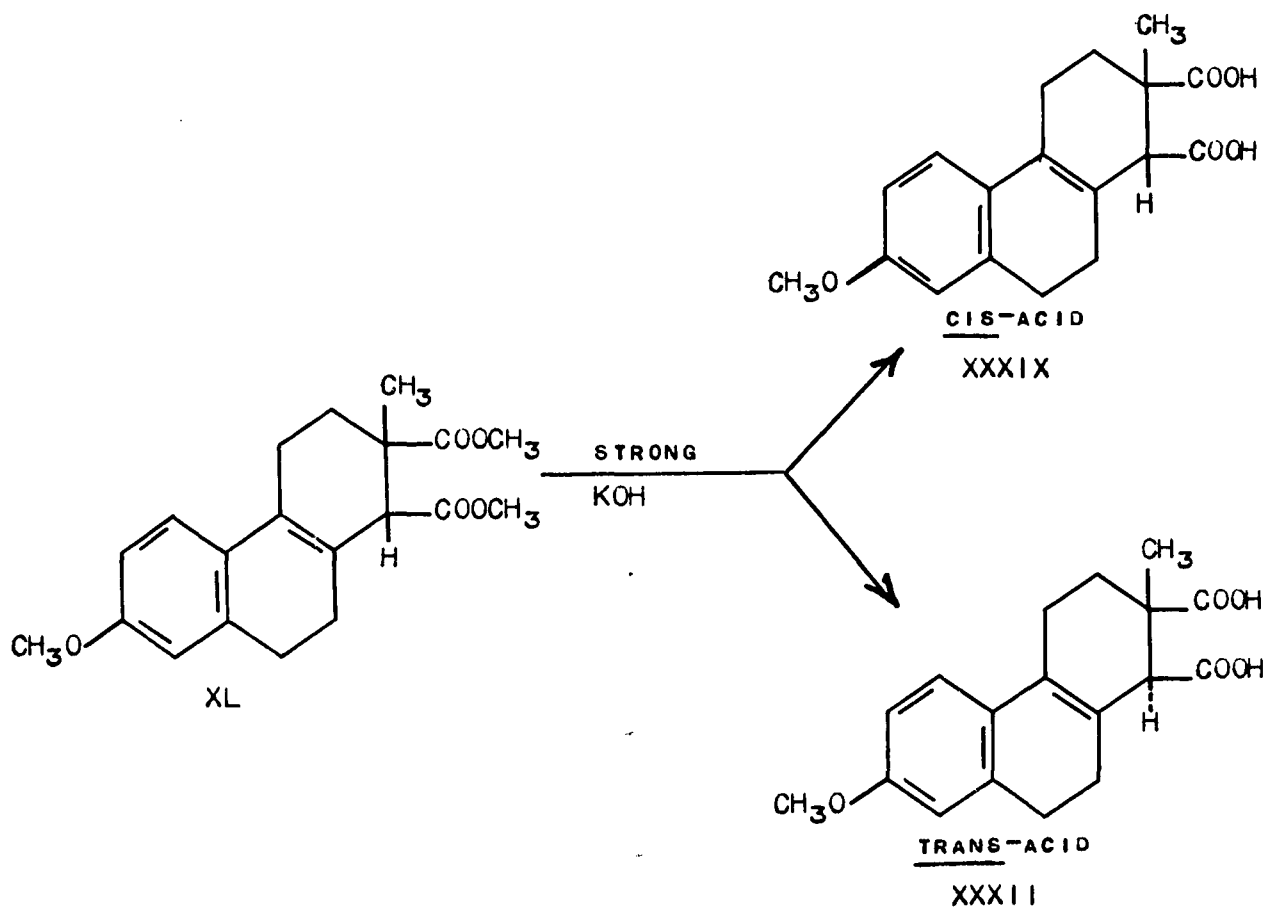
- a) ——— cis-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XLVIII) (in CHCl_3) Max: $\lambda = 290$, $E_{1\%}^{1\text{cm.}} = 540$.
 b) — — — cis-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XLIX) (in EtOH) Max: $\lambda = 274$, $E_{1\%}^{1\text{cm.}} = 494$.
 c) - - - - - dimethyl ester of cis-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (I) (in EtOH) Max: $\lambda = 276$, $E_{1\%}^{1\text{cm.}} = 510$.



Although the diacids of the adducts derived from the Diels-Alder reaction with citraconic anhydride have the same structural formulas as the adducts derived from mesaconic acid, they are stereo-isomeric with the latter and have different properties (m.p., solubility, etc.). Only the 2-methyl derivative is shown in the following formulation.

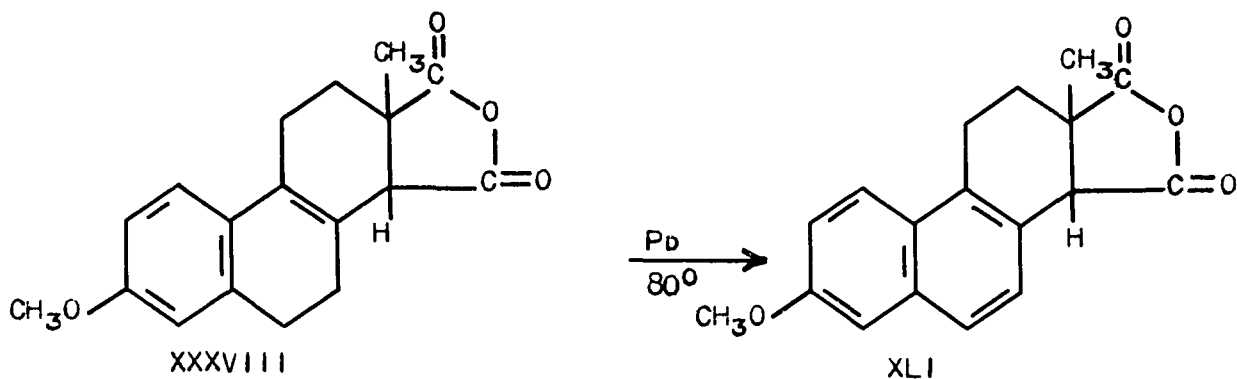
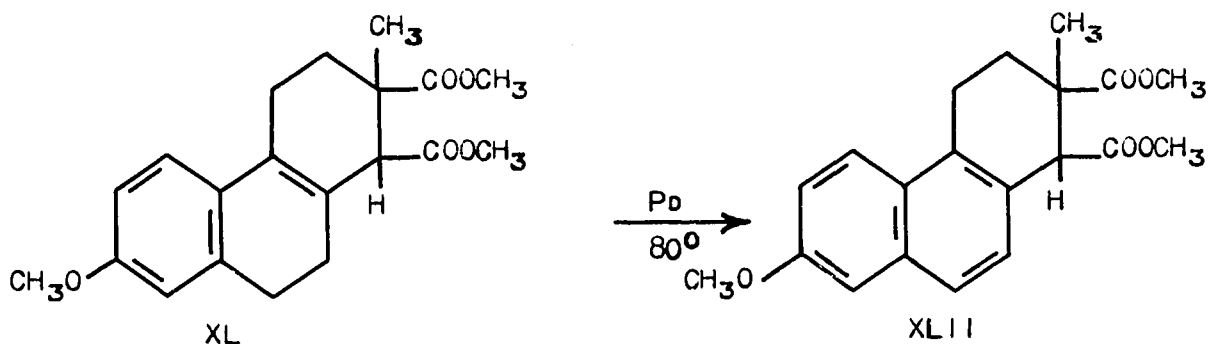


The anhydride adduct was converted into the corresponding cis-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXIX, m.p. 179-180°) by mild alkaline hydrolysis; from the acid the cis-dimethyl ester (XL; m.p. 90-92°) was prepared. When the pure cis-dimethyl ester was hydrolyzed with strong methanolic potassium hydroxide partial epimerization occurred. In addition to the cis acid which was the chief product, there was isolated some of the trans acid (m.p. 206-208°), which was identical with the acid (XXXII) obtained by addition of mesaconic acid to the diene.



This result clearly shows the relationship between the adducts obtained from citraconic and mesaconic acid.

We have found that refluxing of a benzene solution of cis-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic anhydride with palladium was sufficient to effect dehydrogenation of the B ring to yield cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (XLI). Similarly, the dimethyl ester of cis-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid was dehydrogenated in boiling ethanol to the dimethyl ester of cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XLII). The results showed that no epimerization occurred during dehydrogenation.



It was found possible to effect epimerization by alkali in this tetrahydro series also. Some of the trans-2-methyl-7-methoxy-1,2,3,4-tetrahydro-dicarboxylic acid was obtained when the corresponding cis dimethyl ester was hydrolyzed with strong alkali or when treated with triphenylmethylsodium, followed by hydrolysis. The cis configuration seems to be favored over the trans in alkaline medium. Thus, mild half-hydrolysis of the trans dimethyl ester by alkali sufficed to cause epimerization with the formation of a cis product.

Proof of the Configuration of the C/D Ring Junction in the Estrogenic Hormones. A New Synthesis of Isoequilenin.

Hydrolysis of the dimethyl ester of cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XLII) by potassium carbonate in aqueous methanol yielded a separable mixture of the two possible acid esters (XLIII and XLIV). That no epimerization had taken place during the half hydrolysis was proved by the re-formation of the original cis diester from both acid esters by treatment with diazomethane.

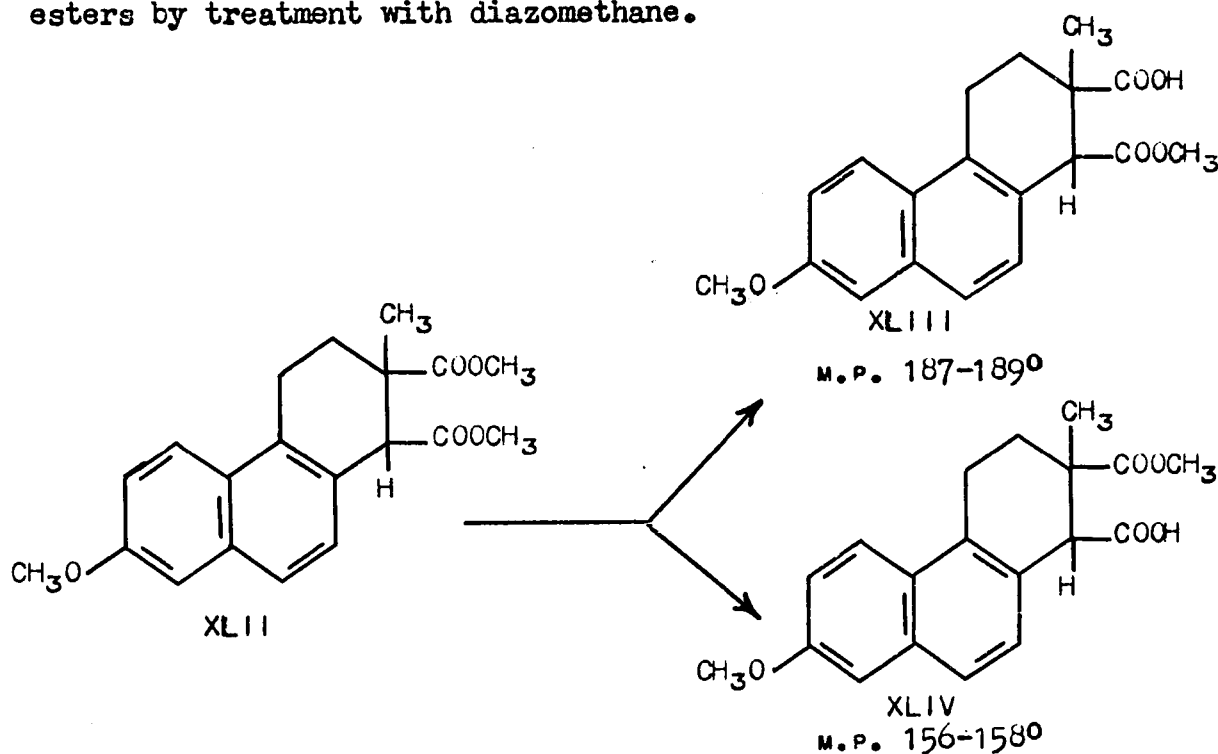
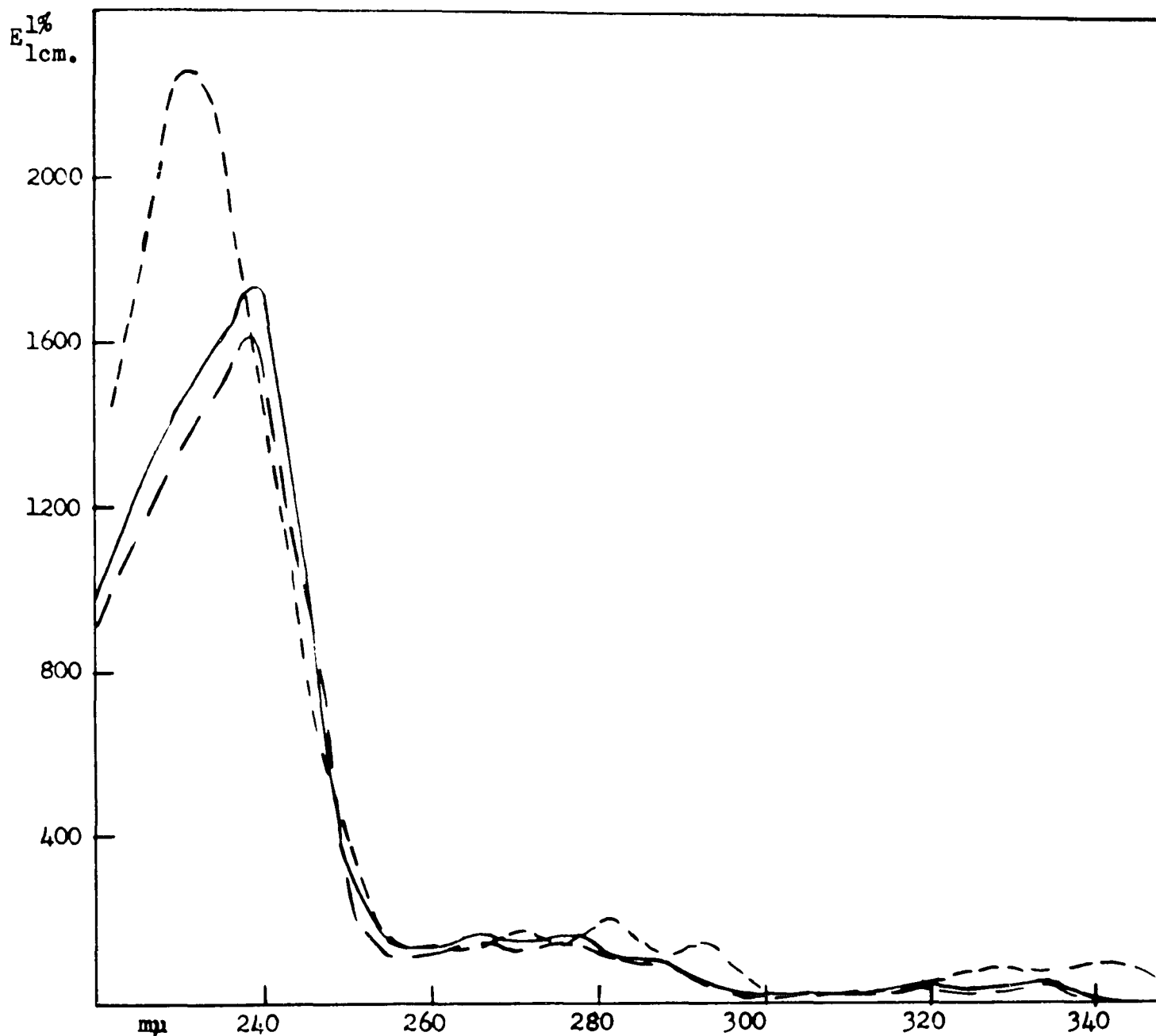


PLATE 8.

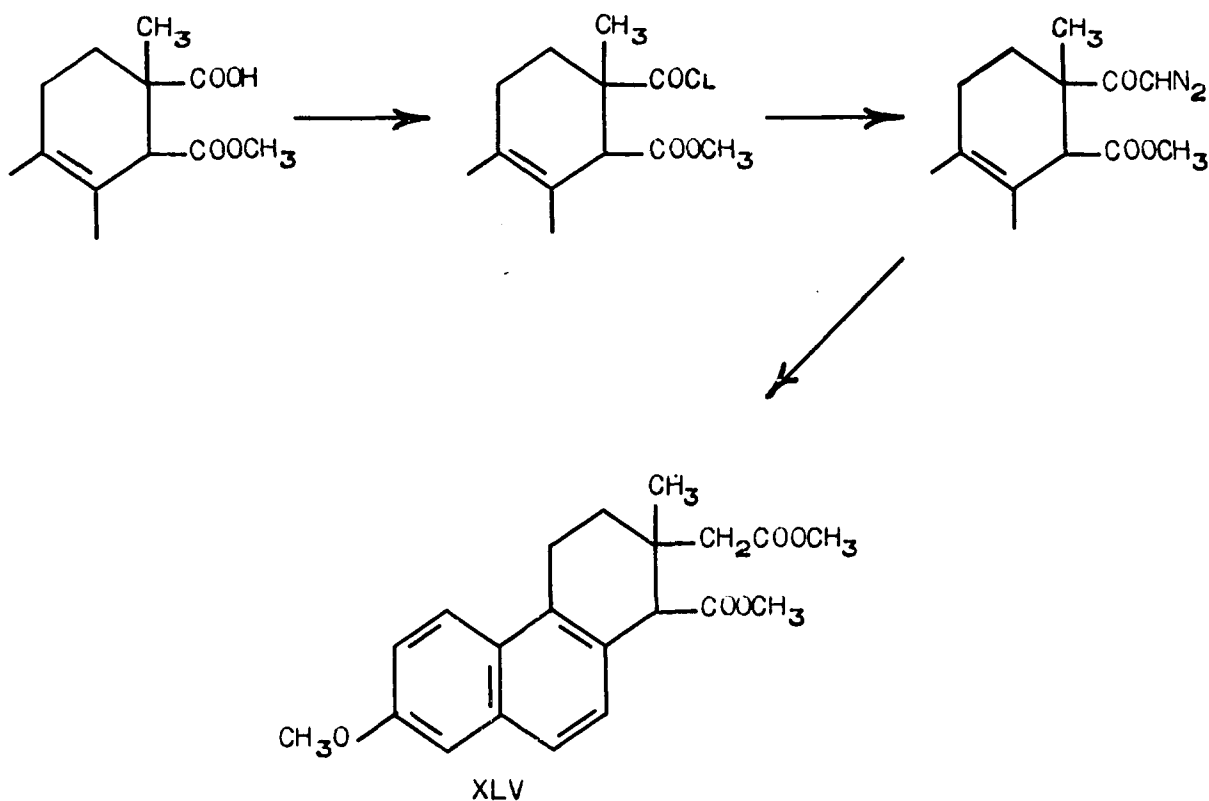


Ultraviolet absorption spectra of:

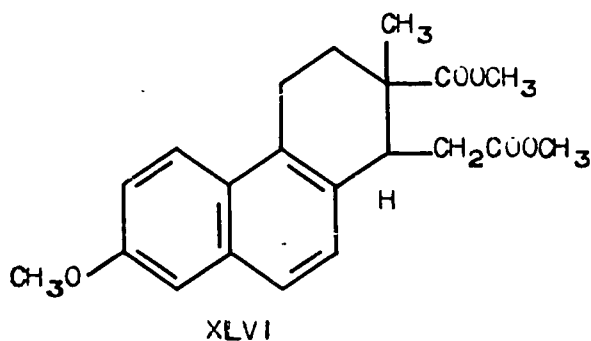
- a) ——— cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid, monomethyl ester (XLIV) (in EtOH) Max: $\lambda = 238.5$,
 $E_{1\%}^{1\text{cm.}} = 1740$
- b) — — — cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid, monomethyl ester (XLIII) (in EtOH) Max: $\lambda = 238$,
 $E_{1\%}^{1\text{cm.}} = 1607$
- c) - - - - equilenin (p. 36) (in EtOH) Max: $\lambda = 231$, $E_{1\%}^{1\text{cm.}} = 2250$

The high melting acid ester was the chief product when cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (XLI) was heated with methanol, while the low-melting acid ester was the major product when the anhydride was treated with sodium methoxide. The absorption spectra of the isomeric acid esters are shown in Plate 8. The structures of the products were proved by the reactions which follow.

Both acid esters were submitted to an Arndt-Eistert synthesis. Each one was treated with oxalyl chloride to form the acid chlorides. The latter were allowed to react with diazomethane in order to form the diazoketones, which were then rearranged in methanol in the presence of silver oxide. The 2-carboxy compound would yield the 2-acetic acid derivative (XLV) by this procedure; the 1-carboxy compound would be expected to



give the dimethyl ester of cis-2-methyl-7-methoxy-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (XLVI).

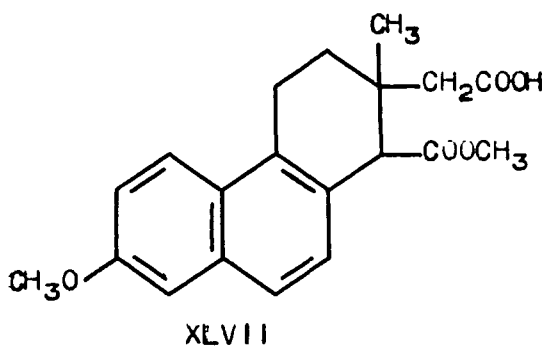


The acetic acid derivative (XLVI) would have the cis configuration since it was derived from the cis carboxylic acid and no inversion occurs in the Arndt-Eistert synthesis. Now, both stereo-isomeric forms of this dimethyl ester are known from the work of Bachmann, Cole and Wilds (13); from one form equilinenin was synthesized and from the other isoequilinenin was prepared. Clearly the reaction will prove the configuration of the estrogenic hormone equilinenin.

When the 187-189° acid ester was carried through the Arndt-Eistert synthesis a liquid product was obtained which yielded no crystalline material when seeded with both forms of XLVI. Hydrolysis with one equivalent of alkali yielded an acid (m.p. 146-148°) which was not equivalent to the acid esters derived

37.

from both forms of XLVI by similar treatment. The product presumably is XLVII although this has not yet been rigidly proved.



The 156-158° acid ester XLIV, surprisingly enough, yielded an acid (m.p. 146-148°) after hydrolysis of the liquid product, which did not depress the melting point of the acid derived from XLVII. However, it also gave, albeit in low yield, a crystalline dimethyl ester which proved to be identical with the acetic acid derivative (XLVI) which is a precursor of isoequilenin. This result proves that isoequilenin has the cis configuration at the C/D ring structure and, hence, the natural hormone, equilenin, has the trans configuration. Since estrone and estradiol have the same configuration at the C/D ring juncture as equilenin, it follows that these two estrogenic hormones also have a trans configuration between the C and D rings. The results substantiate the conclusions previously reached concerning the configurations (14).

Inasmuch as isoequilenin has been prepared from the product obtained in the Arndt-Eistert synthesis, the reactions via the Diels-Alder reaction represent a new synthesis of isoequilenin.

The formation of the identical product from both acid esters may involve an exchange between the ester group and acid chloride group such as has been observed by Cason (14) to occur with simpler aliphatic analogs. Whatever the reaction may be it does not affect the argument in regard to the acetic acid derivative actually identified.

SUMMARY

1. An improved method was devised for the preparation of 6-methoxy-1-tetralone starting from the readily available β -naphthyl methyl ether.
2. The preparation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene from 6-methoxy-1-tetralone and the acetylene Grignard reagent was studied in detail. It is considered that the method described herein can be readily duplicated.
3. A method for the analysis of the acetylene Grignard reagent has been devised.
4. A new series of compounds has been derived from the adduct formed from 1-vinyl-6-methoxy-3,4-dihydronaphthalene and maleic anhydride.
5. The Diels-Alder reaction of 1-vinyl-6-methoxy-3,4-dihydronaphthalene with mesaconic acid has been found to yield two adducts. The structures and configurations of each of the adducts have been rigorously established.
6. It has been shown that several hexahydrophenanthrene derivatives were readily dehydrogenated to tetrahydrophenanthrene compounds at 80°.
7. A cis - to - trans inversion or epimerization was carried out on cis-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid; the product was found to be identical with the trans-2-methylhexahydro adduct obtained from the Diels-Alder

condensation with mesaconic acid.

8. A cis - to - trans inversion of epimerization was carried out on cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid; the esterified trans isomer was found to be identical with the product obtained from the dehydrogenation at 80° of the dimethyl ester of the trans-2-methylhexahydro adduct obtained from the Diels-Alder condensation with mesaconic acid.

9. Two different acid esters from cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid were prepared by several procedures. Both acid esters were submitted to an Arndt-Eistert synthesis.

10. The configuration of the C/D ring juncture in the estrogenic hormones, equilenin, estrone, and estradiol, has been shown to be trans.

11. A new synthesis of isoequilenin, the stereoisomer of equilenin, has been realized via the Diels-Alder reaction.

12. Use was made of ultraviolet absorption spectra to aid in the elucidation of the structures of many of the compounds prepared during this investigation.

EXPERIMENTAL DETAIL

Preparation of 6-Methoxy-1-Tetralone

6-Methoxytetralin

1) From Tetralin

Sulfonation of Tetralin. Sulfuric acid (800 g.) was stirred in a three liter beaker during the addition of tetralin (XI) (660 g.) in 25-50 g. portions. After all of the tetralin was added, the mixture was heated on a steam bath for four hours. A sample of the dark red viscous liquid at this time gave only a faint turbidity when placed in a small amount of water. The warm reaction mixture was added slowly with stirring to three liters of saturated sodium chloride solution. When the mixture was cooled to 25°C. it was filtered and the pale reddish-brown cake was washed by slurring in two liters of the saturated sodium chloride solution. The final washed solid sodium salt of ar-tetralin-2-sulfonic acid (XII) was sucked as dry as possible and used directly in the next step.

Fusion of the Sulfonic Acid (XII) and Methylation. The sodium salt (XII) was added in small portions to 2400 g. of potassium hydroxide and 200 ml. of water heated to 200-210° in a metal beaker. A stirrer and lid were provided to effect thorough mixing and prevention of loss of any of the mixture due to spattering. After each portion of the sulfonate was added a short time was allowed to elapse to permit the somewhat violent fusion reaction to

take place before any more sulfonate was added. Heat was applied continually during the addition so that a final temperature of $300-310^{\circ}$ was reached. The melt was kept at this temperature for about two hours and was then poured into a large-area metal tray. Before the melt had solidified completely, it was broken into small pieces. The latter were then stirred with three liters of water. The resulting aqueous mixture was neutralized carefully with 50% aqueous sulfuric acid. Extraction of the slightly acid mixture with ether yielded an ethereal solution which was concentrated to obtain a dark brown oil. This was dissolved in 10% aqueous sodium hydroxide and the solution was cooled to 10°C . To this solution was added dimethyl sulfate (250 ml.). After stirring for one hour the mixture was extracted with three portions of ether, the combined extracts were concentrated to remove the ether and the residual oil was distilled in vacuo. The fraction (313 g.; 26% yield based on tetralin) boiling at $138-144^{\circ}\text{C}$. and 25-27 mm. was collected and consisted of 6-methoxytetralin. (reported⁶: 29%; b.p. $100-5^{\circ}/3$ mm.)

2) From Anisole

Succinoylation of Anisole. A mixture of 216 g. of anisole (XV), 210 g. of succinic anhydride (XVI) and 500 ml. of nitropropane was stirred at 0°C . in a three-necked flask equipped with a condenser, a stirrer and an addition tube. To this mixture was added a solution of 560 g. of aluminum chloride in one liter of

nitropropane. During the addition the temperature was kept below 2°C. The final mixture was stirred at 2-3°C. for eight hours, allowed to stand for eleven hours and stirred for six hours longer. Then it was poured into two liters of 6N hydrochloric acid and two kilograms of ice. This mixture was stirred well and filtered. The filter cake was dissolved in 1.5 liters of water containing 150 g. of sodium hydroxide. The solution was decolorized and filtered and the filtrate was acidified with hydrochloric acid. The light tan β -p-anisoylpropionic acid (XVII) which resulted was filtered, washed, and dried; m.p. 143-5°; yield 355 g. (reported⁷, 144-6°; 367 g.)

Clemmensen Reduction of the Keto-Acid XVII. Zinc (840 g.) was amalgamated by shaking with a solution of 50 g. of mercuric chloride in 35 ml. of hydrochloric acid and 900 ml. of water. The supernatant liquid was decanted and 525 ml. of water, 1225 ml. hydrochloric acid, 700 ml. of toluene and 350 g. of β -(p-anisoyl)-propionic acid (XVII) were added. This mixture in a 12-liter flask was refluxed for forty-eight hours. At intervals of six hours eight 175 ml. portions of hydrochloric acid were added to the refluxing mixture. The mixture was cooled at the end of the forty-eight hour period and the layers were separated. The aqueous layer was diluted with 1.2 liters of water and extracted with two 700 ml. portions of ether. The extracts were combined with the organic layer obtained from the first separation of layers and added to 2.1 liters of 5% aqueous sodium hydroxide. This alkaline mixture was steam-distilled to remove the organic solvents and the residue

was treated with 60 ml. of dimethyl sulfate at 80°C. After stirring for three-quarters of an hour, the mixture was neutralized carefully with acetic acid and the solution was charcoaled and filtered. The cold filtrate was treated at 10°C. with concentrated hydrochloric acid until definitely acid. After stirring for one hour, the mixture was filtered. The precipitated γ-p-anisylbutyric acid (XVIII) was washed and dried; m.p. 59-60°; yield 294 g. (reported⁷, 59-61°; 285-290 g.)

Ring Closure of Acid XVIII. To a mechanically stirred solution of 194 g. of γ-p-anisylbutyric acid (XVIII) in one liter of dry thiophene-free benzene was added 208.3 g. of phosphorus pentachloride while the temperature was kept at 5-10°C. The resulting colorless solution was warmed to 50°C. for a few minutes and then chilled to 0 to -5°C. To it was added rapidly (about forty seconds) a chilled solution of 175 ml. of anhydrous stannic chloride in 175 ml. of dry thiophene-free benzene. In ten to fifteen minutes the dark green reaction mixture solidified. About 500 g. of ice was added to the contents of the flask, followed by the addition of 500 ml. of hydrochloric acid. 50 ml. of ether was added to hasten hydrolysis of the complex and the mixture was shaken until complete solution occurred. After separating the two layers, the organic layer was washed with several portions of 5% hydrochloric acid, water, 5% aqueous sodium hydroxide, and finally water again. Concentration of the organic fraction yielded a residue which was distilled at 160-5°C./11 mm. and consisted of 7-methoxy-1-tetralone (XX); yield 160 g. (reported⁷, b.p. 160-5°/11 mm.; 161 g.)

Reduction of the Ketone XX. 7-Methoxytetralone (XX)

(88 g.) was dissolved in 275 ml. of ethanol and 10 g. of 5% palladium on charcoal catalyst was added. The mixture was hydrogenated in the Parr type hydrogenator at a pressure of about four atmospheres of hydrogen. When the calculated amount of hydrogen had been absorbed, the mixture was removed from the apparatus and the catalyst was filtered. The filtrate was concentrated in vacuo to remove the solvent, the residue was distilled at 120-128°/6-12 mm.; yield 85 g. and consisted of 6-methoxytetralin (XIV) (reported⁷, b.p. 121-8°/11 mm.; 81 g.). This amount represents a 50% overall yield based on anisole.

3) From β -Naphthol

Methylation of β -Naphthol (XXII). A solution of 550 g. of α -naphthol (XXII) in 900 ml. of methanol and 150 ml. of concentrated sulfuric acid was refluxed for five hours and poured out of the flask before cooling. Upon cooling to room temperature β -naphthyl methyl ether separated as a crystalline solid. It was filtered and washed by slurring with water, by slurring with dilute sodium hydroxide, and with water. The solid was sucked as dry as possible and then recrystallized from methanol. Two crops of the β -naphthyl methyl ether (XXI) were obtained; yield, 521 g.; m.p. 72-3° (reported, 525 g.; 71-2°)

Hydrogenation of the Ether XXI. β -Naphthyl methyl ether (XXI) (380 g.) was dissolved in one liter of glacial acetic acid

and Adams' platinum oxide catalyst (6 g.) was added. The mixture was hydrogenated in a Parr type hydrogenator at a pressure of about four atmospheres of hydrogen. Heating to 70-80° during the hydrogenation was effected by means of an electric heating collar held securely around the outside of the hydrogenation flask. When the hydrogen pressure fell to an amount equivalent to the absorption of the calculated amount of hydrogen, the mixture was removed from the apparatus and the catalyst was removed by filtration. The filtrate was concentrated in vacuo and the residual oil was distilled at 120-128°/8-12 mm.; yield 335 g. and consisted largely of 6-methoxytetralin (XIV).

One gram of this product was refluxed for two hours with 8 ml. of 48% hydriodic acid. Ten milliliters of water was added and about 10 ml. of the solution was distilled. The cloudy distillate was centrifuged. The oil in the bottom of the centrifuge tube dissolved in potassium hydroxide with only the slightest amount of turbidity. Upon acidification of the alkaline solution, a strong turbidity developed and an oil deposited on the walls of the tube. This test and the ultraviolet absorption spectrum (Plate 1) indicated that the product was chiefly the desired 6-methoxytetralin.

Oxidation of 6-Methoxytetralin (XIV). A solution of 248 g. of 6-methoxytetralin (XIV) in 260 ml. of propionic acid and 1127 ml. of glacial acetic acid was stirred at 5-10° while a solution of 243 g. of chromic anhydride in 100 ml. of water and 700 ml. of acetic acid was added dropwise over a period of five hours. The

solution was stirred for sixteen hours longer with the temperature rising gradually to 25°. The solution was then concentrated in vacuo and the black viscous mixture which remained was digested for one-half hour with 2.5 liters of hot water. The aqueous mixture was extracted with two liters of ether and then with three 500 ml. portions of ether. The combined ether extracts were washed with saturated sodium carbonate solution and then with water. The dried ether extract (magnesium sulfate) was concentrated in vacuo and the residue was distilled at 155-165° and 5-10 mm. The yellow distillate quickly solidified and melted at 75-8°; yield 128 g. (47%). Instead of distillation of the ether solution concentrate, the following procedure was employed to advantage: the concentrate was taken up in one liter of benzene and this solution was poured over a column of Brockmann aluminum oxide about 70 cm. long and 2.5 cm. in diameter. Concentration in vacuo of the effluent liquid from such a column with a run of the same size yielded 167 g. (62%) of almost pure 6-methoxy-1-tetralone (V); m.p. 78-9° (reported⁶, 70%; m.p. 77.5°). The product, when allowed to separate by evaporation of a solution slowly, crystallized in the form of thick prisms.

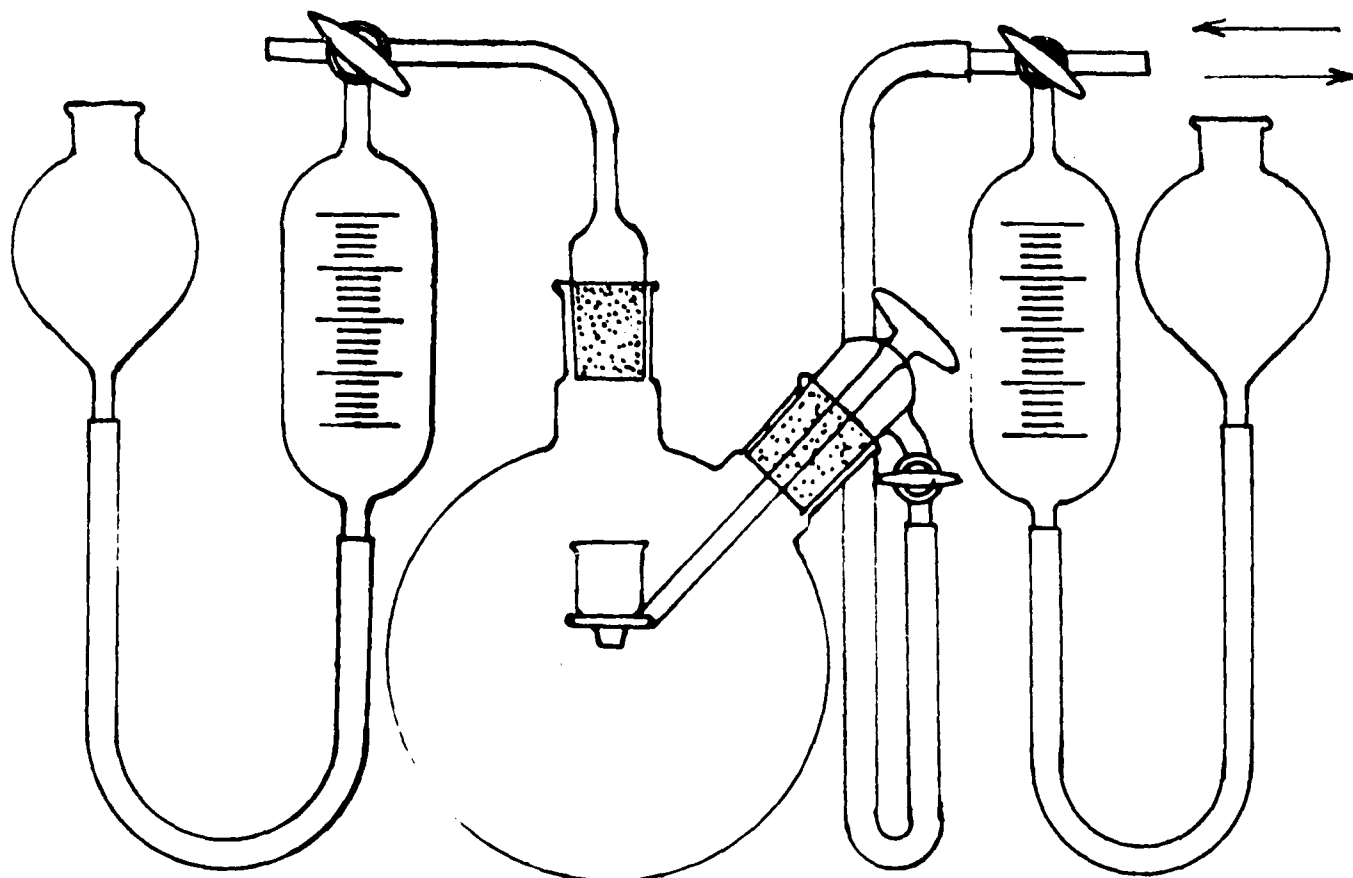
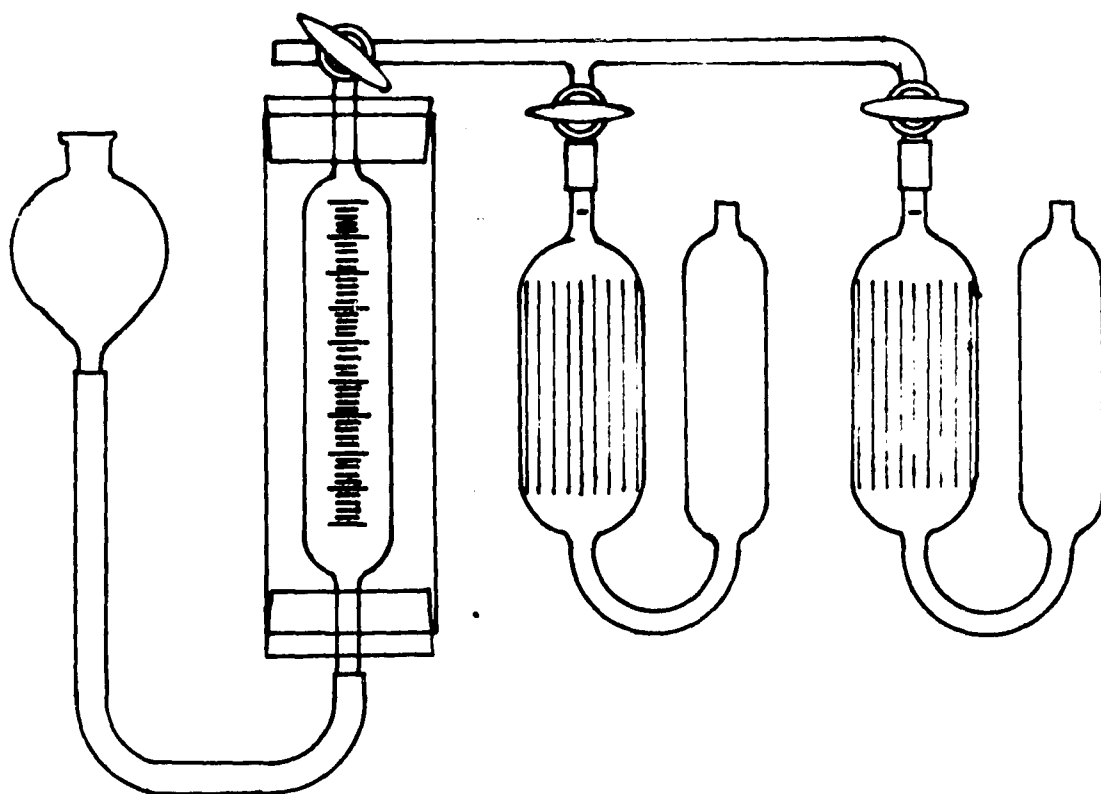
Reaction of 6-Methoxy-1-Tetralone with the Acetylene Grignard Reagent

Preparation and Analysis of the Acetylene Grignard Reagent.

Magnesium (28 g.) and butyl ether (250 ml.) were stirred at room temperature during the slow addition of ethyl iodide (110 ml.). The solution of ethylmagnesium iodide thus prepared was diluted

with 500 ml. of dry benzene and the resulting solution was cooled to $5-10^{\circ}$. Acetylene gas, purified by passing the commercial tank product through water and concentrated sulfuric acid and a calcium sulfate drying tower, was introduced at a moderate rate into the Grignard solution. Mechanical stirring was effected throughout the addition of the acetylene which was continued for one hour at $5-10^{\circ}$, for another hour at 25° and for two hours longer at $50-60^{\circ}$. The solution was allowed to stand for sixteen hours at room temperature and was then treated with acetylene again for one hour longer at $50-60^{\circ}$. Heating was effected by means of a hot water bath surrounding the flask. Aliquots for analysis of the Grignard solution were withdrawn at this point. The apparatus and procedure for this analysis is as follows:

The apparatus pictured in Fig. 1 was constructed. The two main parts are the gas-liberation set-up (A) and the Orsat-type set-up (B). The reaction flask in A was constructed with a movable arm extending into the middle of the flask. On the end of this arm inside the flask was a hook for holding a small glass bucket with a liquid capacity of about 5 ml. In the side of the arm on the outside of the flask was inserted an inlet into the flask which held a stopcock used for the introduction and exit of gases. On the top of the flask was another exit for gases. Both parts were connected to eudiometers which were filled with saturated salt solution and attached to levelling bulbs. Apparatus B was modelled after the

FIG. I. GAS ANALYSIS APPARATUS**A. GAS LIBERATION APPARATUS****B. ORSAT APPARATUS**

usual Orsat type of gas analysis equipment. The gasometer, contained in a water-jacket, was attached at the lower end to a levelling bulb also filled with saturated salt solution. At the upper end of the gasometer was attached a T-tube, one arm of which was connected to a three-way stopcock and the other arm of which was connected to a manifold. This manifold connected the gasometer to two absorption bulbs. These were constructed as pictured and the portions of the bulbs closest to the manifold were filled with many short lengths of 6 mm. glass tubing to provide increased surface area. The parts of the bulbs connected directly to the manifold outlets were constructed of capillary tubing with meniscus marks near the upper end. The operation of the entire apparatus will be obvious from the description of the analysis which follows.

An aliquot of the acetylene Grignard reagent solution is introduced into the bottom of the reaction flask previously swept out with dry nitrogen gas. The bucket is filled with 5 ml. of butyl alcohol and the apparatus is readied for gas evolution by insuring equality of pressure in the two eudiometers. Accompanied by a gentle swirling motion of the flask, the arm is rotated slowly through an angle of about 145° causing a gradual addition of the alcohol to the Grignard solution. Gas evolution occurs and the volume of the evolved gases can be read from the eudiometers after a suitable time has elapsed to insure equilibration. Then the levels of the liquid in the eudiometers may be raised and lowered to cause complete mixing of the evolved gases and the initial nitrogen gas. An aliquot is then conducted out through the stopcock in the side arm over into

the gasometer in (B). The gas in (B) is introduced into one of the absorption bulbs previously filled to the meniscus mark in the capillary tube connecting the bulb to the manifold. The gas is then brought back into the gasometer. (This transfer of the gas from the gasometer into the bulbs is accomplished by means of the levelling bulb attached to the lower end of the gasometer). The process is repeated until a constant volume is attained in the gasometer. This implies a complete absorption of the component gas in the gasometer which was soluble in the particular absorbent in the bulb. The gas is then led into the next bulb and the same procedure is repeated. In actual analysis, one bulb was filled with a solution of mercuric cyanide in potassium hydroxide, a solvent for acetylene gas. The other bulb was filled with concentrated sulfuric acid for the removal of solvent vapors. The final residual gas in the gasometer was considered to consist of nitrogen and any ethane resulting from ethylmagnesium iodide contaminating the acetylene Grignard reagent.

The results which were finally obtained led to the conclusion that the acetylene was quantitatively absorbed from the mixture of evolved gases and nitrogen by the cyanide solution in the absorption bulb. The sulfuric acid, however, failed to absorb solvent vapors and it was necessary to blank out the latter by running an experiment as follows. A mixture of the solvents for the Grignard reagent was introduced into the reaction flask in (A) and the bucket containing the hydrolytic butanol was overturned into this mixture. After

equilibrium due to solvent vapor pressures was reached, the volume in the eudiometers was recorded and an aliquot was passed over into the gasometer in (B). As no decrease in volume transpired during several passes of the gas into each of the absorption bulbs, it was considered valid to apply the volume of blank gases evolved in this experiment to the results obtained when an actual Grignard solution was analyzed

The results of a typical analysis are shown on the following page.

SAMPLE DATA SHEET FOR GAS ANALYSIS

Barometric Pressure 745 mm.
 Temperature 26°C.

Blank

Volume of Evolution Apparatus after Equilibrium of Solvent Vapor	680 ml.	672 ml.
Volume of Evolution Apparatus before Equilibrium of Solvent Vapor	<u>645 ml.</u>	<u>639 ml.</u>
Difference (Solvent Blank)	35 ml.	33 ml.

Aliquot of Acetylene Grignard Solution

Volume of Evolution Apparatus after Liberation .	748 ml.	780 ml.
Volume of Evolution Apparatus before Liberation.	<u>635 ml.</u>	<u>670 ml.</u>
Difference (Gas Liberated)	113 ml.	110 ml.
Aliquot of Total Gas	81.3 ml.	76.0 ml.
Constant Reading of Gasometer after Acetylene Absorption	<u>72.7 ml.</u>	<u>68.6 ml.</u>
Difference (Acetylene in Total Gas Aliquot)	8.6 ml.	7.4 ml.
Constant Reading of Gasometer after Solvent Absorption	<u>72.7 ml.</u>	<u>68.6 ml.</u>
(Absorbable Solvent Vapor in Total Gas Aliquot).	0.0 ml.	0.0 ml.
Total Acetylene in Liberated Gas	79.2 ml.	76.1 ml.
Avg. Total Gas Liberated	111.5 ml.	
Avg. Blank	<u>34.0 ml.</u>	
Difference (Gas Liberated upon Hydrolysis)	77.5 ml.	
Avg. Volume of Acetylene (from Absorption)	77.6 ml.	
Volume of Acetylene Absorbed (S.T.P.)	69.5 ml.	
Milliequivalents of Acetylene	3.1 me.	

Titration of Acetylene Grignard Solution Aliquot

Ml. of 0.1 N Hydrochloric Acid	57.49 ml.	57.12 ml.
Avg. ml. of 0.1 N Hydrochloric Acid	57.30 ml.	
Milliequivalents of RMgI	5.73 me.	

Calculation of % Mono and % Bis

RMgI: 5.73 me.
 C₂H₂: 3.10 me.

If: X = HC≡CMgI (me.)	Then: X + 2Y = 5.73
Y = IMgC≡CMgI (me.)	X + <u>Y</u> = <u>3.10</u>
	Y = 2.63 and X = 0.47

∴ Mixture Contains 85% Bis Compound
 and 15% Mono Compound

Condensation of the Acetylene Grignard Reagent with

6-Methoxy-1-Tetralone (V). To the solution of the acetylene Grignard reagent as prepared above was added 6-methoxy-1-tetralone (V) (20 g.) dissolved in 50 ml. of dry benzene. Mechanical stirring, acetylene introduction and warming to 50-60° were continued for two hours after the addition of the ketone. The mixture was then allowed to stand at room temperature for sixteen hours. Hydrolysis of the reaction mixture was effected by the slow addition of the purple-colored liquid to 200 g. of ammonium chloride in 100 ml. of water and 500 g. of ice. Thorough stirring of this mixture was effected and the resulting mixture was separated into the component organic and aqueous layers. The organic layer was washed with water and then concentrated in vacuo. A bubbler tube connected to a nitrogen tank was used to prevent bumping of the solution during concentration. When the volume of the solution was approximately 30-40 ml. the pale red solution was transferred to a pear-shaped flask equipped with a Vigreux still-head. The material in this flask was subjected to a pressure of about 0.5 mm. and the temperature was raised gradually by means of an oil-bath surrounding the flask. At 70-100° any solid which separated during the removal of the last traces of solvent melted and the resulting red oil began to boil vigorously in the temperature range of 100-110°. The temperature was generally held at this point for about one-half hour to insure complete dehydration of the acetylenic

carbinol. Then the temperature was increased to 150–180°. With the pressure still at 0.5 mm. a pale yellow oil began to distill over slowly. Generally about 9–10 g. of distillate, boiling at 115–120°C./0.5 mm., was collected in a run of this size. (An explosion-proof glass screen was always placed in front of the distillation apparatus during this distillation). If considerable reaction between the ketone and the Grignard reaction had not been effected earlier, a fraction boiling at 120–125°/0.5 mm. came over with the above yellow oil and then solidified in the condenser. Removal of a small amount of this solid and subsequent recrystallization confirmed the conclusion that it was unchanged 6-methoxy-1-tetralone. The 1-ethynyl-6-methoxy-3,4-dihydronaphthalene (VII) obtained as the first fraction gave a strongly positive test with ammoniacal silver nitrate solution.

Reduction of the Eneyne VII. The fraction boiling at 115–120° obtained in the above preparation was dissolved immediately in ethanol, the solution comprising about 9 g. of oil in 50 ml. of solvent. To this solution was added 0.5 g. of 5% palladium on charcoal catalyst. The resulting mixture was hydrogenated at room temperature in a semi-micro hydrogenation apparatus of ordinary design. When reasonably pure eneyne was prepared as in the above step the rate of hydrogen absorption was about 5 ml. per minute. Intermittently during the hydrogenation small samples of the solution were withdrawn and tested with

ammoniacal silver nitrate solution. As soon as no precipitate formed upon the addition of this reagent, the hydrogen absorption was stopped and the mixture was filtered free from the catalyst. The filtrate was concentrated in vacuo to obtain the residual pale yellow oil 1-vinyl-6-methoxy-3,4-dihydronaphthalene (VIII) which reacted instantly with maleic anhydride in benzene; yield 9 g.; 42.5% based on 6-methoxytetralone. (reported², 52%)

The alternative reduction procedure consisted of the following: The distilled eneyne from 20 g. of 6-methoxytetralone was dissolved in 130 ml. of ethanol and 30 g. of zinc dust coated with copper was added to the mixture. The zinc-copper was prepared by shaking 30 g. of zinc dust in a solution of 25 g. of copper sulfate in 500 ml. of water. Most of the supernatant liquid was decanted and the muddy powdered metal was added directly to the ethanolic solution of the eneyne. The mixture thus obtained was refluxed until a negative ammoniacal silver nitrate test was noted with a small sample of the refluxing mixture. Then the mixture was filtered and the cake was washed thoroughly with ethanol. The combined filtrate and washings were concentrated in vacuo to an oily residue which was taken up in ether and dried over magnesium sulfate. The dried solution was concentrated to yield 7-8 g. (35%) of the 1-vinyl-6-methoxy-3,4-dihydronaphthalene which reacted instantly with maleic anhydride in benzene (reported³, 67%) .

Reaction of 1-Vinyl-6-Methoxy-3,4-Dihydronaphthalene with
Dienophiles

With Maleic Anhydride. A solution of 1 g. of maleic anhydride in 10 ml. of benzene was treated with 1 g. of 1-vinyl-6-methoxy-3,4-dihydronaphthalene. The yellow crystalline adduct which formed almost immediately was centrifuged after a few minutes' standing. The solid was recrystallized from dioxane and then from acetone-water yielding 400 mg. of colorless needles of cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XXVI), m.p. 203-4° corr. (reported¹, 201°); U.V. abs. spec., Plate 4 (a).

Hydrolysis of Anhydride XXVI. The maleic anhydride adduct XXVI (300 mg.) was warmed with 5% aqueous potassium hydroxide. The resulting solution was poured into excess cold dilute hydrochloric acid. The white solid was separated by centrifugation, washed with water and dried. Attempt to recrystallize this solid failed but a somewhat pure material was obtained by partial evaporation of a dioxane solution of the solid. The ether-washed microcrystalline cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid (XXVIII) melted at 210-5° corr., weight, 210 mg., U.V. abs. spec., Plate 4 (b).

Anal. Calcd. for C₁₂H₁₇O₅: C, 67.7, H, 5.6. Found: C, 66.9, H, 6.2.

Dimethyl Ester of Acid XXVIII. The above diacid (100 mg.) in 10 ml. of methanol was treated with an excess of diazomethane dissolved in ether. The yellow solution was evaporated in a stream of air and the residue recrystallized from methanol. Prismatic crystals (95 mg.) of the dimethyl ester of cis-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid (XXVII) were obtained, m.p. 115-7° corr. (reported¹, 117°); U.V. abs. spec., Plate 4 (c).

Hydrolysis of the Dimethyl Ester XXVII. The above dimethyl ester (XXVIII) (25 mg.) was heated on the steam bath with 1 ml. of 10% aqueous potassium hydroxide and 2 ml. of ethanol for one hour. The solution was diluted with five volumes of water and then poured into excess cold dilute hydrochloric acid. The precipitated acid was washed and dried, weight, 15 mg., m.p. 210-3° corr., mixed m.p. with diacid XXVIII, 210-4°.

Conversion of Diacid XXVIII to a New Anhydride. The diacid XXVIII (50 mg.) was heated in an atmosphere of nitrogen at 210-220° for 15-20 minutes. The cold melt was recrystallized from benzene and the prisms of cis-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XXIX) melted at 123-4° corr., weight, 20 mg., U.V. abs. spec., Plate 5 (a).

Isomerization of Diacid XXVIII. The diacid XXVIII (40 mg.)

was heated with 0.5 ml. of a 9% solution of dry hydrogen chloride in glacial acetic acid until solution occurred. After standing 30 minutes, the solution had deposited a crop of needles which were separated by centrifugation and washed with ether, weight, 38 mg., m.p. 195-8° corr., U.V. abs. spec., Plate 5 (b'). Mixed m.p. of this new acid, cis-7-methoxy-1,2,3,4,9,10-hexahydro-phenanthrene-1,2-dicarboxylic acid (XXX) and the diacid XXVIII was 170-190° corr.

Isomerization of Diester XXVII. The diester XXVII (40 mg.) was dissolved in 0.2 ml. of the 9% solution of dry hydrogen chloride in glacial acetic acid at room temperature. The solution was diluted with five volumes of water and extracted with ether. The ethereal extract was washed with aqueous potassium carbonate and then water. Finally the neutral extract was dried over magnesium sulfate and evaporated in a stream of air. The residue was recrystallized from methanol. The colorless needles of the dimethyl ester of cis-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXI) melted at 65° corr., weight, 25 mg., U.V. abs. spec., Plate 5 (c').

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.0, H, 6.7. Found: C, 68.5, H, 7.0.

Esterification of the Diacid XXX. The isomerized diacid XXX (15 mg.) in methanol was treated with excess diazomethane in ether. The yellow solution was evaporated in a stream of air and

and the residue recrystallized from methanol. The colorless needles, m.p. $64-5^{\circ}$ corr., gave no depression in the mixed m.p. with the isomerized dimethyl ester (XXXI) obtained above.

3. With Mesaconic Acid. 1-Vinyl-7-methoxy-3,4-dihydronaphthalene (9 g.) was refluxed with a solution of 15 g. of mesaconic acid in 100 ml. of propionic acid for 96 hours. At the end of this time the mixture was cooled somewhat and concentrated in vacuo to remove most of the propionic acid solvent. The residue was taken up in 50 ml. of benzene and filtered from excess mesaconic acid. The solid was washed thoroughly with benzene and the washings were combined with the filtrate. The benzene solution was extracted with 2N aqueous potassium hydroxide. The alkaline extract was washed with ether and then poured into excess hydrochloric acid. The solid which separated was suspended in a small volume of methanol and heated to solution. Upon cooling a tan solid crystallized. Another recrystallization of this solid from methanol gave a white crystalline solid which melted at $185-195^{\circ}$. This material was recrystallized next from a mixture of ethyl acetate and benzene to give a white solid, m.p. $205-210^{\circ}$. A last recrystallization from ethyl acetate yielded 110 mg. of pure trans-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXII) as clusters of colorless needles, m.p. $206-8^{\circ}$ corr. U.V. abs. spec., Plate 6.

Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34, H, 6.37. Found:
C, 68.55, H, 6.54.

The filtrates from the first three recrystallizations were combined and concentrated in a stream of nitrogen. Recrystallization of the residue from methanol containing about 10% of water gave three successive crops of a diacid fraction melting at 240-250°. Further recrystallization of the combined crops from methanol yielded 340 mg. of heavy plates of pure trans-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXIII), m.p. 248-250° corr. U.V. abs. spec., Plate 6.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34, H, 6.37. Found:
C, 68.16, H, 6.39.

Degradation of the trans-1-Methyl Adduct XXXIII. trans-1-Methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXIII) (m.p. 248-250°) (100 mg.) was mixed with 50 mg. of 5% palladium on charcoal and heated at 300-315° for fifteen minutes in a stream of nitrogen. The cooled mixture was extracted with acetone and the catalyst on charcoal was removed by filtration and the filtrate concentrated in a stream of nitrogen to dryness. The residue was extracted with 1N sodium hydroxide and the insoluble

*The analyses recorded in this section were performed by Mr. Charles Childs, Mrs. Patricia Ramey and Miss Jere Saladonis. Grateful thanks are hereby extended to these members of the Microanalytical Section of the Parke, Davis and Company Research Laboratories.

portion separated by centrifugation. This white solid was recrystallized from methanol. The colorless plates of 1-methyl-7-methoxyphenanthrene melted at $131-2^{\circ}$ corr. Mixed m.p. with an authentic sample: $130-3^{\circ}$.

Degradation of the trans-2-Methyl Adduct XXXII. The same degradation was carried out on trans-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid as on the 1-methyl isomer described in the preceding experiment. The end product of the degradation of the 2-methyl isomer was a crop of colorless needles of 2-methyl-7-methoxyphenanthrene, m.p. $142-3^{\circ}$ corr. Mixed m.p. with an authentic sample: $140-2^{\circ}$.

Esterification of the trans-1-Methyl Adduct XXXIII. The trans-1-methyl diacid XXXIII (80 mg.) in 15 ml. of methanol was treated with excess diazomethane in ether. Evaporation of the yellow solution in a stream of air gave a residue which was recrystallized from methanol-water. The thick colorless needles of the dimethyl ester of trans-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXVI) melted at $83-4^{\circ}$ corr., weight, 68 mg.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.9; H, 6.9.

Dehydrogenation of the Dimethyl Ester XXXVI. The dimethyl ester XXXVI (30 mg.) of the trans-1-methyl adduct was dissolved in 10 ml. of absolute ethanol and refluxed with 30 mg. of 5% palladium on charcoal for 30 hours. The mixture was filtered and the filtrate evaporated in a stream of nitrogen. After two recrystallizations of

the residue from methanol the dimethyl ester of trans-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XXXVII) was obtained as colorless plates, m.p. 134-5° corr. Mixed m.p. of this diester with a sample of the diester obtained by Bachmann and Scott (12). Showed no depression.

Esterification of the trans-2-Methyl Adduct XXXII. The trans-2-methyl diacid XXXII (20 mg.) was dissolved in methanol and treated with an excess of diazomethane in ether. The yellow solution was evaporated in a stream of air and the residue was recrystallized from methanol. The slender needles of the dimethyl ester of trans-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XXXIV) (18 mg.) melted at 67-8° corr.

Dehydrogenation of the Dimethyl Ester XXXIV. The dimethyl ester XXXIV (15 mg.) of the trans-2-methyl adduct was dissolved in 10 ml. of absolute ethanol and refluxed with 15 mg. of 50% palladium on charcoal for 27 hours. The cooled reaction mixture was filtered and concentrated to dryness in a stream of nitrogen gas. The solid residue was recrystallized from methanol. The colorless cubic crystals (12 mg.) of the dimethyl ester of trans-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XXXV) melted at 157-8° corr.

Anal. Calcd. for C₂₀H₂₂O₅: C, 70.2; H, 6.5. Found: C, 69.9; H, 6.7.

With Citraconic Anhydride. 1-Vinyl-6-methoxy-3,4-dihydronaphthalene (9.0 g.) and citraconic anhydride (20 g.) were dissolved in benzene and the solution was refluxed for 48 hours. The solution was concentrated in vacuo on the steam bath to remove solvent and excess citraconic anhydride. The residue was treated with 50 ml. of 10% aqueous potassium hydroxide and the mixture was warmed on the steam bath for fifteen minutes. The cooled mixture was extracted with ether and the dried ether layer yielded 1.5 g. of crude 6-methoxy-1-tetralone after concentration in vacuo. The aqueous alkaline layer was poured into 15 ml. of concentrated hydrochloric acid and 100 ml. of water. The resulting semi-solid mass which separated was removed by filtration and was then heated in a stream of nitrogen at 190-195°C. for 20 minutes. The cooled melt was taken up in 10 ml. of acetone and 25 ml. of ethyl acetate. After scratching inner walls of the vessel and allowing the solution to stand for two hours, there deposited a crop of 2.2 g. of almost colorless cubic crystals, m.p. 161-2° corr., which consisted of cis-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XXXVIII) (reported², m.p. 163-163.5°). Addition of 5 ml. of petroleum ether (b.p. 60-70°) to the filtrate caused the separation of a crop of colorless needles which, after recrystallization from ethyl acetate-petroleum ether, melted at 126-8° and consisted of cis-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid anhydride (XLVIII)

(reported², m.p. 127-8°), U.V. abs. spec., Plate 7.

(In the above preparation of the cis anhydride adducts, the procedure of Bachmann and Chemerda (2) was followed for the most part. However, in the experiment described above, a separation of the two isomeric adducts was effected more suitably by solubility differences rather than by mechanical separation as described by the earlier investigators).

Hydrolysis of the cis-1-Methyl Adduct XLVIII. The cis-1-methyl anhydride adduct XLVIII (50 mg.) was warmed with 150 mg. of potassium hydroxide in 5 ml. of water until solution occurred. The solution was poured into excess dilute hydrochloric acid and the precipitated solid was separated by centrifugation. This solid was recrystallized from methanol. The colorless irregular plates (30 mg.) of cis-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XLIX) melted at 135-7° corr., U.V. abs. spec., Plate 7.

Anal. Calcd. for C₁₈H₂₀O₅: C, 68.3; H, 6.3. Found: C, 68.2; H, 6.4.

Esterification of Diacid XLIX. The cis-1-methyl diacid XLIX (10 mg.) was treated with excess diazomethane in ether. The yellow solution was concentrated in a stream of air and the residue was recrystallized from methanol. The colorless prisms (8 mg.) of the dimethyl ester of cis-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydro-

phenanthrene-1,2-dicarboxylic acid (L) melted at 84° corr.

(reported², m.p. $83-83.5^{\circ}$). U.V. abs. spec., Plate 7.

Hydrolysis and Esterification of the *cis*-2-Methyl Adduct

XXXVIII. The *cis*-2-methyl anhydride adduct XXXVIII (930 mg.) was heated with 1.5 g. of potassium hydroxide in 27 ml. of water on a steam bath for fifteen minutes. The clear solution was poured into 200 ml. of 3N hydrochloric acid at $5-10^{\circ}$. The white solid which separated was filtered, washed and dried and melted at $184-6^{\circ}$. This solid was dissolved in 15 ml. of methanol and treated at 5° with an excess of diazomethane in ether. After standing for one-half hour at room temperature the yellow solution was evaporated in a stream of nitrogen and the dimethyl ester was recrystallized from a 5:2 methanol-water mixture. The crystalline dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XL) melted at $90-2^{\circ}$ corr. (reported², $91-92^{\circ}$) and weighed 780 mg.

Epimerization of the *cis*-2-Methyl Diester XL. The dimethyl ester XL of the *cis*-2-methyl adduct (800 mg.) was refluxed in a mixture of 11.2 g. of potassium hydroxide in 14 ml. of water and 36 ml. of methanol for 20 hours. A white crystalline precipitate settled out during the first hour of refluxing. After 20 hours, the mixture was cooled and filtered. The precipitate was dissolved in 25 ml. of water and poured into excess dilute hydrochloric acid. The solid (600 mg.) which precipitated was filtered, washed and dried, m.p. $176-8^{\circ}$. This solid is practically pure *cis*-2-methyl

7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXIX) (reported⁴, m.p. 179-180°). Proof of this structure was obtained by esterification with diazomethane resulting in the formation of the corresponding dimethyl ester XI, m.p. 90-2°.

The filtrate from the separation of the crystalline deposit found in the alkaline reaction mixture was concentrated in vacuo to remove the methanol. The residue was diluted with an equal volume of water and poured into an excess of dilute hydrochloric acid. The solid which separated was filtered, washed, dried and then recrystallized from methanol. The clusters of needles, m.p. 206-8°, weight, 85 mg., proved to be identical with the trans-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXXII) obtained in the Diels-Alder reaction of the diene and mesaconic acid. Mixed m.p. of the epimerization product and the adduct diacid, 205-8° corr.

Dehydrogenation of the cis-2-Methyl Adduct XXXVIII. The cis-2-methyl anhydride adduct XXXVIII (2.1 g.) was refluxed with 1.0 g. of 5% palladium on charcoal in 50 ml. of benzene for 42 hours. The catalyst was removed by filtration and the filtrate concentrated in vacuo. The residue was recrystallized from benzene. The colorless prisms (1.2 g.) of cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid anhydride (XII) melted at 180-2° corr. Bachmann and Chemerda (2) reported m.p. 185-6° (after recrystallization from ethyl acetate-benzene) for the product obtained by dehydrogenation at 315-320°.

Dehydrogenation of the *cis*-2-Methyl-Hexahydro Diester XL.

The *cis*-2-methyl-hexahydro dimethyl ester XL (50 mg.) was dissolved in 12 ml. of absolute ethanol and refluxed with 50 mg. of 5% palladium on charcoal for 27 hours. The catalyst was removed by filtration and the filtrate was concentrated in a stream of air. The residue was crystallized from methanol. The white chalky needles (45 mg.) of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XLII) melted at 99-100° corr. (reported², m.p. 100-101°).

Epimerization of *cis*-2-Methyl-Tetrahydro Diester XLII. The *cis*-2-methyl-tetrahydro diester XLII (450 mg.) was dissolved in dry benzene and treated with 18 ml. of a solution of 0.105 milliequivalents of sodium triphenylmethyl per milliliter. The persistent red colored solution was allowed to stand for 1/2 hour and was then treated with 50 ml. of water containing about 0.5 ml. of concentrated hydrochloric acid. The almost colorless mixture was extracted with benzene and the dried extract was concentrated to a crystalline residue. The residue was digested with 4N potassium hydroxide on the steam bath for 1/2 hour. The alkaline mixture was extracted with ether and the ethereal layer drawn off. Upon acidification of the aqueous layer, an oily material separated. This was extracted with ether and the ethereal extract dried over magnesium sulfate. Concentration of this dried solution yielded 200 mg. of solid which was taken up in methanol. The methanolic solution was treated with an excess of diazomethane in ether.

The yellow solution was concentrated in vacuo and the residue was recrystallized from methanol. The first crop of crystals which separated melted at 145-155° and upon a second recrystallization from methanol melted at 155-6°. Mixed m.p. of this material with the dimethyl ester of the trans-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XXXV) obtained in the dehydrogenation of the trans-2-methyl adduct derivative described above, 155-7° corr.

Mild Half Hydrolysis of the trans-2-Methyl-Tetrahydro Diester

XXXV. The trans-2-methyl-tetrahydro diester XXXV (100 mg.) in 10 ml. of methanol and 3 ml. of 0.1N sodium hydroxide were refluxed on the steam bath for 22 hours. The methanol was removed by concentration in vacuo and the residue was diluted with two volumes of water. The alkaline solution was poured into excess dilute hydrochloric acid. The gummy solid was extracted with ether. The dried ethereal layer was concentrated in vacuo and the residue, from which no crystallizable material could be isolated, was taken up in methanol. The methanolic solution was treated with excess diazomethane in ether. Upon evaporation of the yellow solution in a stream of air, an amorphous residue was obtained. Upon standing and seeding with a crystal of the dimethyl ester of cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (XLII), the mixture crystallized for the most part. In fact, a crop of 73 mg. of the cis dimethyl ester (m.p. 96-90°) was finally isolated. No other identifiable product was obtained.

Isomeric Acid Esters of *cis*-2-Methyl-7-Methoxy-1,2,3,4-Tetrahydrophenanthrene-1,2-Dicarboxylic Acid. *cis*-2-Methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (XLI) (600 mg.) was added to a solution of sodium methoxide prepared from 1 g. of sodium and 100 ml. of anhydrous methanol; a clear solution was formed in a few minutes. The solution was poured into 75 ml. of dilute hydrochloric acid and the colorless solid which precipitated was extracted into benzene. The benzene solution after having been dried over magnesium sulfate yielded 420 mg. of a colorless solid on evaporation; m.p. 150-170°. A solution of the solid in methanol was allowed to evaporate slowly (two days) to a small volume; under these conditions two types of crystals separated: scattered clumps of needles and large thick prisms. The two types of crystals were separated mechanically. By recrystallization of the prisms from ethyl acetate, *cis*-1-carboxy-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLIV) was obtained as colorless prisms; yield, 150 mg.; m.p. 156-157°. U.V. abs. spec., Plate 8.

Anal. Calcd. for C₁₉H₂₀O₅: C, 69.5; H, 6.14. Found: C, 69.36; H, 6.31.

By recrystallization of the clumps of needles from ethyl acetate *cis*-1-carbomethoxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLIII) was obtained as colorless needles; yield, 50 mg., m.p. 187-189° (reported³, 186-188°). Mixed m.p. of XLIV and XLIII, 150-183°. U.V. abs. spec., Plate 8.

The isomeric acid esters on treatment with diazomethane yielded the same dimethyl ester of cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid; m.p. 98-100°, mixed m.p. 97-9° corr.

Both acid esters were also obtained when 300 mg. of the dimethyl ester was refluxed with 300 mg. of potassium carbonate, 5 ml. of water and 12 ml. of methanol for twenty hours. From the product by the procedure described above chiefly the 187-9° melting acid ester was isolated; only 50 mg. of the lower-melting isomer was obtained.

The best yield of the high-melting acid ester was obtained by the procedure of Bachmann and Chemarda (2). A methanolic solution of 400 mg. of the anhydride was refluxed for twenty-three hours, and then evaporated. Recrystallization of the product from ethyl acetate gave 200 mg. of colorless needles; m.p. 187-189°.

Arndt-Eistert Reaction on cis-1-Carbomethoxy-2-Methyl-7-Methoxy-1,2,3,4-Tetrahydrophenanthrene. To a solution of 1.2 ml. of oxalyl chloride in 1.2 ml. of benzene was added 175 mg. of the acid-ester (XLIII) (m.p. 187-189°); in a few minutes a clear yellow solution resulted. After two hours the liquids were removed at room temperature under reduced pressure; 1 ml. of dry benzene was added and then removed under reduced pressure. A solution of the acid chloride in benzene was added to an ethereal solution containing an excess of diazomethane (prepared from 2.5 ml. of 4-methyl-4-(methylnitrosoamino)-2-butanone). Evolution of gas was observed.

After two days at room temperature the solution was filtered and evaporated under reduced pressure. The residue, presumably the diazoketone, was a pale yellow viscous liquid.

A suspension of 50 mg. of silver oxide in 5 ml. of anhydrous methanol was refluxed on a steam bath until a silver mirror was formed (fifteen minutes). Then a solution of the diazoketone in a few ml. of methanol was added along with 50 mg. of silver oxide and the whole was refluxed for eight hours. Evaporation of the filtered solution yielded a viscous yellow liquid which could not be made to crystallize.

A solution of the product in 10 ml. of benzene was passed through a column (150 mm. x 7 mm.) of aluminum oxide (Fisher Scientific Co.). A yellow band appeared near the top of the column. Six 10 ml. portions of benzene (eluates collected in separate flasks) served to wash through 100 mg. of colorless liquid. The yellow material on the column was finally eluated by benzene-methanol and methanol.

The colorless liquid (100 mg.), which did not crystallize when seeded with the alpha (m.p. 126°) or beta (m.p. 114°) forms of the dimethyl ester of 7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid, ^(XLVI) was hydrolyzed by refluxing with a solution of 0.28 ml. of N sodium hydroxide (sufficient for one ester group) in 2.5 ml. of methanol for three hours. The methanol was removed by evaporation in a current of air and water

and a little alkali were added to dissolve the sodium salt of the acid ester. A small quantity of insoluble material was extracted into ether, the clear aqueous solution was acidified with hydrochloric acid and the precipitated acid ester was extracted with ether. Evaporation of the ether left a colorless liquid which crystallized readily when scratched under ether-petroleum ether. The colorless solid was collected on a filter; weight, 50 mg.; m.p. 143-145°. The compound, presumably cis-1-carbomethoxy-2-methyl-2-carboxymethyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLVII), crystallized from ether-petroleum ether in colorless needles; m.p. 146-148°.

Arndt-Eistert Reaction on cis-1-Carboxy-2-Carbomethoxy-2-Methyl-7-Methoxy-1,2,3,4-Tetrahydrophenanthrene. When 180 mg. of the acid ester (XLIV) (m.p. 156-157°) was added to a solution of 1.2 ml. of oxalyl chloride in 1.2 ml. of benzene a crust of solid formed on the bottom and adhered to the glass. By tapping and swirling, the solid was dislodged and finally (fifteen minutes) went into solution. After two hours the yellow solution was evaporated under reduced pressure, and the residue treated with 1 ml. of dry benzene, which was then removed under reduced pressure. The residual acid chloride was added to ethereal diazomethane and the diazoketone was rearranged exactly in the manner described for its isomer in the preceding section.

A solution of the product, a viscous yellow liquid, in 5 ml.

of benzene and 40 ml. of petroleum ether (60-75°) was passed through a column of alumina (150 mm. x 7 mm.) which had been wet with petroleum ether. The following fractions were collected:

1. 40 ml. p.e. + 5 ml. benzene ---- nothing on evaporation
2. 8 ml. p.e. + 2 ml. benzene ---- nothing
3. 5 ml. p.e. + 5 ml. benzene ---- nothing
4. 5 ml. p.e. + 5 ml. benzene ---- trace of colorless liquid
5. 10 ml. benzene ---- 45 mg. colorless liquid
6. 10 ml. benzene ---- 30 mg. colorless liquid
7. 10 ml. benzene + 1 ml. methanol ---- 30 mg. viscous yellow liquid
8. 10 ml. benzene ---- viscous yellow liquid

Small amounts of methanol were added to each fraction and the solutions allowed to evaporate slowly but no crystals appeared except in #7.

The colorless liquids in fractions 4, 5, and 6 were combined and hydrolyzed by boiling with a solution of 0.22 ml. of N sodium hydroxide in 2 ml. of methanol for three hours. The acid ester was isolated as described in the preceding preparation; yield, 45 mg. of colorless solid; m.p. 144-147°. From ether-petroleum ether it crystallized in little buttons and needles; m.p. 146-148° alone and when mixed with the product (m.p. 146-148°) obtained from the isomeric acid ester.

Fractions 7 and 8 were combined and dissolved in 10 ml. of benzene and passed through a 25 mm. x 7 mm. column of alumina

and washed with two 10 ml. portions of benzene, one of 1:1 benzene-chloroform, and finally chloroform. The first 10 ml. fraction contained colorless liquid which crystallized readily on scratching under methanol; the second and third fractions contained nothing and the last ones contained viscous yellow gum. The crystals from the first fraction were collected on a filter; yield, 10 mg.; m.p. 124-126°. When mixed with authentic alpha form (m.p. 126-127°, precursor of isoequilenin) of the dimethyl ester of cis-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (XLVI) the melting point was 125-127°. From methanol the product crystallized in clusters of thick colorless plates; m.p. 126-127° alone and when mixed with the alpha form; the melt solidified readily on cooling and on reheating melted at 126-127°.

Ultraviolet Absorption Spectra

The data required for the ultraviolet absorption spectra recorded during the present investigation were obtained by the members of the Physical Chemistry Section of the Research Laboratories of Parke, Davis and Company. Grateful acknowledgment is hereby extended to Dr. J. M. Vandenberg and his assistants, Misses Denise Lundquest, Jere Saladonis and Patricia Welch.

TABLE OF COMPOUNDS PREPARED

Acetylene Grignard reagent	47
β -p-Anisoylpropionic acid (XVII)	42
γ -p-Anisylbutyric acid (XVIII)	43
γ -p-Anisylbutyric acid chloride (XIX)	44
* <u>cis</u> -1-Carbomethoxy-2-carbomethoxymethyl-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLV)	70
<u>cis</u> -2-Carbomethoxy-1-carbomethoxymethyl-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLVI)	72
<u>cis</u> -1-Carbomethoxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLIII)	69
* <u>cis</u> -2-Carbomethoxy-1-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLIV)	69
* <u>cis</u> -1-Carbomethoxy-2-carboxymethyl-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XLVII)	70
1-Ethynyl-6-methoxy-3,4-dihydronaphthalene (VII)	53
1-Ethynyl-6-methoxytetralol-1 (VI)	53
bis (6-Methoxy-3,4-dihydronaphthyl) acetylene (XXIII) ..	53
* <u>cis</u> -7-Methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (XXX)	57
* _____, anhydride (XXIX)	57
* _____, dimethyl ester (XXXI)	58
<u>cis</u> -7-Methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic acid (XXVIII)	56, 57

*Isolated and characterized for the first time.

_____ , anhydride (XXVI)	56
_____ , dimethyl ester (XXVII)	57
6-Methoxytetralin (XIV)	41, 45
6-Methoxy-1-tetralone (V)	46
7-Methoxy-1-tetralone (XX)	44
* <u>cis</u> -1-Methyl-7-methoxy-1,2,3,4,9,10-hexahydro- phenanthrene-1,2-dicarboxylic acid (XLIX)	64
_____ , anhydride (XLVIII)	63
_____ , dimethyl ester (L)	64
<u>cis</u> -2-Methyl-7-methoxy-1,2,3,4,9,10-hexahydro- phenanthrene-1,2-dicarboxylic acid (XXXIX)	65
_____ , anhydride (XXXVIII)	63
_____ , dimethyl ester (XL)	65
* <u>trans</u> -1-Methyl-7-methoxy-1,2,3,4,9,10-hexahydro- phenanthrene-1,2-dicarboxylic acid (XXXIII)	60
_____ , dimethyl ester (XXXVI)	61
* <u>trans</u> -2-Methyl-7-methoxy-1,2,3,4,9,10-hexahydro- phenanthrene-1,2-dicarboxylic acid (XXXII) ...	59, 65
* _____ , dimethyl ester (XXXIV)	62
<u>cis</u> -2-Methyl-7-methoxy-1,2,3,4-tetrahydro- phenanthrene-1,2-dicarboxylic acid anhydride (XLI)	66
<u>cis</u> -2-Methyl-7-methoxy-1,2,3,4-tetrahydro- phenanthrene-1,2-dicarboxylic acid, dimethyl ester (XLII)	67, 68
<u>trans</u> -1-Methyl-7-methoxy-1,2,3,4-tetrahydro- phenanthrene-1,2-dicarboxylic acid, dimethyl ester (XXXVII)	61
* <u>trans</u> -2-Methyl-7-methoxy-1,2,3,4-tetrahydro- phenanthrene-1,2-dicarboxylic acid, dimethyl ester (XXXV)	62, 67
β -Naphthyl methyl ether (XXI)	45

<u>α</u> - β -Tetralin sulfonic acid, sodium salt (XII)	41
β -Tetralol	41
1-Vinyl-6-methoxy-3,4-dihydronaphthalene (VIII)	54, 55

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