

SYNTHESIS OF STEROID PRECURSORS

by

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A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

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1957

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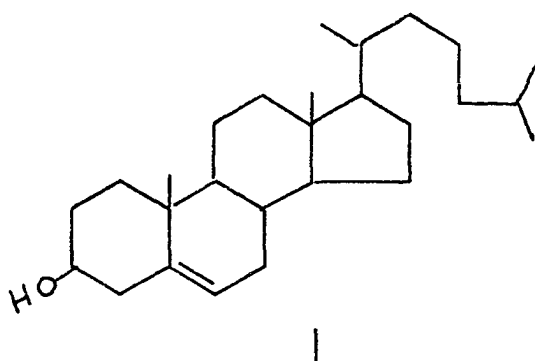
INTRODUCTION

The purpose of this investigation was the synthesis of a tetracyclic steroid precursor in a simple and direct manner. With dihydroresorcinol serving as potential ring D, it was hoped to achieve a synthesis of a tetracyclic compound by successive Robinson cyclohexenone synthesis in a D-C-B-A sequence.

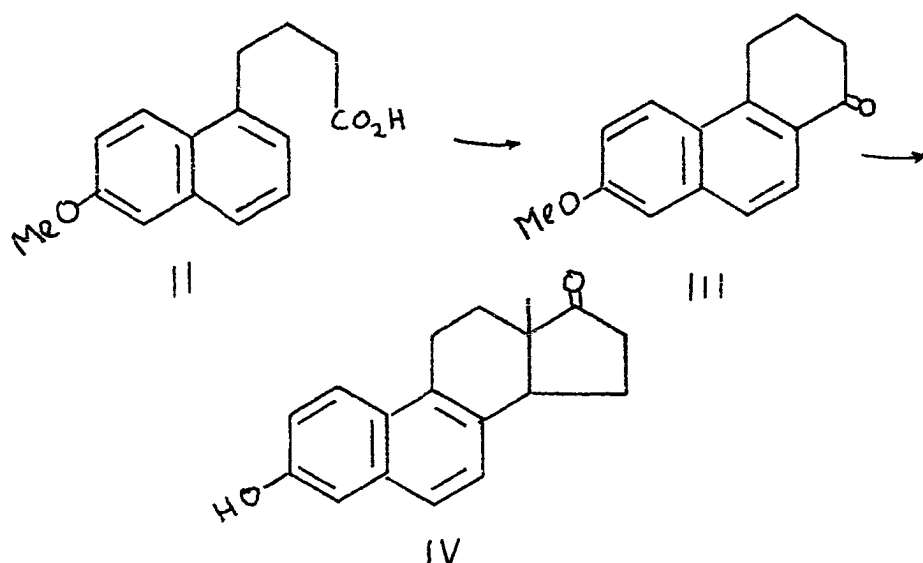
HISTORICAL

Early Syntheses

Since the elucidation of the structure of cholesterol I by Rosenheim and King (1) and Wieland and Dane (2) in 1932, many steroid syntheses have been described. (3, 4, 5, 6)



In 1939 Bachmann, Cole, and Wilds (7) accomplished the first total synthesis of a steroid. Starting with a commercially available substituted naphthalene, the acid II was



synthesized and cyclized to the tricyclic methoxyketone III.

It required ten steps for the construction of ring D and hence the completion of the synthesis of (+)-equilenin IV by a AB-C-D ring build-up. Compound III was reacted with methyl oxalate and sodium methoxide and the resulting glyoxylic ester was heated to eliminate carbon monoxide. The C/D angular methyl group was introduced by ordinary alkylation methods. Reaction of this latter substance with zinc and methyl bromoacetate, followed by treatment with thionyl chloride and pyridine and alkaline hydrolysis gave an unsaturated acid. Reduction with sodium amalgam, hydrolysis of the least hindered carbomethoxyl group, followed by an Arndt-Eistert diazoketone rearrangement gave a compound which was ready to be cyclized into ring D. Cyclization by Dickman procedures, hydrolysis of the carbomethoxyl group (which also split the methoxyl group) afforded the desired compound IV.

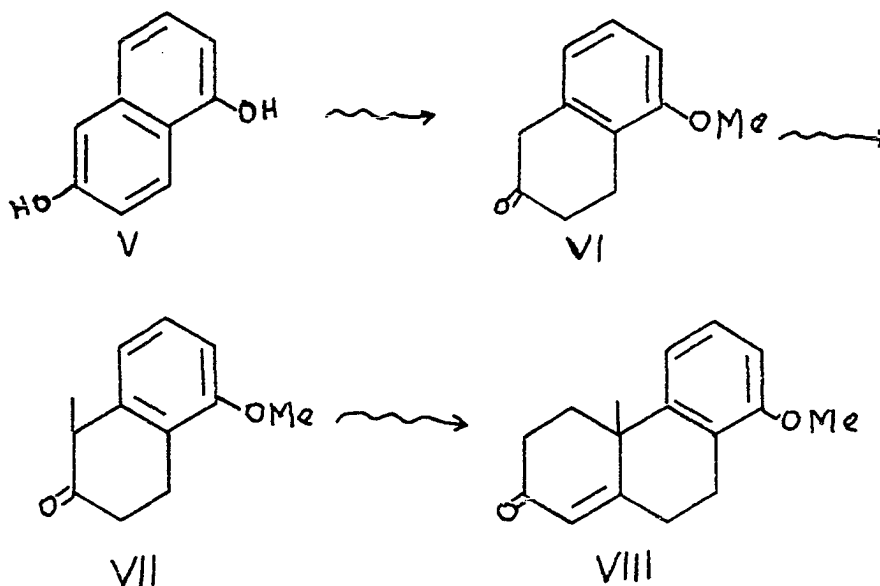
W. S. Johnson and co-workers (8) achieved the synthesis of (±)-equilenin by a similar route as that of Bachmann and co-workers, except for the method of incorporation of ring D into the nucleus. Starting with the ketone III, a hydroxymethylene-ketone was formed by reaction with ethyl formate and sodium methoxide. Conversion of its oxime into an isoxazole, followed by ring fission to give the sodio-derivative of a cyano-ketone and addition of methyl iodide yielded a

methylated cyano-ketone. The remainder of ring D was formed in one step by means of a Stobbe condensation with methyl succinate and potassium tert-butoxide. The rest of the details followed those mentioned for the previous synthesis.

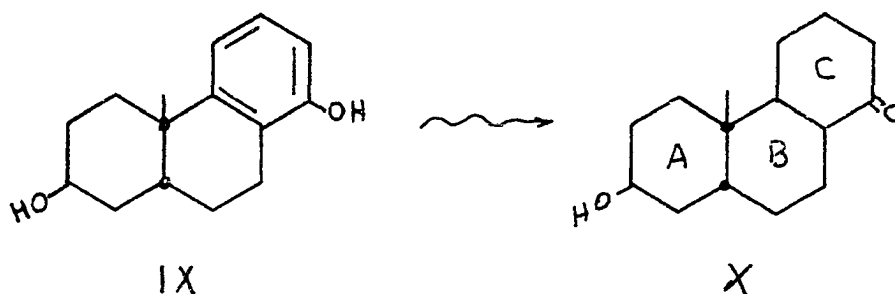
Total Synthesis of Non-Aromatic Steroids

In 1951 two different total syntheses of non-aromatic steroids were announced almost simultaneously by the laboratories of Robinson and Conforth in England and Woodward and his associates in America.

The "Oxford" synthesis (9) represented a BC-A-D sequence of ring construction. Methylation of 1,6-dihydroxynaphthalene V, Birch reduction and hydrolysis led to 5-methoxy-2-tetralone VI. Treatment of VI with sodium methoxide and



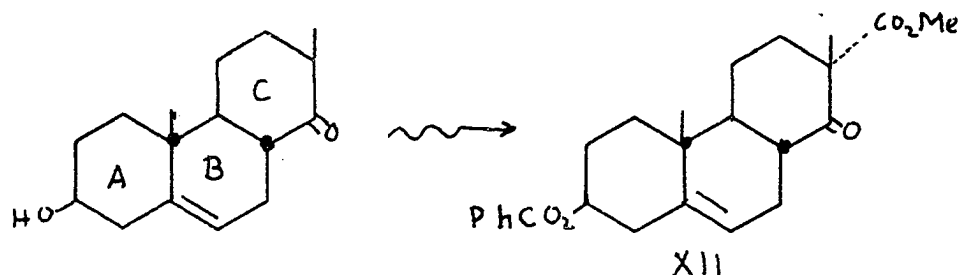
methyl iodide gave the methylated ketone VII. The tricyclic ketone VIII was formed by the reaction of VII with diethylaminobutanone methiodide and potassium ethoxide. Hydrogen iodide treatment of the ketone VIII gave a phenolic ketone which was then hydrogenated to yield the diol IX stereospecifically.



Selective acetylation of the ring A hydroxyl group, catalytic hydrogenation of ring C and oxidation yielded two isomeric ketones, the desired one X in the smaller amount. This substance was identical with a diketone obtainable by oxidative degradation of deoxycholic acid and of cholesterol (10a, 10b).

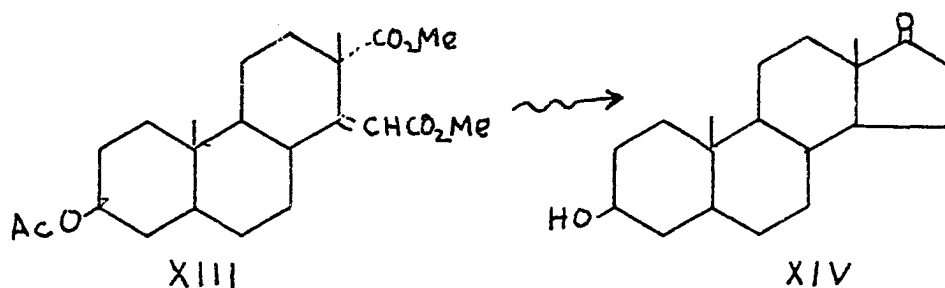
Conversion of X, which previously had a potential C/D angular methyl group introduced, into XI proceeded by bromination of ring A, followed by dehydrobromination (11). The enol acetate of this ketone was treated with potassium amide in liquid ammonia and the new diketone was reduced with lithium aluminum hydride by a method devised by Birch (12) to give a diol. Protection of the ring A hydroxyl

group as the triphenylmethyl ether, oxidation of the ring C hydroxyl group, and the removal of the protecting group gave the ketone XI.



Introduction of a methoxycarbonyl group in the benzoate of XI was effected by treatment with sodium triphenylmethide followed by carbon dioxide. The resulting β -keto acids were esterified at once with diazomethane (13) leading to two keto esters of which the desired product XII is shown above.

A Reformatsky reaction, followed by hydrolysis, gave two epimeric hydroxy-acid esters. The more easily isolated

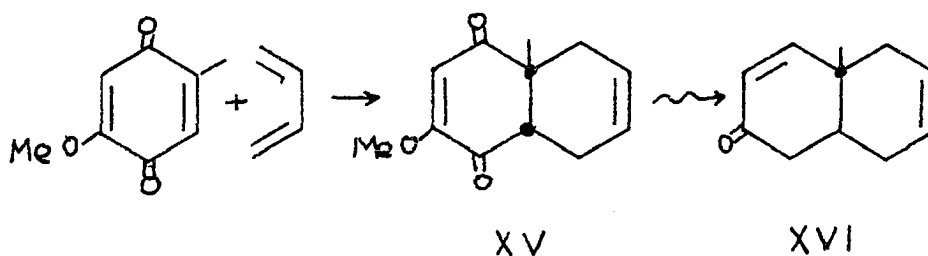


epimer was hydrogenated, acetylated, esterified, and dehydrated to give the etiallobilienic ester XIII.

Hydrogenation of the double bond in compound XIII,

Dieckmann cyclization and hydrolysis led to epiandrosterone XIV.

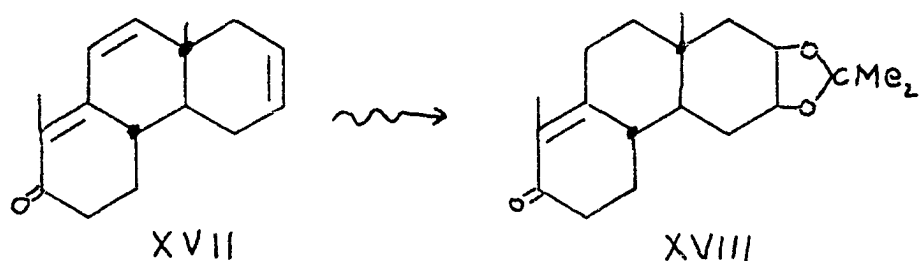
The "Harvard" synthesis (14) involved a C-D-B-A pathway. A Diels-Alder condensation between methoxytoluquinone and butadiene led to the adduct XV (15). Reduction of the ketone XV by lithium aluminum hydride gave a diol, which



upon treatment with mineral acid hydrolyzed the enol ether grouping while at the same time dehydrating the intermediate hydroxy ketone to give an unsaturated ketol. Removal of the remaining hydroxyl group was achieved by heating its acetate with zinc in acetic anhydride to give the desired product XVI.

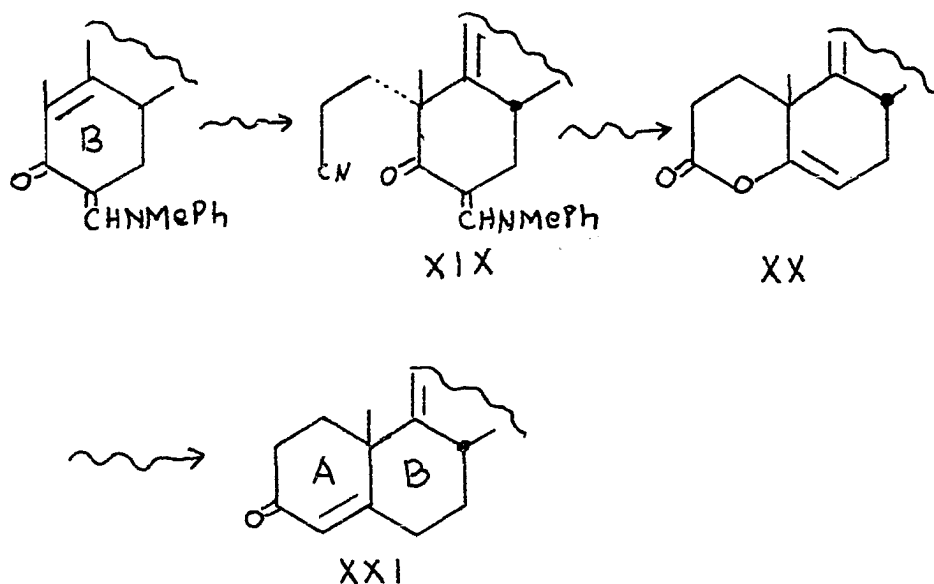
Ring B was introduced by adding ethyl vinyl ketone to the hydroxymethylene derivative of XVI. Cyclization and removal of the activating group to give the tricyclic ketone XVII was accomplished by warming with alkali.

Treatment of the tricyclic ketone XVII with osmium tetroxide gave two cis-glycols. The major product was converted into its acetonide. Selective reduction of the acetonide in benzene solution over palladium on strontium



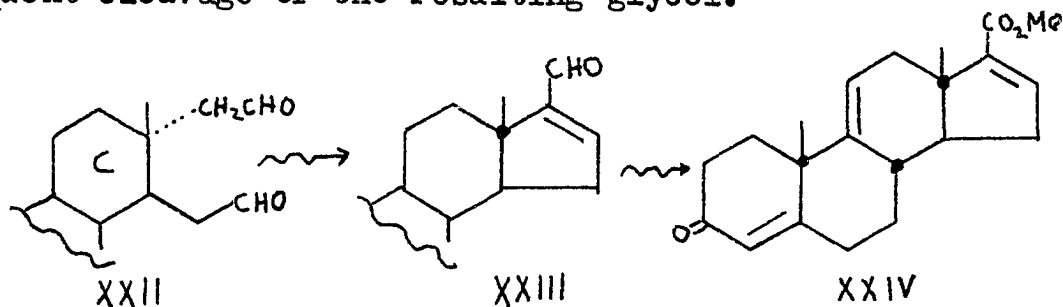
carbonate gave the compound XVIII.

The methylanilinomethylene derivative of XVIII was treated with Triton B and acrylonitrile to give two epimeric ketonitriles, one being represented by part formula XIX. Removal of the blocking group, followed by hydrolysis of



the nitrile yielded a keto acid (16a, 16b). Acetic anhydride-sodium acetate treatment gave the enol-lactone XX which by successive treatment with methylmagnesium iodide and alkali produced the tetracyclic ketone XXI.

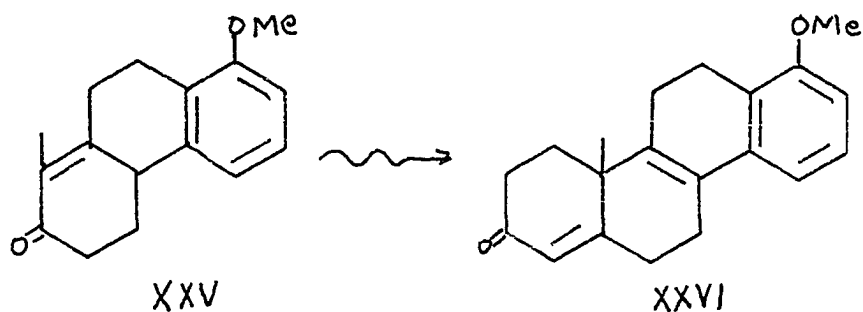
In order to modify ring D, the acetonide XXI was treated with periodic acid to give the dialdehyde XXII by means of hydrolysis of the isopropylidene grouping and subsequent cleavage of the resulting glycol.



Ring closure by piperidine acetate yielded mostly the desired aldehyde XXIII. Oxidation of the aldehyde followed by esterification gave a racemic mixture XXIV which was identical in every respect with a known compound.

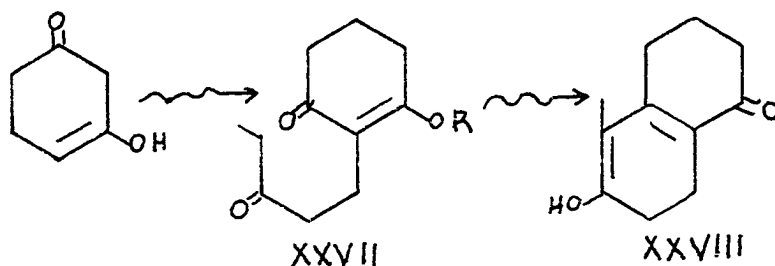
First Wisconsin Synthesis

Starting with the β -tetralone used in the Oxford synthesis, W. S. Johnson and co-workers (17) synthesized ($\pm$)-epiandrosterone. Rings C and D were provided by the β -tetralone, while the first ring extension was accomplished by treatment with 1-diethylamino-3-pentanone methiodide to give XXV, followed by methyl vinyl ketone to yield the tetracyclic ketone XXVI. The reduction of ring D, introduction of the C/D angular methyl group, and ring contraction followed methods similar to those already discussed.



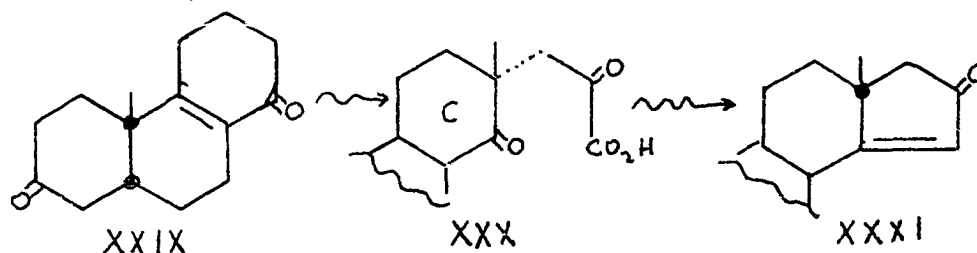
Second Wisconsin Synthesis

In 1953, Wilds and co-workers (18a, 18b) completed earlier work which led to the synthesis of $(\pm)$ -3-oxoetianate. Treatment of dihydroresorcinol with 1-diethylamino-3-pentanone methiodide gave an adduct which was converted into its enol ether XXVII, cyclized, and then hydrolyzed to the unsaturated keto-enol XXVIII.



Ring A was introduced by treatment of XXVIII with methyl vinyl ketone. The resulting ketone was partially hydrogenated to the ketone XXIX.

The mono-ethylene ketal of XXIX was prepared and methylated via its hydroxymethylene derivative. Reaction of this product with sodium triphenylmethide and methyl

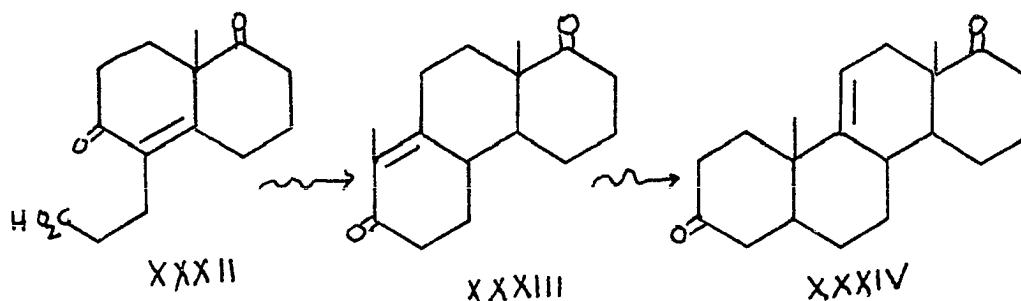


bromoacetate gave, after hydrolysis, two epimeric acids XXX. Conversion of these acids into methyl ketones was accomplished by reaction of the acid chloride with tert-butyl malonate followed by an acid catalyzed decarboxylation. Cyclization with sodium methoxide afforded the ketone XXXI, which could be modified very readily to desired known compounds.

Ciba Synthesis

Certain aspects of this synthesis had similarities to the preceding one. However instead of the methyldihydro-resorcinol being potential ring C, it was now destined to become ring D. Addition of the chloroketone $\text{Cl-CH}_2\text{-CH}_2\text{-CO(CH}_2)_3\text{CO}_2\text{Et}$ obtained from ethylene and glutaric ethyl ester chloride afforded the compound XXXII (19). Hydrogenation produced two stereoisomeric acids, the trans-decalin in larger amount.

In order to construct ring B it was necessary to transform the carboxyl group into an ethyl ketone. This was done with the trans-isomer by esterification with diazomethane,



protection of the keto groups as ethylene ketals, formation of the dimethylamide (by reaction of the ester with dimethyl aminomagnesium iodide), and the preparation of the desired ethyl ketone by the Grignard reaction with ethylmagnesium bromide. Finally, hydrolysis of the ketal groups, and alkaline cyclization produced the tricyclic ketone XXXIII. A correlation of this compound with that from the Harvard synthesis was then made.

By means of methyl vinyl ketone and sodium ethoxide below 0° C, followed by alcoholic alkali to dehydrate the intermediate ketol, the tetracyclic ketone XXXIV was realized. By further modifications known D-homosteroids were produced.

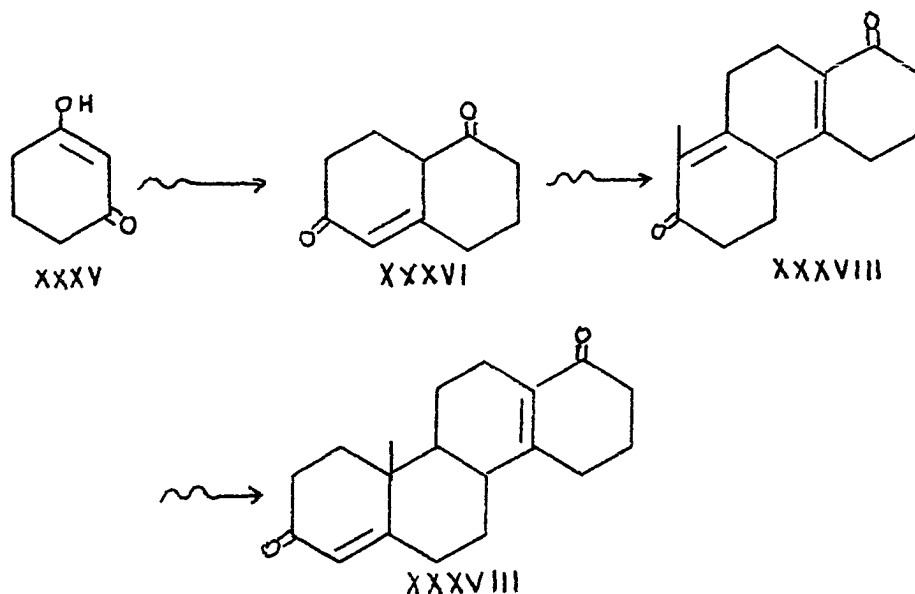
Limitation of space will not permit the enclosure of all steroid syntheses. However, mention should be made of the very elegant synthesis of cortisone by Sarett and co-workers (20a, 20b). This synthesis had the unique distinction of being completely stereospecific, the desired

stereoisomerides always predominating.

Finally, the hydrochrysene approach to steroid total synthesis by W. S. Johnson (21) should also be mentioned.

DISCUSSION

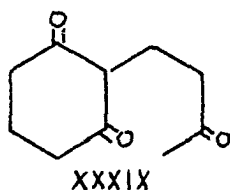
The original goal of the present work was the synthesis of a tetracyclic steroid precursor. It was hoped that successive Michael reactions of dihydroresorcinol XXXV with methyl vinyl ketone, ethyl vinyl ketone, and methyl vinyl ketone would lead to XXXVI, XXXVII, and XXXVIII, respectively, in a manner similar to the synthesis of a tricyclic ketone by Wilds and co-workers (18a, 18b).



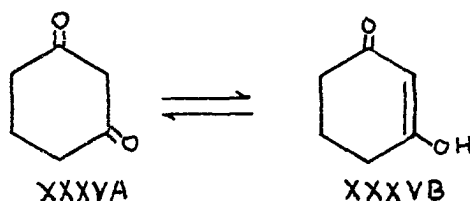
Because of the absence of experimental data in the Wilds paper, the procedure used by Wendler and co-workers (22) for the synthesis of Δ^4 -9-methyloctalin-3,8-dione was followed. Their method involved the use of triethylamine as the base for the addition of methyl vinyl ketone to

2-methylcyclohexan-1,3-dione.

The preparation of the Michael adduct XXXIX led to an oil which resisted base catalyzed cyclization to XXXVI, merely yielding back unchanged starting material. At each step the liquids were distilled at high vacuum under an atmosphere of nitrogen.



The lack of cyclization was not too surprising in view of the 100% enolic character (XXXVB) of dihydroresorcinol (23, 24, 25, 26, 27).



In strong base XXXIX would be expected to exist as the enolate anion of the β -diketone, thus preventing intramolecular aldolization from taking place. It therefore became obvious that, as in the case of Wilds and co-workers (18a, 18b), cyclization would have to be preceded by enol ether formation. The Michael adduct was treated with diazomethane to produce the methyl ether whose ultraviolet spectrum (λ_{max} , 245, ϵ 16,500) was identical with that of the starting material. The infrared spectrum differed from the

latter in its absence of peaks in the 2.8μ to 3.4μ region.

The methylated material was treated with potassium tert-butoxide to effect cyclization. Again an oil was produced which after purification by distillation gave only ambiguous spectral results: ultraviolet spectrum, $\lambda_{\text{max.}}$ $243\text{ m}\mu$ (ϵ 9,040); infrared spectrum, 5.8μ and 6.15μ .

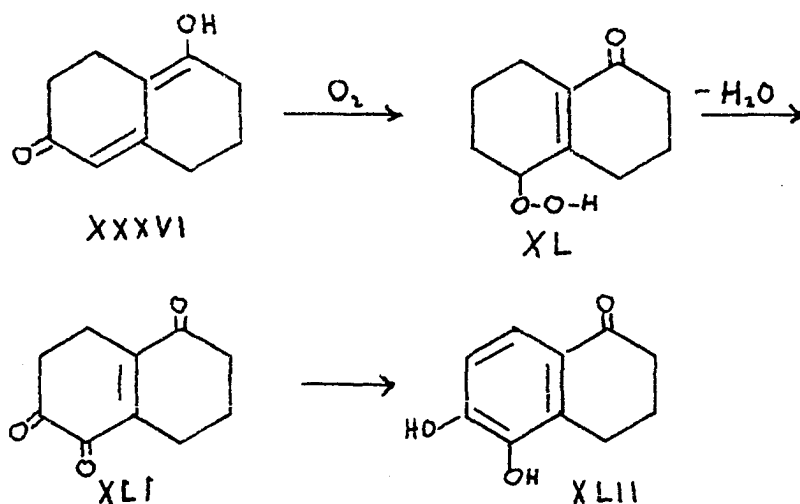
At this time an improvement in the separation of the oily products was needed. Therefore all oils obtained by the previous three-step procedure were chromatographed on a silicic acid-Celite column. Upon elution with petroleum ether-ether mixture (1:4), a solid compound insoluble in chloroform was obtained. Its ultraviolet spectrum had two maxima, one at $237\text{ m}\mu$ (ϵ 17,000) and the other at $287\text{ m}\mu$ (ϵ 12,000). Its infrared absorption revealed a hydroxy band at 2.9μ , and conjugated ketone absorption at 6.1μ , and aromatic absorption at 6.2 and 6.4μ . The analysis of this substance led to an empirical formula $\text{C}_{10}\text{H}_{10}\text{O}_3$. The compound could be hydrogenated to give a new low melting substance with an ultraviolet spectrum of a phenol: $\lambda_{\text{max.}}$ $280\text{ m}\mu$ (ϵ 17,900). The infrared spectrum showed the loss of the conjugated ketone peak. Acetylation of the phenol yielded a diacetate, $\text{C}_{14}\text{H}_{14}\text{O}_5$, whose infrared spectrum revealed the low wavelength peaks at 5.65 and 5.95μ , characteristic of carbonyl groups of phenyl esters (5.78 - 5.82μ).

All spectral evidence indicated that the unknown substance was a phenol. The infrared data showed the presence of two distinct hydroxyl peaks, therefore the problem was to determine the relationship between the two groups. 1,2-dihydroxy compounds as represented by catechol absorb in the $280\text{ m}\mu$ region (28), 1,3-dihydroxy compounds such as resorcinol have maxima in the $275\text{ m}\mu$ region, while 1,4-dihydroxy compounds like hydroquinone absorb in the $295\text{ m}\mu$ region (29). These data indicated that the unknown substance was 1,2-dihydroxy substituted. Since on hydrogenation the compound suffered hydrogenolytic loss of a carbonyl group, the latter had to be at a benzyl position. Based on this evidence and on mechanistic reasoning, the structure XLII was assigned to the unknown substance.

A possible path for the formation of the β -tetralone is shown below. The bicyclic ketone XXXVI (enol form) in the presence of base and oxygen is able to form the hydroperoxide XL. The anion formed in basic medium at position five of the hydroperoxide is capable of elimination of hydroxide ion yielding XLI which enolizes to the more stable product XLII.

By analogy Wilds and co-workers (18b) reported that compound XXVIII was oxidized to the 6-hydroxy diketone in the presence of alkali.

Now that a synthesis of a bicyclic structure had been achieved, there remained the prevention of oxidation. The



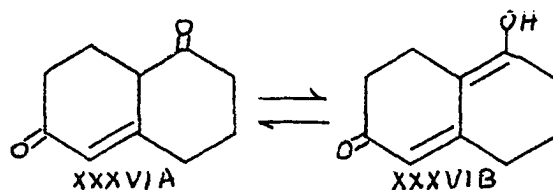
preparation of the bicyclic ketone XXXVI was again undertaken using the same conditions listed previously, except that after each reaction the product was chromatographed on a silicic acid-Celite column, elution being effected with mixtures of petroleum ether-ether.

The adduct upon such treatment was eluted as a colorless oil. The ultraviolet spectrum had a single maximum at $245\text{ m}\mu$ (ϵ 4,440). Dihydroresorcinol has a maximum at $253\text{ m}\mu$ (ϵ 21,400), thereby one would have expected the mono-C-alkylated product to exhibit a shift of about $5\text{ m}\mu$ in the direction of higher wavelengths. The infrared spectrum showed a small hydroxyl peak at 2.85μ and a broad band at $3.2\text{-}3.4\mu$. Absorption in the saturated (5.8) and unsaturated (6.1) carbonyl region was present. Dihydroresorcinol has a

broad hydroxyl band at $3.0-3.2\mu$, with unsaturated ketone absorption at 5.9μ and unsaturated absorption at 6.2μ .

Diazomethane treatment of the adduct produced another oil after chromatography whose ultraviolet spectrum was identical in every respect to that of starting material. However, the infrared spectrum showed the loss of hydroxyl absorption. The appearance of two carbonyl peaks, 5.8μ and 5.9μ was evident.

Potassium tert-butoxide treatment of the enol ether, followed by chromatography yielded a solid material, m.p. $162-63^{\circ}\text{C.}$, after elution with petroleum ether-ether in a 1:4 ratio. The solid material had one absorption peak in the ultraviolet at $298\text{ m}\mu$ (ϵ 18,000). Enolic hydroxyl absorption at $3.2-3.4\mu$ was evident in the infrared. A saturated ketone peak at 5.8μ and an unsaturated carbonyl peak at 6.1μ followed by two peaks at 6.2 and 6.4μ completed the region of most interest of the spectrum. Had the bicyclic ketone XXXVI been the unknown substance, the spectral data would not have fit, since such a compound would be expected to show ultraviolet absorption in the $245-250\text{ m}\mu$ region. Certainly no hydroxyl absorption in the infrared would be possible with such a structure, and the presence of two peaks in the double bond region ($6.2-6.4$ micron) was also rather unexplicable in terms of structure XXXVI. However, if one were dealing with a keto-enol mixture as illustrated below, compound XXXVIB might fit a structure which



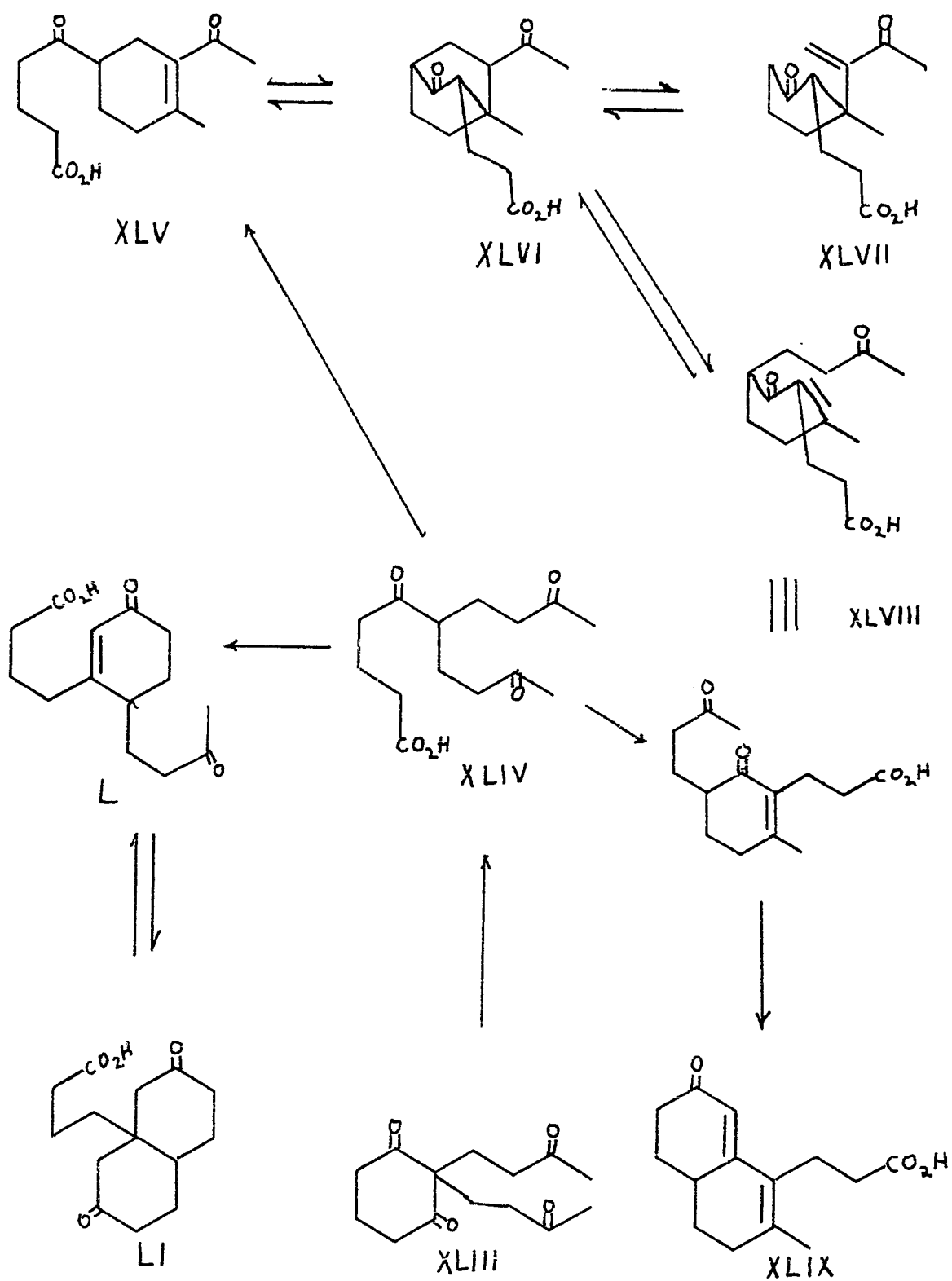
would explain most of the spectral characteristics exhibited by the substance. Such a compound is conjugated, and therefore the ultraviolet absorption would be expected to be shifted to higher wavelengths (310 $m\mu$ region), the observed peak, however, being at 298 $m\mu$. The infrared spectrum appeared to be reasonable, since an enol might be expected to show several double bond peaks. In order to see whether or not the solvent was playing a role in the possible equilibrium, the infrared spectrum was run by the KBr pellet method, yielding the same spectrum as that in chloroform. The ultraviolet spectrum in cyclohexane showed a peak at 283 $m\mu$ (ϵ 10,300), while in 0.1 N sodium hydroxide shifted the maximum to 308 $m\mu$ (ϵ 3,200).

The compound exhibited acidic character as indicated by its solubility in base as well as the above-mentioned ultraviolet spectrum in base. Attempted acetate formation by three different methods was fruitless. Reaction with 2,4-dinitrophenylhydrazine and hydroxylamine hydrochloride also bore no results. Hydrogenation in neutral medium over Pd/C afforded an oil which after chromatography also failed to yield a 2,4-dinitrophenylhydrazone. No ultraviolet absorption was present, while the infrared showed the loss of the

unsaturated carbonyl and double bond peaks. Hydroxyl and saturated carbonyl absorption was still present. The possibility of the unknown solid being the enol ether was dismissed when acid hydrolysis failed to yield a new product, but gave only starting material. With all of the data at hand, the only possible conclusion one is able to arrive at is that the unknown compound must be an acid.

If this conclusion is correct, one must be able to formulate a pathway by which the substance could arise. Therefore the mechanistic scheme on page 22 is presented. If one formulates bis-C-alkylation of dihydroresorcinol with methyl vinyl ketone, compound XLIII would be formed. In the presence of base and water (the methyl vinyl ketone is used as an azeotropic mixture containing water) the dihydroresorcinol ring could undergo cleavage to yield XLIV. Aldolization between the two butanone side chains would result in the acid XLV. Whether aldolization takes place prior to cleavage cannot be determined. A Michael reaction would then give the bicyclic compound XLVI which is in equilibrium with its double bond isomer XLVII. Compound XLVII can be excluded from consideration since it would not possess any of the necessary spectral requirements. Further reaction in the presence of base would yield the cyclic acid XLVIII. Final aldolization would lead to the bicyclic acid XLIX.

Another route whereby aldolization had occurred between



the keto acid side chain and one of the butanone moieties would give compound XLVIII directly by aldolization or the bicyclic acid XLVI by a Michael reaction. These two routes would therefore lead to the same end-product XLIX.

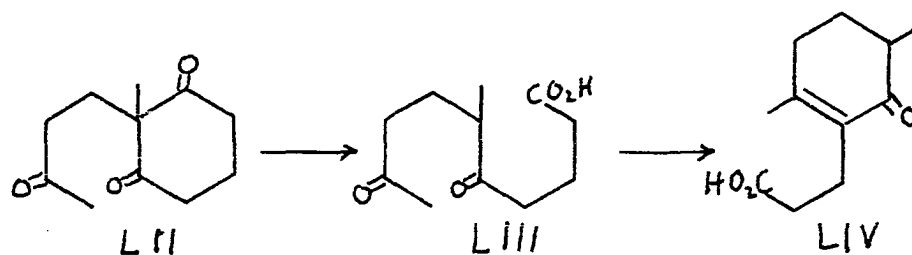
The remaining pathway may be depicted by aldolization to yield the acid L which may undergo a Michael reaction to form the bicyclic structure LI. This latter structure would not fit any of the data at hand; therefore it may be discarded from any consideration.

All experimental data agreed with structure XLIX. The infrared spectrum was satisfactory since the compound contained a carboxyl group, an unsaturated carbonyl grouping, and two double bonds which would explain the two peaks in the 6.2 to 6.4 μ region. The ultraviolet spectrum fitted a substituted conjugated carbonyl system. Using Woodward's rules (3, 4, 5, 6) a calculated value of 298 m μ was obtained which was identical with the observed maximum.

Analysis of the compound showed it to be a C₁₄H₁₈O₃ molecule, corresponding to a 2:1 methyl vinyl ketone-dihydroresorcinol reaction product. Lithium aluminum hydride reduction gave a new solid which possessed all of the spectral requirements for a dienediol system. The saturated carbonyl (5.8 μ) and unsaturated carbonyl (6.1 μ) peaks had disappeared. The ultraviolet spectrum showed the compound to be a substituted diene system having a maximum at 245 m μ

(21,700). Manganese dioxide oxidation (30) of the enol led to a new product which had the spectral properties of a conjugated enone system (identical to compound XLIX). Appearance of an unsaturated carbonyl group (6.1μ) was noted. The appearance of a single maximum at $300 \text{ M}\mu$ ($\epsilon 13,400$) in the ultraviolet indicated a substituted conjugated dienone system. Esterification of the original acid yielded an oil whose infrared spectrum showed only the loss of hydroxyl absorption ($3.2\text{--}3.4 \mu$) and no other changes from starting material. The ultraviolet spectrum was also identical with that of starting material.

The structure of the compound leading to XLIX had yet to be assigned. Wendler and co-workers (22) found that in the presence of sodium ethoxide and water the adduct LII, which arises from the reaction of 2-methyl-cyclohexan-1,3-dione and methyl vinyl ketone, underwent cleavage to form the acid LIII. Cyclic β -diketones, which are disubstituted at the α -position, are extremely susceptible to ring cleavage by

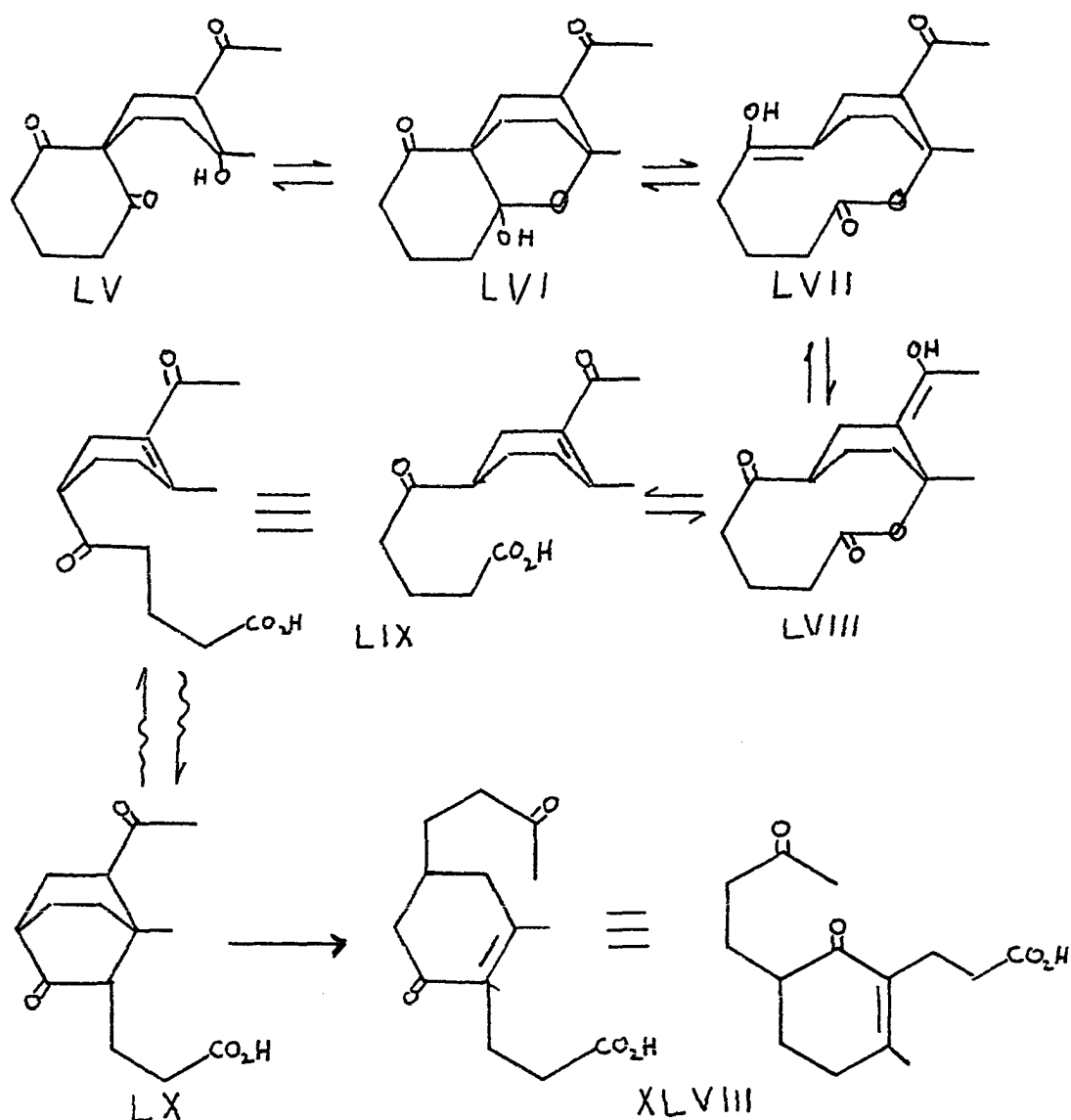


alkaline reagents (31). LIII cyclized in the presence of strong base to form the acid LIV. Reported cases of 1,5-diketone ring closures (32) indicate that the predominant

course of cyclization proceeds with involvement of the carbonyl center which is flanked to the least extent by adjacent substitution. In the scheme proposed on page 22, this phenomenon would fit extremely well.

The previous discussion has been predicated on the fact that water has played a role in the mechanism. However, a very plausible mechanism involving an internal aldol condensation (33, 34, 35, 36) may be portrayed which lends itself to the preferred course of reaction. Starting with the bis-C-alkylated compound XLII presented earlier, the first aldol could occur between the two butanone side chains giving the spiro-compound LV. The remarkable feature of this compound is that the stereochemical relationship between the hydroxyl group and the ring ketone is such that hemiketal formation is easily envisaged, thereby producing the substance LVI. Ring opening in basic solution would yield the ten-membered ring product LVII which is in equilibrium with its tautomer LVIII. Ring opening would then yield the acid LIX. The bicyclic product LX would arise from a Michael reaction, and could then cleave in the direction of the acetyl group yielding the acid XLVIII (see page 26).

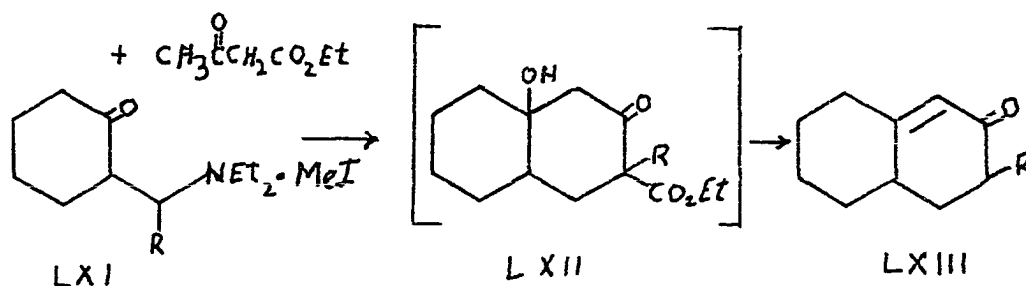
It is therefore proposed that the first product isolated from the reaction of dihydroresorcinol and methyl vinyl ketone in the presence of triethylamine is the compound LXII. The spectral data would support such a structure. The ultraviolet spectrum would be that of a disubstituted



enone calculated to be 237 $m\mu$. The spectrum has its maximum at 245 $m\mu$, but the acid LV reported by Wendler and co-workers (22) is also an α, β -disubstituted unsaturated ketone and its spectrum has a maximum at 243 $m\mu$. The infrared data could also be explained since there would be a saturated and unsaturated peak, as well as hydroxyl absorption. The

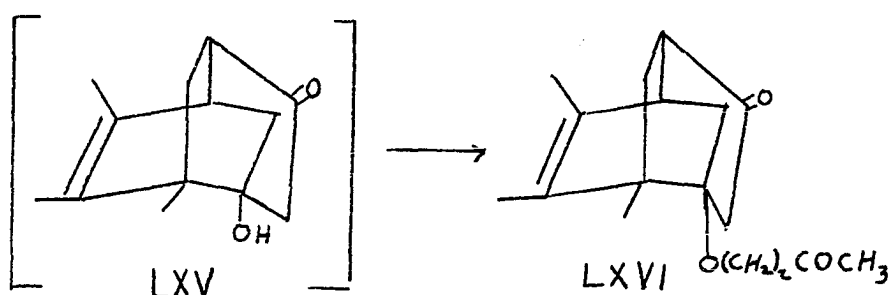
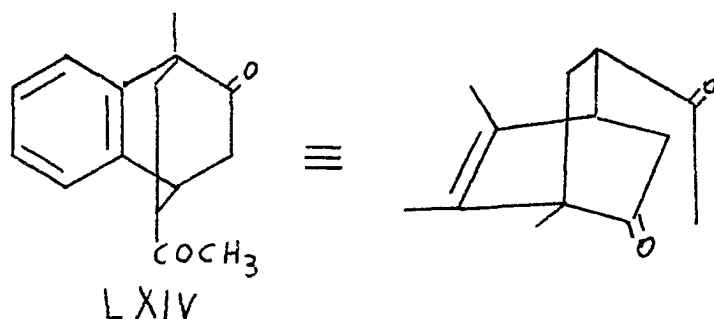
disappearance of the hydroxyl peak upon diazomethane treatment would also be explained. Formation of a 2,4-dinitrophenylhydrazone afforded a $C_{26}H_{24}O_{10}N_8$ compound which checked with the analytical results obtained.

A mechanism such as that just illustrated is not without precedent. Logan and co-workers (37) have treated the Mannich base LXI with various substituted acetoacetic esters in the presence of sodium ethoxide to give compounds of the type LXIII. The anion LXII of the aldol product is capable of undergoing intramolecular transesterification followed by a base catalyzed ring opening and decarboxylation. No unsaturated ester has been isolated from the reaction (38).



Wenkert and Stevens (36) report that during their studies involving acid and base condensations of various vinyl ketones with 1-methyl-2-naphthol an internal aldol has occurred. The ketone LXIV may undergo an internal aldol in the presence of base with simultaneous β -addition to methyl vinyl ketone to yield LXVI.

In order to clarify the nature of the genesis of the bis-C-alkylated compound XLIII which arises from the reaction



of methyl vinyl ketone and dihydroresorcinol, the possibility of O-alkylation followed by a reverse Michael was considered. However, due to the spectral data of Meek and co-workers (39), given below, the idea was discarded.

	<u>Enol</u>	<u>Enol ether</u>
Unsubstituted	253 m μ	249 m μ
2-methyl	251	255
2,2,5,5,-tetramethyl	207 274	

The feasibility of both O- and C-alkylation was checked by taking the methyl vinyl ketone adduct and subjecting it to a lithium aluminum hydride reduction. If any O-alkylation

had occurred in the beginning, under the acid work-up conditions the enol ether would have been cleaved thereby yielding an unsaturated ketone. The infrared spectrum was devoid of any carbonyl absorption and merely had a hydroxyl peak at 3.0μ , thereby eliminating the possibility of O-alkylation.

In order to verify the fact that the second step of the synthesis, namely diazomethane treatment of the methyl vinyl ketone adduct, would not be necessary for production of the final acid XLIX, equal portions of the adduct were taken and one reacted with diazomethane. The two parts were then subjected to cyclization conditions (potassium tert-butoxide).

From each part, the acid XLIX was isolated, thereby proving the original premise that diazomethane treatment led only to esterification, which had no effect upon the mechanism portrayed.

That bis-C-alkylation did occur was not too surprising for Nazarov and co-workers (38, 40) have shown by synthetic experiments that dihydroresorcinol, like dimedon, is non-selective towards methyl iodide. During the preparation of 2-methylcyclohexan-1,3-dione (43% yield), some 2,2,-dimethylcyclohexan-1,3-dione was also formed.

Wendler and co-workers (22) report that attempts to form the Michael adduct LII by conventional methods (37, 41) using Mannich bases in the presence of sodium alkoxides were unsuccessful. Similar efforts with methyl vinyl ketone were

also to no avail. Only by resorting to such a weak base as triethylamine was the desired compound produced. This result is in harmony with the results of the Russian workers mentioned above who used potassium carbonate in aqueous acetone. It would therefore seem extremely plausible that triethylamine would be capable of effecting the conversion of LV to XLVIII.

The strong base, potassium tert-butoxide, would then be needed to effect the cyclization of XLVIII to XLIX. This result is in line with those of Wenkert and Stevens (36) who also found that strong base was needed for such intramolecular condensations.

As a final point the reason for Wilds' isolation of a mono-adduct with dihydroresorcinol requires explanation. Perhaps the use of a Mannich base instead of methyl vinyl ketone is sufficient to account for the contrast of results with the present work. Unfortunately in the absence of experimental data, nothing definite can be concluded.

SPECTRA

Ultraviolet spectra were run in 95% ethanol using a Beckman model DU quartz spectrophotometer. All infrared absorption spectra were recorded using a Baird Double Beam infrared spectrophotometer.

Chloroform was the solvent used for the spectra except for that of 3,4,5,6-tetrahydro-7-methyl-8- β -carboxyethyl-naphthadiene-2(1H)-one and 3,4-dihydro-5,6-dihydroxy-1(2H)-naphthalenone which were run in KBr pellet.

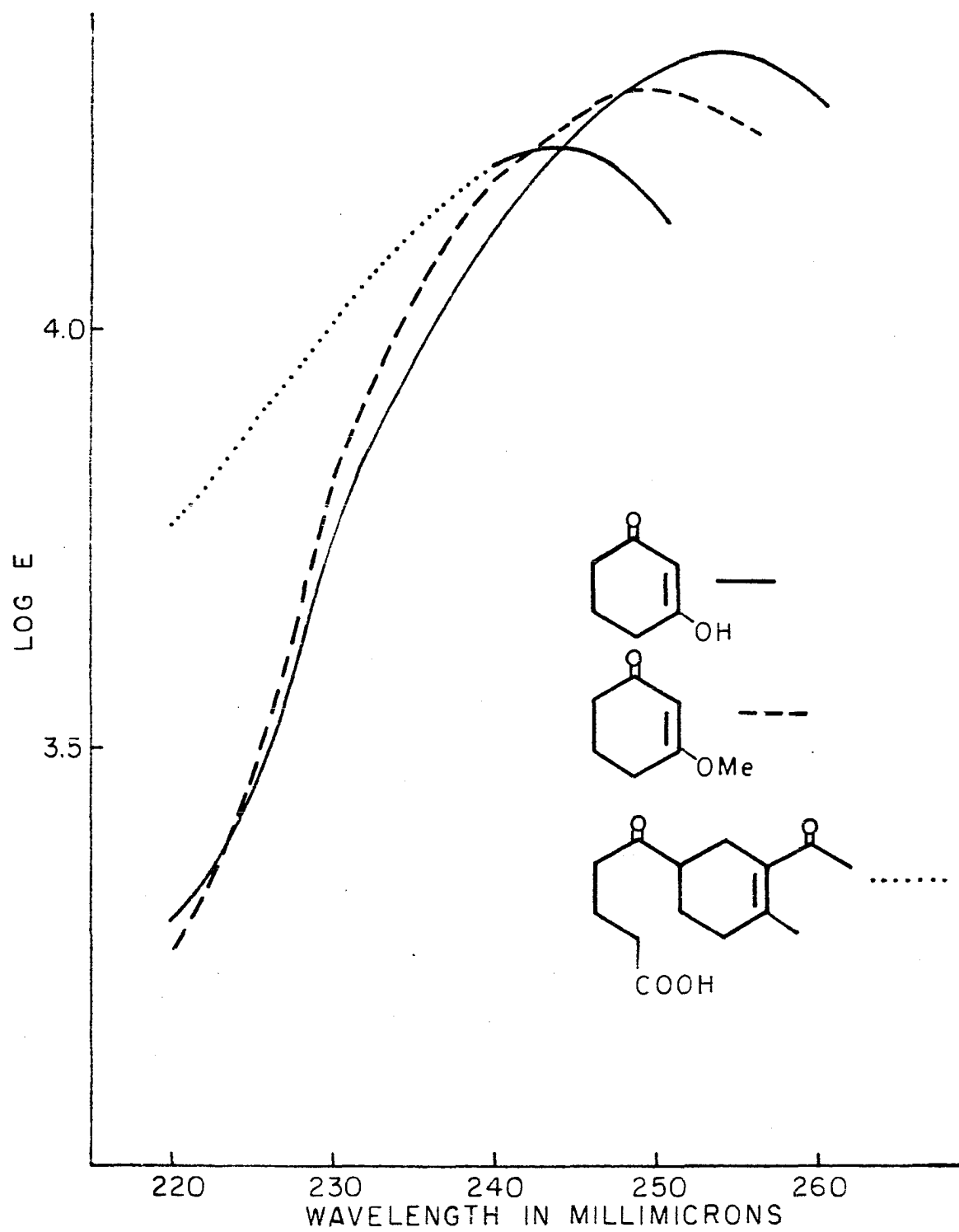


Figure 1. Ultraviolet spectra

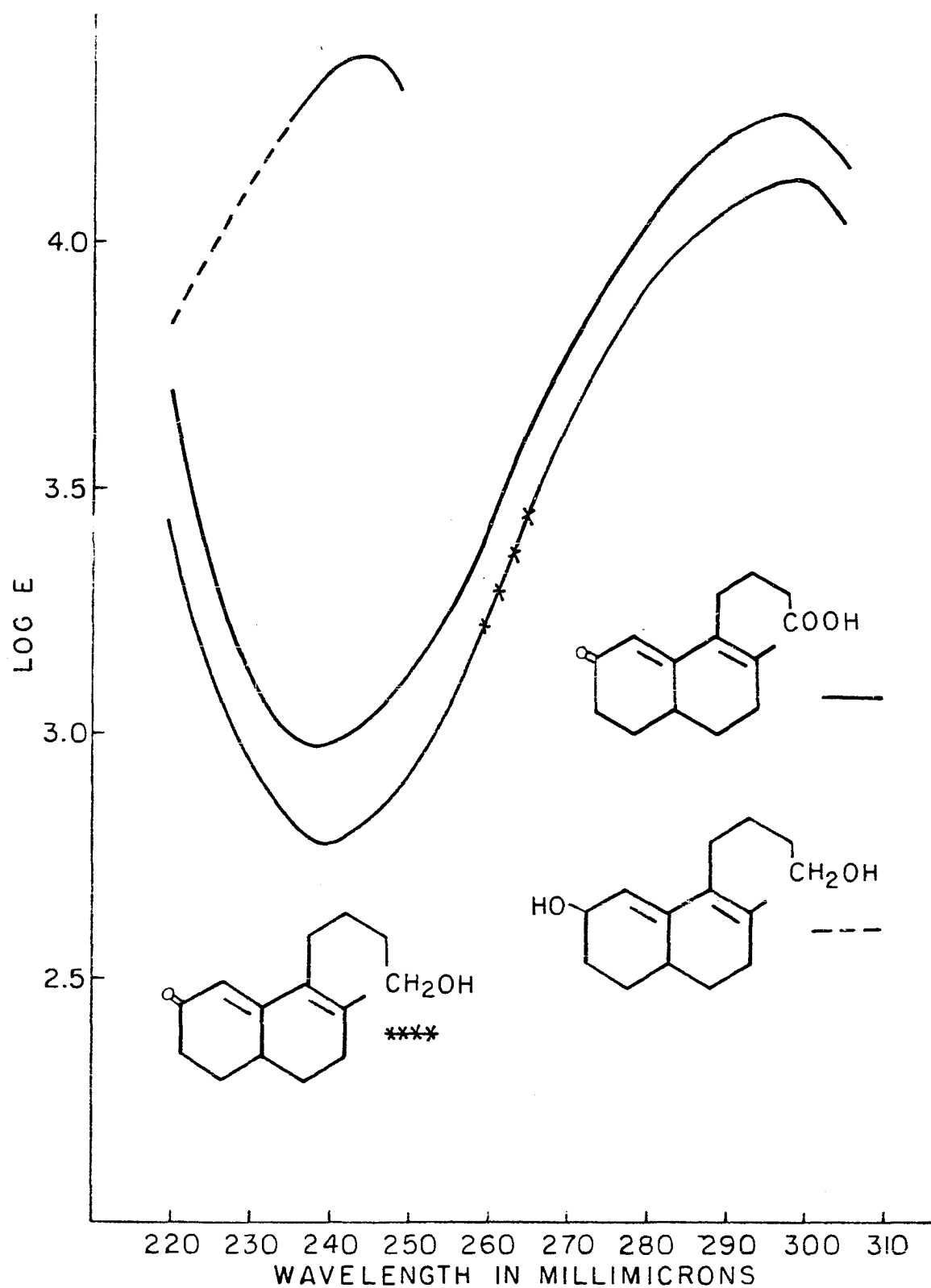


Figure 2. Ultraviolet spectra

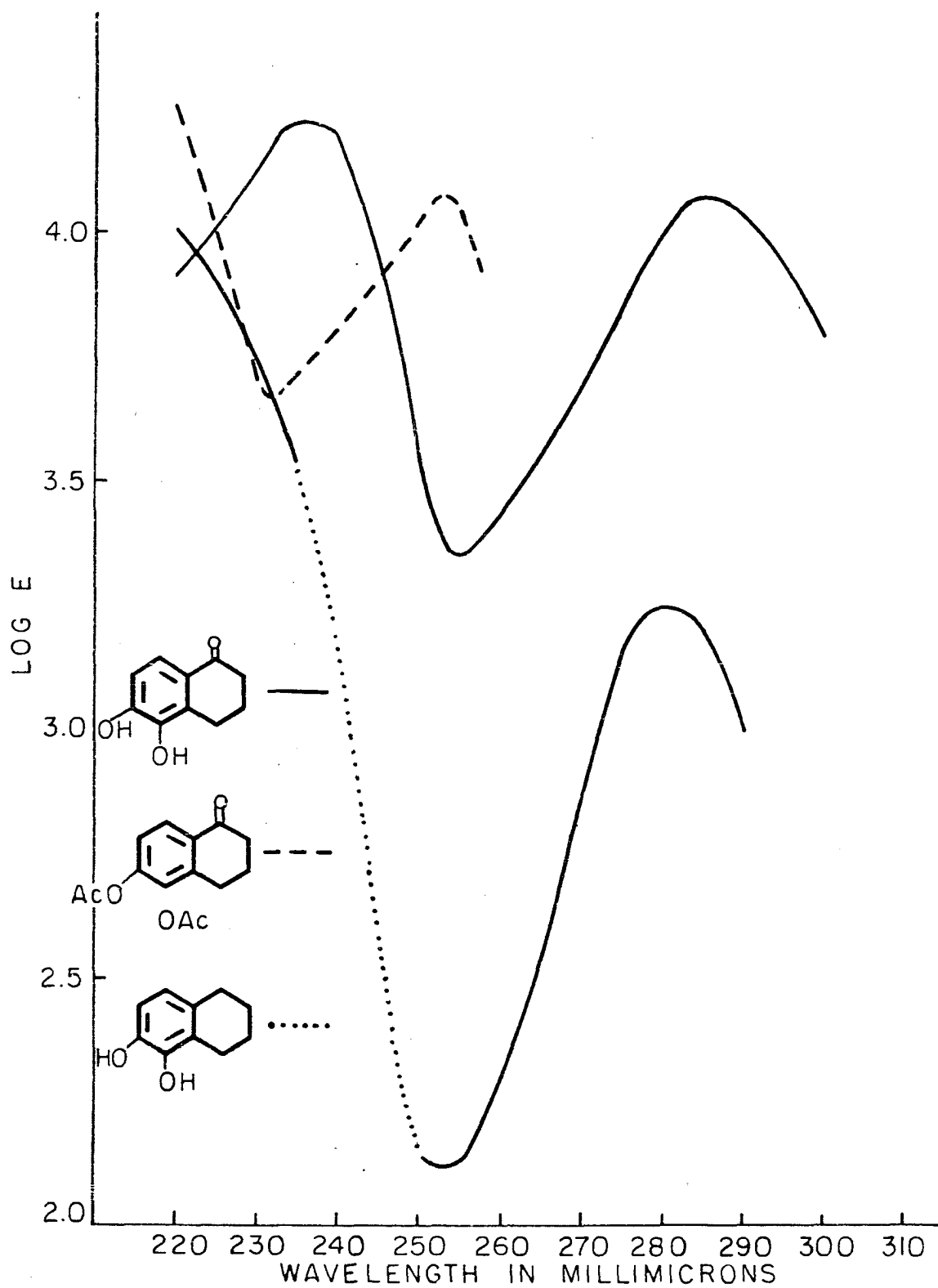


Figure 3. Ultraviolet spectra

Figure 4. Infrared spectra

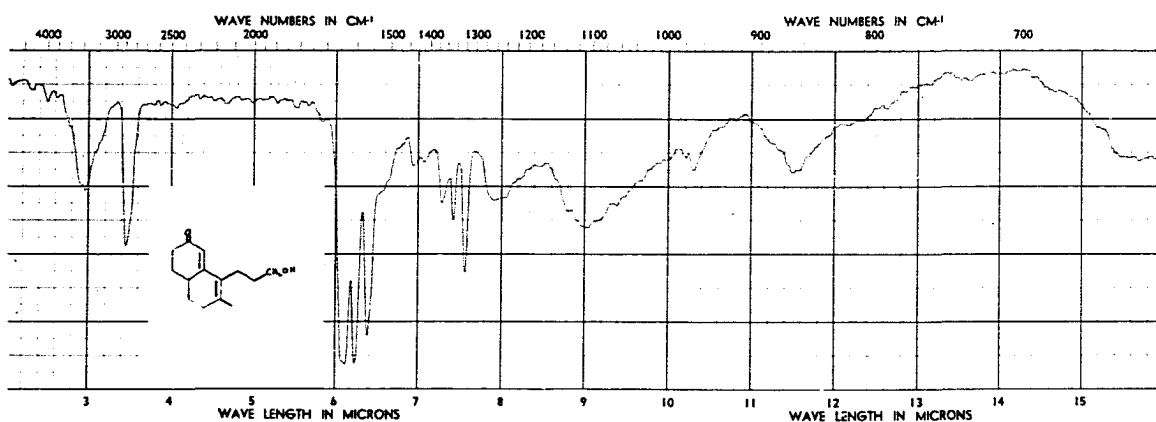
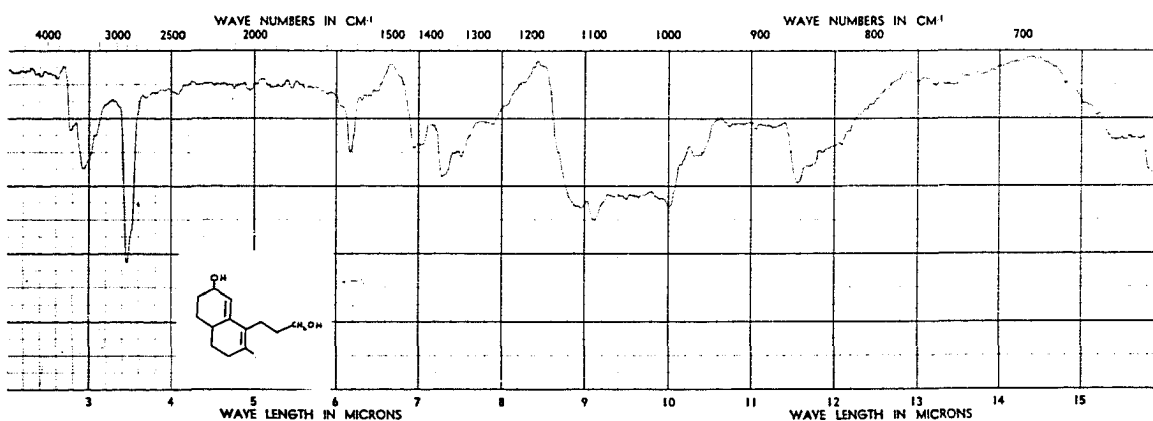
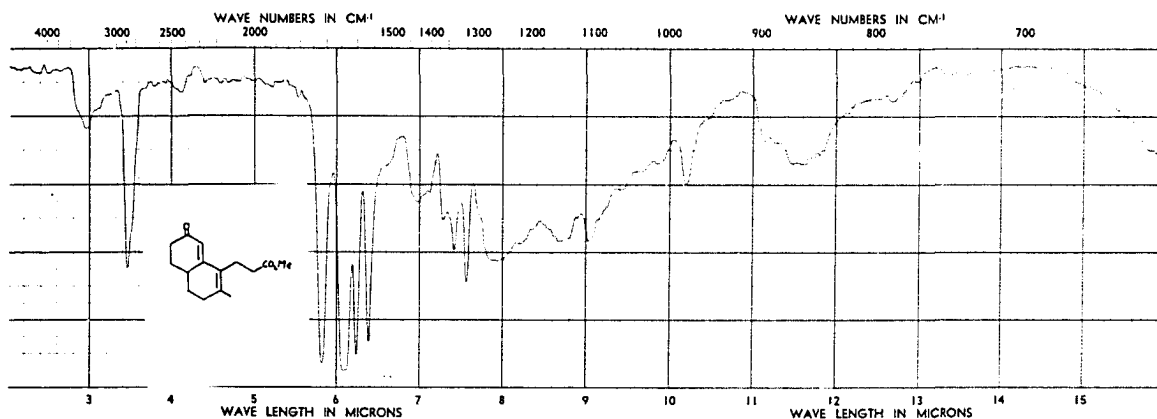


Figure 5. Infrared spectra

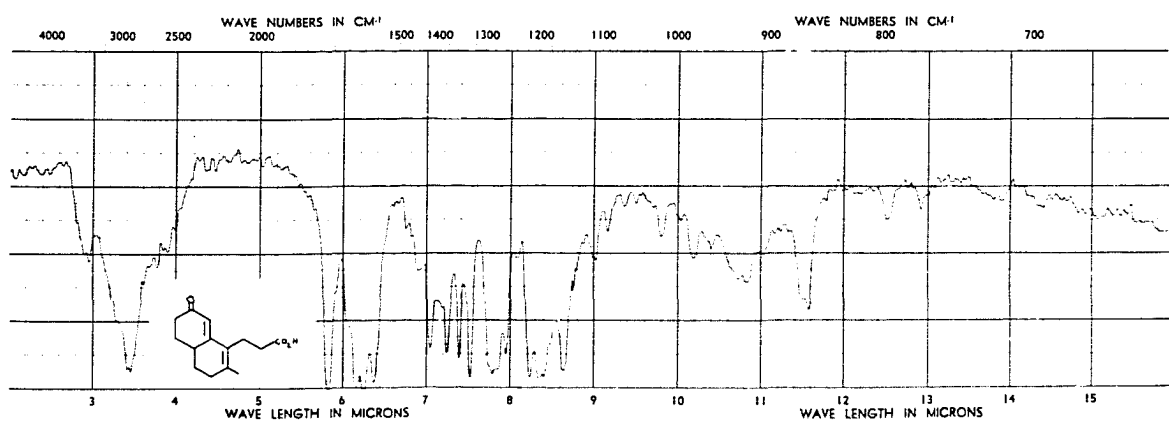
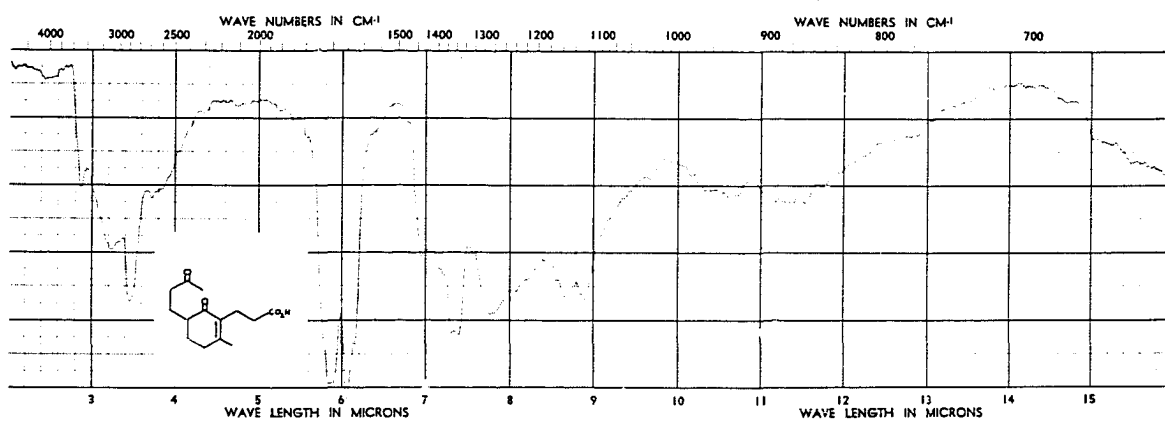
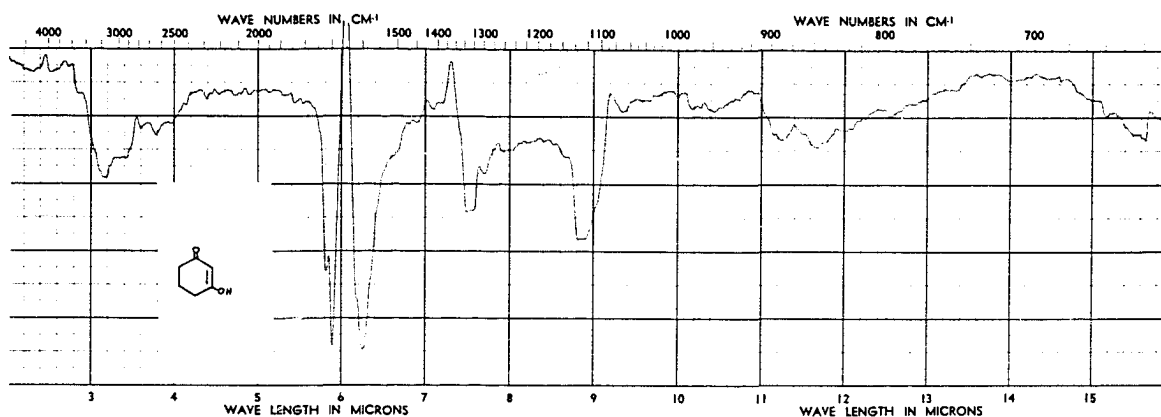
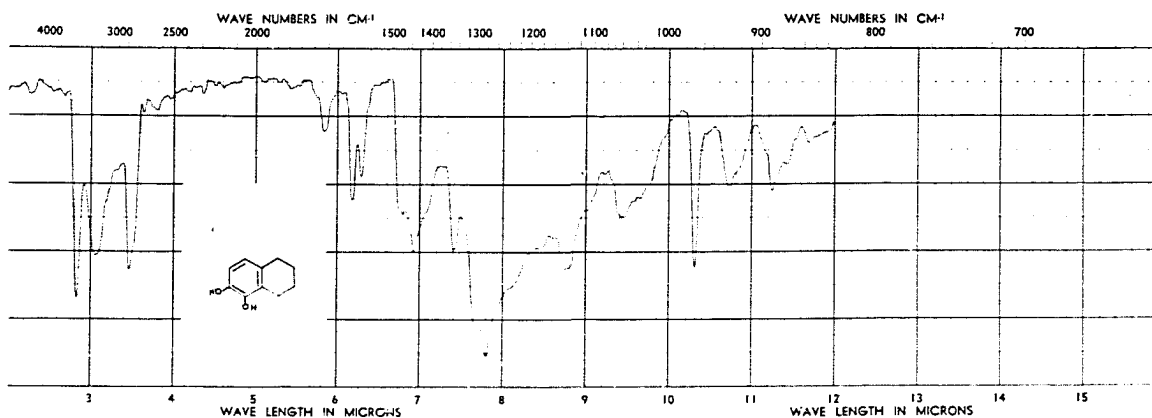
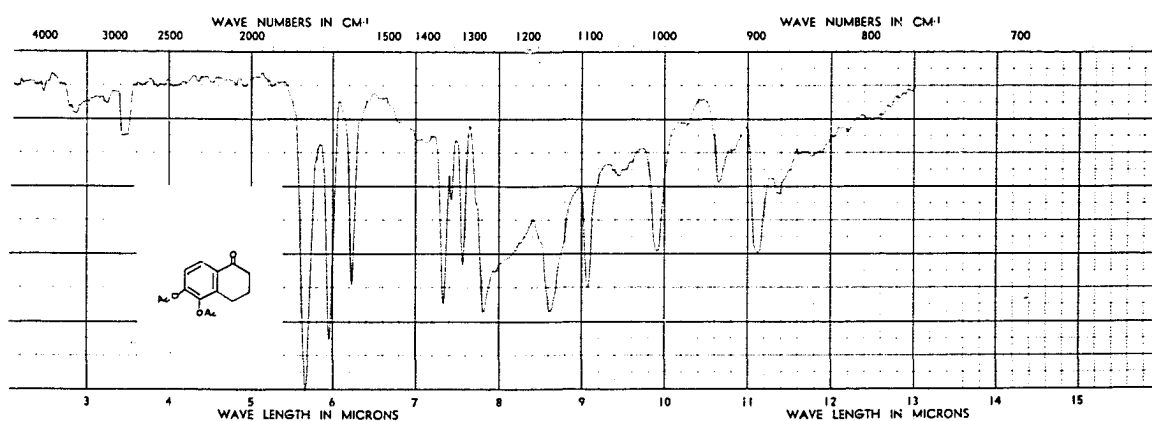
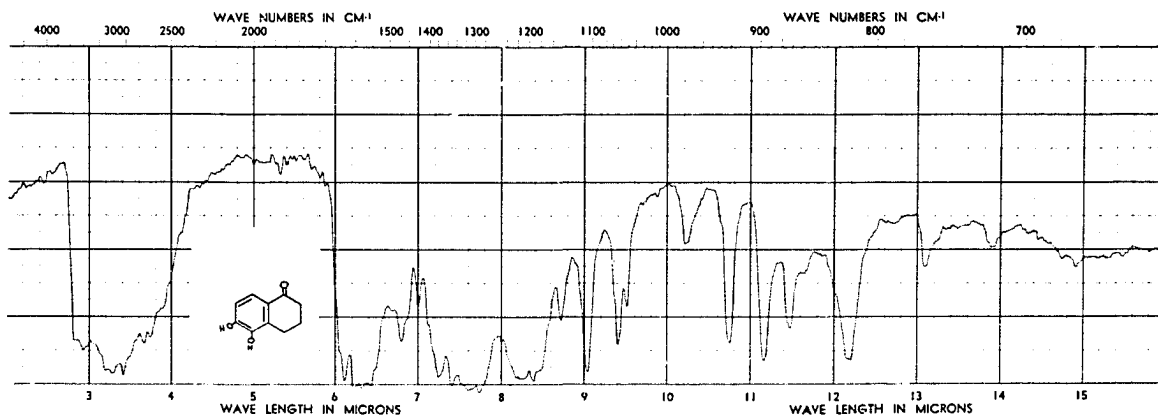


Figure 6. Infrared spectra



EXPERIMENTAL

All melting points are corrected unless otherwise stated. The term petroleum ether refers to the fraction b. p. 60-70° C. Microanalysis were performed by Weiler and Strauss Microanalytical Laboratory, Oxford, England; and Midwest Microlab Inc., Indianapolis, Indiana.

Adsorbents for Chromatography

The silicic acid-Celite absorbent was prepared by mixing equal weights of Celite and 100 mesh silicic acid.

Preparation of Dihydroresorcinol XXXV

To a solution of 36 g. of sodium hydroxide was added 82.5 g. of resorcinol yielding a light red colored solution. To this solution, 15 g. of Raney nickel catalyst (42) was added and the resulting mixture hydrogenated at 50 lbs. pressure for 48 hrs. or until 60 lbs. of hydrogen had been taken up. After the allotted time, the solution was decanted, and the liquid acidified with concentrated hydrochloric acid until acid to congo red paper. Upon cooling, crystallization took place. The solid was separated by filtration and recrystallized from benzene. The water layer

which settled to the bottom was withdrawn, and the benzene solution cooled until crystals appeared. Since at the low pressure used, complete hydrogenation was never acquired, and it took as many as fifteen to twenty recrystallizations to remove all of the resorcinol. It was found that if the second recrystallization was made from ethanol, the amount of recrystallization was reduced. Washing from boiling petroleum ether was also found to be helpful, just as using a fritted glass funnel. The pure product has a m.p. of 103-4° C.

Synthesis of Δ^2 -2- β -carboxyethyl,3-methyl,5- γ -butanone-cyclohexene-1-one XLVIII

8.85 g. (0.078 moles) of dihydroresorcinol was dissolved in 155 ml. of methyl alcohol to which 14 ml. of freshly distilled methyl vinyl ketone was added. Then 1.5 ml. of distilled triethylamine was added to the stirred solution which was under an atmosphere of nitrogen (dry). This procedure was almost identical to that reported by Wendler and co-workers (22). After approximately 20 hrs. the solution which had now become slightly orange in color, was evaporated in vacuo. A deep orange oil remained which was placed on a silicic acid-Celite column. Elution with petroleum ether-ether 20:1 ration gave a colorless liquid in 59.9% yield.

When nearly all of the material had been removed from

the column, a solid material could be isolated. This substance had the same spectral characteristics of the liquid. Recrystallization from ether afforded a white needle-like solid m.p. 65-6° C.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.7; H, 7.94. Found: C, 66.34; H, 7.98.

Ultraviolet spectrum. λ_{max} . 245 m μ (ϵ 16,500)

The 2,4-dinitrophenylhydrazone of LX melted at 225-6° C. Recrystallization from dimethyl formamide-ethanol yielded yellow crystals.

Anal. Calcd. for $C_{26}H_{24}O_{10}N_8$: C, 51.4; H, 3.95; N, 18.45. Found: C, 50.8; H, 4.35; N, 18.3.

Preparation of 3,4,5,6-tetrahydro-7-methyl-8- β -carboxyethyl-naphthadiene-2(1H)-one XLIX

Equimolar quantities of potassium metal and the Michael adduct LX were used. Clean potassium metal was allowed to dissolve in calcium hydride distilled tert-butyl alcohol. When dissolution was complete, the base was added dropwise to an ice-cold solution of LX under an atmosphere of nitrogen. When the addition of the base was completed, the stirred solution was allowed to stand at room temperature for six to eight hours. The mixture was neutralized with 2.5 N. hydrochloric acid, extracted with chloroform, and dried over sodium sulfate.

Removal of solvent yielded a dark oil which was placed on a prepared silicic acid-Celite column. A solid substance appeared after elution with 4:1 petroleum ether-ether. Recrystallization from benzene gave a white crystalline solid, m.p. 162-3° C.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.7; H, 7.69. Found: C, 71.6; H, 7.64.

Ultraviolet spectrum. $\lambda_{\max}$. 298 m μ (ϵ 18,000)

Lithium Aluminum Hydride Reduction of XLIX

Dry tetrahydrofuran was prepared by refluxing with sodium wire, and distilled onto lithium aluminum hydride. The mixture was again refluxed and distilled under an atmosphere of nitrogen.

To the dry tetrahydrofuran the acid XLV was added. This solution was added dropwise to a stirred solution of dry tetrahydrofuran and lithium aluminum hydride, taking all of the necessary precaution to insure dryness. When all of the solution had been added, the mixture was refluxed for one hour. After this period of time, the excess lithium aluminum hydride was decomposed with water. The solid was filtered off and washed with chloroform, and the resulting solution dried over sodium sulfate. Evaporation of the solvent yielded a white solid. Recrystallization from benzene afforded white platelets m.p. 117-18° C.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.6; H, 9.92. Found:
C, 76.36; H, 9.69.

Ultraviolet spectrum. $\lambda_{\max}$. 245 $m\mu$ (ϵ 21,700)

Oxidation of 3,4,5,6-tetrahydro-7-methyl-8- β -hydroxyethyl-
naphthadiene-2(1H)-ol

Manganese dioxide was prepared by the method of Mancera and co-workers (43) in the following manner. To a stirred aqueous solution of manganous sulfate held at 90° C. a water solution of potassium permanganate was added until a pink coloration remained in the supernatant liquid. The mixture was stirred at 90° for fifteen minutes longer. The manganese dioxide was filtered off and washed thoroughly with hot water. The catalyst was dried overnight at a temperature of 135° C.

A chloroform solution of compound XLV was mixed with 25 mg. of manganese dioxide. The solution was stirred rapidly by means of a paddle stirrer for 10 hrs. At the end of this period of time, another small charge (10 mg.) of catalyst was added and the reaction mixture allowed to stir overnight.

The solid material was filtered off and washed with chloroform. Removal of the solvent gave a white solid, m.p. 60° C. Recrystallization from ether afforded small white needles, m.p. 63-4° C.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.4; H, 9.1. Found:

C, 75.73; H, 9.12.

Ultraviolet spectrum. $\lambda_{\max}$. 300 m μ (ϵ 13,400)

Purification of 3,4-dihydro-5,6-dihydroxy-1(2H)-
naphthalenone XLII

The compound was recrystallized from benzene solution to yield a white crystalline product in the form of needles, m.p. 195-96° C.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.3; H, 5.63. Found:

C, 66.9; H, 5.94.

Ultraviolet spectrum. $\lambda_{\max}$. 238 m μ (ϵ 17,000),
 $\lambda_{\max}$. 285 m μ (ϵ 12,000)

Acetate of XLII

The acetate was prepared according to the procedure of Shriner and Fuson (44). Recrystallization of the solid from ethanol gave a white solid, m.p. 125-26° C.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.2; H, 5.34. Found:

C, 64.5; H, 4.97.

Ultraviolet spectrum. $\lambda_{\max}$. 253 m μ (ϵ 11,800)

Hydrogenation of XLII

125 mg. of the dihydroxytetralone XL were dissolved in 25 ml. of ethanol and 50 mg. of 10% Pd/C catalyst added.

Hydrogen uptake was very rapid, and nearly the total amount reacted within thirty minutes. The mixture was allowed to stand for one hour longer. The calculated amount of hydrogen was 35 ml.; actual uptake was 36 ml. The catalyst was filtered off, and the resulting solution evaporated. An oil remained which was chromatographed on silicic acid-Celite. Elution with 10:1 petroleum ether-ether yielded a white solid. Recrystallization from benzene gave small white platelets, m.p. 69.5-70.5° C. on a Fisher-Johns melting point block.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.3; H, 7.3. Found:

C, 73.6; H, 7.35.

Ultraviolet spectrum. $\lambda_{max.}$ 280 m μ (ϵ 17,900)

SUMMARY

An attempted synthesis of a tetracyclic steroid precursor led only to bicyclic systems with interesting chemical genesis.

Probable mechanisms for the formation of these compounds are presented.

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ACKNOWLEDGEMENTS

The role of the major professor is hereby dutifully noted. Special mention should be made of the extraordinary patience and guidance shown by Dr. Ernest Wenkert during the course of the many studies performed at this institution.

Extreme thanks are due to Professor George S. Hammond for his many thoughtful and helpful "sermons".

The author is indebted to the Institute for Atomic Research, Iowa State College, for the use of the infrared spectrophotometer without which this research could not have been accomplished. A big thank you is in order to E. Miller Layton whose cooperation in running the largest share of the infrared spectra is greatly appreciated.

A final note of thanks is reserved for Professor W. Ben King whose patience and shining example in the field of teaching has always held the greatest of respect by this author. It is difficult to express in words the great admiration shown by this individual for the inspiration derived from the several years of contact while working for Professor King. Thank you!