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Uses of integer programming in problems of optimization and their computational aspects

Dale David Grosvenor
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PHOTOCHEMICAL STUDIES ON UNSATURATED KETONES

by

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and

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VITA

The author was born on a farm near Livingston, Wisconsin on February 20, 1933 to Mr. and Mrs. T. E. Griswold. He attended Platteville High School at Platteville, Wisconsin and was graduated in May, 1950. In September of 1950 he enrolled at Wisconsin State College at Platteville, Wisconsin and attended this school until May, 1952. In September of 1952 he transferred to the University of Wisconsin and attended that institution for one year.

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INTRODUCTION

Photochemistry in the past ten years has grown from the curiosity status to a position of practical value and theoretical significance. It is now evident that one may accomplish structural changes in organic molecules, by means of a single photochemical reaction, that would be virtually impossible through classical methods. Reactions of preparative value (1) are becoming more abundant with each passing year.

Undoubtedly, the photochemical interconversions that have earned the title of "most valuable" are in the Vitamin D_2 series (2). Although relatively uninvestigated commercially, the photoisomerizations in the steroid field (3) offer exceptionally interesting structural changes that have a high potential for biological activity.

In any compilation (4, 5, 6, 7) of photochemical reactions, it is readily apparent that much too little is known about the mechanisms of photochemical reactions. At present, certain theories (7, 8, 9), relating to photochemical mechanisms, exist. But as is true in any new field, they must still undergo the critical tests of time and further investigation.

Many of the previous accomplishments in the photochemical field arise from the photoisomerization reactions of unsaturated carbonyl compounds. The scope of this thesis falls within this general area.

Included in this investigation were examples of a simple

photochemical dimerization, a photochemical valence tautomerization of a cyclic dienone and light induced rearrangements involving a cross-conjugated dienone as well as a simple α,β-unsaturated ketone.

The design of the work mainly involved synthesis and structure proof rather than a mechanistic approach. Nevertheless, most mechanistic conclusions in the field of photochemistry (or for that matter in chemistry) are arrived at after the fact. The investigations in this work are by no means exceptional. It must be emphasized, however, that definite attempts, with some success, were made to incorporate previously gained knowledge into the work.

HISTORICAL

Photochemical Reactions of Homocyclic, Unsaturated Ketones

The reactions of unsaturated ketones, under the influence of light, can in general be divided into four categories, based upon the type of product formed. They are:

a. Simple dimerization reactions forming cyclobutane derivatives.

b. Rearrangement reactions wherein the gross structure of the molecule is changed.

c. Photochemically induced valence tautomerization reactions.

d. Light catalyzed addition reactions.

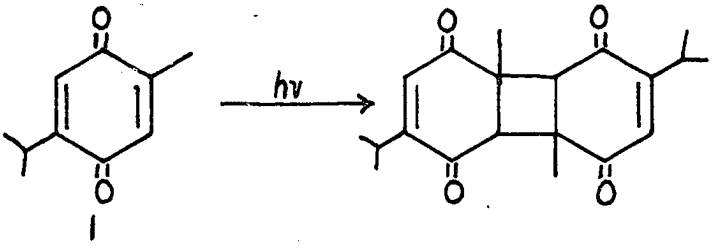
Category c can in many cases be included in b. The division is made to differentiate between reactions initiated by excitation of the carbonyl group and those reactions that may or may not be initiated by a diene system in conjugation with the carbonyl group. This breakdown has an added advantage. The systems studied in this research fit very nicely into the first three categories. As no examples of category d were included in this study, the reader is referred to the previously cited reviews (1, 6, 7).

This categorization necessarily omits a vast quantity of photochemistry pertaining to unsaturated carbonyl compounds e.g., unsaturated acids and esters, unsaturated lactones and

pyrones, to name a few.

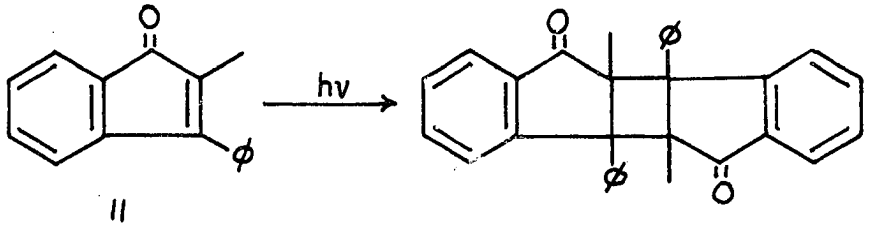
Dimerization reactions

Photochemical dimerization reactions of cyclic, unsaturated ketones have long been known. One of the earliest reports is that of Liebermann and Ilinskii (10), who found that thymoquinone (I) readily forms a dimeric product in the



I

presence of sunlight. Since that time, many quinones (4) have been found to dimerize in a similar fashion. de Fazi (11) found that 2-methyl-3-phenylindone (II) forms a dimer upon

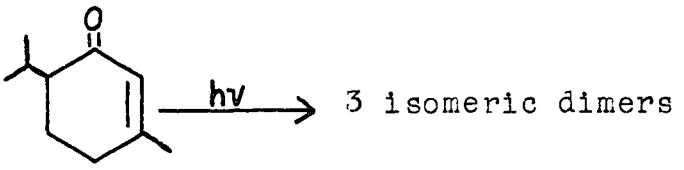


II

irradiation. The truxones, as these dimers have been named, have been formed from several indone systems (12).

In 1930 Triebs (13) reported that 2-cyclohexenone, 3-methyl-2-cyclohexenone and 3,5-dimethyl-2-cyclohexenone form dimers under the influence of light. Three years later Triebs (13) isolated three isomeric dimers from the irradi-

ation of piperitone (III).



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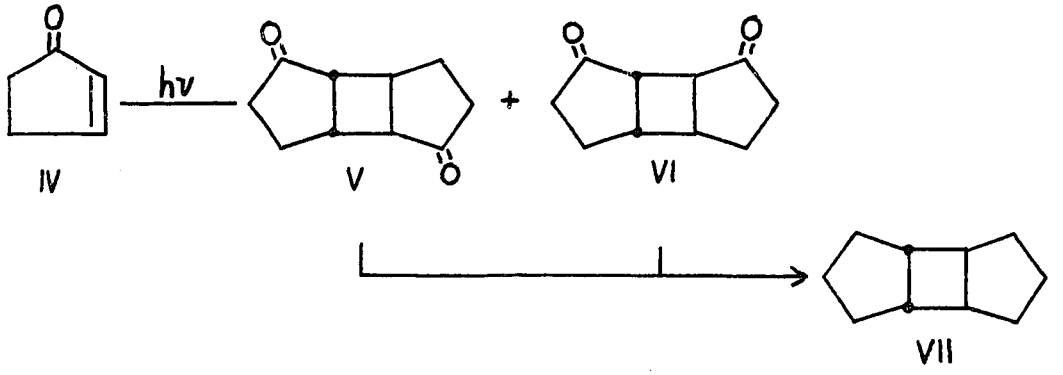
The complete structure of the previous 2-cyclohexenone dimers is still in doubt. Only recently has the complete structure of a dimer of this type been fully elucidated.

Eaton (14) irradiated cyclopentenone (IV) and isolated equal amounts of two dimers (V and VI). V and VI were shown to give the same hydrocarbon (VII) after Wolff-Kishner reduction. In this way V and VI were shown to be isomeric in



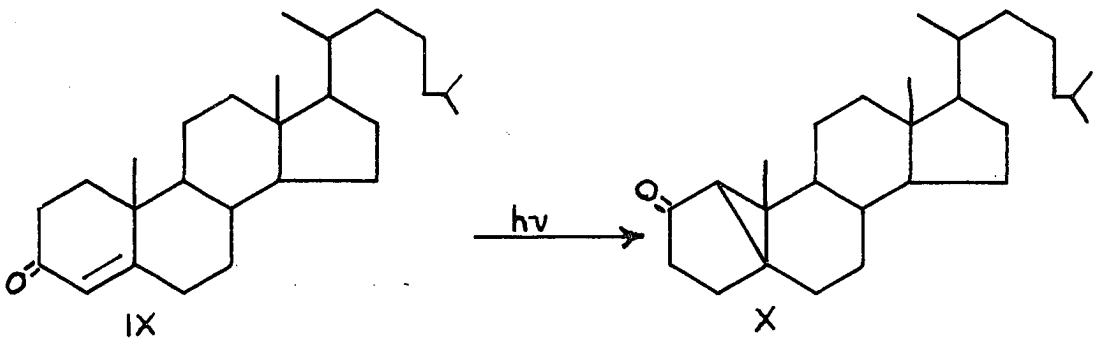
IV V VI VII

relation to the positions of the carbonyl groups. The stereochemistry around the cyclobutane ring was determined through a nuclear magnetic resonance study on derivatives of the dimers.

Photochemical rearrangements of 2-cyclohexenones and cross-conjugated cyclohexadienones

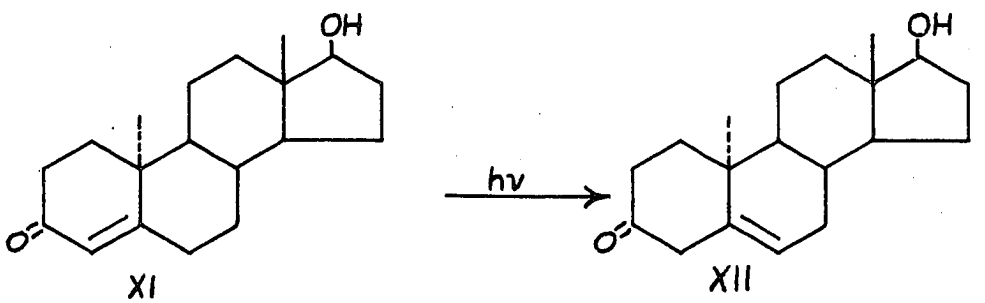
The number of photochemical rearrangements involving 2-cyclohexenones is very limited. Kwie et al. (15) irradiated

Δ^4-cholesten-3-one (IX) in tertiary-butyl alcohol and obtained the cyclopropyl ketone X (lumi-cholestenone).



IX X

In a remarkable reaction (16) 10α-methyltestosterone (XI) gave only XII when irradiated in tertiary-butyl alcohol.

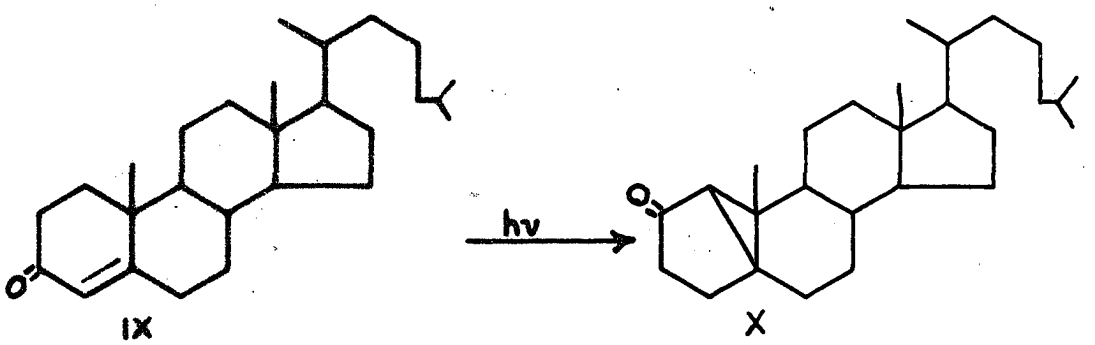


XI XII

The migration of the double bond to the five position indicates the effects of the 10α-methyl on A/B ring chemistry as compared to the well-known 10β-methyl compound. The photochemical conversion of α,β-unsaturated ketones to β,γ-unsaturated ketones via the enol is a well-known reaction. The reader is referred to reference 7 for a review on photochemical enolization reactions.

Chapman et al. (17) isolated several products from the irradiation of 4,4-dimethylcyclohexenone (XIII). The nature

Δ^4-cholesten-3-one (IX) in tertiary-butyl alcohol and obtained the cyclopropyl ketone X (lumi-cholestenone).



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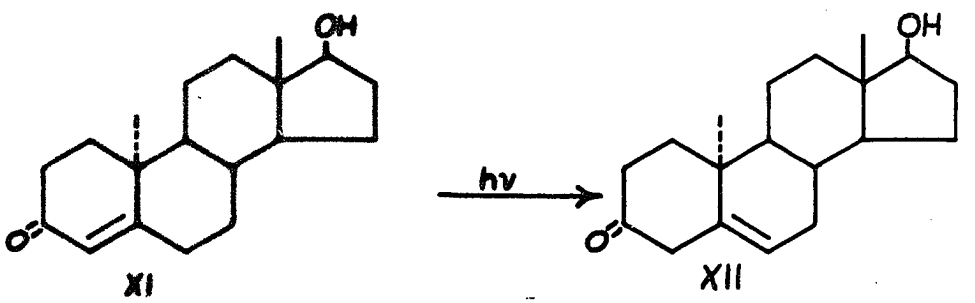

XI XII

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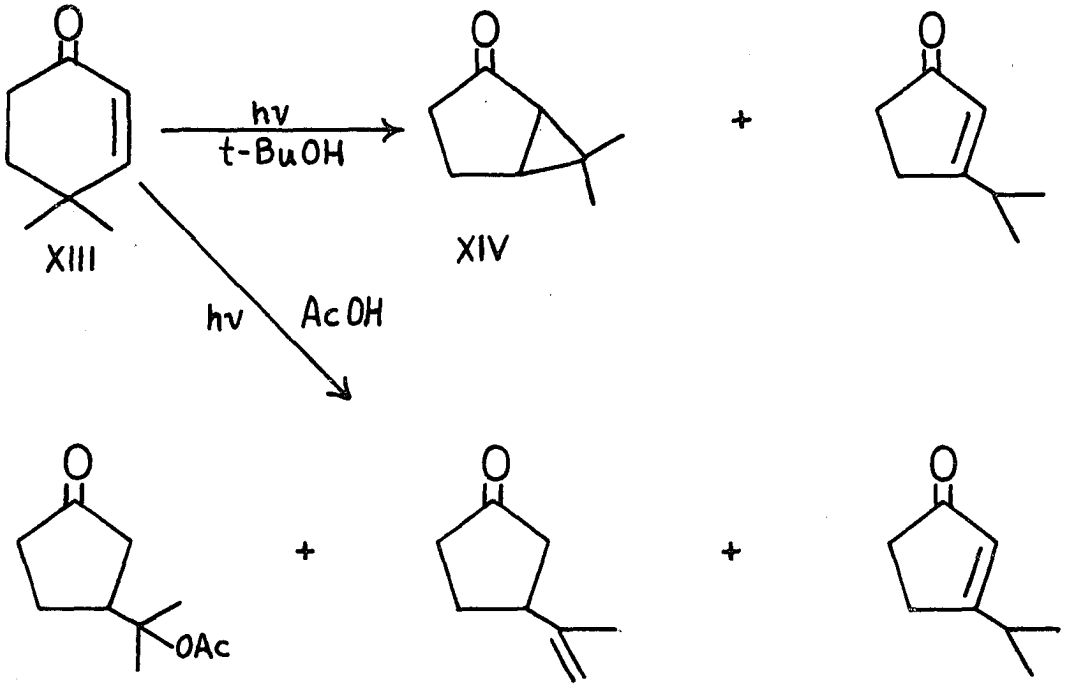
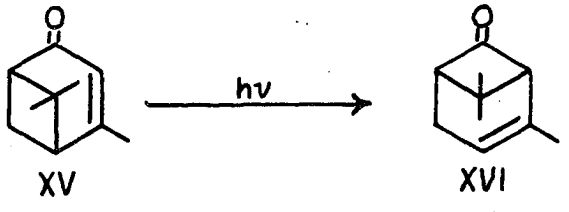
Chapman et al. (17) isolated several products from the irradiation of 4,4-dimethylcyclohexenone (XIII). The nature

of the photoproducts was found to be solvent dependent. XIV is the analog in this series to lumi-cholestenone (X).



The photochemical transformation (18) of verbenone (XV) to chrysanthenone (XVI) illustrates a different type of



photochemical rearrangement.

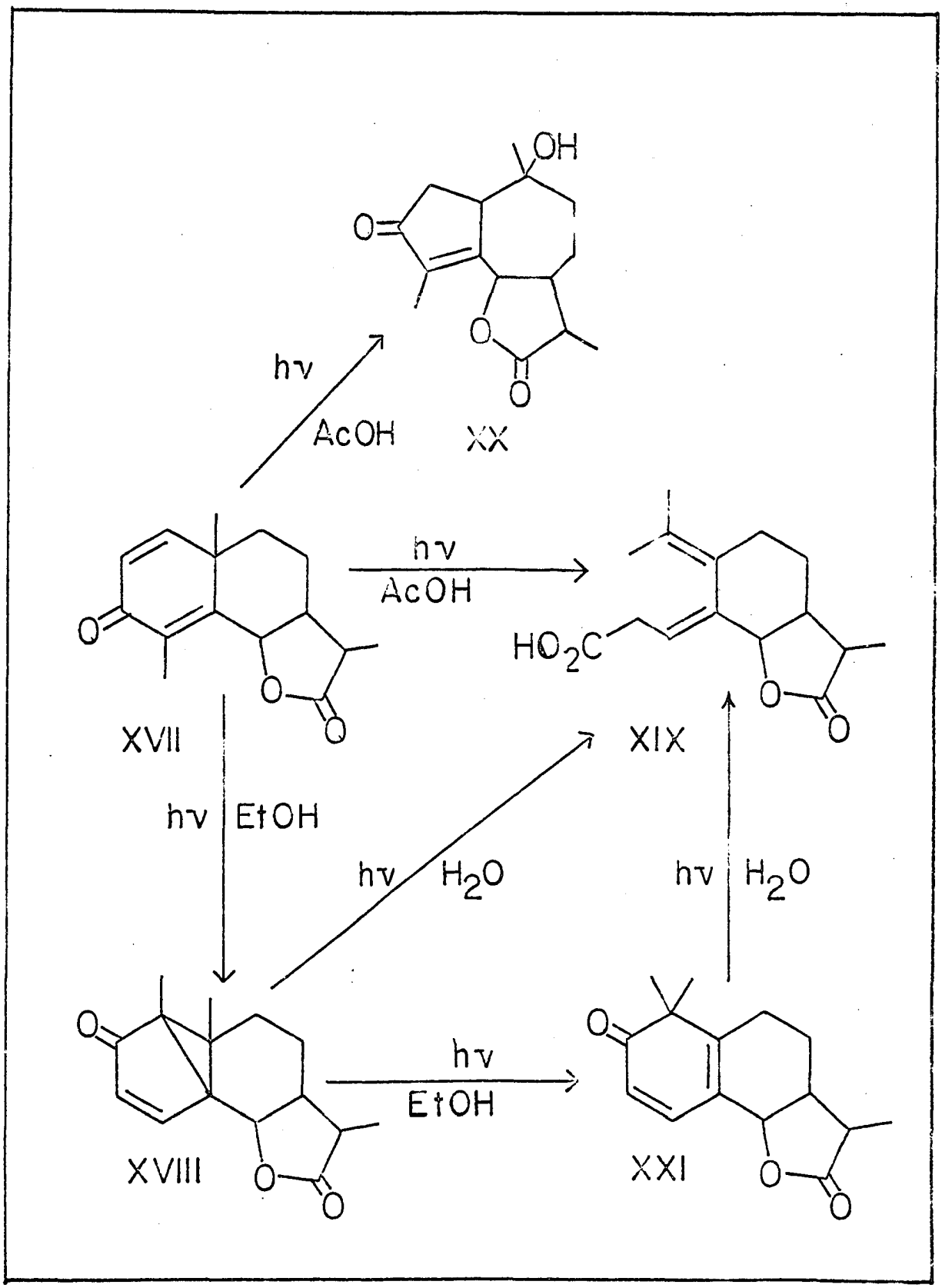
The cross-conjugated cyclohexadienones have received a great deal of attention in the field of photochemistry. Some of the most novel rearrangements have been shown to take place with these compounds. The basis for much of this chemistry was laid in the santonin series (19, 20, 21).

Santonin (XVII) is readily converted to lumi-santonin (XVIII) by irradiation in neutral solution. When santonin is irradiated in acetic acid, both photosantonic acid (XIX) and isophotosantonic acid lactone (XX) are isolated. Lumi-santonin, although not isolated from acetic acid irradiations, can be converted to XIX by irradiation in that solvent. Chapman and Englert (22) have recently found that lumi-santonin is converted to the dienone XXI by irradiation in neutral solution in the absence of water. With water present, XXI is quickly converted to XIX under the influence of light. The photochemical conversions in the santonin series are shown in Figure 1, page 10.

Steroids have played an important role in the photochemistry of cross-conjugated cyclohexadienones. The steroid nucleus offers a wide variety of structural isomers as well as a wide selection of functional groups and sites of unsaturation.

The 1-dehydrotestosterone series has received intensive study. Irradiation of 4-methyl-1-dehydrotestosterone (XXII) has been shown (23) to give cleanly XXIII. 2,4-Dimethyl-1-dehydrotestosterone (23, 24) undergoes an identical reaction. These reactions are analogous to the santonin to lumi-santonin transformation.

Figure 1. Photochemical transformations of santonin (19, 20, 21, 22)


OH
O
O
O
hν
AcOH
XX
hν
AcOH
O
O
O
XVII
HO2C
O
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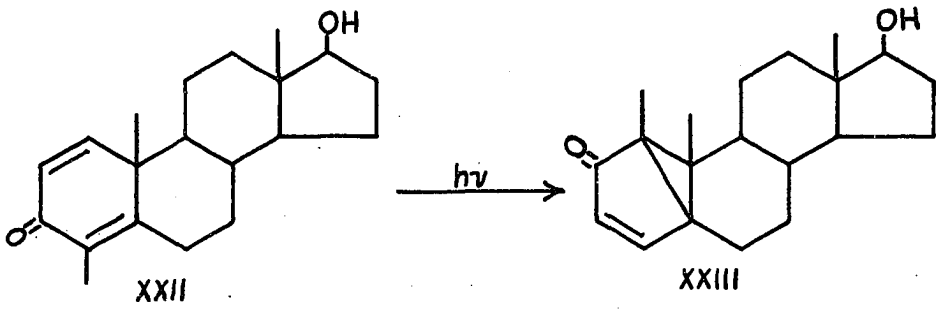
XXI



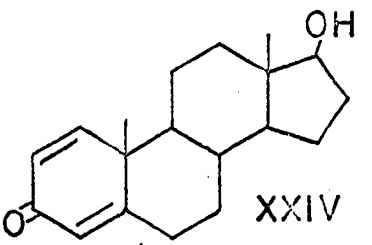
XXII XXIII

The parent compound, 1-dehydrotestosterone (XXIV), does not undergo a clean photochemical reaction as do the 4-methyl and 2,4-dimethyl derivatives. The products from the irradiation of 1-dehydrotestosterone in acetic acid (25) are shown in Figure 2, page 13. This reaction is illustrated as all of the isolated photoproducts from any of the irradiations were found in the acetic acid irradiation. The photochemistry of XXIV was found to be very sensitive to changes in solvent (26). XXV is isolated in high yield if XXIV is irradiated in dioxane using 254 mu light (19). The ketonic photoproducts were themselves irradiated to determine the origin of the phenols as well as the ketones. Table 1 shows the results of the various photo-reactions.

It is evident that this work consumed much time, patience and knowledge. A study such as this is a credit to the photochemical field as well as to organic chemistry.

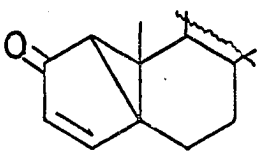
Another example of the santonin to lumi-santonin type isomerization was reported by Barton et al. (27). 3β-Acetoxylanosta-5,8-dien-7-one (XXXVII) on irradiation in

Figure 2. Photochemical transformations of 1-dehydrotestosterone in acetic acid (25)

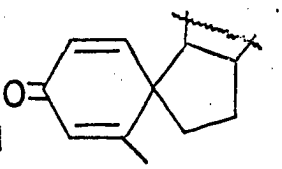


XXIV

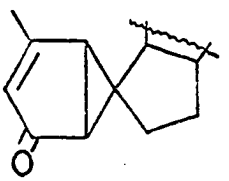
hv | AcOH



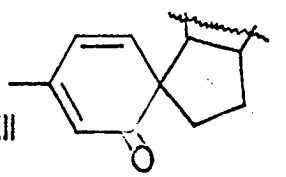
XXV



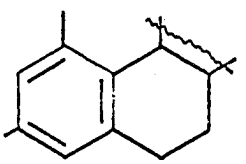
XXVI



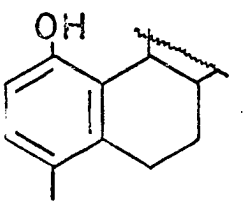
XXVII



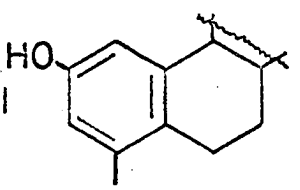
XXVIII



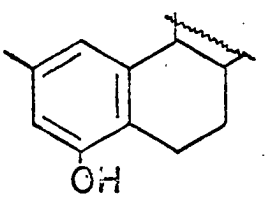
XXIX



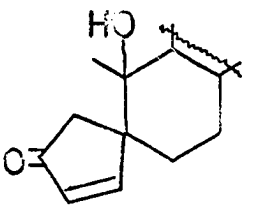
XXX



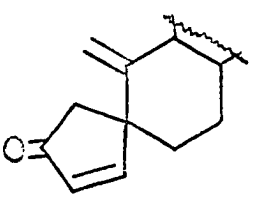
XXXI



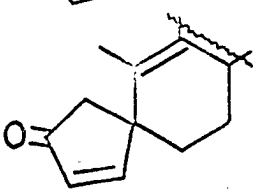
XXXII



XXXV



XXXIV



XXXIII

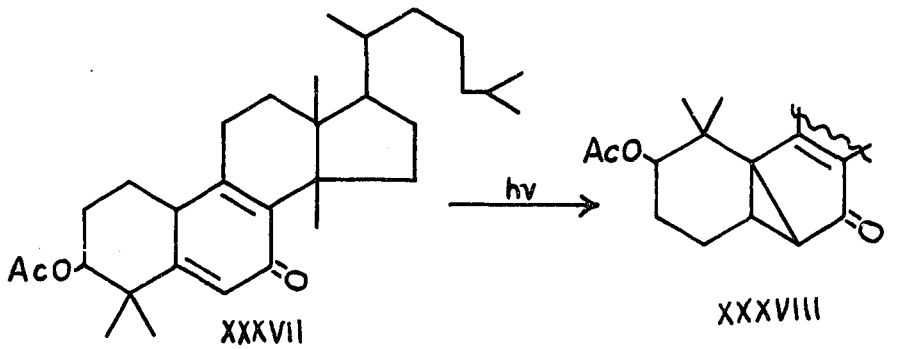
XXXVI

unknown product

Table 1. Photoproducts and their precursors from the irradiation of 1-dehydrotestosterone (25)

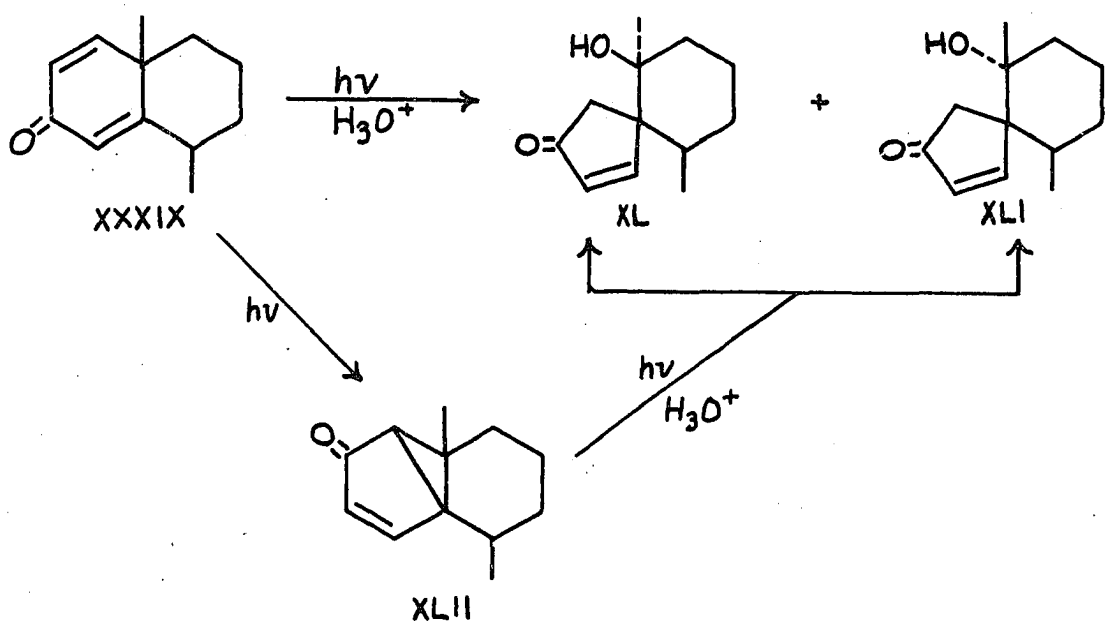
Compound irradiated	Solvent	Products
XXIV	dioxane	XXV, XXVI, XXVII, XXVIII, XXIX, XXX, XXXI, XXXII, XXXVI
XXIV	H_2O-AcOH	XXXI, XXXV
XXIV	CH_3OH	XXIX, XXXII
XXVI	dioxane	XXVII, XXVIII, XXIX
XXV	dioxane	XXVII, XXXI
XXVII	dioxane	XXVIII, XXXII, XXX

ethanol gives XXXVIII. This reaction is stereospecific since the 10-epi-isomer of XXXVII gives an isomer of XXXVIII (27).

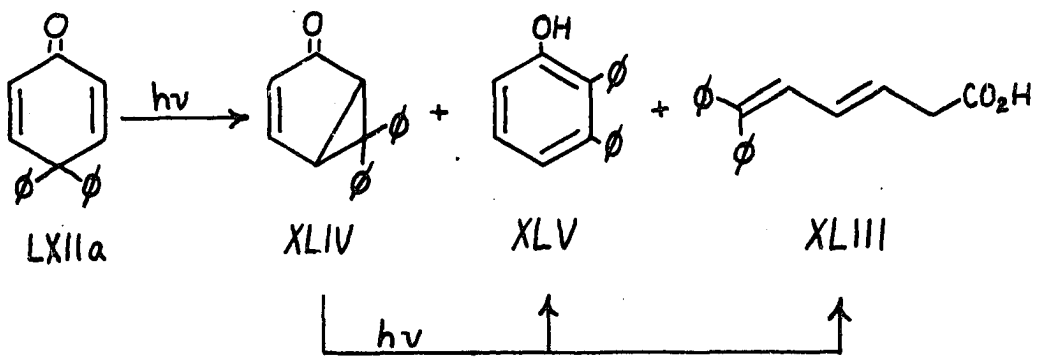


XXXVII XXXVIII

Rearrangements analogous to those found with 1-dehydrotestosterone (XXIV) have been found by Kropp and Erman in the model system XXXIX (28). Irradiation of XXXIX in aqueous, refluxing acetic acid gives XL and XLI. Irradiation of XXXIX at 20° gives XLII an analog of lumi-santonin. Further irradiation of XLII with water present gives XL and XLI.



Irradiation of 4,4-diphenylcyclohexadienone (29) (XLIIa) in dioxane gives the acid XLIII as the major product. Photoketone, XLIV, was isolated in small yield and was found to be intermediate to XLV and XLIII. This reaction sequence has been used as a vehicle for delineation of a general theory of the photochemical reactions of ketones (9).



Barton and Taylor (30) have reported that irradiation of prednisone acetate (XLVI) gives products not expected from a lumi-santonin type rearrangement; leaving the 11-keto group as the causative factor. Irradiation of XLVI in refluxing acetic acid gives XLIX which is analogous to the isophoto-santonic acid lactone rearrangement in the santonin series. The phenol L was obtained by irradiation of XLVI in dioxane. The acid-catalyzed rearrangement of XLVII to LI is of some interest in itself. For the complete reaction sequence, see Figure 3, page 18.

A completely different type of photochemical rearrangement was observed by van Tamelen et al. (31) in the irradiation of LII in aqueous acetic which gives the ring-opened compound LIII. The path of this reaction is not well understood.

The photochemical conversion of LIV to LV was reported by Staudinger and Bereza (32) in 1911. The irradiation was

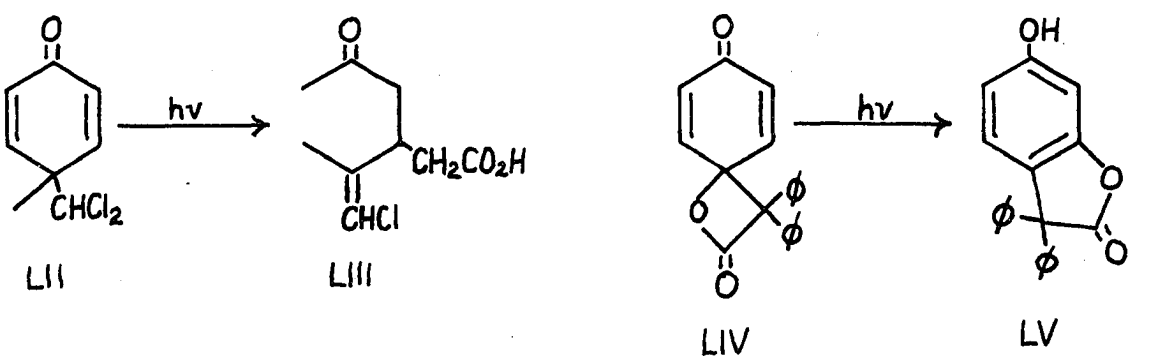
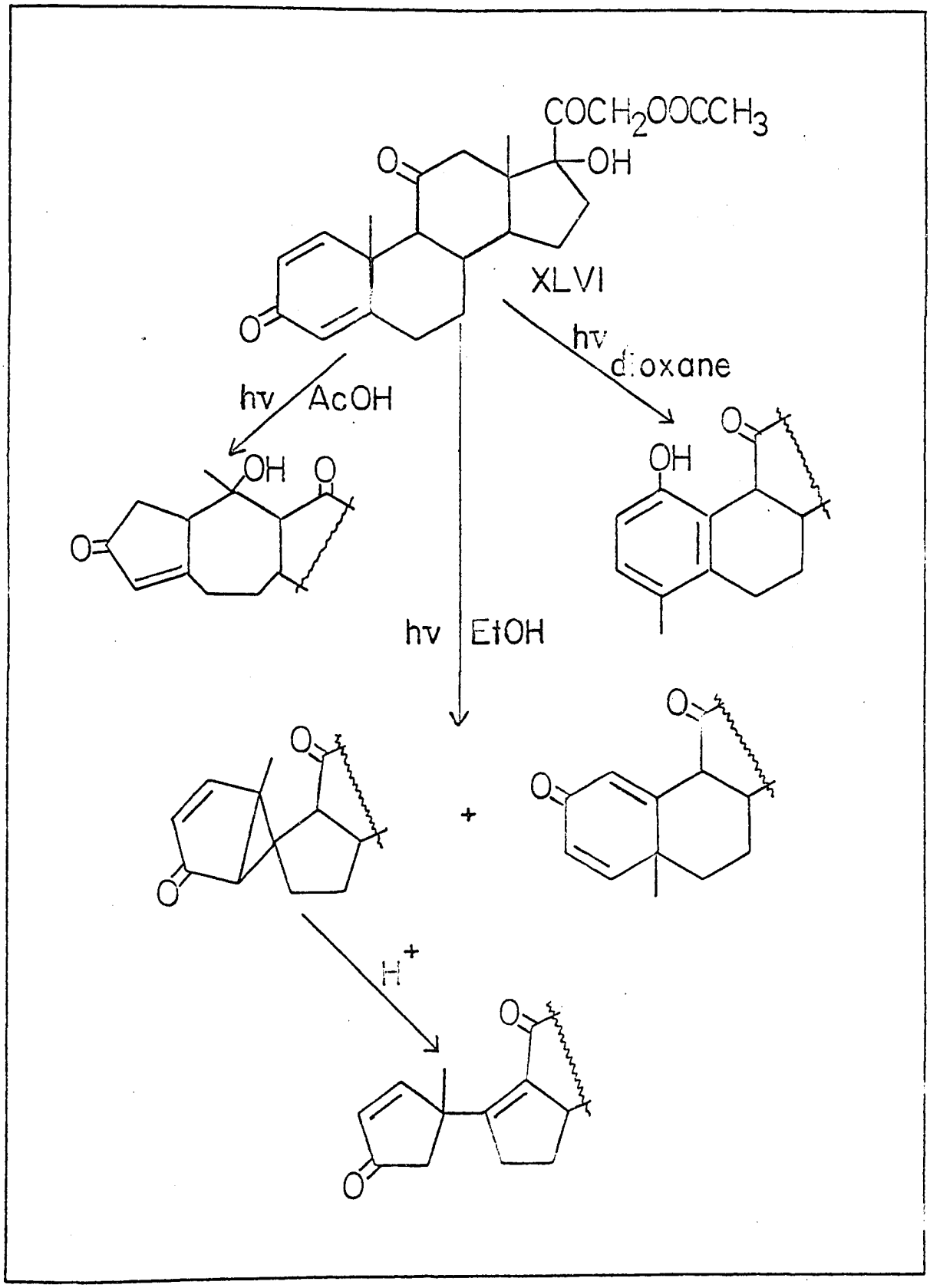
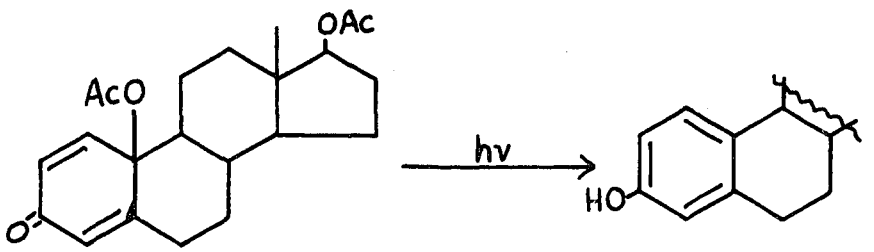


Figure 3. Photochemical conversions of prednisone acetate (30)


COCH2OOCCH3
OH
O
O
XLVI
hv dioxane
hv AcOH
OH
O
O
OH
O
hv EtOH
O
O
+
O
O
H+
O
O

carried out in benzene and has been fully confirmed by unambiguous synthesis of the product.

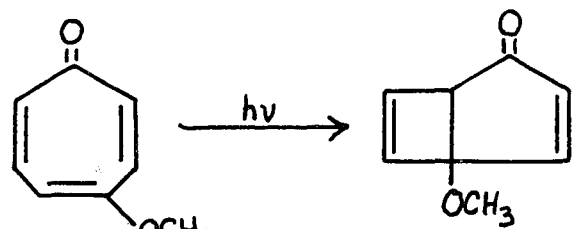
Irradiation of LVI in dioxane gives LVII (33). This reaction is analogous to the expulsion of α-substituents from α-heteroatom substituted ketones.



LVI LVII

The photochemistry of the cycloheptadienones

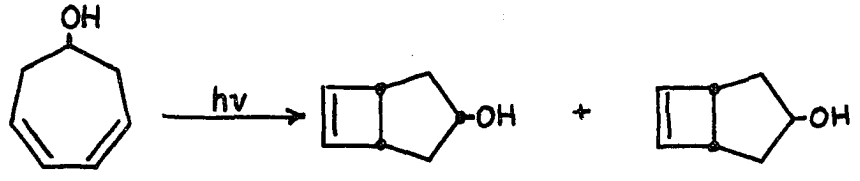
The photochemistry of the cycloheptadienones was previously (see page 3) classified under the general category "photochemical valence tautomerizations". Compounds containing a troponoid system are noted for this type of reaction. An example is the conversion of gamma-tropolone methyl ether (LVIII) to the tauotmeric product LIX (34). As no original work with these systems was accomplished in this study, the



LVIII LIX

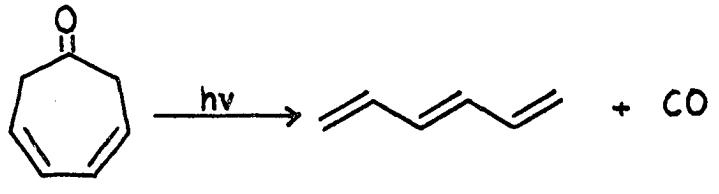
reader is referred to a previously cited review (7).

The results of this study, pertaining to the cycloheptadienones, were supplementary to those of D. J. Pasto (35). Findings from both studies have been published in complete form (36). The irradiation of 3,5-cycloheptadienol (LX) by Borden (37) is included in the complete publication (36).



LX

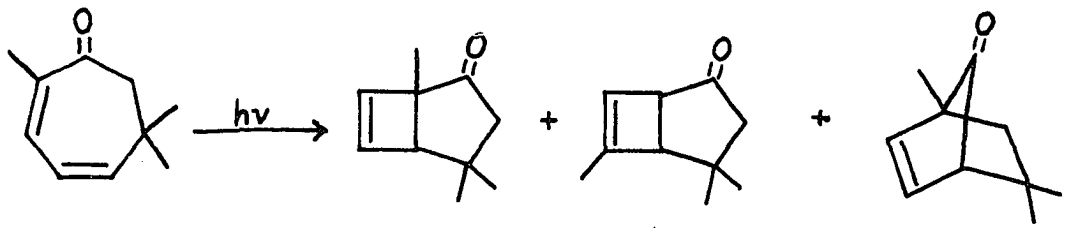
Chapman and Borden (38) have shown that 3,5-cycloheptadienone (LXI) does not give the expected ring-closed product.



LXI

2-Methyl-3,5-cycloheptadienone was shown to give 1,3,5-heptatriene upon irradiation.

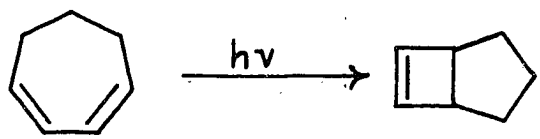
Irradiation (39, 40) of eucarvone (LXII) in aqueous acetic acid gave three products. The novel bicyclic product LXIII was not isolated when the irradiation was conducted in



LXII LXIII

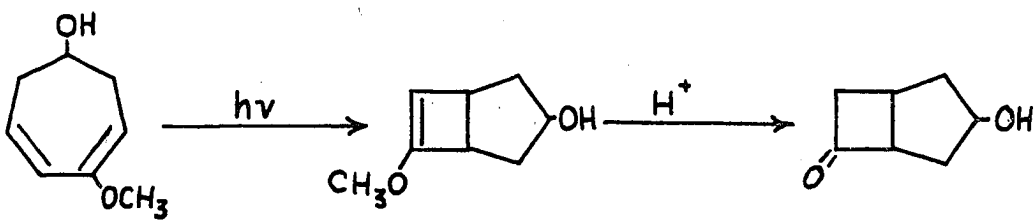
neutral solution.

Dauben and Cargill (41) irradiated 1,3-cycloheptadiene (LXIV) and obtained LXV in good yield.



LXIV LXV

Irradiation of LXVI gives the photoproduct LXVII (35, 36). The structure was easily proven by acid hydrolysis to the ketone, LXVIII, which exhibited a cyclobutanone absorption



LXVI LXVII LXVIII

maximum in the infrared.

It is evident from the above reactions that the light-

induced valence tautomerization reactions of conjugated cycloheptadienes and their derivatives offer a convenient entrance into the bicyclo[3.2.0]heptane system.

The reaction of gamma-tropolone methyl ether and tropone with Grignard and hydride reagents

This study completed an investigation initiated by D. J. Pasto (35, 42). The combined results have been published (43) in complete form.

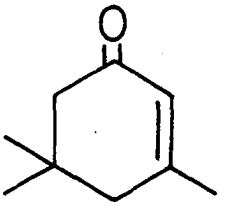
For the sake of clarity, no attempt was made to divide the results into two groups. The pertinent results of Pasto are included in the Discussion and mention is made when it is not the author's work.

RESULTS AND DISCUSSION

Structural Studies on the Isophorone Dimers

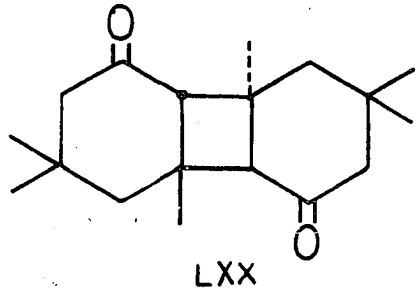
At the time this project was begun, no reports could be found in the literature elucidating the structures of the cyclohexenone dimers. The advent of nuclear magnetic resonance seemed to provide a tool with which to solve this problem if the selected system could be interpreted.

After determining which cyclohexenones were available, isophorone (LXIX) and its possible dimers appeared amenable to an n.m.r. study, combined with a minimum amount of degradative chemistry. The decision to study LXIX was based upon the observation that all protons were isolated from each other by substituent groups.

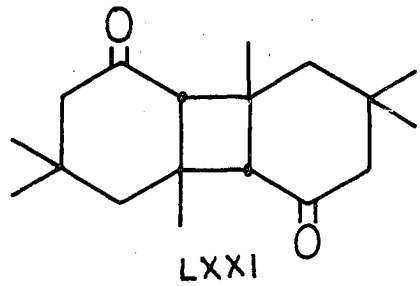


LXIX

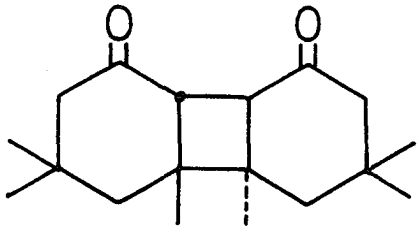
Upon irradiation, any cyclohexenone can give four possible dimeric isomers assuming cis fusion (14) of the parent rings. The four possible dimers for LXIX are LXX, LXXI, LXXII and LXXIII. It appeared that n.m.r. could provide considerable assitance in the proof-of-structure of these com-



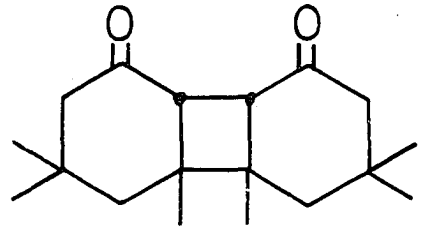
LXX



LXXI



LXXII



LXXIII

pounds.

Irradiation of LXIX produced two dimers. The compounds are designated Dimer I and Dimer II relative to their elution order from the chromatography column. The relative proportion of Dimer I, m.p. 211-3°, to Dimer II, m.p. 187.5-189°, is very dependent upon conditions of the irradiation. Irradiation in ethanol-water solution with General Electric sunlamps gave Dimer I and Dimer II in a 1:5 ratio. Irradiation of LXIX as a neat liquid with a Hanovia Type A mercury lamp gave a 2:1 ratio respectively.

The infrared spectrum, Figure 5, page 37, of Dimer I shows a 5.94 u carbonyl which is higher than expected for a cyclohexanone ring. Figure 5, page 37, shows the infrared

spectrum of Dimer II which also has a high carbonyl at 5.93 u. The bands (3.40, 6.90 and 8.10 u) associated with cyclobutane rings are not readily assignable (44).

The n.m.r. spectrum of Dimer I, Figure 7, page 41, is extremely simple and for this reason affords little information. The spectrum does indicate the high symmetry in the molecule. This spectrum, as well as the following, are discussed more completely on page 31.

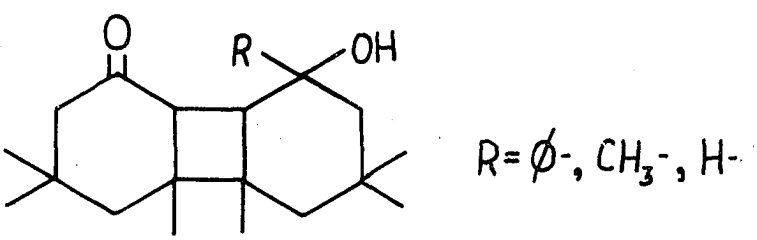
The n.m.r. spectrum of Dimer II, Figure 7, page 41, is the exact opposite of the previous spectrum. The spectrum is extremely complicated and the coupling found could not originally be explained.

The cyclobutyl protons in both spectra appear as singlets at 7.50τ for Dimer I and 7.20τ for Dimer II. The appearance of these protons as singlets is another indication of symmetry.

The structures of the crystalline photoproducts from cyclohexenones upon irradiation have been generally considered dimeric. Triebs (13) determined molecular weights but obtained poor results. The molecular weights of the isophorone dimers were determined. Dimer I, by Rast in camphor, has a molecular weight of 294 (theory - 276.4, 6% variance). Dimer II, by Rast in camphor, shows a molecular weight of 264 (4.4% variance). The molecular weight of Dimer II by vapor osmometry in benzene is 274. These values substantiate dimeric

structure for Dimer I and Dimer II.

As the previous spectral data did not provide definitive structural information, attempts were made to prepare certain derivatives that could be studied spectrally. The reactions attempted were directed toward formation of compounds in which only one carbonyl had undergone reaction. Compounds such as these would have the symmetry of one ring destroyed producing new peaks in their n.m.r. spectra while leaving the peaks of the unreacted ring nearly the same. Many of the reactions were tried on the dimer mixture as it came from the irradiation. If the reaction succeeded, it was repeated on the pure isomers. In attempts to form structures such as LXXIV, the dimers were reacted with Grignard reagents. The dimer



LXXIV

mixture was reacted with phenyl magnesium bromide but no reaction occurred. Methyl magnesium iodide also gave no reaction.

To prepare LXXIV where R equals hydrogen, the dimer mixture was reacted in high dilution with an equimolar amount of lithium aluminum hydride. After workup only diol (no carbonyl

absorption in the infrared) and unreacted dimers were isolated.

As addition reactions on the carbonyls proved unfeasible, another approach was taken. Dimer II was reacted with an excess of isopropenyl acetate using sulfuric acid as catalyst. The di-enol acetate of Dimer II (m.p. 95-7°) was isolated. The infrared spectrum, Figure 5, page 37, showed the characteristic (45) 5.71 u carbonyl and 5.97 u double bond absorption. The n.m.r. spectrum, Figure 8, page 43, is discussed on page 34.

The dimer mixture was reacted with an equimolar quantity of ethylene glycol to form a mono-ketal derivative. The crude solid isolated from the reaction was chromatographed giving unreacted dimers and a product corresponding to a mono-ketal of one of the dimers. The infrared spectrum of the mono-ketal, Figure 6, page 39, has a 5.92 carbonyl indicating a Dimer II derivative. To determine which dimer gave the mono-ketal, the pure isomers were reacted. Dimer II readily gave the same mono-ketal.

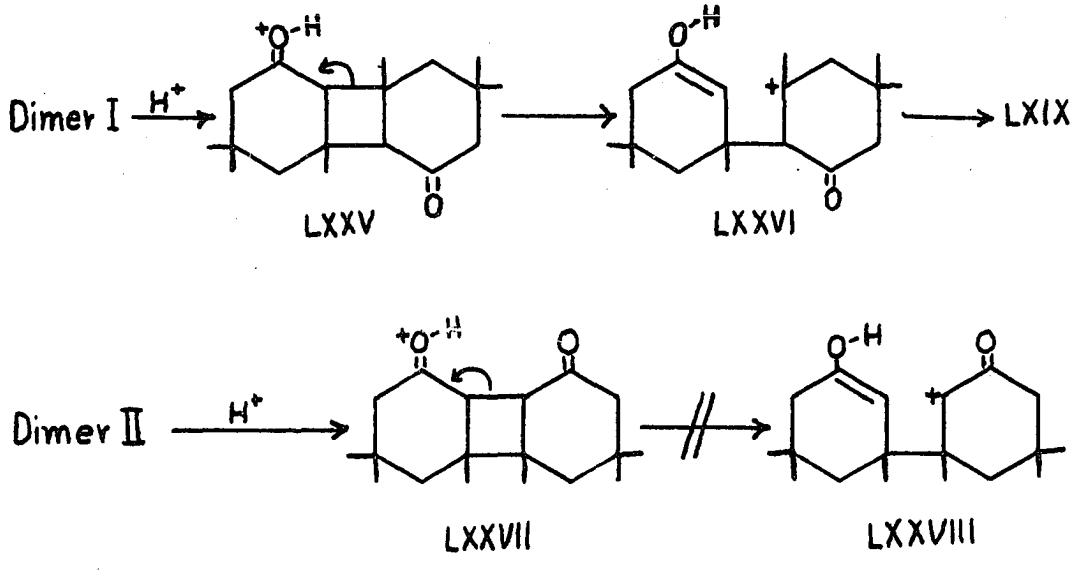
Four attempts were made to form the mono-ketal of Dimer I. The catalysts used were sulfuric acid and p-toluene sulfonic acid. The only product isolable from these reactions in greatly reduced quantities was Dimer I. These reactions indicated that Dimer I was unstable toward acids.

As stability towards strong acid might have structural

significance (46), the dimers were treated with concentrated sulfuric acid. The reactions were run simultaneously to ascertain identical conditions. Dimer II was briefly heated in concentrated sulfuric acid and allowed to remain in the acid overnight. Upon workup with water, Dimer II was isolated unchanged in 63% yield.

Dimer I, treated in an identical manner, gave no solid material on dilution with water. The aqueous solution was extracted with ether and vapor phase chromatographic analysis showed isophorone (LXIX) as the only product.

The sulfuric acid reactions brought out an important factor that must be related to a structural difference between the dimers. Mechanistically, this factor may be viewed as follows:



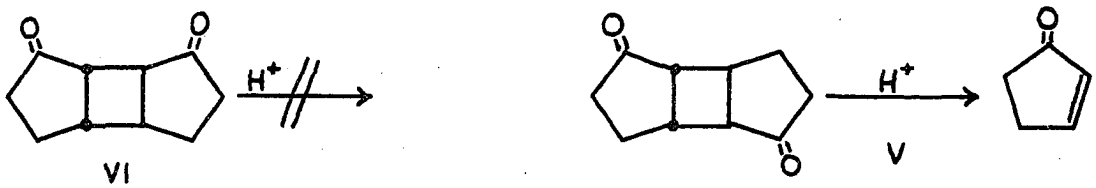
In both reactions with sulfuric acid, the first step is undoubtedly protonation of a carbonyl oxygen to LXXV and LXXVII. With Dimer I, a cyclobutane bond in LXXV cleaves allowing formation of intermediate LXXVI. The breaking of this bond leaves a relatively stable tertiary carbonium ion on one ring and the enol form of a ketone on the other. The breaking of the bridging bond in LXXVI in a retro-Michael-type reaction forms LXIX.

In the case of Dimer II, protonation can occur to LXXVII. Breakage of the cyclobutane bond causes the formation of a positive charge on a carbon adjacent to a carbonyl group. The formation of an intermediate such as LXXVIII is extremely difficult due to the partially positive character of the carbonyl carbon. Even if the LXXVII to LXXVIII conversion were possible, more difficulty would be expected in formation of the secondary carbonium ion on LXXVIII.

It is apparent that the above mechanisms neglect stereochemistry on the cyclobutane ring. In a reaction as rigorous as this, it is extremely difficult to envision how the arrangement of protons and methyl groups on the cyclobutane ring could effect this reaction. The important structural feature is the head-to-head or head-to-tail relationship of the carbonyls.

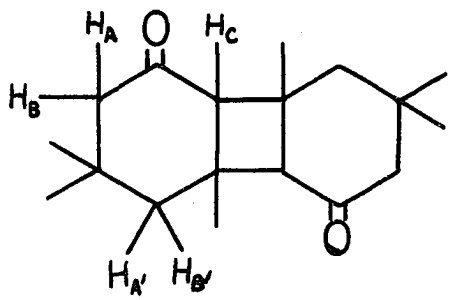
The general utility of this reaction can not be evaluated without further examples. It appears from the work by Eaton (14), who isolated V and VI (see page 5), that this

reaction may not operate for these compounds. Acid catalyzed reactions in moderate yield were run on V. No reactions were reported on VI other than the Baeyer-Williger oxidation and the Wolff-Kishner reduction. V and VI may react as shown below



when the acid reagent is concentrated sulfuric acid. In any case, the reaction must be highly dependent upon the type of carbonium ion formed.

From the previous reactions, the structure of Dimer I is shown as LXXIX. The stereochemistry on the cyclobutane ring



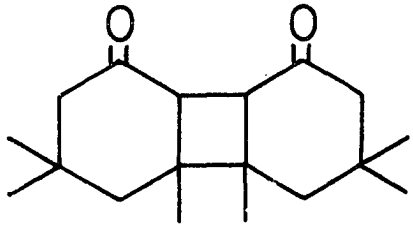
LXXIX

can not be obtained from the above data, but Eaton's work (14) on V and VI suggests that the cyclohexanone rings should be trans (see LXX, page 24). Construction of the cis-isomers (LXXI and LXXIII) with Dreiding models shows an exceptional amount of 1,3-diaxial interactions between four methyl groups.

Flipping the cyclohexanone rings to the remaining conformation causes intermeshing of these rings. The twist conformation could not be formed without immediately flipping into the boat conformation. An interesting feature of the models of all the isomers is their inability to assume a chair conformation for the cyclohexanone rings.

The n.m.r. spectrum of Dimer I, Figure 5, page 37, suggests identical conformations in both six-membered rings. The Dreiding model indicates that a twist conformation removes all 1,3-diaxial methyl interactions and causes all methylenes to become identical with their counterpart in the other ring. The only remaining conformations appear to be boat conformations which have considerable steric repulsion. In view of these arguments, the singlet at 8.17 τ is assigned to the gamma-methylene (H_B) and the singlet at 7.82 τ to the alpha-methylene (H_A). The cyclobutyl protons (H_C) are seen at 7.50 τ. The different methyl peaks are not readily assigned.

Dimer II is shown by LXXX. The previous arguments per-



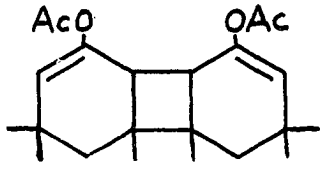
LXXX

taining to structure are also applicable in this case. The trans structure (LXXII) embodies fewer steric interactions in

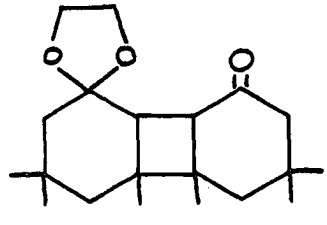
the model than does the cis (LXXIII).

The n.m.r. spectrum of Dimer II, Figure 7, page 41, is difficult to interpret. The alpha-methylenes (H_A and H_B) appear as an AB pattern centered at 7.75 τ. The gamma-methylenes (H_A' and H_B') also occur as an AB pattern centered at 8.25 τ. A segment of the spectrum is shown in Figure 4, page 34, along with pertinent data. The two high field peaks in each AB pattern are further split. Recent information (47) indicates this splitting is a result of long range coupling between 1,3-diequatorial protons. The Dreiding model of Dimer II shows no conformational arrangements that can account straightforwardly for the splitting observed. The exact structure of Dimer II remains unknown.

It was previously shown that Dimer II formed a di-enol acetate and a mono-ketal derivative. The gross structure of these compounds are shown as LXXXI and LXXXII respectively.



LXXXI

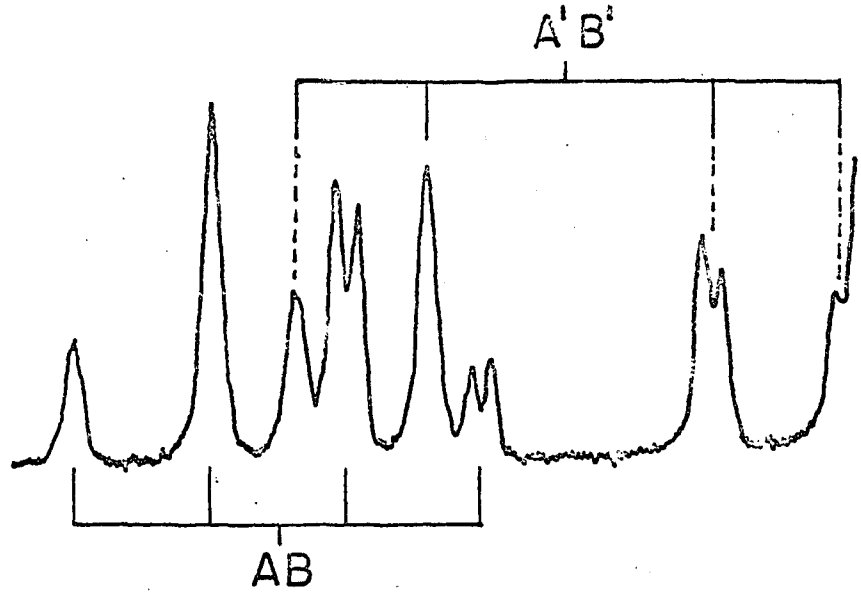


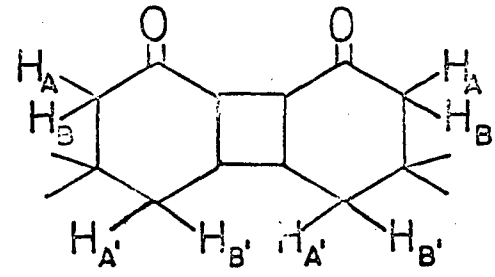
LXXXII

The n.m.r. spectra of these compounds are shown in Figure 8, page 43. The spectrum of LXXXII is more complicated than the parent compound.

The spectrum of LXXXI is interpretable. The olefinic

Figure 4. Segment of the nuclear magnetic resonance spectrum of Dimer II





LXXX

J_{AB} = 14·4 c.p.s. $J_{A'B'}$ = 15 c.p.s.

$J_{BB'}$ = 1·25 c.p.s.

ν_A = 147 c.p.s. $\nu_{A'}$ = 125·5 c.p.s.

ν_B = 123 c.p.s. $\nu_{B'}$ = 84·5 c.p.s.

protons are at 4.85 τ and the cyclobutyl protons at 7.64 τ. The acetate methyl occurs at 7.94 τ. The gamma-methylenes form an AX pattern with peaks at 8.25 and 8.61 τ. Even though assignments can be made, the spectrum affords little structural information.

It has been apparent throughout this work that the isophorone dimers are not usual organic compounds. Characteristic reactions failed to work. The spectra showed anomalies for which there are no analogs. The study must be considered a failure from the standpoint of original objective. However, the data collected may be of use in further studies.

In the process of this study, a single dimer of 3-methylcyclohexenone was isolated. Thte infrared spectrum is shown in Figure 6, page 39. The infrared spectrum (5.93 u) as well as irradiation conditions indicate the head-to-tail isomer. No work was accomplished on this compound.

The Photochemistry of Testosterone Acetate

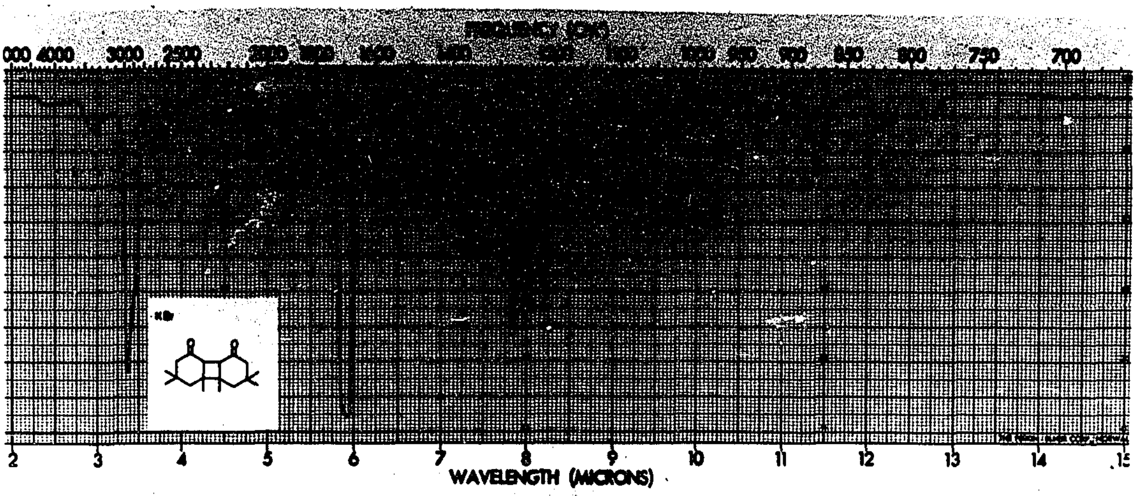
Prior to this study, the photochemical rearrangements of cyclic, unsaturated ketones were limited mainly to the cross-conjugated dienones (see Historical). With the advent of the polar photochemical mechanism, attention was focused upon simple, cyclic α,β-unsaturated ketones, as they too should rearrange according to this mechanism. In order to test this hypothesis, a system such as the following was

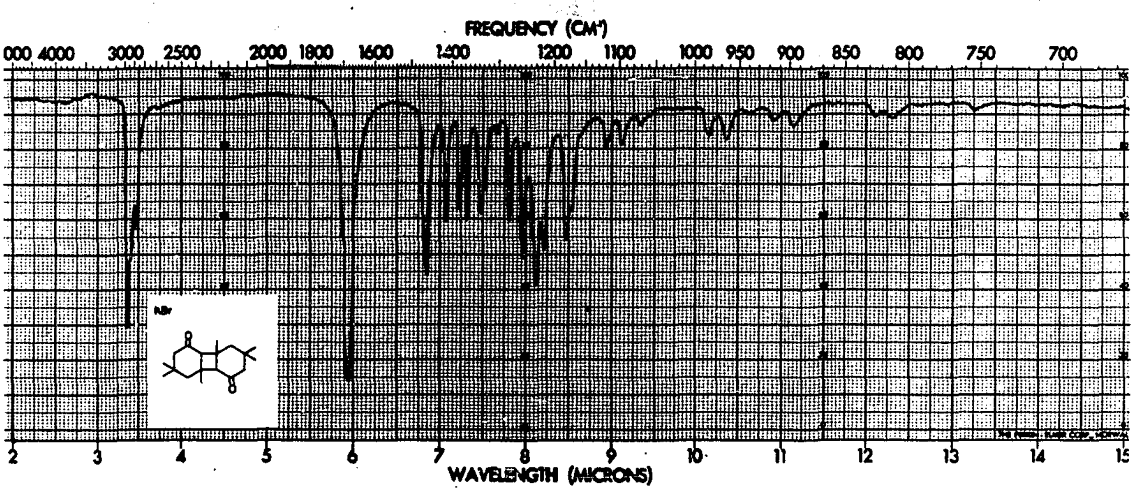
Figure 5. Infrared spectra

Top - Dimer II

Middle - Dimer I

Bottom - Dimer II di-enol acetate


000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
KBr
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
KBr
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

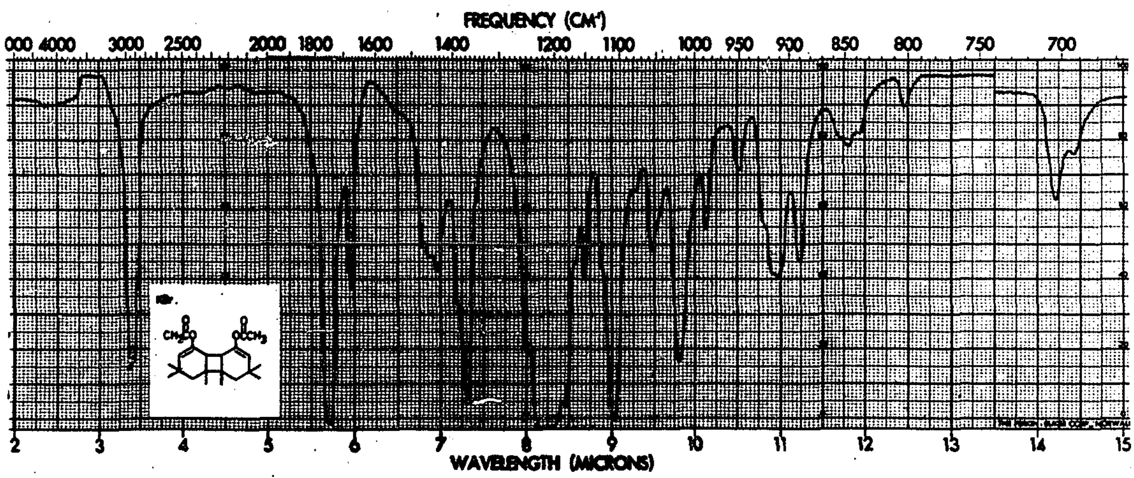
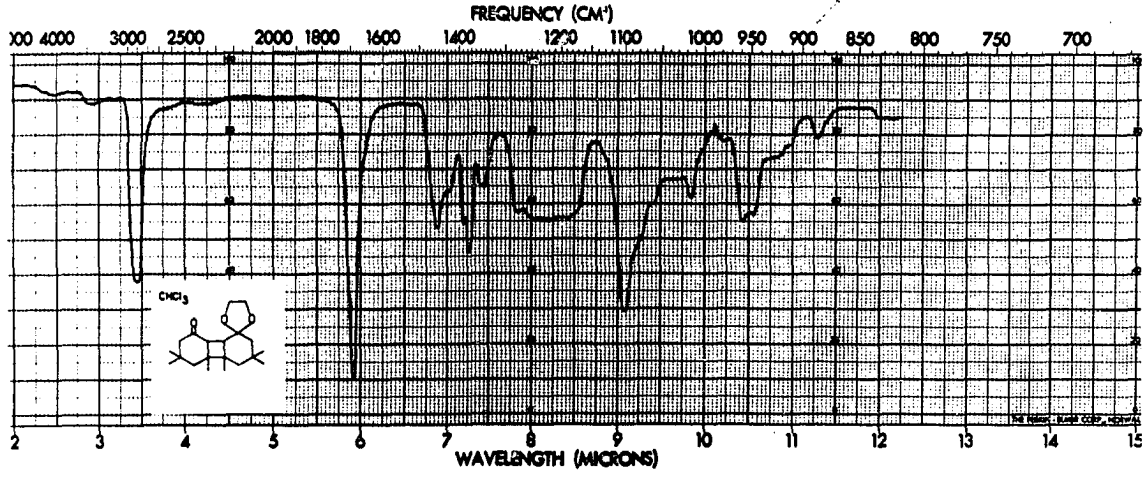

FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
KBr
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Figure 6. Infrared spectra

Top - Dimer II mono-ketal

Bottom - 3-Methylcyclohexenone dimer


FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

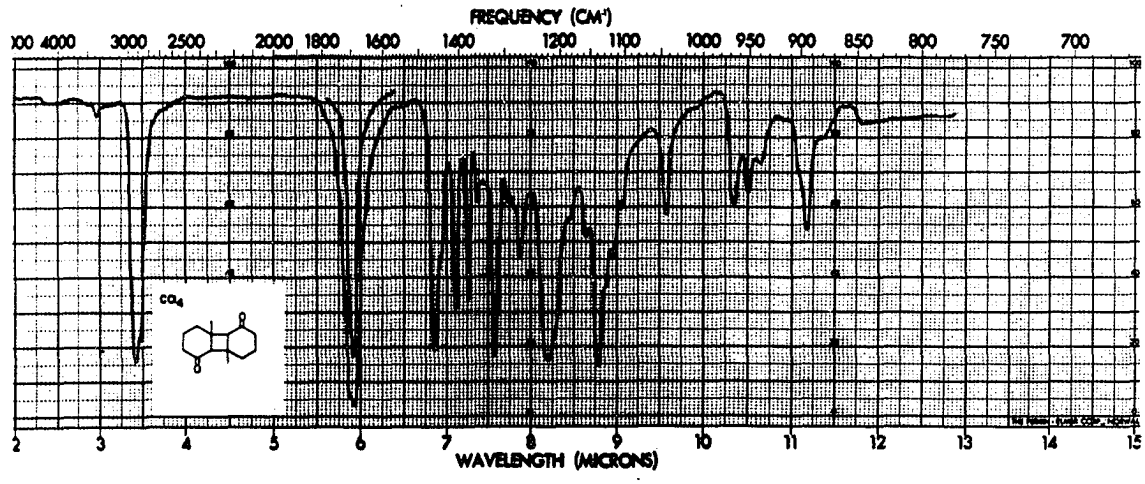
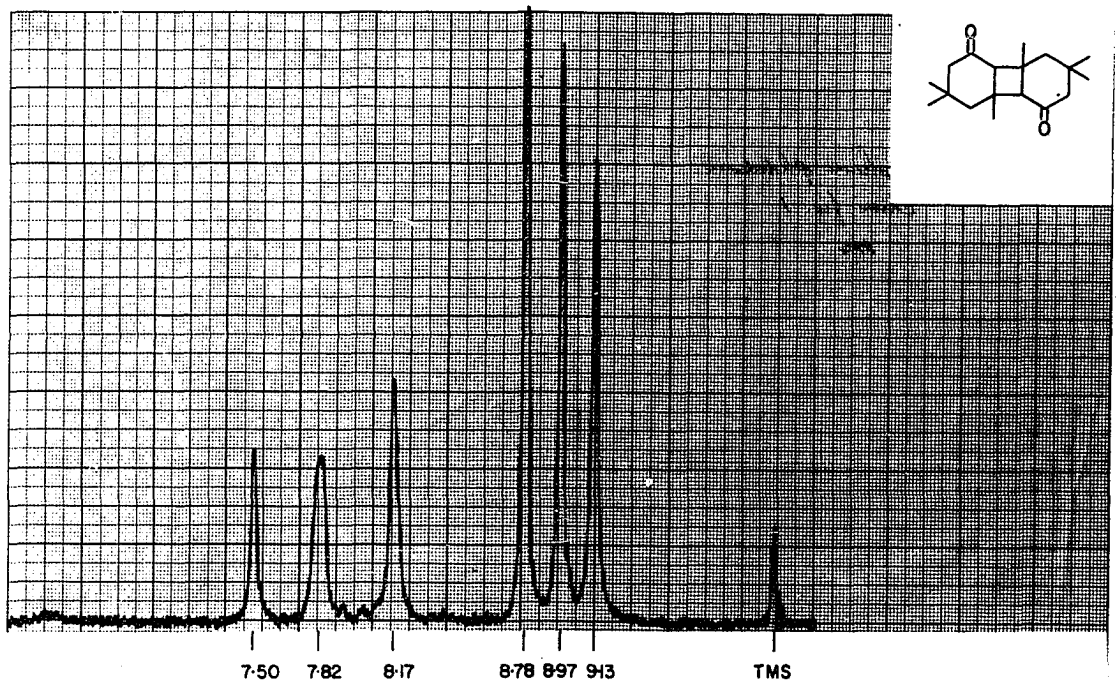

FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Figure 7. Nuclear magnetic resonance spectra

Top - Dimer I

Bottom - Dimer II


7·50
7·82
8·17
8·78
8·97
9·13
TMS
TAU

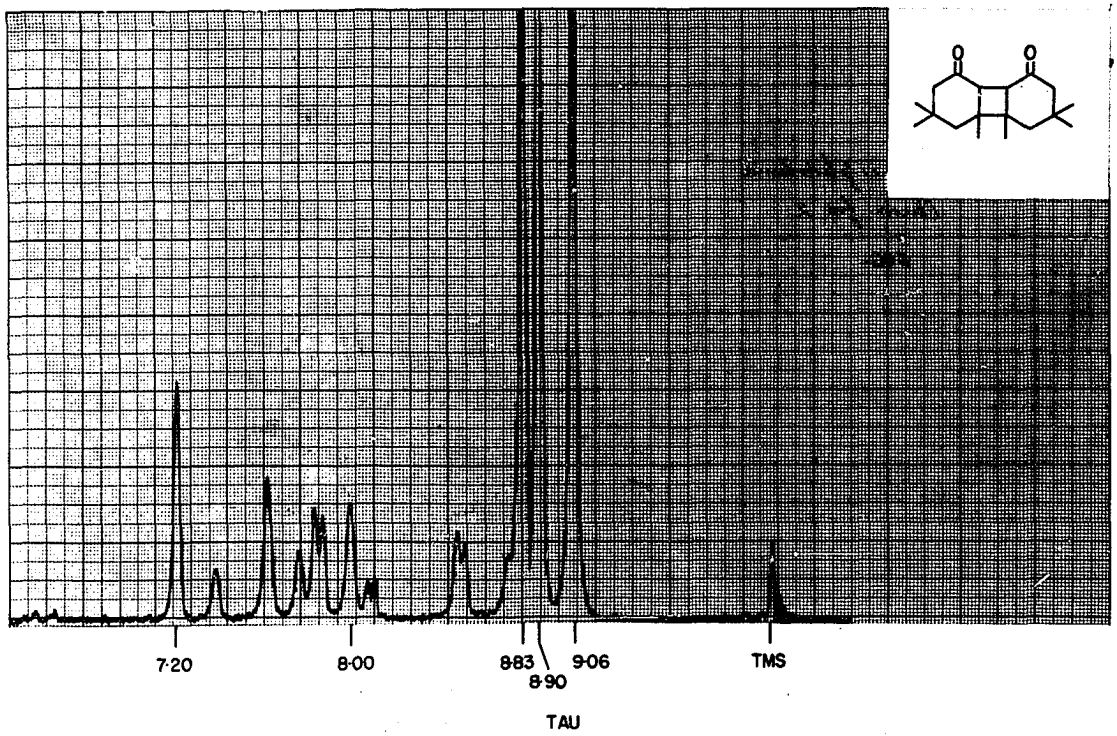
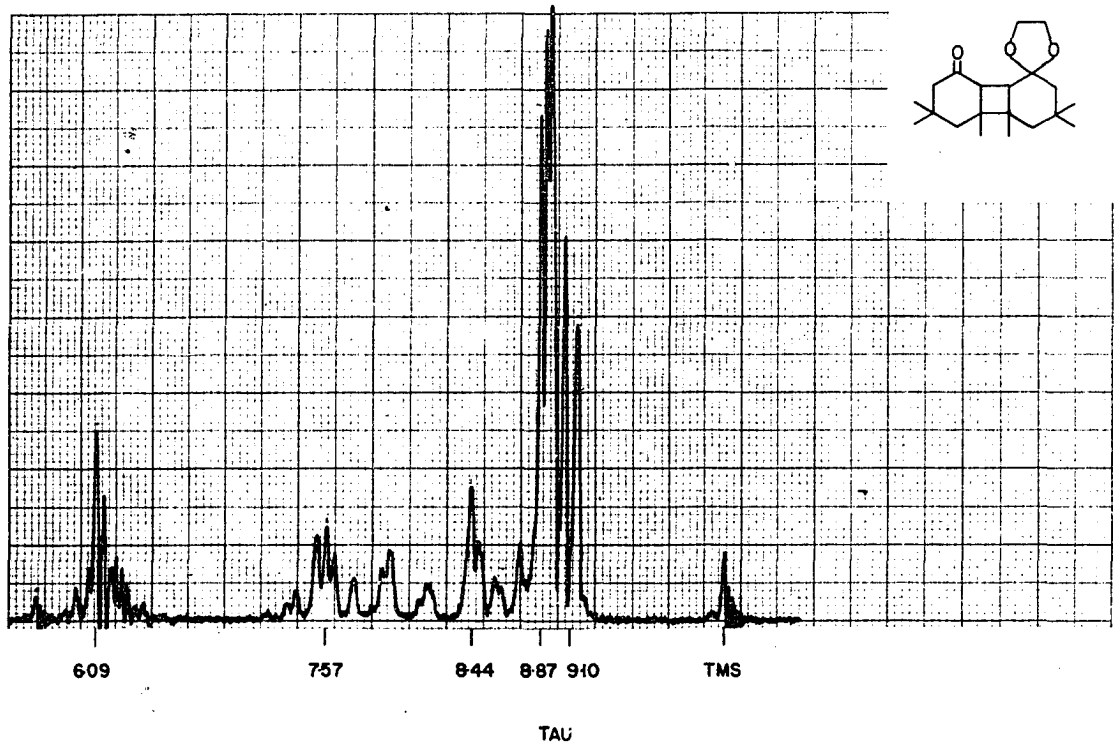
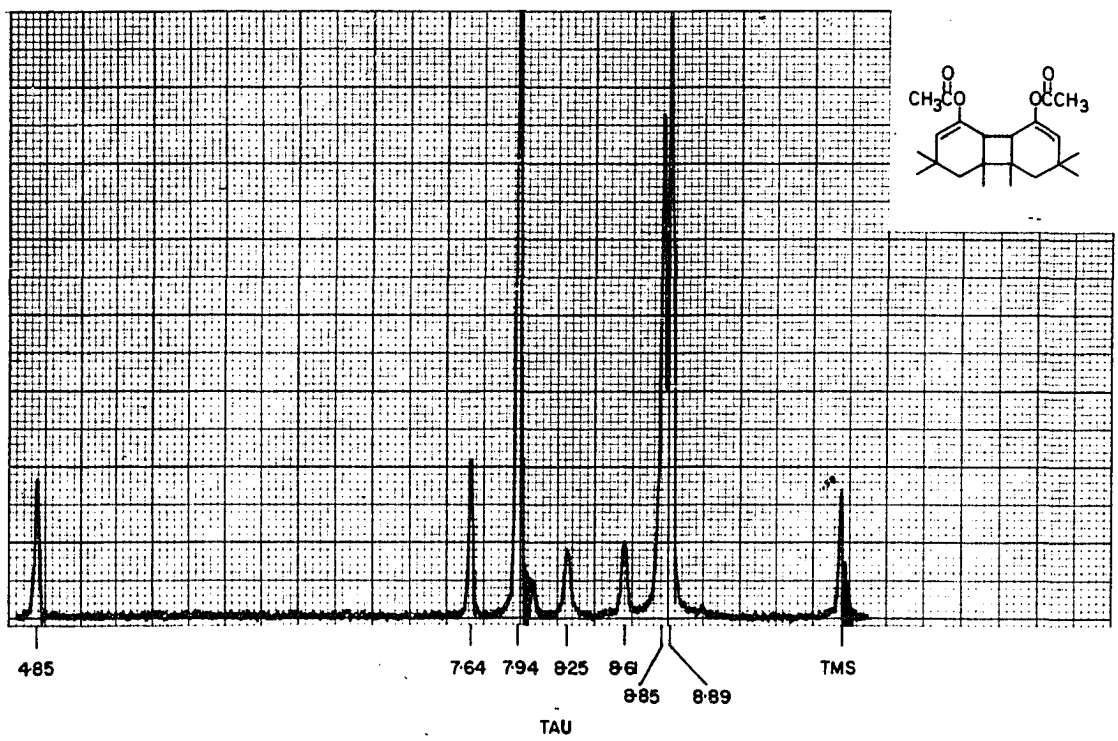

7·20
8·00
8·83
8·90
9·06
TMS
TAU

Figure 8. Nuclear magnetic resonance spectra

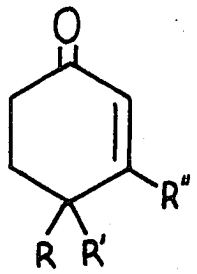
Top - Dimer II mono-ketal

Bottom - Dimer II di-enol acetate

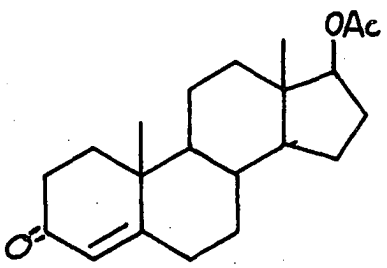

6·09
7·57
8·44
8·87
9·10
TMS
TAU


CH3CO
OCCH3
4·85
7·64
7·94
8·25
8·61
8·85
8·89
TMS
TAU

sought:



Over the years the steroids have supplied organic chemists with many ready-made systems. The partial structure above was available in several steroid systems. The steroid selected was testosterone acetate (LXXXIII), a member of the androstane series. The infrared spectrum, Figure 11, page 63,



LXXXIII

and the n.m.r. spectrum, Figure 17, page 75, of LXXXIII are included for comparative purposes.

The chemistry of steroids is quite different as compared to usual organic compounds. A steroid is considered to be a large hydrocarbon whose physical properties are tremendously effected by substituent groups. The neophyte is often amazed at the physical differences displayed by a steroidal alcohol and its corresponding acetate. A guiding principle, when

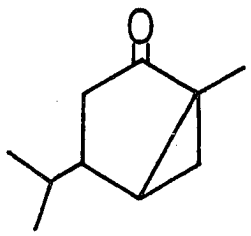
working with a steroid, is that it "wants" to be a solid. Its purity decides whether or not solidification occurs. The best criterium of purity of a steroid is the melting point. Melting behavior assumes an important role in characterizing these compounds.

Vapor phase chromatography has introduced a substantial change in steroid chemistry. The work reported in this section could not have been accomplished without the benefit of this technique. One can not assume, however, that the peak on a vapor phase chromatography trace is a sufficient criterion of purity.

The solvent in all of the irradiations of LXXXIII was tert-butyl alcohol. Previous work (see the following section) indicated that this alcohol was an excellent solvent for rearrangement reactions as it is a poor nucleophile. The irradiations were conducted in Pyrex, effectively excluding light below 300 mu.

Irradiation of LXXXIII produced two photoproducts which were readily separated by column chromatography on Woelm neutral alumina. For convenience, the photoproducts were designated photo-testosterone acetate (LXXXIV), m.p. 167-9°, and lumi-testosterone acetate (LXXXV), m.p. 109-109.5°. These products were isolated in 32 and 25% yield, respectively; unchanged testosterone acetate (LXXXIII) was recovered in 43% yield.

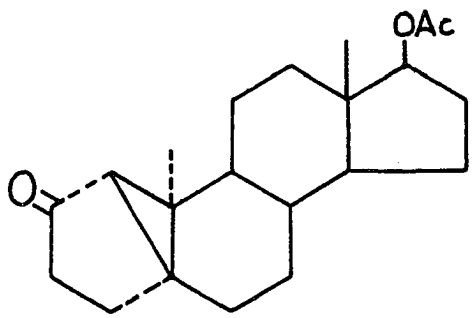
The infrared spectrum, Figure 11, page 63, of photo-testosterone acetate (LXXXIV) shows the presence of the 17-acetate (5.77 and 8.19 u) and a 5.84 carbonyl group. The latter can be ascribed to either a cyclohexanone or a dihydro-umbellulone (48) (LXXXVI) structure [5.81 u; λ_{max}^{alc} 210 mu (2,470)]. The ultraviolet spectrum of LXXXIV shows



LXXXVI

$\lambda_{max}^{95\%\ ethanol}$ 209 mu (5,200). The specific rotation of LXXXIV is $[\alpha]_d^{31} = 32.2^\circ$ (c. = 0.906, $CHCl_3$).

The physical constants indicate that photo-testosterone acetate is identical to "dihydro-ketone-A_3" isolated (26) by acetylation and hydrogenation of XXV (see page 13). The physical data recorded for dihydro-ketone-A_3 are: m.p. 164-5°;



LXXXIV

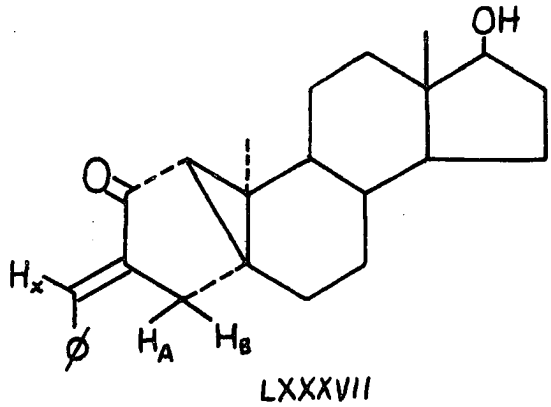
ν_{max} = 5.78, 5.84, 7.97 (KBr); λ_{max} = 212 mu (6,030); $[\alpha]_D$ = 37° and peaks in the n.m.r. at 9.22, 8.82, 7.97 and 5.40 τ. The n.m.r. spectrum of LXXXIV, Figure 17, page 75, agrees well with the reported spectrum. The spectrum shows the 18 and 19-methyls at 9.22 and 8.83 τ respectively, while the 17-acetate methyl appears at 7.97 τ.

The sharp singlet at 8.29 τ is difficult to assign as it sits on the proton mass generated by the remainder of the steroid. Kwie et al. (15) found a similar peak at 8.50 τ in the n.m.r. spectrum of lumi-cholestenone (X) and assigned it to the cyclopropyl methine. The peak was not assigned by Dutler et al. (26), in the spectrum of XXV, although it was present. The peak does occur in all the compounds of this type prepared in this study and is tenatively assigned to the cyclopropyl methine proton on carbon one.

An authentic sample of dihydro-ketone-A_3, prepared by the method of Dutler et al. (26), was obtained from Dr. P. Kropp (c.f., Kropp and Erman (28)). The sample had a melting point of 168-9°. The mixed melting point of LXXXIV and the authentic sample showed no depression. The infrared spectra of LXXXIV and the authentic sample (Figure 11, page 63) were superimposable.

Further proof of structure was obtained from the reaction of LXXXIV with benzaldehyde and methanolic base giving the colorless, mono-benzal derivative LXXXVII (m.p. 240-241.5°;

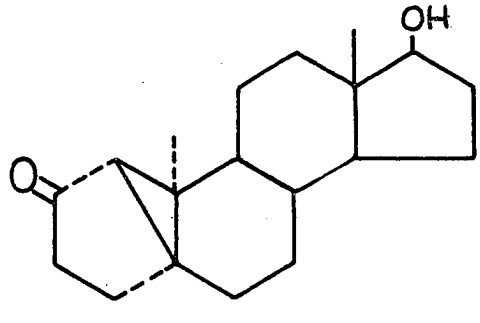
2.78, 2.90, 5.92 and 6.16 u, Figure 12, page 65; $\lambda_{max}^{95\%\ ethanol}$ 299 mu (2,710), 229 mu (960), 223 mu (951)). The n.m.r. spectrum, Figure 18, page 77, is as expected for LXXXVII.



LXXXVII

The spectrum shows an ABX pattern with the symmetrical AB portion centered at 7.02 τ (J_{AB} = 18 c.p.s., J_{AX} and J_{BX} are approximately 1 c.p.s.). The X portion is buried under the aromatic proton signals of the benzylidene group (2.22 to 2.82 τ). By deuteration, the sharp singlet at 8.10 τ is assigned to the 17-hydroxy proton. The 18 and 19-methyls appear at 9.25 and 8.94 τ respectively.

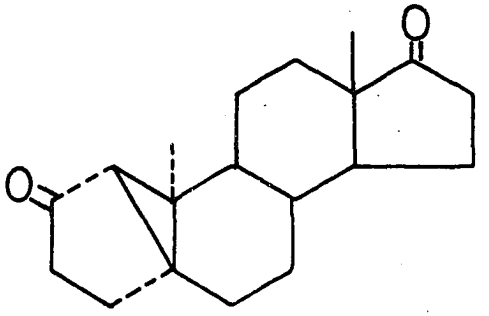
Saponification of LXXXIV in methanolic base gave phototestosterone (LXXXVIII; m.p. 204-5°; 2.77, 2.90, 5.88 u,



LXXXVIII

Figure 12, page 65; $\lambda_{max}^{95\%\ ethanol}$ 208.8 mu (6,470)). The n.m.r. spectrum of LXXXVIII, Figure 18, page 77, shows an 8.36 τ peak assignable to the cyclopropyl methine proton. The 17-hydroxy proton is buried at 7.97 τ as determined by deuteration. The 18 and 19-methyls appear at 9.28 and 8.84 τ respectively. The spectrum of this compound is extremely similar to that of LXXXIV.

Oxidation of LXXXVIII with chromic oxide in pyridine gave the diketone LXXXIX (m.p. 153-4°; 5.78, 5.88 u, Figure 12, page 65; $\lambda_{max}^{95\%\ ethanol}$ 208.7 mu (6,720) and 283.5 mu (111)). The n.m.r. spectrum, Figure 21, page 83, also shows the sharp singlet at 8.38 τ, indicating the cyclopropyl methine proton.

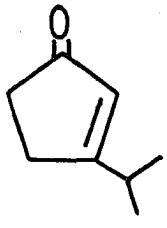


LXXXIX

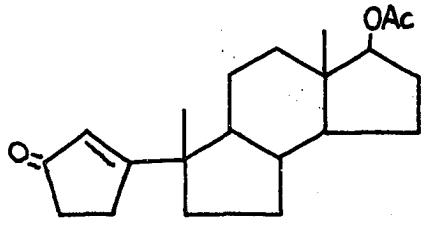
The infrared spectrum, Figure 13, page 67, of the second photoproduct, lumi-testosterone acetate (LXXXV), is somewhat anomalous in that it shows three carbonyl bands at 5.75, 5.84 and 5.94 u. Yates and Williams (49) report infrared bands at 5.82 and 5.90 u for 3-phenyl-2-cyclopentenone. A strong double bond absorption is present at 6.25 u as well as the

ester band (45) at 8.07 u. Strong absorption at 232 mu (18,600) in the ultraviolet combined with the infrared data, indicated an α,β-unsaturated ketone.

The n.m.r. spectrum of LXXXV, Figure 19, page 79, provided the first definitive evidence for the gross structure. The highly split doublet centered at 7.61 τ is extremely similar to the A_2B_2X pattern (centered at 7.56 τ) found in the n.m.r. spectrum of 3-isopropylcyclopentenone (17) (LXXXIXa). The olefinic proton at 4.20 τ is allylically split into an



LXXXIXa



LXXXV

unsymmetric triplet and is identical to that found at 4.20 τ in the spectrum of LXXXIXa. The remainder of the spectrum shows the 18 and 19-methyl groups at 9.24 and 8.88 τ respectively. The 17-acetate methyl appears at 8.05 τ and the 17-methine proton at 5.45 τ. Consideration of the above data and mechanistic argument suggested LXXXV for lumi-testosterone

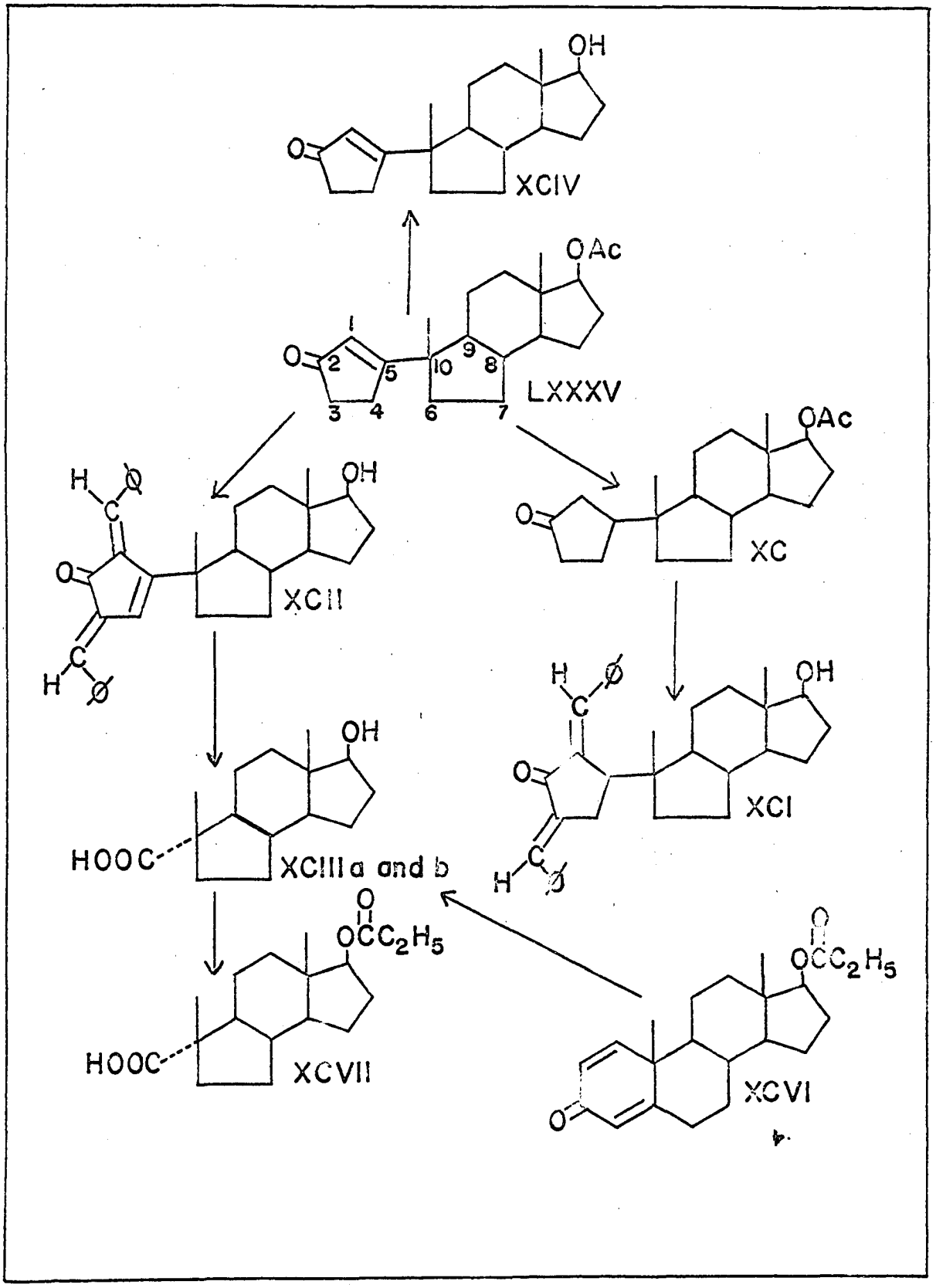
acetate.

Structure LXXXV was established in the following manner (Figure 9, page 53). Catalytic hydrogenation of LXXXV (one equivalent absorbed) gave dihydro-lumi-testosterone acetate (XC, m.p. 84-6°). The infrared spectrum of XC, Figure 14, page 69, shows a 5.74 u carbonyl group. The ester band at 8.08 u indicates that the cyclopentanone and the acetate carbonyl absorptions are coincident. The n.m.r. spectrum of XC, Figure 21, page 83, shows the 19-methyl at 9.25 τ. The 18-methyl appears as two peaks at 9.10 and 9.13 τ. The hydrogenation thus appears to have given unequal amounts of the two possible isomers. The 17-acetate methyl appears at 8.05 τ and the 17-methine proton at 5.45 τ.

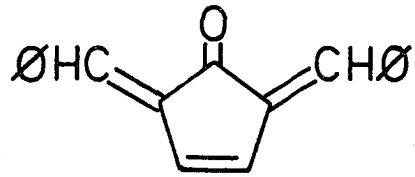
The reaction of dihydro-lumi-testosterone acetate (XC) with excess benzaldehyde in methanolic base gave XCI (m.p. 190-2°; 2.78, 2.90, 5.92, 6.15, 6.20 (shoulder) and 6.35 u, Figure 14, page 69; $\lambda_{max}^{95\%\ ethanol}$ 231 mu (16,800) and 348 mu (32,100)). The spectral data agree very well for a dibenzylidenecyclopentanone structure. Dibenzylidenecyclopentanone, itself, shows peaks in the infrared at 5.95, 6.17, 6.22 (shoulder) and 6.37 u, while absorption in the ultraviolet (50) occurs at $\lambda_{max}^{ethanol}$ 344 mu (27,500). The formation of the dibenzal derivative shows the cyclopentanone moiety of LXXXV is attached through a β-position.

In attempts to prepare the mono-benzal derivative of

Figure 9. Reactions of lumi-testosterone acetate (LXXXV)


OH
O
XCIV
OAc
1
O
2
5
10
9
8
3
4
6
7
LXXXV
OAc
XC
H
Ø
C
O
OH
XCII
XCI
HOOC
XCIII a and b
O
OC2H5
XCVII
XCVI

LXXXV, only the dibenzal derivative XCII (m.p. 186-187.5°; 2.75, 2.88, 5.87, 6.17 and 6.24 u, Figure 13, page 67; $\lambda_{max}^{95\% \text{ ethanol}}$ 317 mu (31,300) and 225 mu (shoulder, 15,000) was isolated. The spectral data indicate the presence of a 2,5-dibenzylidene-3-cyclopentenone moiety (XCV) in XCII.



XCV

2,5-Dibenzylidene-3-cyclopentenone (51) shows $\lambda_{max}^{ethanol}$ 316 mu (38,900) and 232-4 mu (11,700) in the ultraviolet and bands at 5.89, 6.18 and 6.25 u (shoulder) in the infrared. The n.m.r. spectrum of XCII, Figure 20, page 81, shows the 18 and 19-methyls at 9.20 and 8.68 τ respectively. The 17-hydroxyl proton by deuteration occurs at 8.49 τ and the 17-methine proton occurs at 6.30 τ. The aromatic region (2.02 to 3.01 τ) is unassignable but the proton integration shows 13 protons. The integration furnishes further evidence for mono-substitution on a β-position of the cyclopentenone moiety of LXXV.

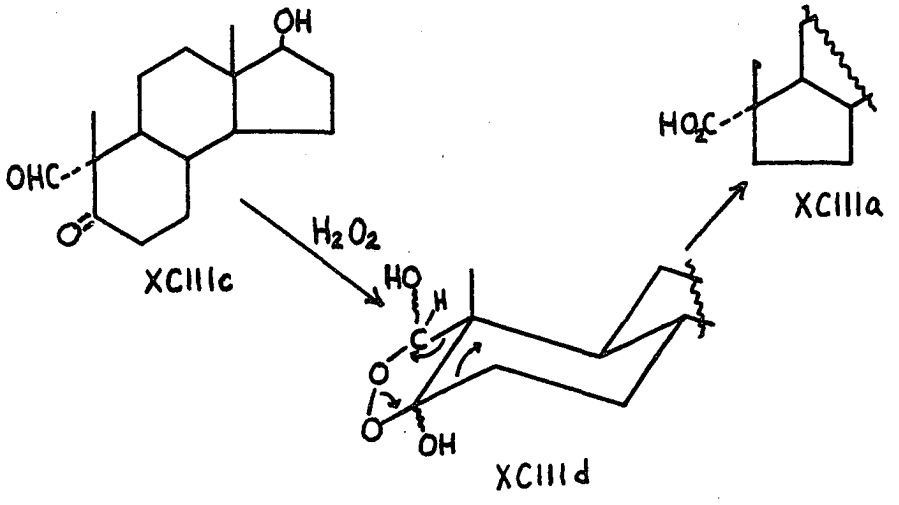
The previous reactions and the spectral evidence cited, establish the A-ring structure of lumi-testosterone acetate (LXXXV). The reactions to this point prove nothing about the remainder of the molecule (especially ring B) and the stereochemistry around carbon six.

Recently, Caspi et al. (52) reported the isolation of XCIIIa from the ozonolysis of 1-dehydrotestosterone propionate (XCVI, Figure 9, page 53).

If the cyclopentenone ring of LXXXV could be removed leaving the 5-carbon a carboxyl group, the conversion would provide XCIIIb or the 6-epimer. In either circumstance, the structure and stereochemistry of LXXXV would be known. The conversion was accomplished by degradation of XCII. XCII was first acetylated to prevent oxidation of the 17-hydroxyl group. Crude XCII acetate in ethyl acetate was ozonized with a large excess of ozone. Oxidation of the ozonide with 30% hydrogen peroxide, basic workup and chromatography gave benzoic acid and XCIIIb in small yield. The melting point finally obtained for XCIIIb was 189.5-191°. The reported melting point of XCIIIa was 189-190° (52). An infrared spectrum of XCIIIa was obtained from Dr. Caspi. A comparison of the spectra of XCIIIa and XCIIIb is shown in Figure 15, page 71. The spectra are identical in every respect.

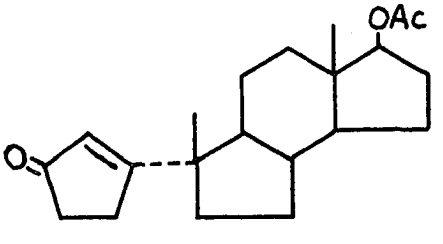
The n.m.r. spectrum of XCIIIb, Figure 20, page 81, shows peaks at 9.25, 8.85, 6.34 and 3.82 τ. Peaks were reported (51) in the n.m.r. of XCIIIa at 9.28, 8.88 and 6.34 τ.

The stereochemistry of XCIIa was not rigorously determined by Caspi et al. (52). Formation of XCIIIa from XCIIIc is entirely reasonable (53). The collapse of XCIIId as



indicated allows the methyl group to remain beta as shown.

As the melting point of XCIIIb differed slightly from the reported value, XCVII was prepared by the reaction of XCIIIb with propionic anhydride in pyridine. After purification, the melting point of XCVII was 151-2° (literature (52) m.p. 151-2°). The infrared spectrum of XCVII is shown in Figure 13, page 67. The infrared spectrum of XCVII obtained from Dr. Caspi is shown in Figure 16, page 73. The infrareds are identical. The structure of lumi-testosterone acetate thus must be LXXXV.

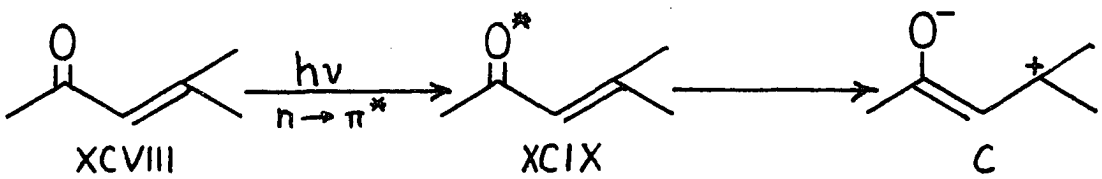


LXXXV

The remaining reaction performed in this series (see Figure 9, page 53) was the saponification of LXXXV to lumi-testosterone (XCIV, m.p. 148.5-150°; 2.78, 2.94, 5.88, 5.97 and 6.27 u, Figure 14, page 69; $\lambda_{max}^{95\%\ ethanol}$ 232.2 mu (18,900) and 297.7 mu (87)). The n.m.r. spectrum is shown in Figure 19, page 79. The sharp singlet at 7.90 τ is the 17-hydroxyl proton.

The rearrangement of testosterone acetate (LXXXIII) to photo-testosterone acetate (LXXXIV) is analogous to the photochemical rearrangement of santonin (XVII) to lumi-santonin (XVIII), Figure 1, page 10. The difference lies in the absence of the double bond at the 1-position in testosterone acetate. The observation that this bond is unnecessary for rearrangement lends further credence to the polar mechanism (7, 9) in photochemical reactions.

Previous evidence (9, 53) indicates the original excitation of unsaturated ketones occurs through an $n \rightarrow \pi^*$ transition (XCVIII ⟶ XCIX). This assumes the use of Pyrex or filter



solutions cutting off all light below 300 mu. As the irradiations of testosterone acetate were conducted in Pyrex, the excitation must have been of this type.

The electronic transitions (9) necessary to proceed from the singlet state (XCIX) to the polar intermediate (C, perhaps a triplet state) are at present obscure. As it is readily evident that the polar state C is the important intermediate in these rearrangements, a discussion of the electronic transitions necessary would only be speculation until more evidence is available.

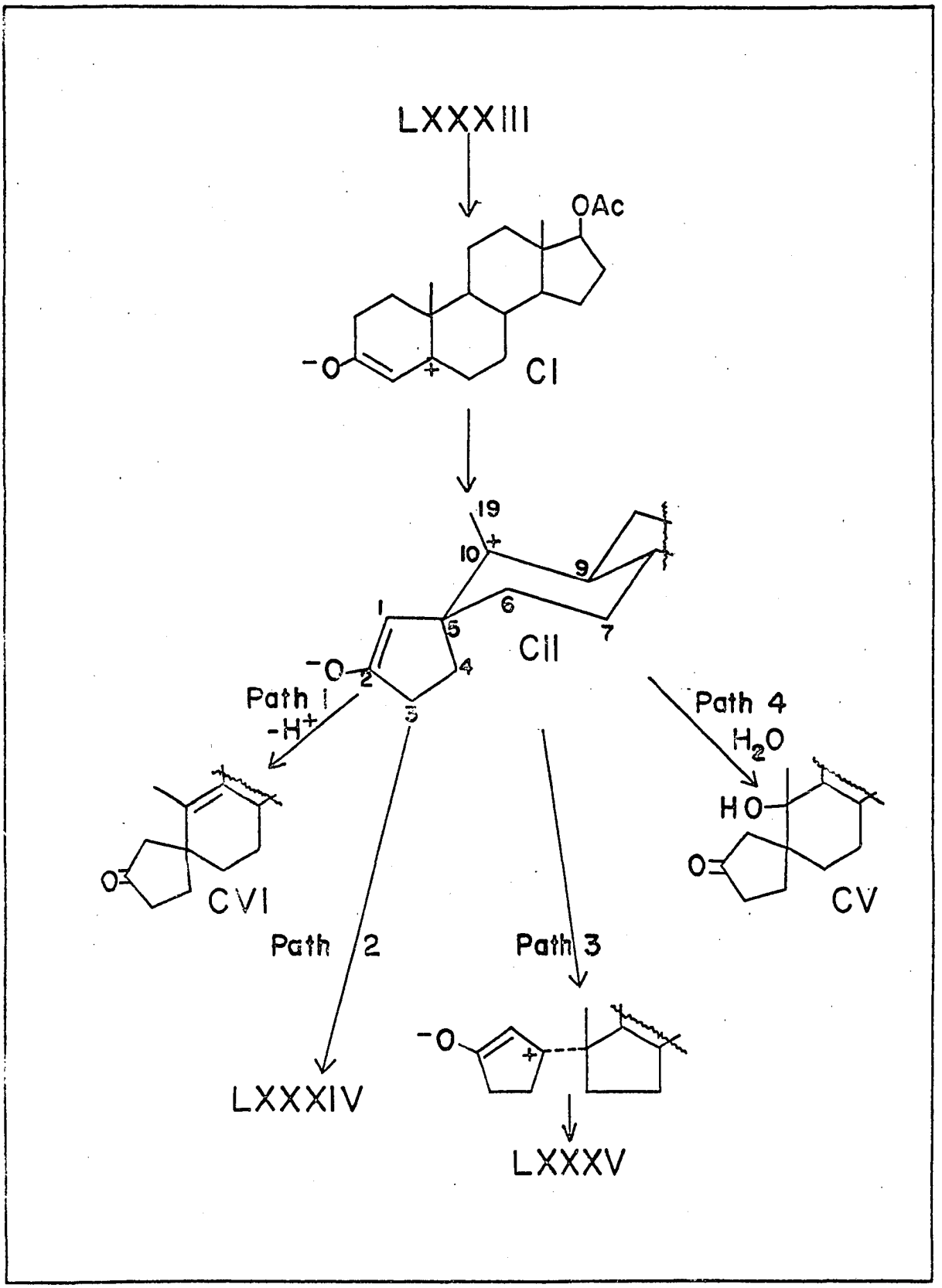
The intermediate CI in the testosterone acetate series is an analog of C. The structures relating to the following mechanistic discussion are shown in Figure 10, page 60. The numbering system used below is shown on structure CII.

The existence of intermediate CII has been amply demonstrated (25, 26, 28) by the isolation of compounds with the same ring structure. The use of CII provides a logical mechanism to LXXXIV and LXXXV.

Intermediate CII has four pathways leading to charge neutralization through which it may proceed. Paths 1 and 4 are not observed in this reaction. The presence of water and/or acetic acid is a necessary prerequisite of these pathways.

The stereochemistry of Path 2 has been most effectively proven by Wenger *et al*. (53) by the synthesis of 10α-methyltestosterone (XI, page 6). The rearrangement involves the migration of the 1-5 bond to position 10 from above the plane of the 10-carbonium ion.

Figure 10. Photochemical mechanism


LXXXIII
OAc
-O
CI
19
10
9
1
6
5
7
CII
-O
2
4
3
Path 1
-H+
Path 4
H2O
HO
O
CVI
CV
Path 2
Path 3
LXXXIV
-O
LXXXV

The stereochemistry of the carbonium ion at carbon 10 is extremely important. To form the ion, the 5-10, 9-10, and 19-10 bonds must lie in the same plane. The 19-methyl group allows this to occur as the 5-10 and 9-10 bonds are effectively prevented from moving by the rather tightly locked ring system. In this way, the 19-methyl remains mainly beta (above molecular plane). The representation of CII in Figure 10 corresponds fairly closely to the Dreiding model.

The shift of the 5-6 bond in Path 3 must necessarily force the 19-methyl up or down. The breakage of the 5-6 bond causes the cyclopentane ring to drop away; forcing the 19-methyl much nearer its original angular position. This allows the new bond (6-10) to effectively form from the side and the 19-methyl remains beta in LXXXV. The above observations were made after a careful study using Dreiding models.

The above description indicates a stepwise mechanism. The collapse of CII may be, and probably is, concerted. This would not alter the stereochemistry.

The Photochemistry of Spiro-(4,5)-deca-1,4-diene-3-one

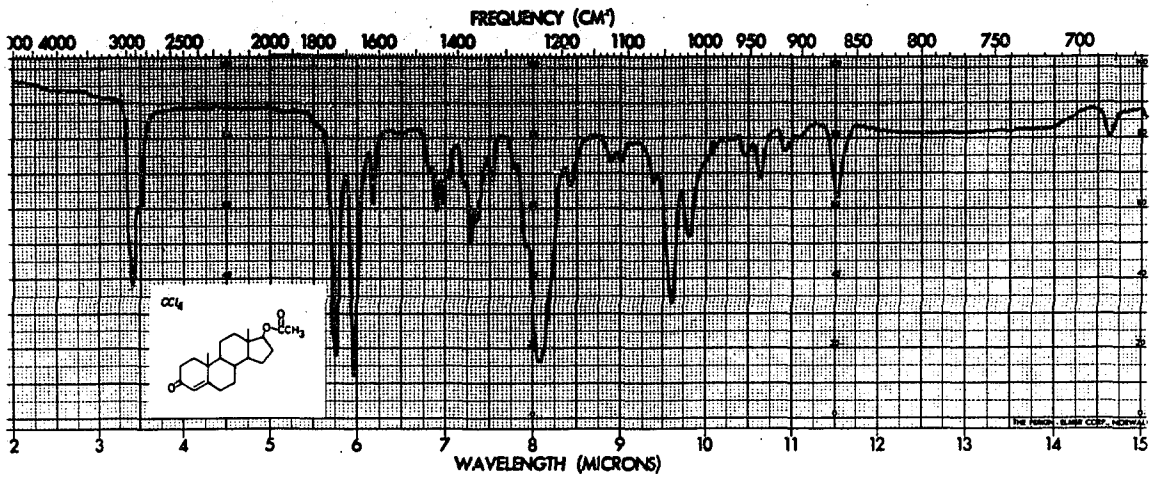
The photochemistry (see Historical) of the cross-conjugated cyclohexadienones has been a complex and rewarding field. The recent synthesis (56) of spiro-(4,5)-deca-1,4-diene-3-one (CVII) made available a unique system. Not only is CVII a cross-conjugated cyclohexadienone, but also a spiro

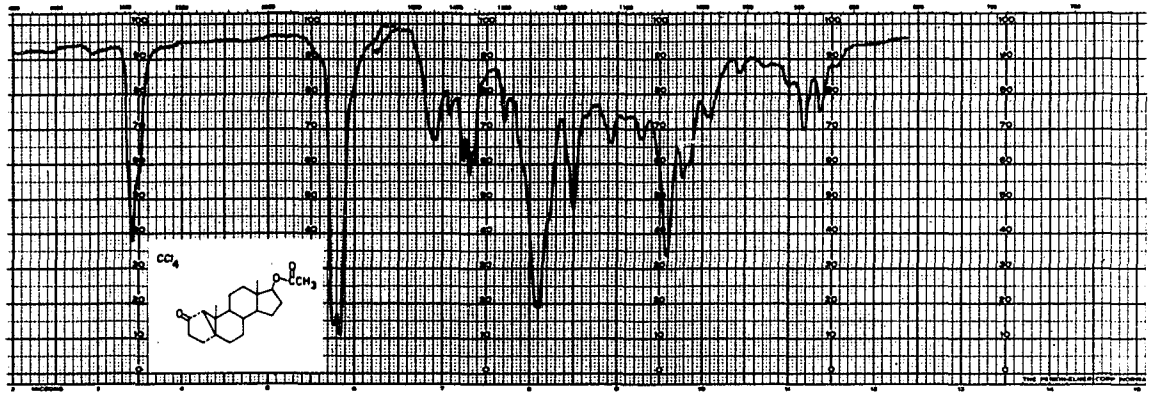
Figure 11. Infrared spectra

Top - Testosterone acetate (LXXXIII)

Middle - Photo-testosterone acetate (LXXXIV)

Bottom - Authentic sample (28) of dihydro-ketone-A_3 (26)


FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
CCl4


CCl4

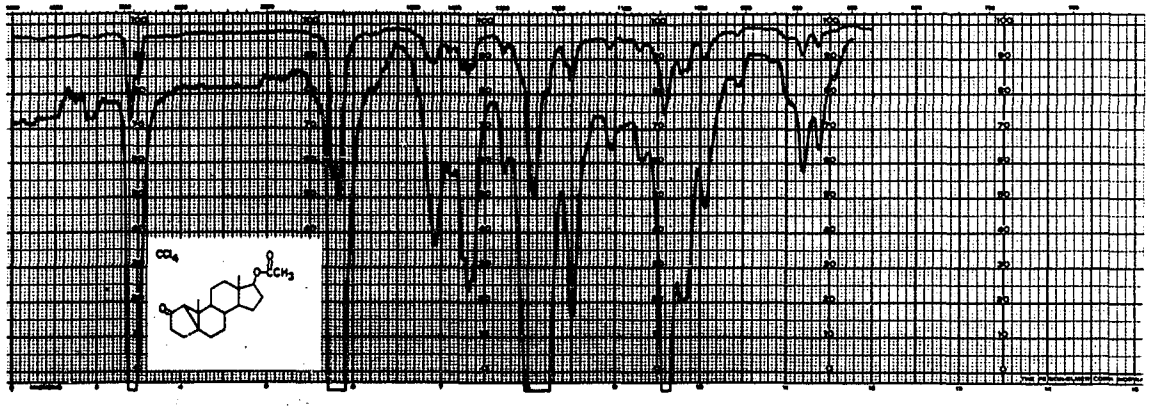
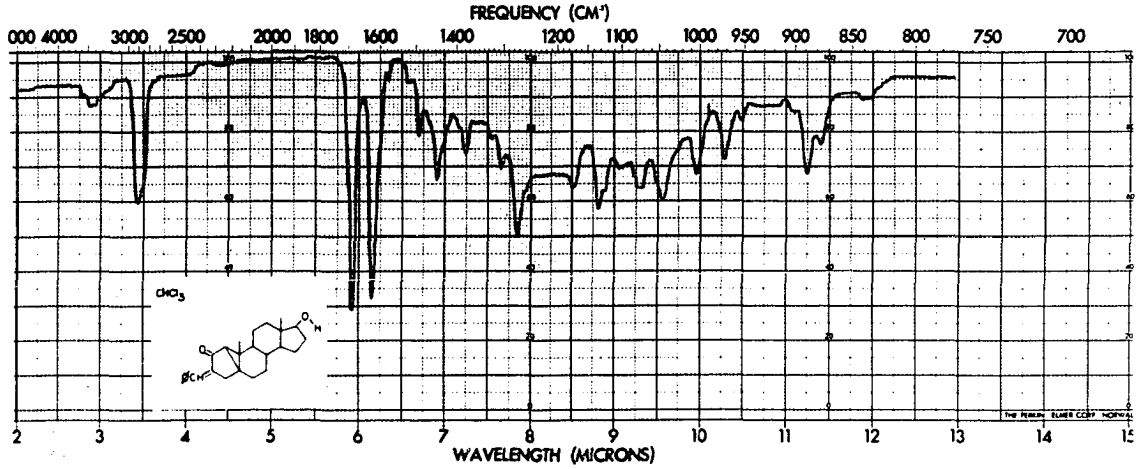

CCl4

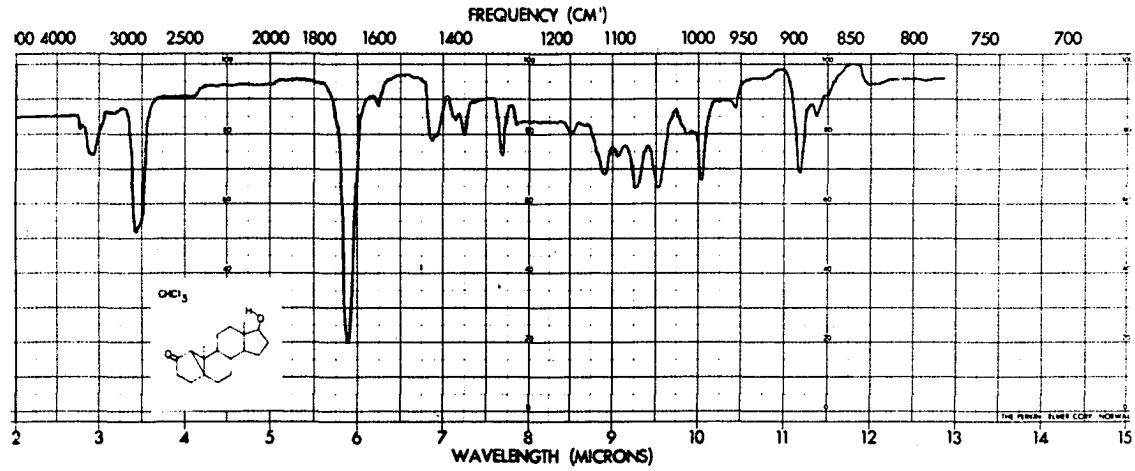
Figure 12. Infrared spectra

Top - Mono-benzal derivative of photo-testosterone (LXXXVII)

Middle - Photo-testosterone (LXXXVIII)

Bottom - 17-Keto-photo-testosterone (LXXXIX)


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CHCl3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
00 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CHCl3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

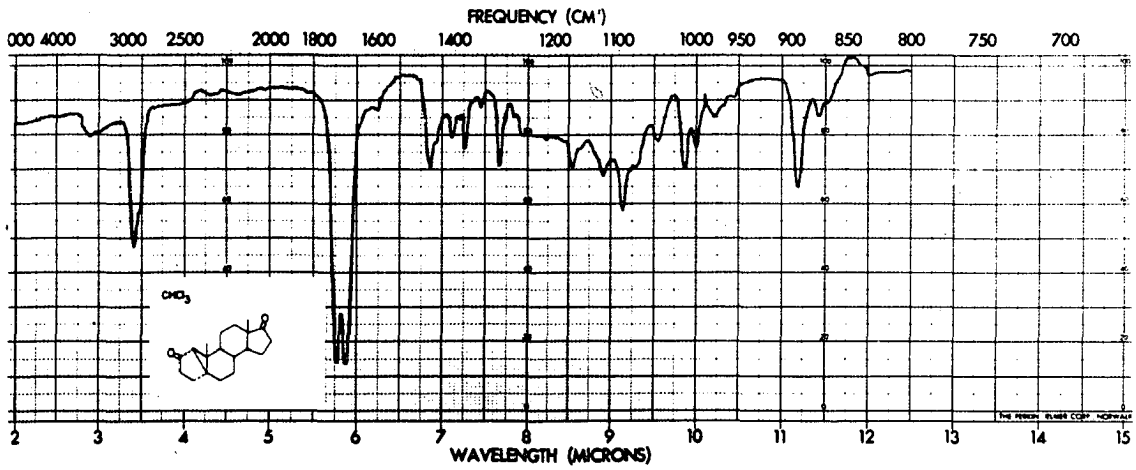
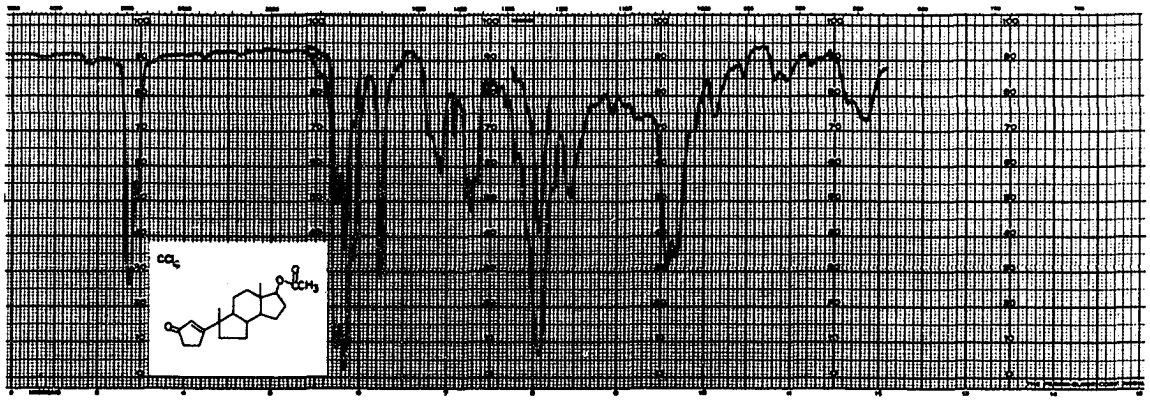

FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CHCl3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

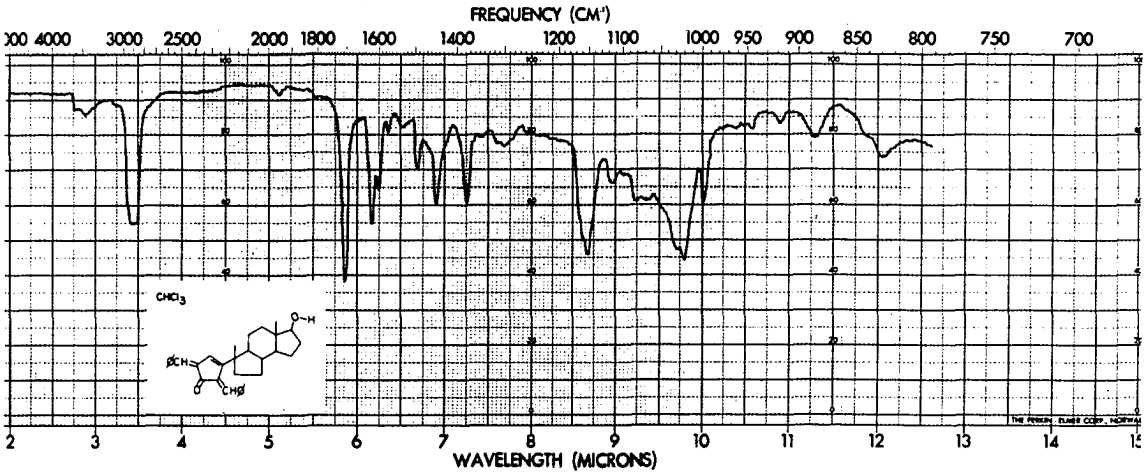
Figure 13. Infrared spectra

Top - Lumi-testosterone acetate (LXXXV)

Middle - Dibenzal derivative (XCII) of lumi-testosterone acetate

Bottom - 3-Carboxy-3,5a-dimethyl-6-propionoxy-as-hydrindacene (XCVII)


CCl_4


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
$CHCl_3$
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

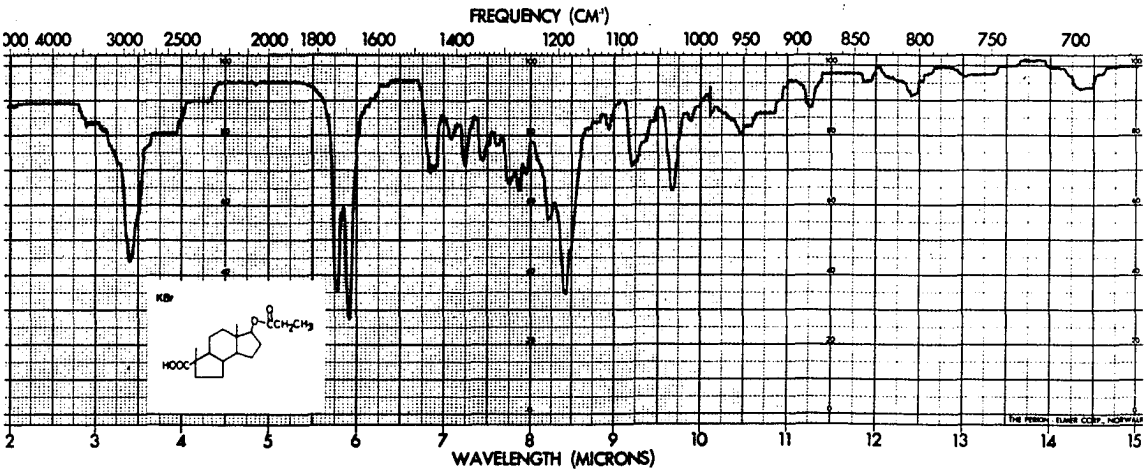
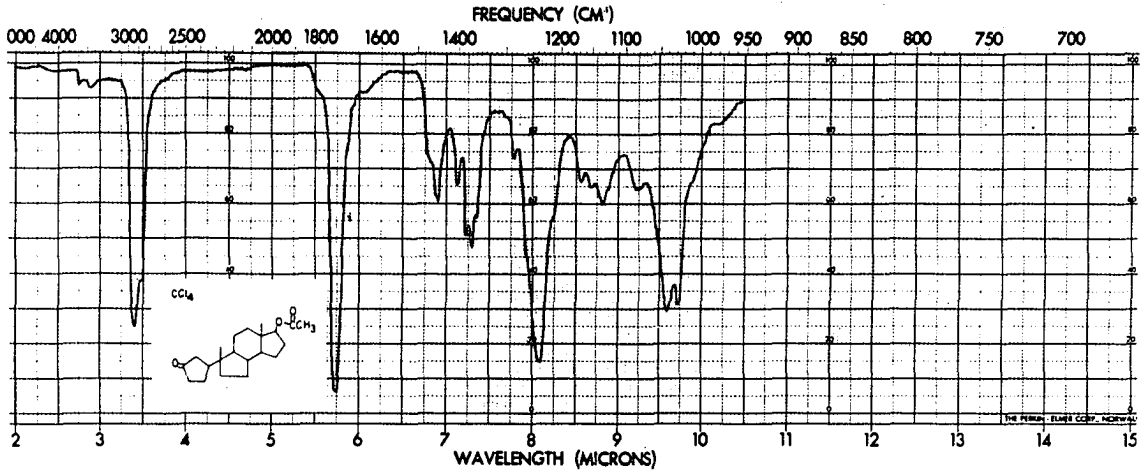

FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
KBr
HOOC
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

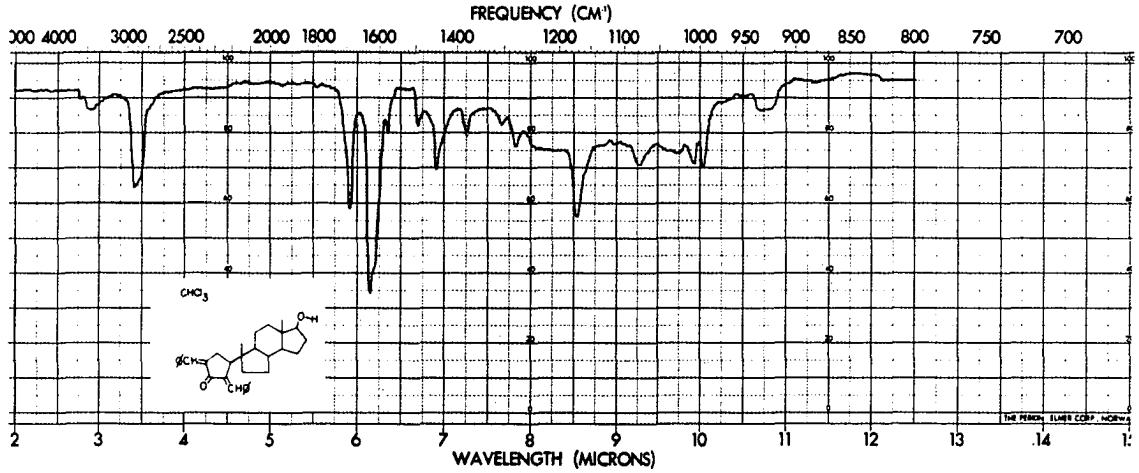
Figure 14. Infrared spectra

Top - Dihydro-lumi-testosterone acetate (XC)

Middle - Dibenzal derivative (XCI) of dihydro-lumi-testosterone acetate (XC)

Bottom - Lumi-testosterone (XCIV)


FREQUENCY (CM¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CCl4
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CHCl3
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

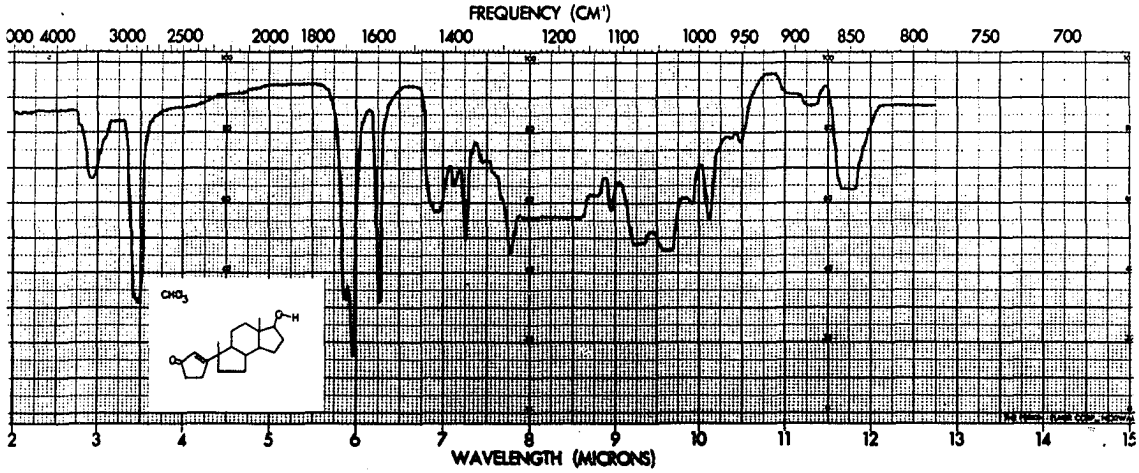

FREQUENCY (CM¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CHCl3
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 15. Infrared spectrum

Top - 3-Carboxy-3,5a-dimethyl-6-hydroxy-as-hydrindacene (XCIIIa) (50)

Bottom - XCIIIb

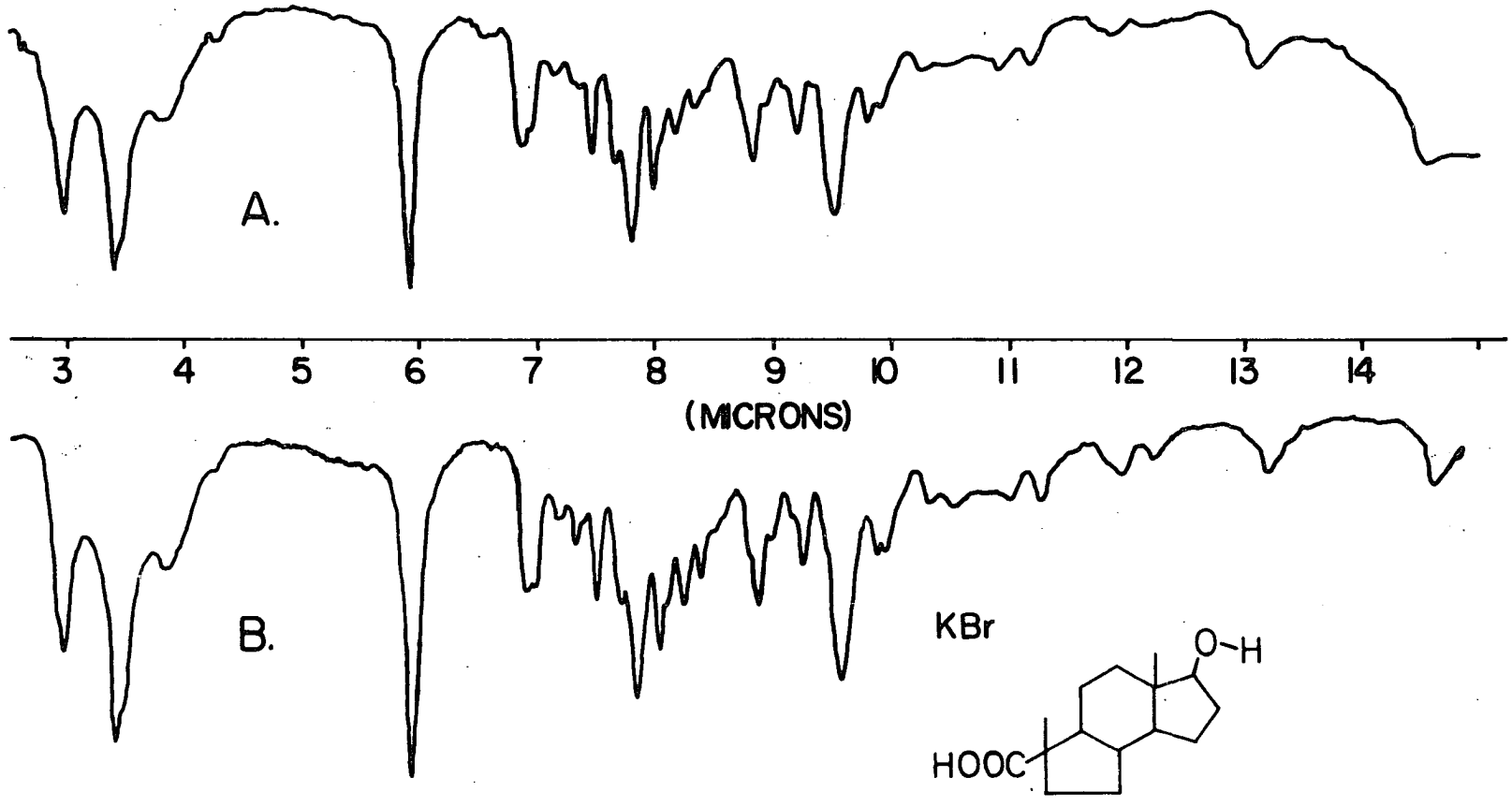

A.
3
4
5
6
7
8
9
10
11
12
13
14
(MICRONS)
B.
KBr
O-H
HOOC

Figure 16. Infrared spectrum of 3-carboxy-3,5a-dimethyl-6-propionoxy-as-hydrindacene (50) (XCVII)

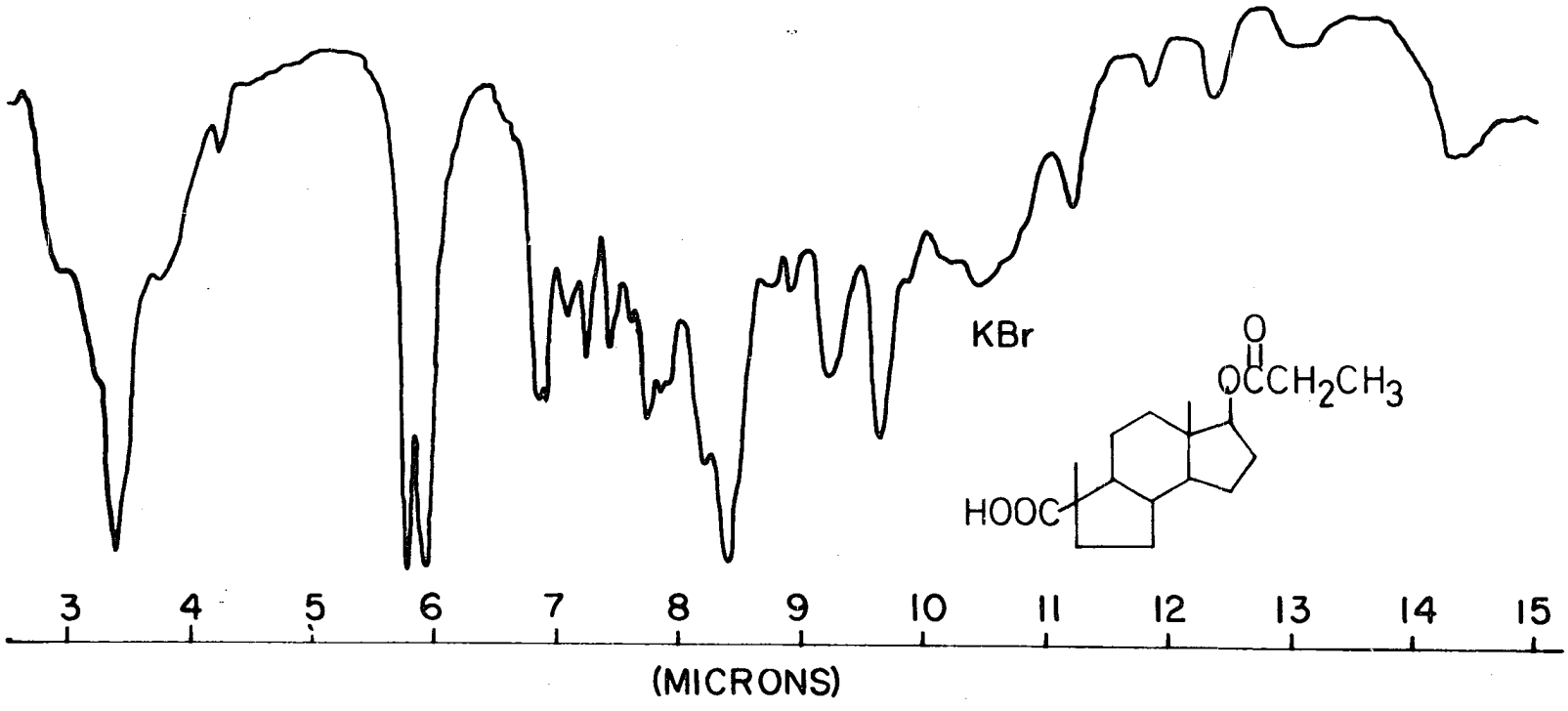
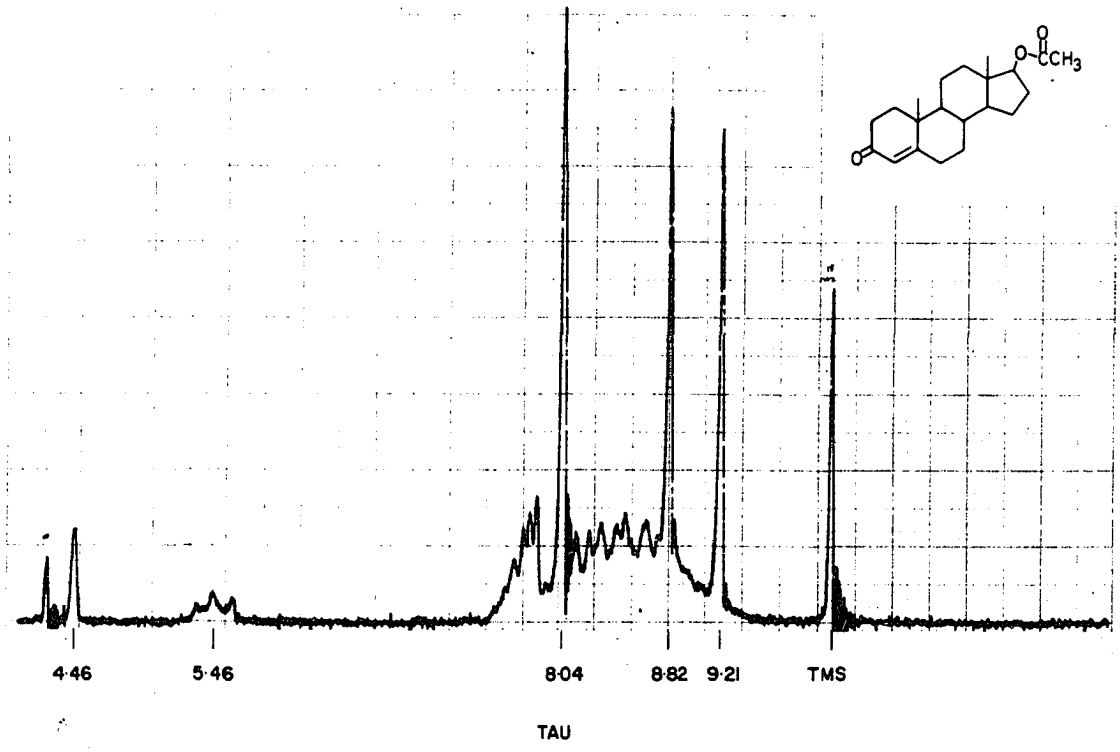

KBr
O
OCCH2CH3
HOOC
3
4
5
6
7
8
9
10
11
12
13
14
15
(MICRONS)

Figure 17. Nuclear magnetic resonance spectra

Top - Testosterone acetate (LXXXIII)

Bottom - Photo-testosterone acetate (LXXXIV)


4·46
5·46
8·04
8·82
9·21
TMS
TAU

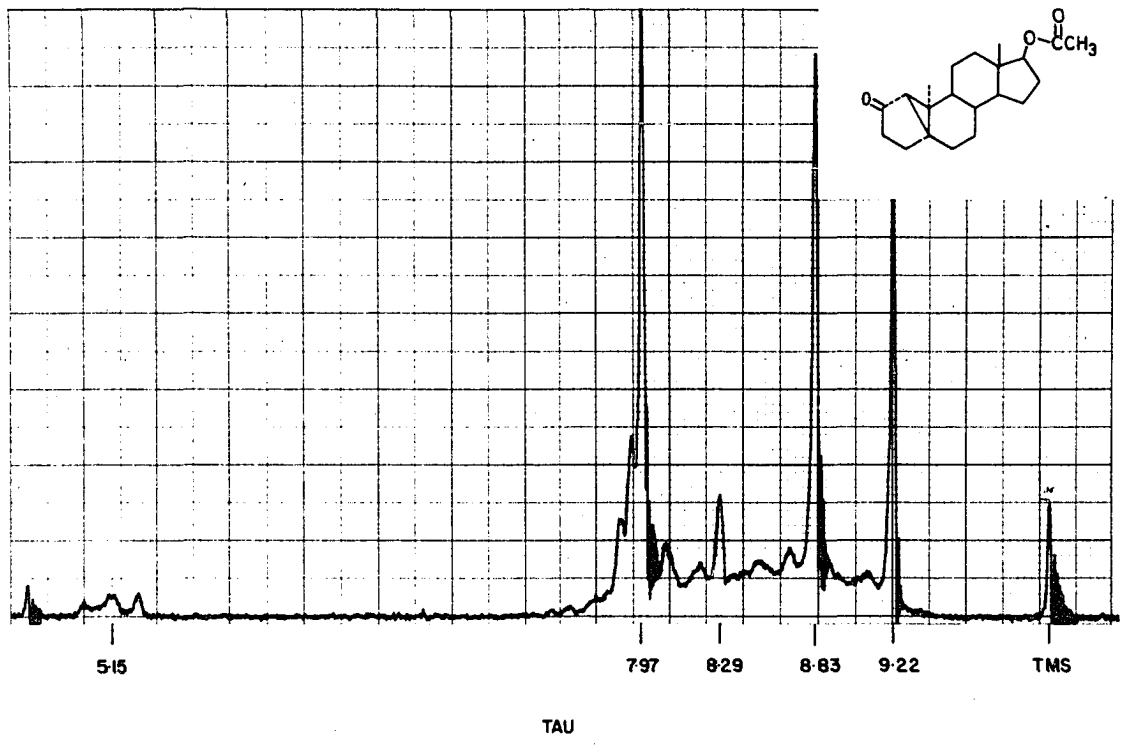
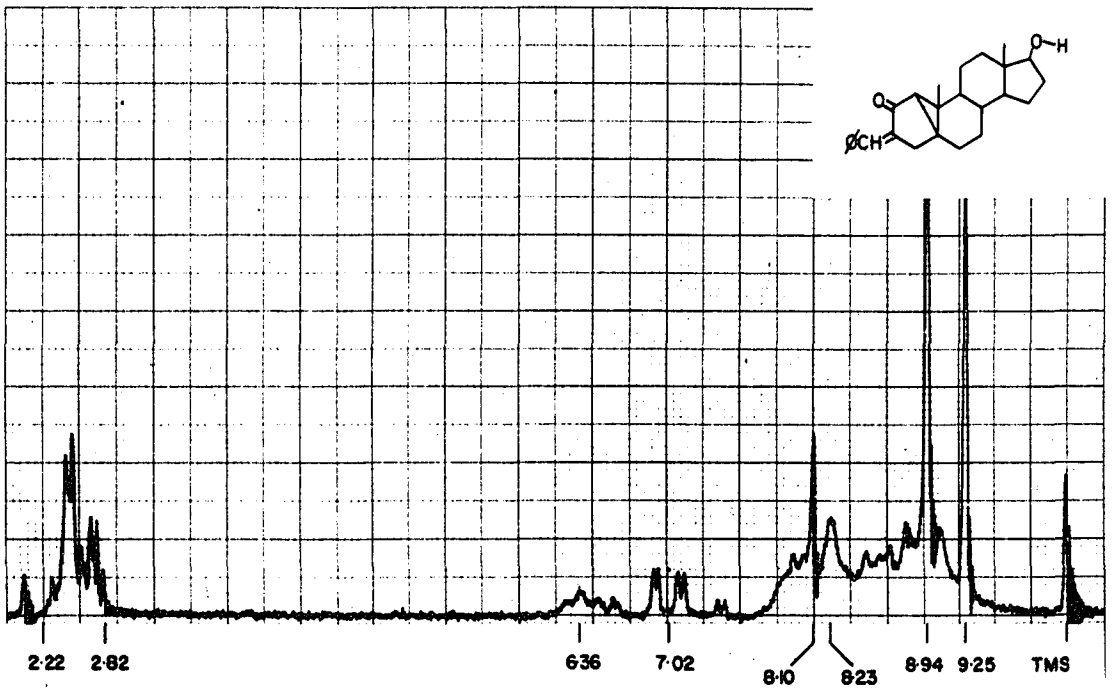

5·15
7·97
8·29
8·83
9·22
TMS
TAU

Figure 18. Nuclear magnetic resonance spectra

Top - Mono-benzal derivative (LXXXVII) of photo-testosterone acetate (LXXXIV)

Bottom - Photo-testosterone (LXXXVIII)


O
H
O
ØCH
2·22
2·82
6·36
7·02
8·10
8·23
8·94
9·25
TMS
TAU

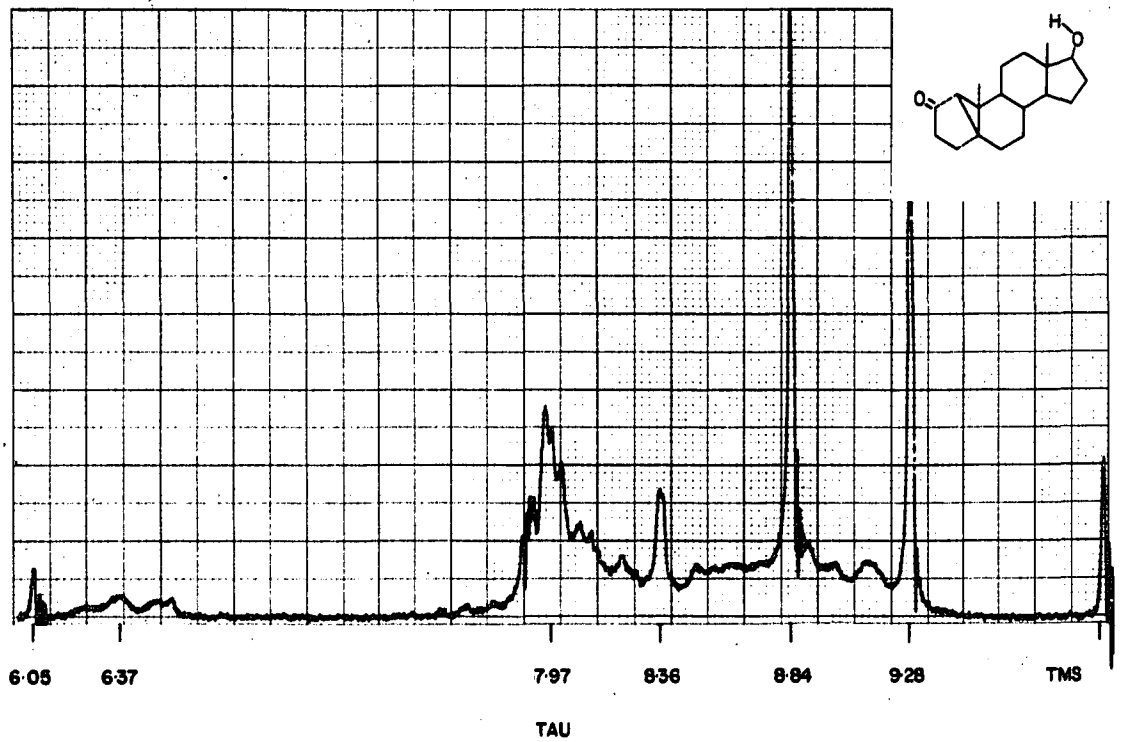
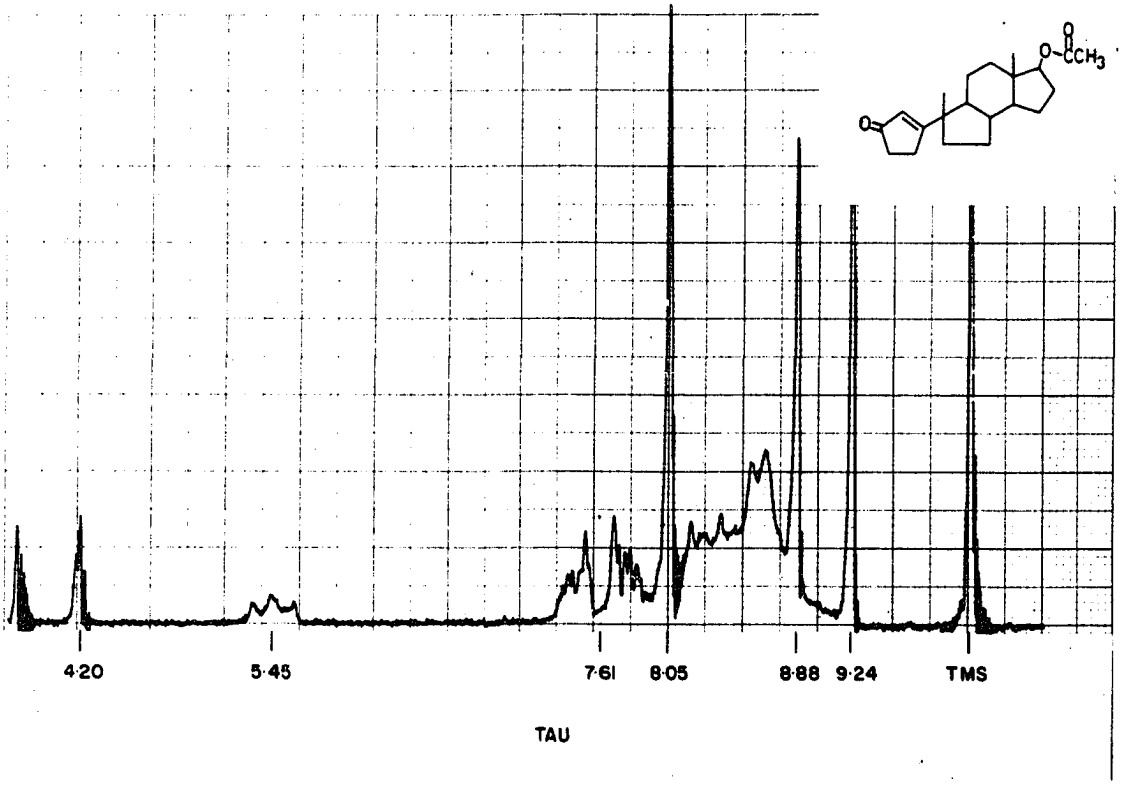

H
O
O
6·05
6·37
7·97
8·36
8·84
9·28
TMS
TAU

Figure 19. Nuclear magnetic resonance spectra

Top - Lumi-testosterone acetate (LXXXV)

Bottom - Lumi-testosterone (XCIV)


4·20
5·45
7·61
8·05
8·88
9·24
TMS
TAU

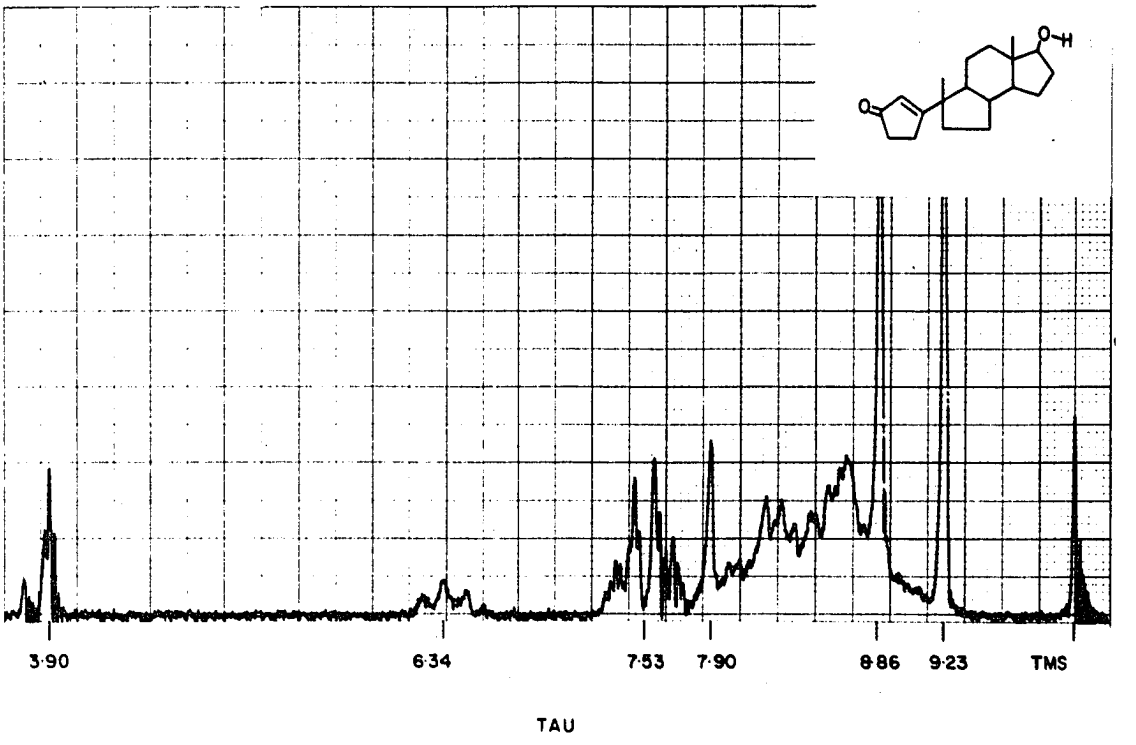
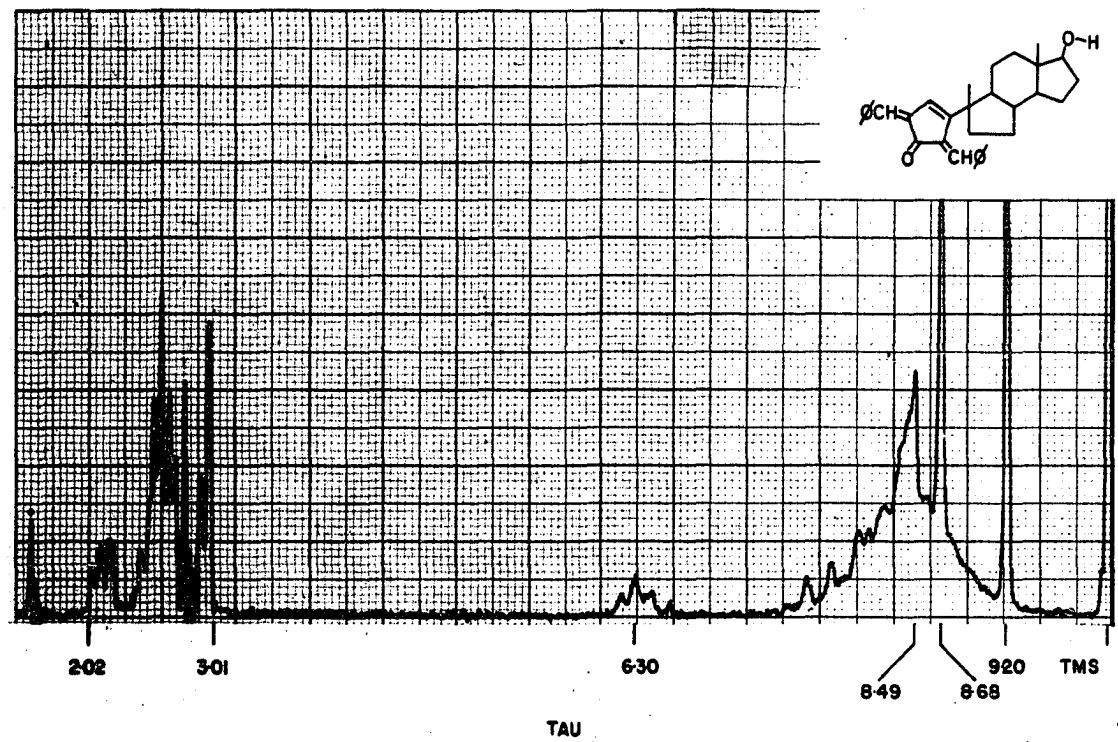

3·90
6·34
7·53
7·90
8·86
9·23
TMS
TAU

Figure 20. Nuclear magnetic resonance spectra

Top - Dibenzal derivative (XCII) of lumi-testosterone acetate (LXXXV)

Bottom - 3-Carboxy-3,5a-dimethyl-6-hydroxy-as-hydrindacene (XCIIIb)


O-H
ØCH
O
CHØ
2·02
3·01
6·30
8·49
8·68
9·20
TMS
TAU

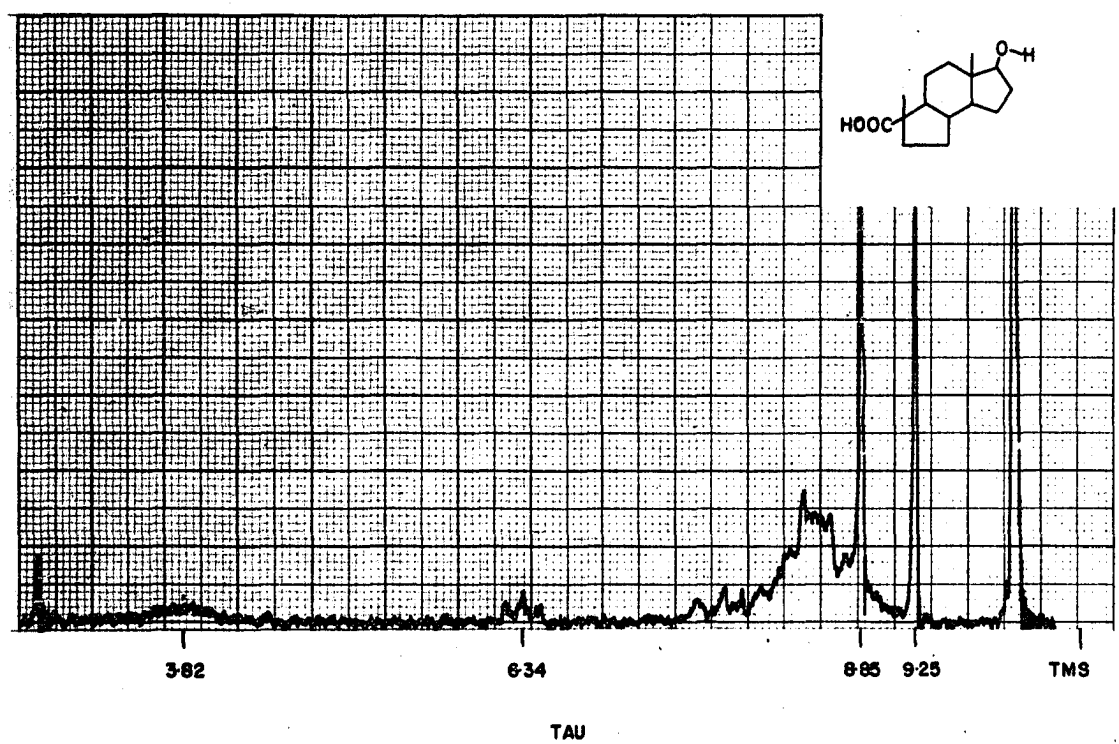
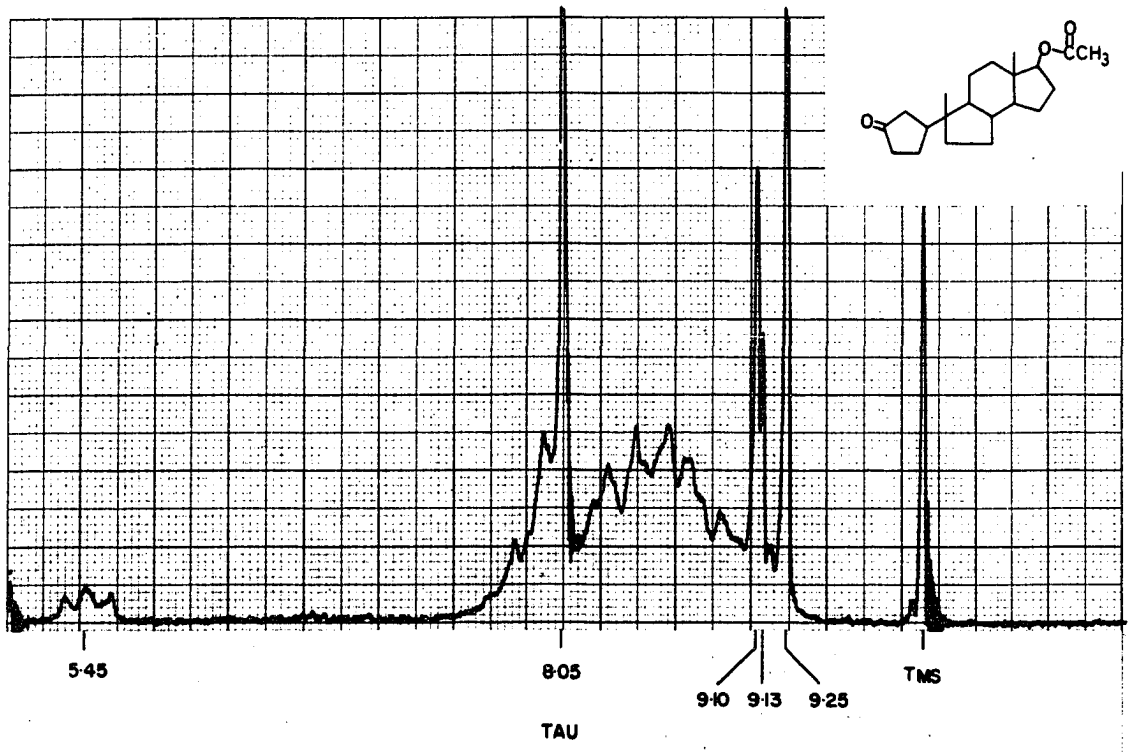
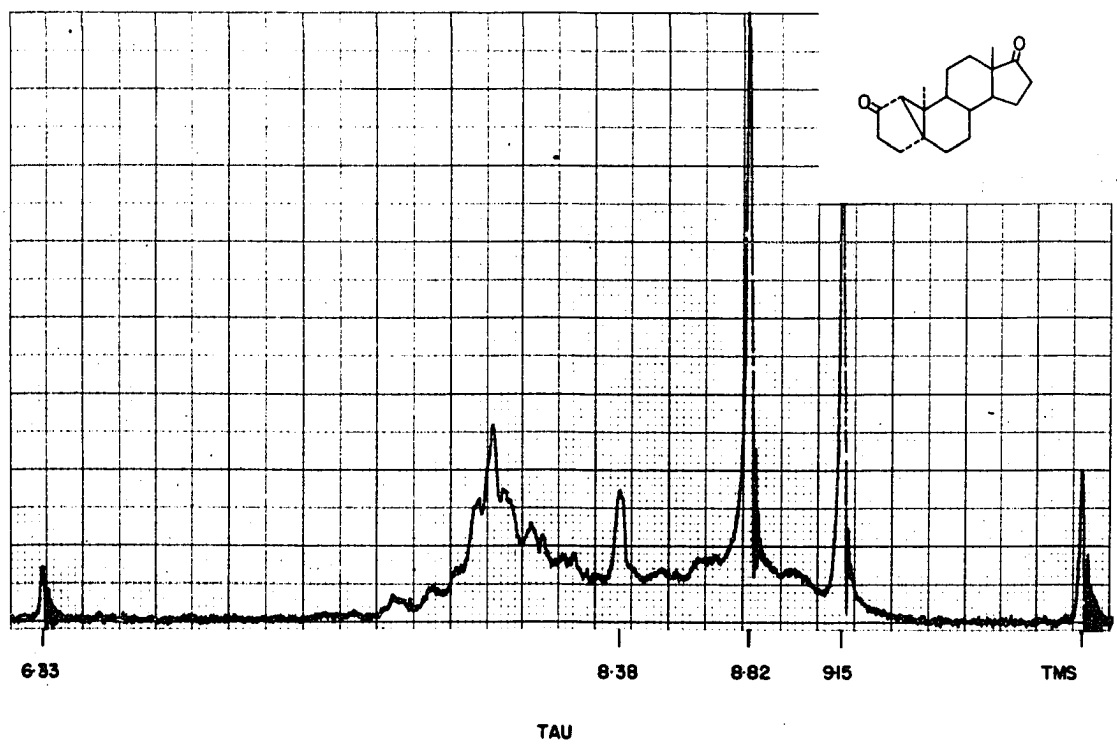

O-H
HOOC
3·82
6·34
8·85
9·25
TMS
TAU

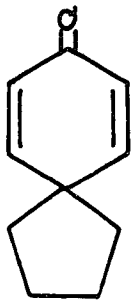
Figure 21. Nuclear magnetic resonance spectra

Top - Dihydro-lumi-testosterone acetate (XC)

Bottom - 17-Keto-photo-testosterone (LXXXIX)


O
O
CCH3
5·45
8·05
9·10
9·13
9·25
TMS
TAU


O
O
6·33
8·38
8·82
9·15
TMS
TAU



CVII

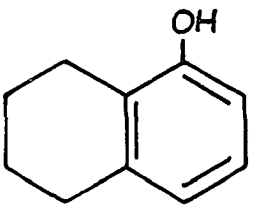
compound which represents a structural type hitherto unstudied photochemically. The infrared spectrum of CVII is shown in Figure 22, page 93. The n.m.r. spectrum, Figure 24, page 97, shows the four olefinic protons as two superimposed AB patterns with J_{AB} = 10 c.p.s. The protons of the spiro-pentane ring appear at 8.15 τ.

The irradiation of CVII was accomplished using a General Electric UA-3 mercury lamp. The irradiation flask was constructed of Pyrex, effectively cutting off light of wavelength below 300 mu. The flask was cooled by internal glass cooling coils through which tapwater was circulated.

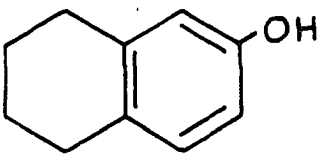
To determine the effects of solvent, CVII was irradiated in ether, tert-butyl alcohol and glacial acetic acid. From the irradiation of CVII in ether, four compounds were isolated by column chromatography on silicic acid. The spiro-dienone was later shown to be stable on silicic acid (see Experimental) and to the conditions of the acetic acid irradiation.

The first compound was an artifact of the spiro-dienone preparation and will be covered later. The second compound was found to be 5,6,7,8-tetrahydro-1-naphthol (CVIII; m.p. 66-8°, 2.76, 6.31, 6.83 and 9.77 u, $\lambda_{max}^{95\% \text{ ethanol}}$ 273 mu (1,340) and 279 mu (1,340) (57)) and was isolated in 30% yield. An infrared comparison, Figure 22, page 93, of CVIII and authentic 5,6,7,8-tetrahydro-1-naphthol shows the compounds are identical. The mixed melting point of the two compounds showed no depression. The n.m.r. spectrum of CVIII is shown in Figure 25, page 99. The proton integration shows four benzyl protons (7.41 τ), four methylene protons (8.31 τ), one hydroxyl proton (4.17 τ) and three aromatic protons (3.06 to 3.69 τ).

The third compound isolated in 15% yield was identified as 5,6,7,8-tetrahydro-2-naphthol (CIX; m.p. 57.5-59°; 2.76,



CVIII



CIX

6.17, 6.66 and 10.84 u; $\lambda_{max}^{95\% \text{ ethanol}}$ 281.3 mu (2,250) (57)). An infrared comparison, Figure 22, page 93, of CIX and authentic 5,6,7,8-tetrahydro-2-naphthol shows superimposable spectra. The mixed melting point of the two compounds showed no depres-

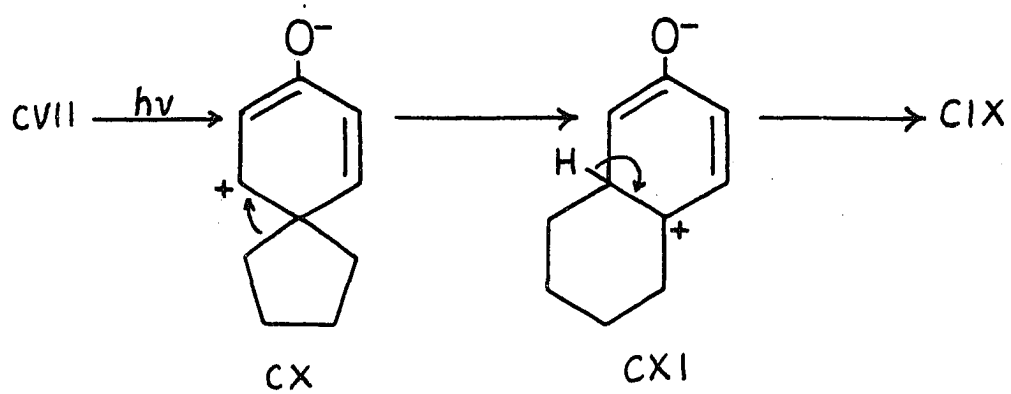
sion. The n.m.r. spectrum of CIX is shown in Figure 24, page 97. The hydroxyl proton was buried in the aromatic proton signals which extended from 3.09 to 3.65 τ (four protons). The benzylic protons appear at 7.44 τ (four protons) and the methylene protons at 8.35 τ (four protons).

The structure of the last compound (m.p. 140-1°) isolated from the irradiation of CVII in ether was not elucidated. The infrared spectrum, Figure 23, page 95, shows carbonyl bands at 5.84 and 5.97 u. The compound absorbed in the ultraviolet at 230 mu. The ebullioscopic molecular weight in benzene was 160. This compound was only isolated from ether irradiations and was never isolated in sizeable amounts.

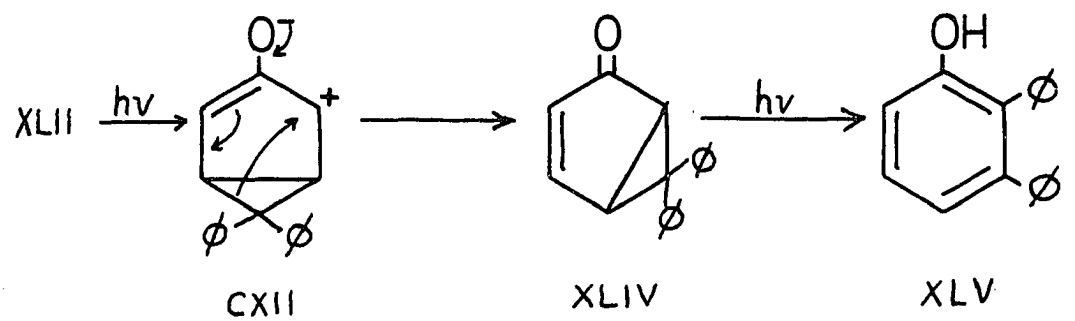
The irradiation of the spiro-dienone (CVII) in tert-butyl alcohol also gave the two naphthols. The yield of 5,6,7,8-tetrahydro-1-naphthol (CVIII) was 27.5%. CIX was isolated in 20% yield.

Irradiation of the spiro-dienone in glacial acetic acid gave 5,6,7,8-tetrahydro-1-naphthol (CVIII) in 19% yield and CIX in 41% yield.

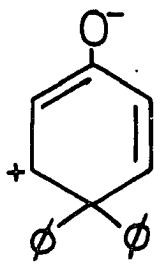
The formation of CIX is readily rationalized through the polar intermediate CX. Alkyl migration of a spiro-pentane bond in CX forms the intermediate CXI which aromatizes to CIX by loss of a proton. A priori, the polar mechanism predicts this product.



5,6,7,8-Tetrahydro-1-naphthol (CVIII) would not have been an expected product without the singular work of Zimmerman and Schuster (9), who studied the photochemistry of 4,4-diphenylcyclohexadienone (XLII, see page 15). The formation of XLIV was rationalized through the polar intermediate CXII.

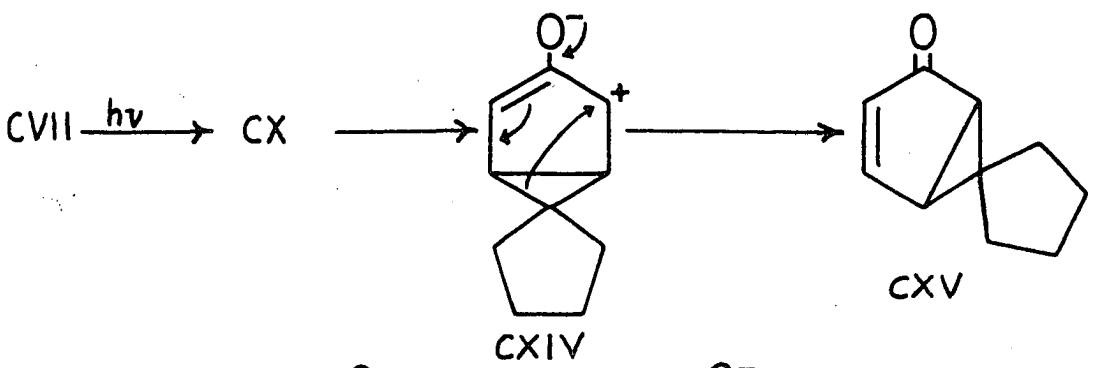


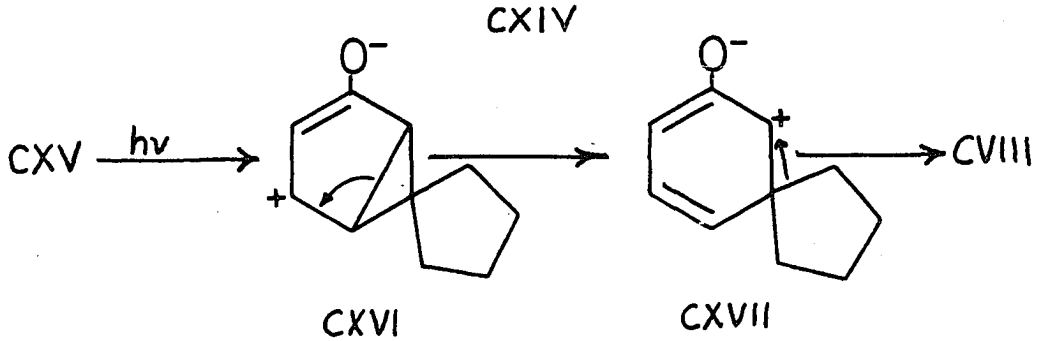
According to Zimmerman and Schuster (9), the excitation process leading to CXII does not involve a polar intermediate such as CXIII. Throughout this study, an intermediate of this type (CXIII) has been used extensively. This intermediate (CXIII) can be used to advantage when predicting products of photochemical reactions. It should be noted that both



CXIII

excitation processes lead to CXII and this intermediate provides a reasonable explanation for the formation of CVIII.





A ketone (CXV), analogous to XLIV, was not isolated from any of the irradiations of the spiro-dienone. Zimmerman and Schuster (9) found XLIV to be quite unstable to isolate under the conditions used in this study. The irradiation of CXV

giving 5,6,7,8-tetrahydro-1-naphthol is thus analogous to the formation of 2,3-diphenylphenol (XLV) from XLIV.

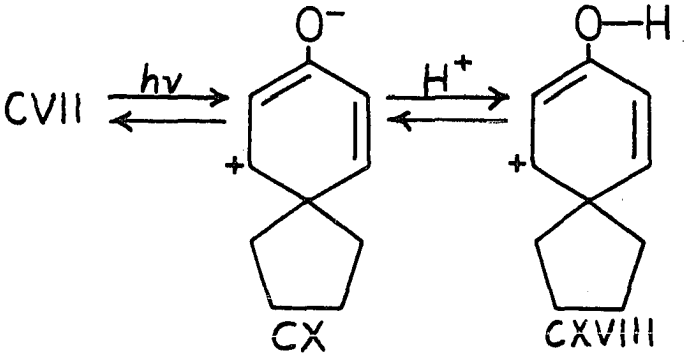
Table 2 records the yield data from the irradiations of CVII in various solvents. It is apparent that an aprotic

Table 2. Yields of tetrahydronaphthols in selected solvents

Solvent	% CVIII	% CIX	$\frac{\%\ \text{CVIII}}{\%\ \text{CIX}}$
Ether	34[a]	17[a]	2
Tert-butyl alcohol	27.5	20	1.4
Acetic acid	19	41	0.5

[a]Corrected for weight of cyclic ether artifact present in sample.

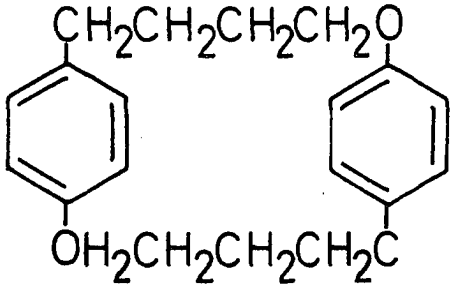
solvent favors formation of CVIII while protic solvents favor CIX. It would be desirable to observe protonation of the polar intermediate (CX) giving CXVIII. However, careful examination of CX and CXVIII provides no information which



would indicate that either CX or CXVIII should be preferentially converted to one product.

Another explanation may involve the stabilization of the polar intermediate (CX) through solvent association. A polar solvent may stabilize the charges; allowing a 1,2-alkyl shift to become the predominating reaction. The evidence at hand does not provide an obvious explanation for the dramatic change in product ratio with changes in solvent.

In the irradiation of CXII in ether, a solid was isolated in 12% yield which proved to be an artifact from the preparation of CXII (see Experimental, page 148). The compound (CXIX; m.p. 132-132.5°) showed no carbonyl or hydroxyl absorption in the infrared (Figure 23, page 95). CXIX showed absorption in the ultraviolet at $\lambda_{max}^{95\%\ ethanol}$ 277 mu (1,160) and 285 mu (855). The osmometric molecular weight in benzene was 294. The previous evidence suggests the following structure:



CXIX

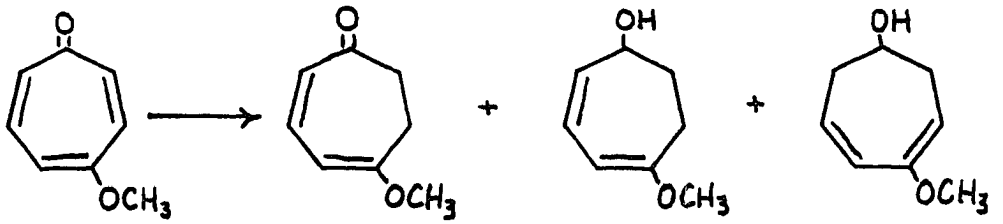
The n.m.r. spectrum, Figure 25, page 99, supports this structure. The four aromatic protons appear as an AB pattern (J_{AB} = 8.4 c.p.s.) with an approximate center at 3.48 τ. The

methylenes (4 protons) on carbons attached to oxygen appear at 6.08 τ and the benzylic methylenes (4 protons) appear at 7.58 τ. The broad peak at 8.52 τ is assigned to the saturated methylenes (4 protons). CXIX can be considered a cyclic dimer of 4-p-hydroxyphenyl-1-butanol.

Reactions of gamma-Tropolone Methyl Ether and Tropone with Grignard and Hydride Reagents

It should be emphasized that the chemistry in this section was accomplished in close cooperation with the work of D. J. Pasto (35). Much of the work is supplementary and some is repetitive. Due to the limited extent of this work, the reader is advised to refer to both theses or the published papers (34, 36, 42, 43) resulting from them.

The reaction of lithium aluminum hydride with gamma-tropolone methyl ether (LVIII) was studied prior to this work. The products from this reaction were shown to be CXX, CXXI, and CXXII. The ketone CXX was easily separated from the



LVIII CXX CXXI CXXII

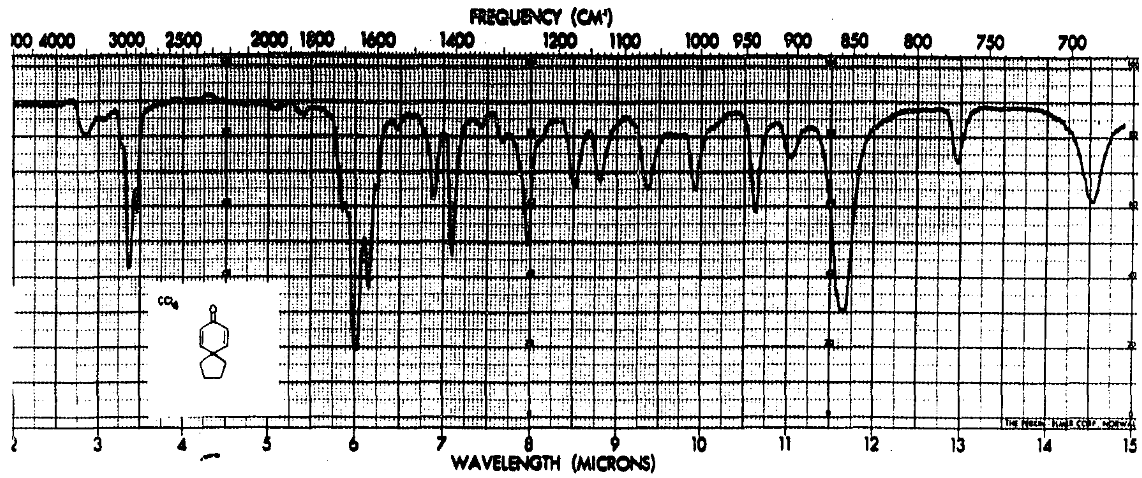
alcohols by column chromatography on basic alumina. The infrared spectrum of CXX is shown in Figure 29, page 119.

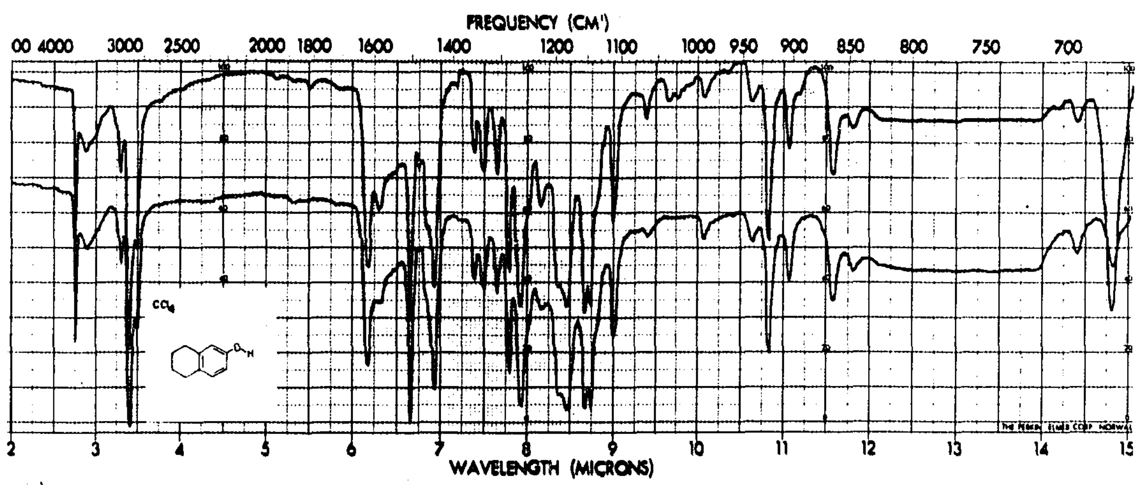
Figure 22. Infrared spectra

Top - Spiro-(4,5)-deca-1,4-diene-3-one CVII

Middle - Top, 5,6,7,8-Tetrahydro-2-naphthol CIX
Bottom, Authentic sample

Bottom - Top, 5,6,7,8-Tetrahydro-1-naphthol CVIII
Bottom, Authentic sample


FREQUENCY (CM⁻¹)
WAVELENGTH (MICRONS)
CCl4


FREQUENCY (CM⁻¹)
WAVELENGTH (MICRONS)
CCl4

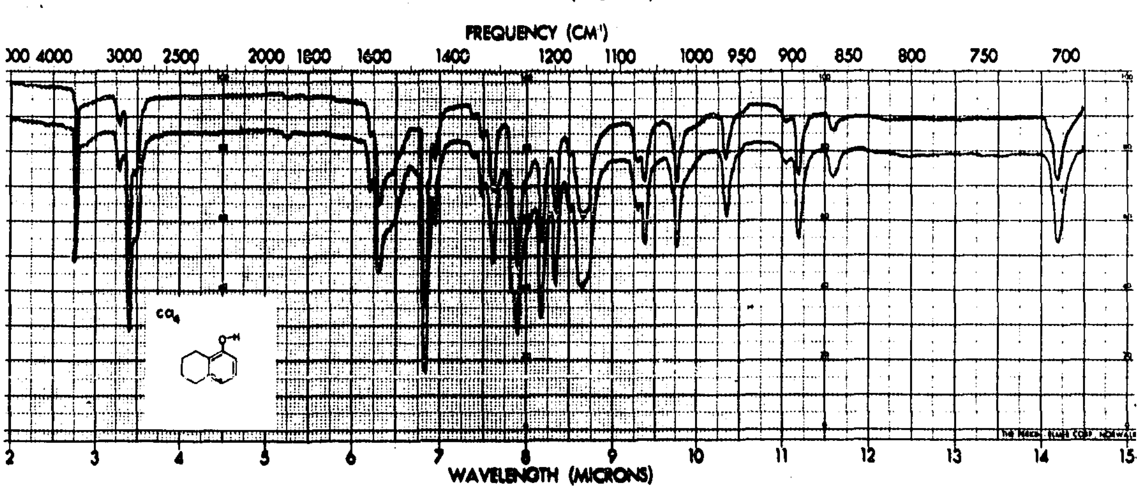
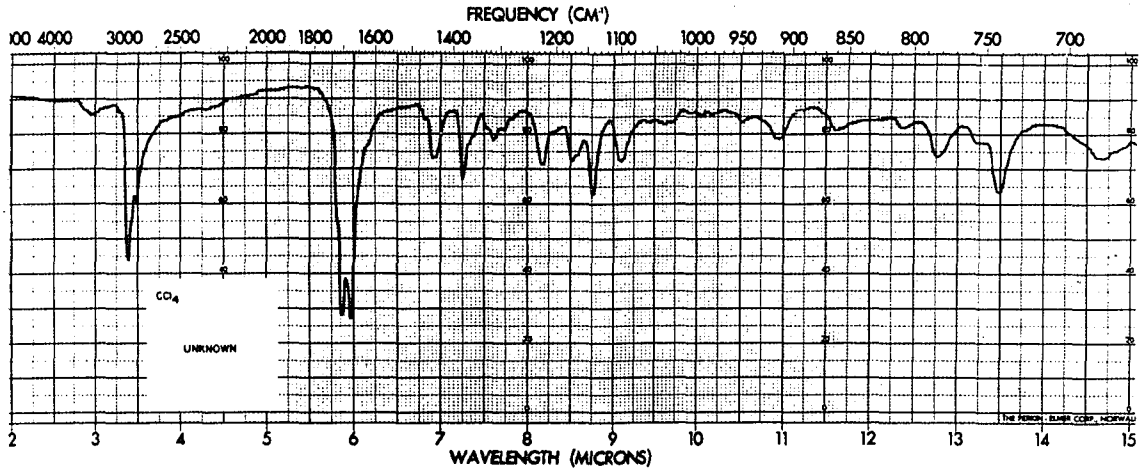

FREQUENCY (CM⁻¹)
WAVELENGTH (MICRONS)
CCl4

Figure 23. Infrared spectra

Top - Unknown compound from irradiation of CVII in ether

Bottom - Cyclic ether CXIX


FREQUENCY (CM⁻¹)
00 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CCl_4
UNKNOWN
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

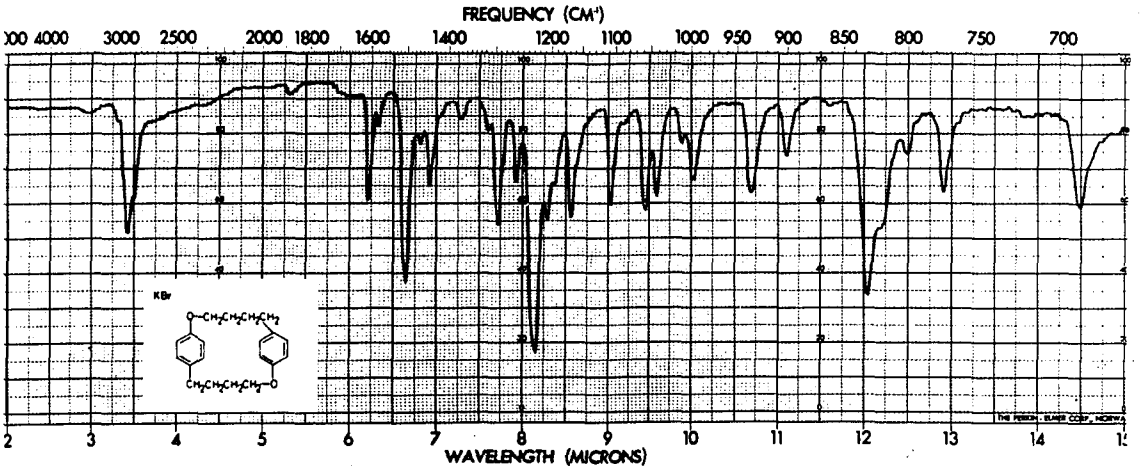
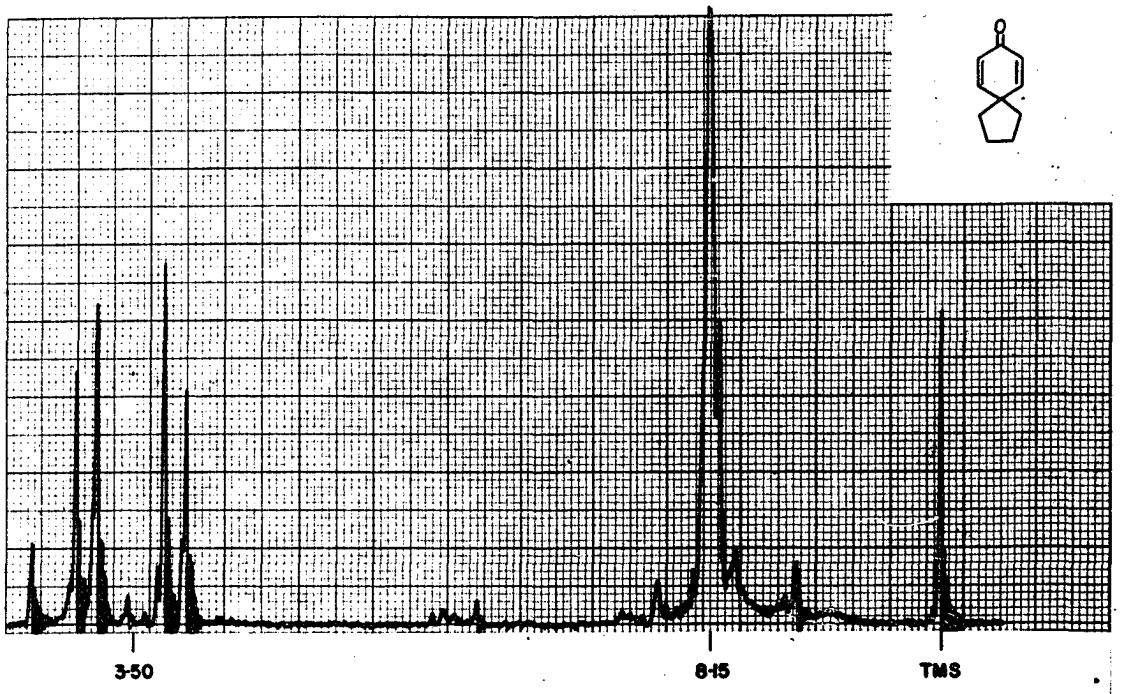

FREQUENCY (CM⁻¹)
00 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
KBr
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 24. Nuclear magnetic resonance spectra

Top - Spiro-(4,5)-deca-1,4-diene-3-one CVII

Bottom - 5,6,7,8-Tetrahydro-2-naphthol CIX


3·50
8·15
TMS
TAU

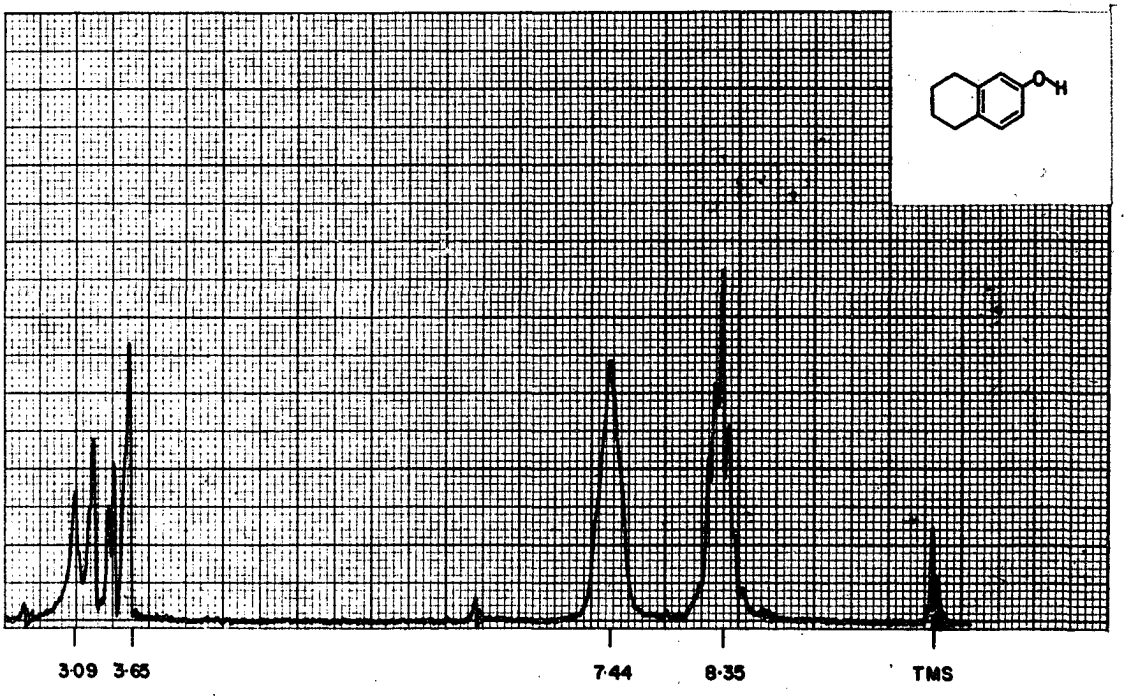
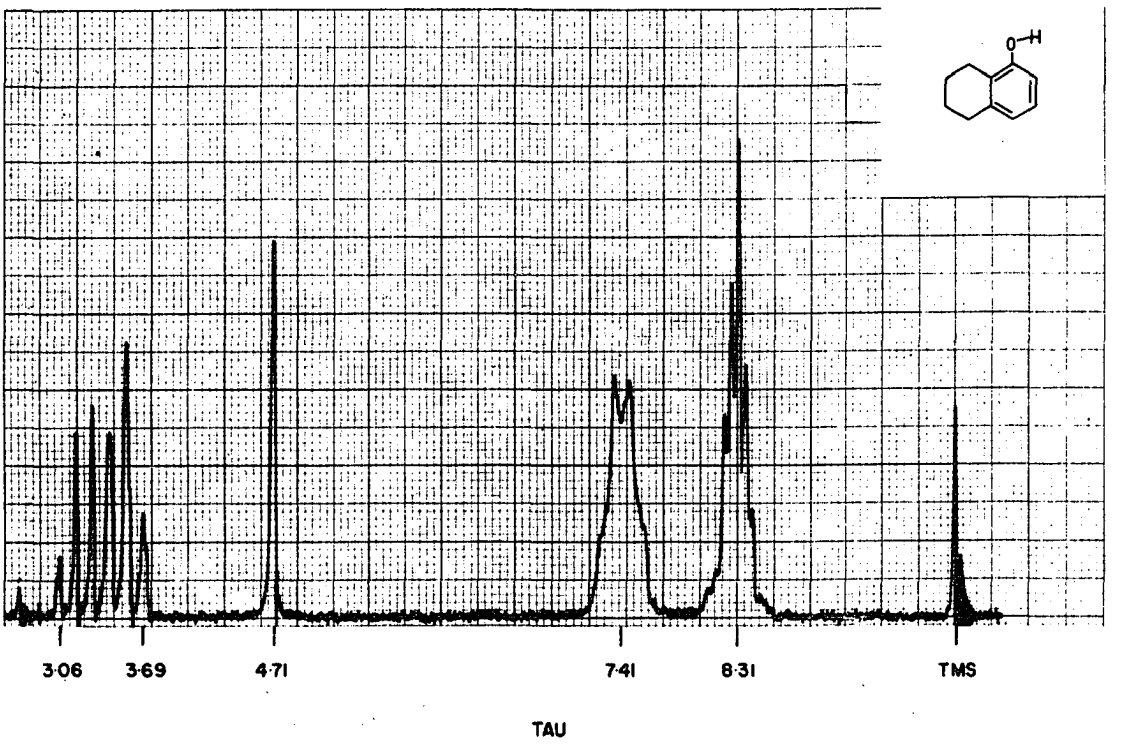
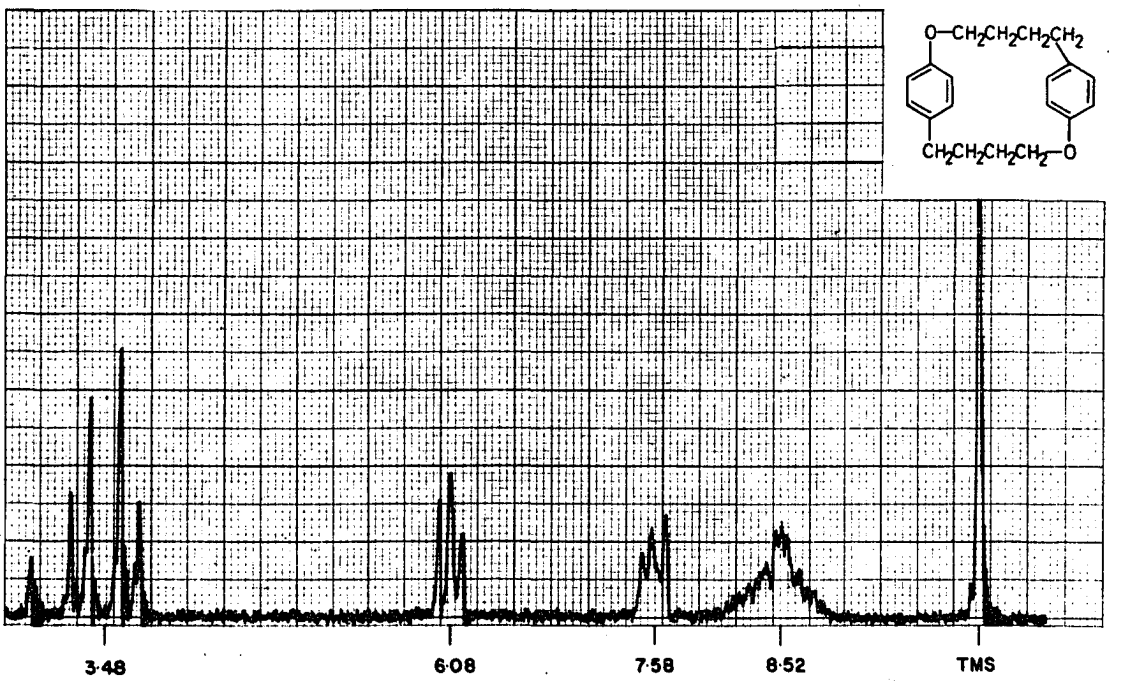

3·09
3·65
7·44
8·35
TMS
TAU

Figure 25. Nuclear magnetic resonance spectra

Top - 5,6,7,8-Tetrahydro-1-naphthol CVIII

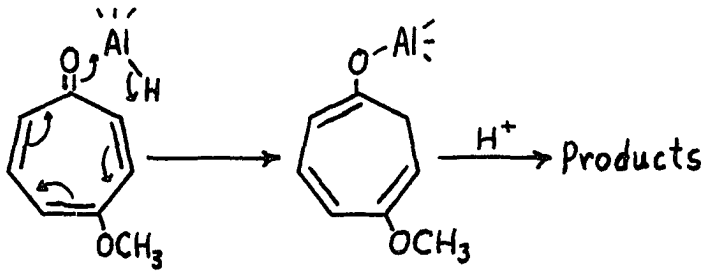
Bottom - Cyclic ether CXIX


O—H
3·06
3·69
4·71
7·41
8·31
TMS
TAU


O—CH2CH2CH2CH2
CH2CH2CH2CH2—O
3·48
6·08
7·58
8·52
TMS
TAU

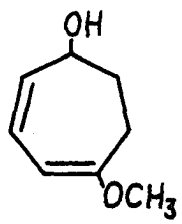
The n.m.r. spectrum, Figure 32, page 125, offers further proof for the structure of CXX. Pasto (35) reported the separation of CXXI and CXXII by vapor phase chromatography. The proof of structure of CXXII is shown on page

The isolated products indicate a novel 1,8-addition of

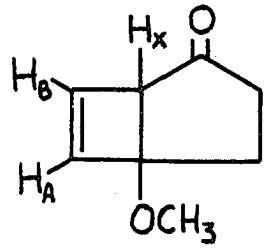


hydride to the tropolone ring. For a more comprehensive discussion of the previous mechanism, see references 35 or 43.

The reactions of CXX were studied further. The reduction of CXX with lithium aluminum hydride gave 5-methoxy-2,4-cycloheptadienol (CXXIII; 2.99, 3.53, 6.09 and 6.20 u, Figure 29, page 119; $\lambda_{max}^{95\%\ ethanol}$ 256 mu (7,590)). Pasto (35) showed that CXXI is identical to CXXIII by a vapor phase chromatographic comparison.



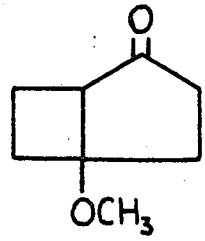
CXXIII



CXXV

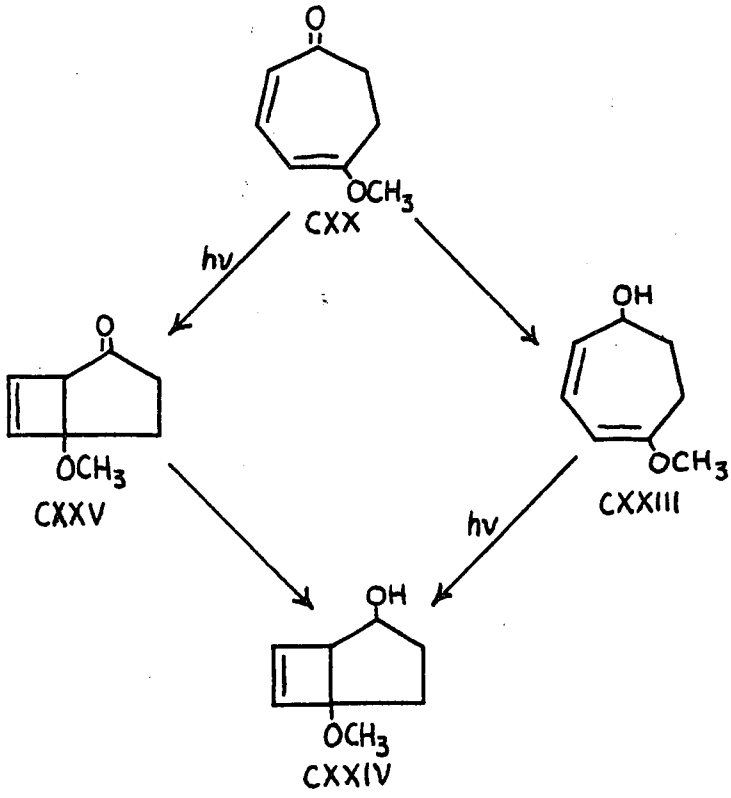
290 mu with an extinction coefficient of 100 or less. The facile ring-opening of CXXV in various solvents explains this anomaly and is discussed later. The n.m.r. spectrum, Figure 32, page 125, of CXXV gives positive proof of structure. At high field, the cyclopentanone methylenes appear at 7.76 τ. The bridgehead methoxyl group is present at 6.68 τ. The bridgehead proton, H_X, occurs as a closely split singlet at 6.90 τ. The expansion of H_X shows it to be a very complex multiplet. The olefinic protons, H_A and H_B, appear to be part of an ABX system with J_{AB} = 2.8 c.p.s. The expansion of the olefinics shows the H_A proton as a clean doublet while proton H_B appears as four peaks. This indicates that proton H_A is not coupled to H_X (J_{AX} = 0) while H_B is coupled weakly (J_{BX} = 1 c.p.s.).

Further proof of structure was obtained by catalytic hydrogenation of CXXV with one mole of hydrogen. The product isolated was identical in infrared absorption to tetrahydro-photo-gamma tropolone methyl ether (CXXVI).



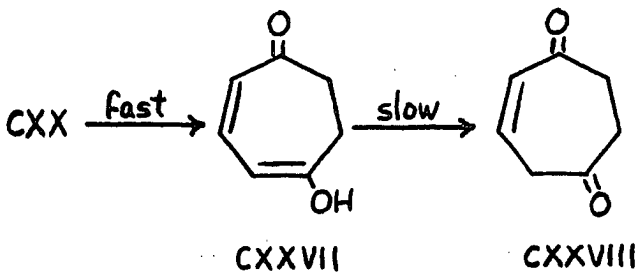
CXXVI

Reduction of CXXV with lithium aluminum hydride gave 5-methoxybicyclo[3.2.0]hept-6-en-2-ol (CXXIV). An infrared comparison of this product with the alcohol obtained from the irradiation of CXXIII, showed them to be identical. The reaction sequence previously completed is shown below:



In an ultraviolet study, Pasto (35) has shown that CXX undergoes the acid and base conversions shown in Figure 26, page 106. The first (hydrolytic) steps were not studied by Pasto. Figure 27, page 108, shows the rates of hydrolysis of CXX in various media at room temperature.

The dissolution of CXX in dilute acid produces a nearly quantitative yield of CXXVII in less than 1.5 minutes as evi-



CXXVII CXXVIII

denced by the 342 mu absorption in the ultraviolet. The 342 mu peak decays while the 235 mu absorption of CXXIX builds up. The rate of this conversion is shown by curve B in Figure 27, page 108.

The basic hydrolysis of CXX is somewhat different. The immediate, quantitative formation of a 342 mu absorption again shows an extremely rapid hydrolysis (2.1 minutes) of CXX to CXXVII. Curve A in Figure 27 shows the hydrolysis rate of CXX in base as well as acid. The decay of the 342 mu absorption (Curve C, Figure 27) in base is related to the appearance of the 414 mu absorption of CXXVIII and the 361 mu absorption

Figure 26. Ultraviolet study (35) of various cycloheptanone derivatives

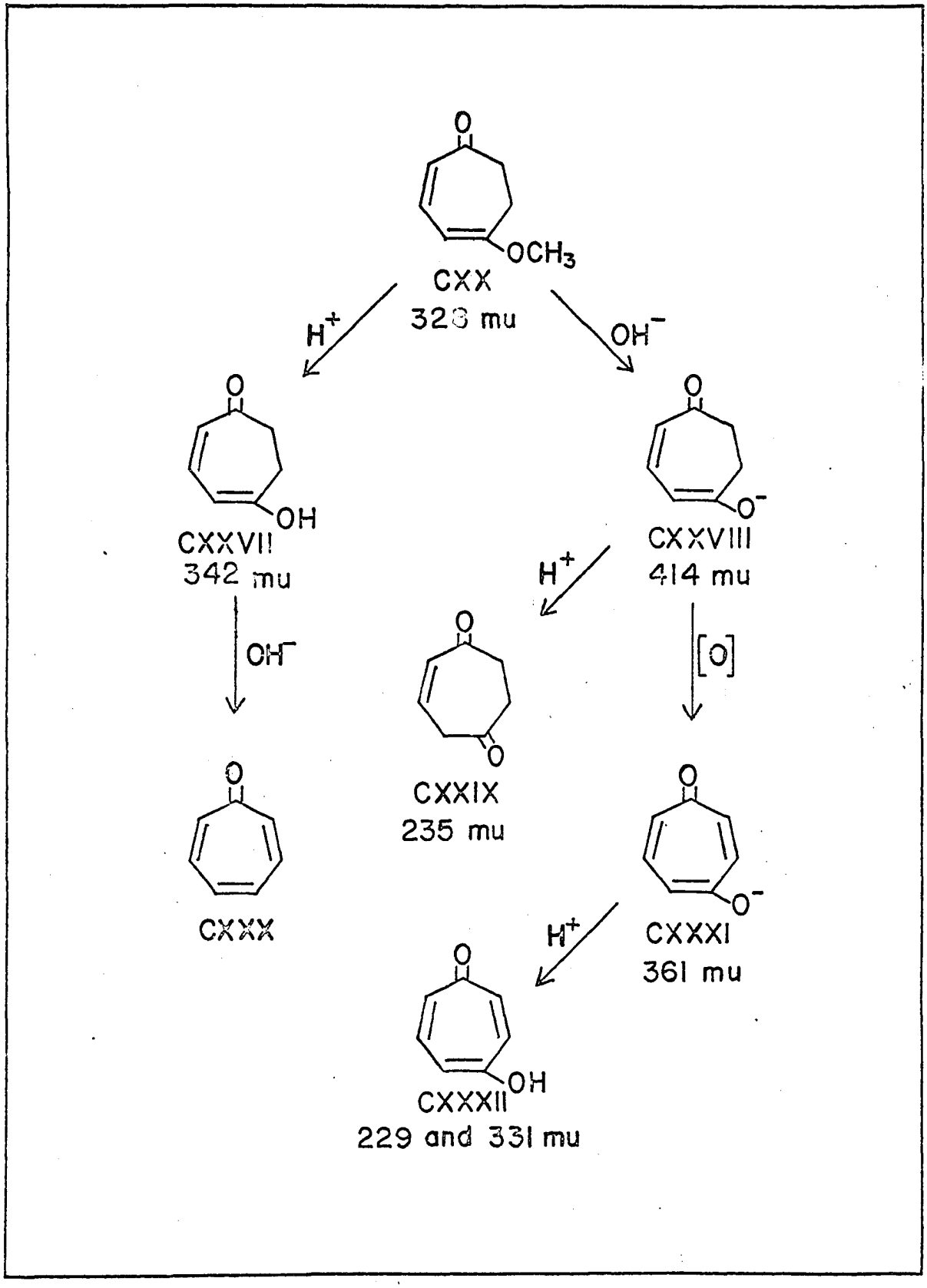

O
OCH3
CXX
326 mu
H+
OH−
O
OH
CXXVII
342 mu
O
O−
CXXVIII
414 mu
OH−
H+
[O]
O
O
CXXIX
235 mu
O
CXXX
O
O−
CXXXI
361 mu
H+
O
OH
CXXXII
229 and 331 mu

Figure 27. Hydrolysis reaction rates

A. Conversion of 5-methoxy-2,4-cycloheptadienone (CXX) to 5-hydroxy-2,4-cycloheptadienone (CXXVII) in 0.0955N H_2SO_4 at 23°C

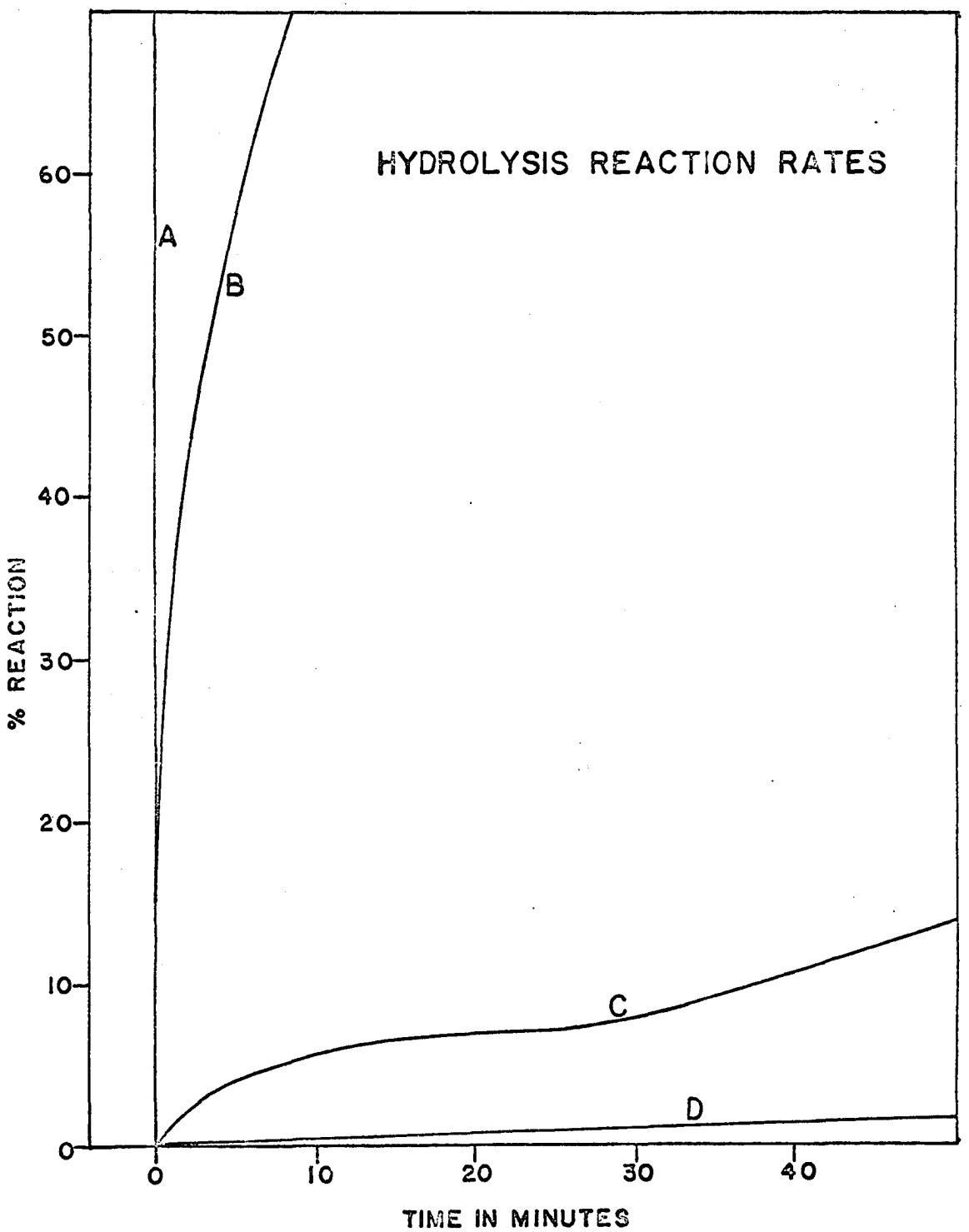
and

Conversion of 5-methoxy-2,4-cycloheptadienone (CXX) to 5-hydroxy-2,4-cycloheptadienone (CXXVII) in 0.0842N NaOH at 23°C

B. Conversion of 5-hydroxy-2,4-cycloheptadienone (CXXIX) to 2-cycloheptene-1,5-dione (CXXIX) in 0.0955N H_2SO_4 at 23°C

C. Hydrolysis of 5-hydroxy-2,4-cycloheptadienone (CXXVII) in 0.0842N NaOH at 23°C

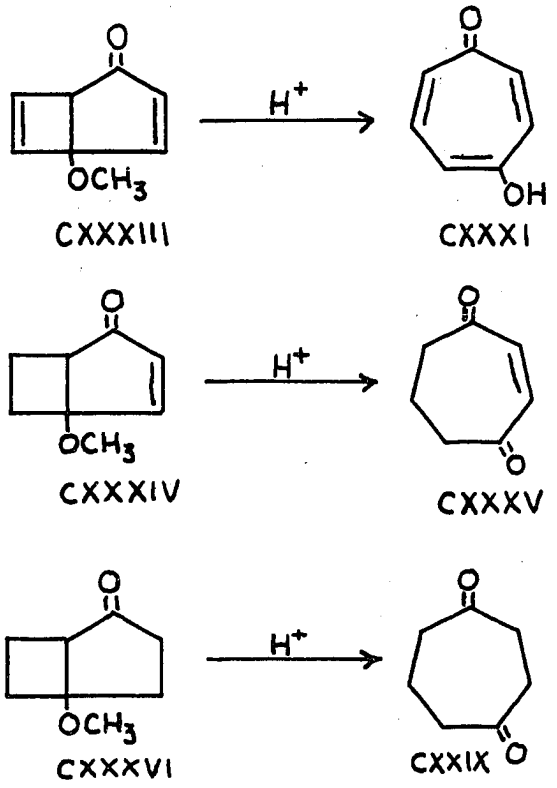
D. Hydrolysis of 5-methoxy-2,4-cycloheptadienone (CXX) in 95% ethanol at 23°C


HYDROLYSIS REACTION RATES
A
B
C
D
% REACTION
60
50
40
30
20
10
0
0
10
20
30
40
TIME IN MINUTES

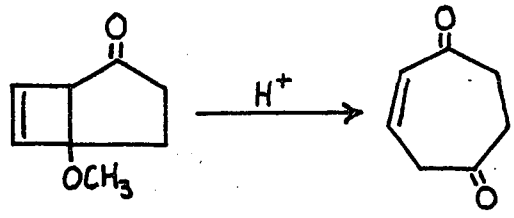
of CXXI observed by Pasto (Figure 26). As Pasto's reaction was run at 90°, curve C in Figure 27 would expectedly show a slow rate of decay of CXXVII. The temperature difference undoubtedly caused Pasto to miss this reaction as it would be too fast at 90°.

Curve D in Figure 27, page 108, shows the rate of hydrolysis of CXX in 95% ethanol at room temperature. The hydrolysis was extremely slow. The reaction in the ultraviolet is complicated by the absorption position of CXX (328 mu) and CXXVII (342 mu). After long periods of time the data are meaningless.

Pasto (35) has previously shown that the following reactions occur in acid.



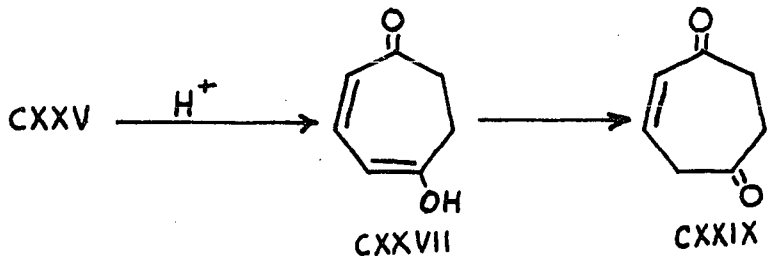
The relative ring-opening rates under the conditions indicated are shown in Figure 28, page 112. In the same study, the ring-opening of CXXV to CXXIX was observed in acid.



CXXV CXXIX

A study of the ring-opening rates of CXXV was undertaken and the results are shown by curves B, C, D, F, and G in Figure 28, page 112.

The ring-opening reaction of CXXV in dilute acid to CXXVII is extremely fast (approximately 1.5 minutes) and is



CXXVII CXXIX

shown by curve B, Figure 28. Curve C is the second half of the reaction and shows CXXVII going to CXXIX.

Ring opening of CXXV to CXXVII in dilute base is shown by curve D in Figure 28. This ring-opening reaction is very

Figure 28. Hydrolysis and ring-opening reaction rates

A. Ring opening of 5-methoxybicyclo[3.2.0]heptan-2-one (CXXXVI) in 0.1N HCl at 22°C (35)

B. Ring opening of 5-methoxybicyclo[3.2.0]hept-6-en-2-one (CXXV) in 0.1074N H_2SO_4 at 23°C

C. Conversion of 5-hydroxy-2,4-cycloheptadienone (CXXVII) to 2-cycloheptene-1,5-dione (CXXIX) in 0.1074N H_2SO_4 at 23°C

D. Ring opening of 5-methoxybicyclo[3.2.0]hept-6-en-2-one (CXXV) in 0.0948N NaOH at 23°C

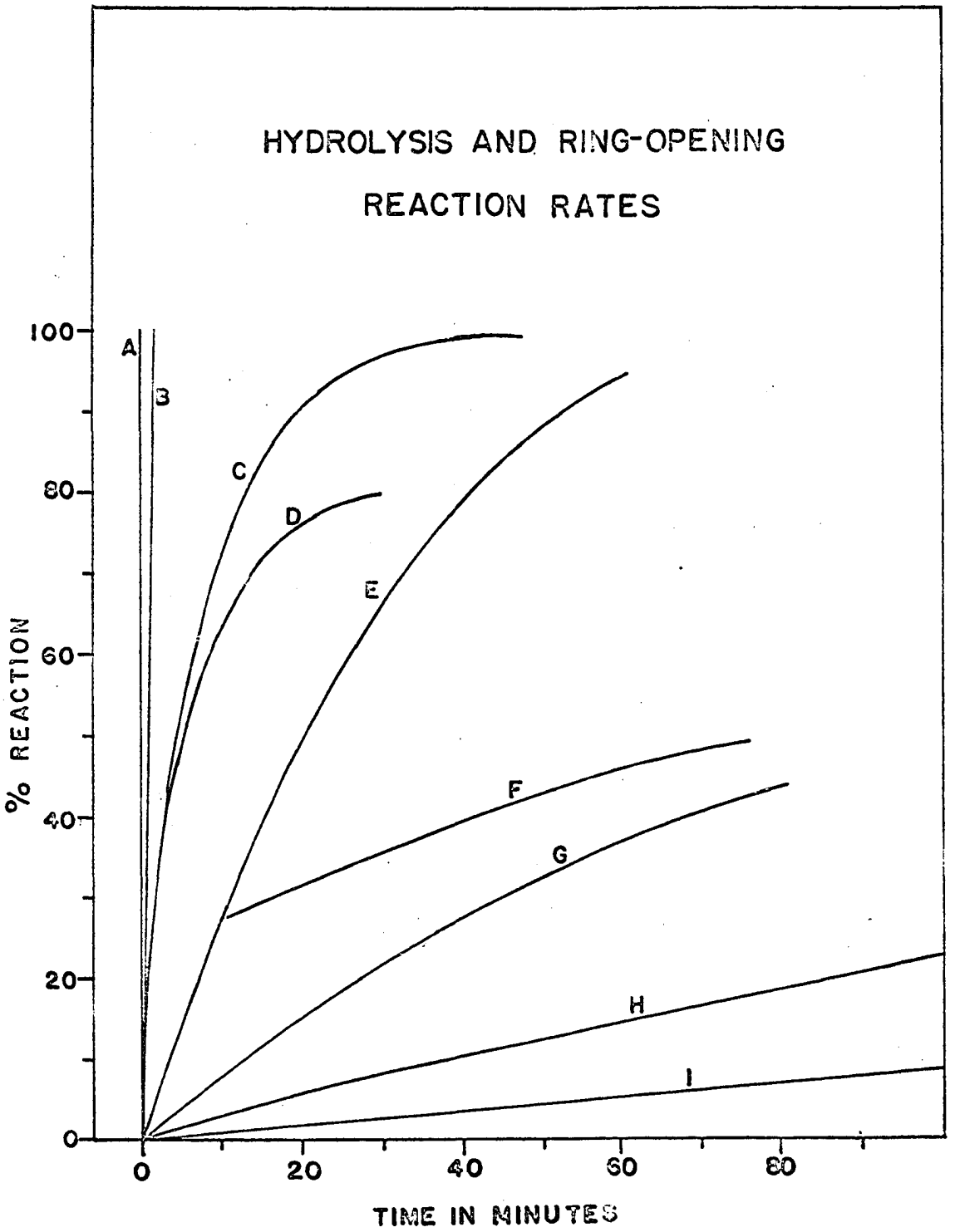
E. Ring opening of 5-methoxybicyclo[3.2.0]heptane-2-one (CXXXVI) in 0.001N HCl at 65°C (35)

F. Ring opening of 5-methoxybicyclo[3.2.0]hept-6-en-2-one in 95% ethanol at 23°C

G. Extrapolation of curve F

H. Ring opening of 5-methoxybicyclo[3.2.0]hept-3-en-2-one in 0.1N H_2SO_4 at 80°C (35)

I. Ring opening of photo-gamma-tropolone methyl ether in 0.1N H_2SO_4 at 80°C (35)

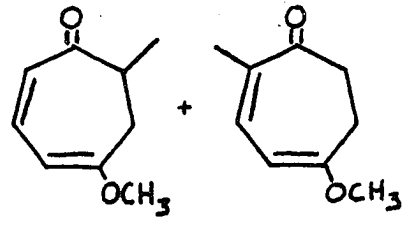

HYDROLYSIS AND RING-OPENING
REACTION RATES
% REACTION
100
80
60
40
20
0
A
B
C
D
E
F
G
H
I
0
20
40
60
80
TIME IN MINUTES

fast in base.

The curve (F) showing the ring-opening of CXXV in 95% ethanol is anomalous. This is undoubtedly due to the ability of CXXV to open on standing. Crude extrapolation of F back to an artificial origin and offsetting this curve to the correct origin gives G.

These data show that ring opening in CXXVI > CXXV >> CXXIV > CXXXIII. The reader is referred to reference 35 for a fine mechanistic discussion of the data.

The reaction of methyl magnesium iodide with gamma-tropolone methyl ether (LVIII) was studied by Pasto (35). Chemical evidence indicated that the ketonic fraction of the product was a 9:1 mixture of CXXXVIII and CXXXIX. The

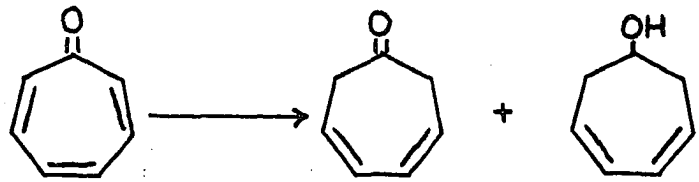


CXXXVIII CXXXIX

reaction was repeated in order to take advantage of a new nuclear magnetic resonance instrument. The ketones isolated were shown by vapor phase chromatography to be a 9:1 mixture as indicated above. The infrared spectrum, Figure 30, page 121, is identical to that obtained by Pasto. The compounds

showed $\lambda_{max}^{95\%\ ethanol}$ 201 mu (8,430) and 331 mu (7,160). The n.m.r. spectrum, Figure 33, page 127, conclusively proved the structure of the major isomer, CXXXVIII. The olefinic region shows three protons (CXXXIX has only two) which have a pattern identical to the olefinic protons of CXX.

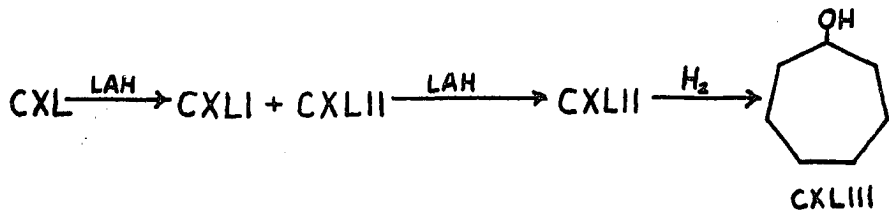
The reaction of tropone (CXL) with lithium aluminum hydride has been shown (35) to give mainly two products, 3,5-cycloheptadienone (CXLI) and 3,5-cycloheptadienol (CXLII).



CXL CXLI CXLII

The structure of the ketone was conclusively proven by catalytic hydrogenation and formation of the known 2,4-dinitrophenylhydrazone. The structure of CXLII was not conclusively proven.

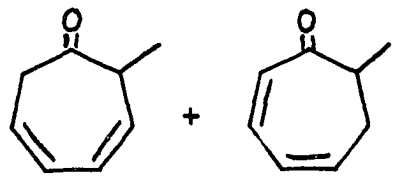
The structure of CXLII was proven in this study by another route. Reduction of tropone with lithium aluminum hydride gave the above mixture. Without isolation, the products were immediately reduced again with the hydride reagent. This step converted the CXLI present to CXLII. Vapor phase chromatography showed three compounds; with one approximating 60% of the mixture. The major isomer was shown to be



CXLII by absorption in the ultraviolet at $\lambda_{max}^{95\%\ ethanol}$ 243 mu (4,440). The infrared spectrum showed no carbonyl absorption.

The crude 3,5-cycloheptadienol was catalytically reduced to cycloheptanol (CXLIII). Vapor phase chromatography of CXLIII showed the same retention time alone and mixed with authentic cycloheptanol. Reaction of CXLIII with 3,5-dinitrobenzoyl chloride gave cycloheptyl 3,5-dinitrobenzoate, m.p. 80° (reported (59) 79°).

The reaction of tropone (CXL) with methyl magnesium iodide was shown by Pasto (35) to yield a mixture of ketones, CXLIV and CXLV. The addition of the methyl group to the two position of tropone was by catalytic hydrogenation of the



CXLIV CXLV

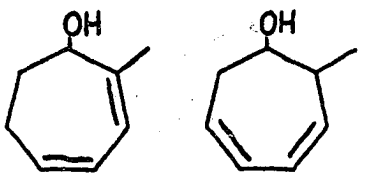
mixture to 2-methylcycloheptanone (CXLVI) which was identified by vapor phase chromatography.

The reactions were repeated to obtain further and more positive proof. The reaction of tropone with methyl magnesium iodide gave a 19:1 mixture of the two ketones by vapor phase analysis. The compounds showed absorption in the ultraviolet at $\lambda_{max}^{95\%\ ethanol}$ 246 mu (5,170) and 291 mu (806). The ultraviolet spectrum shows that CXLIV is the major isomer as the conjugated cycloheptadienone should absorb at approximately 292 mu (59). The absorption at 291 mu is the small amount of CXLV present in the mixture. The infrared spectrum, Figure 30, page 121, shows a 5.86 u carbonyl characteristic (45) of an unconjugated cycloheptanone. The n.m.r. spectrum, Figure 33, page 127, further supports this structure. The methyl group at 8.79 is split into a symmetrical doublet indicating attachment of the methyl to a carbon bearing one hydrogen.

Catalytic hydrogenation of CXLIV and CXLV gave 2-methylcycloheptanone (CXLVI; 5.88 u, Figure 31, page 123). The 2,4-dinitrophenylhydrazone was prepared and found to melt at 116-7° (reported (60) 121-2°) after several recrystallizations. The mixed melting point with authentic 2-methylcycloheptanone 2,4-dinitrophenylhydrazone (m.p. 120-1°) showed no depression and melted at 120-121.3°.

Reduction of the ketone mixture (CXLIV and CXLV) with lithium aluminum hydride gave a mixture of isomeric alcohols,

CXLVII and CXLVIII. The infrared spectrum of the mixture is



CXLVII CXLVIII

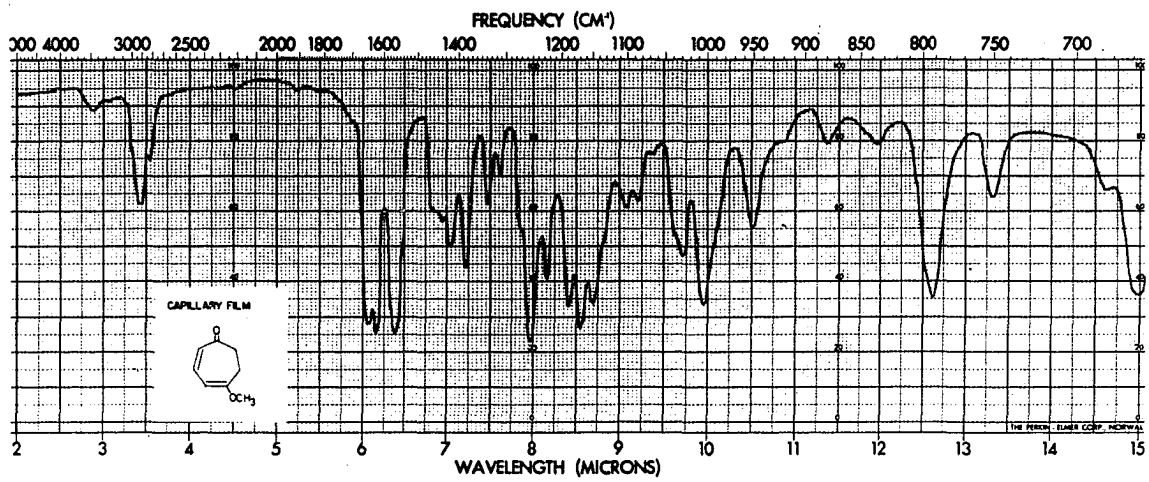
shown in Figure 31, page 123. The structures of the alcohols are assigned from ultraviolet absorptions at 241 and 247 mu. The absorption at 241 mu compares well with 1,3-cycloheptadiene (242 mu in ethanol) and confirms CXLVIII. Application of Woodward's rules (2) to CXLVII would predict a 268 mu absorption for CXLVII which is not observed.

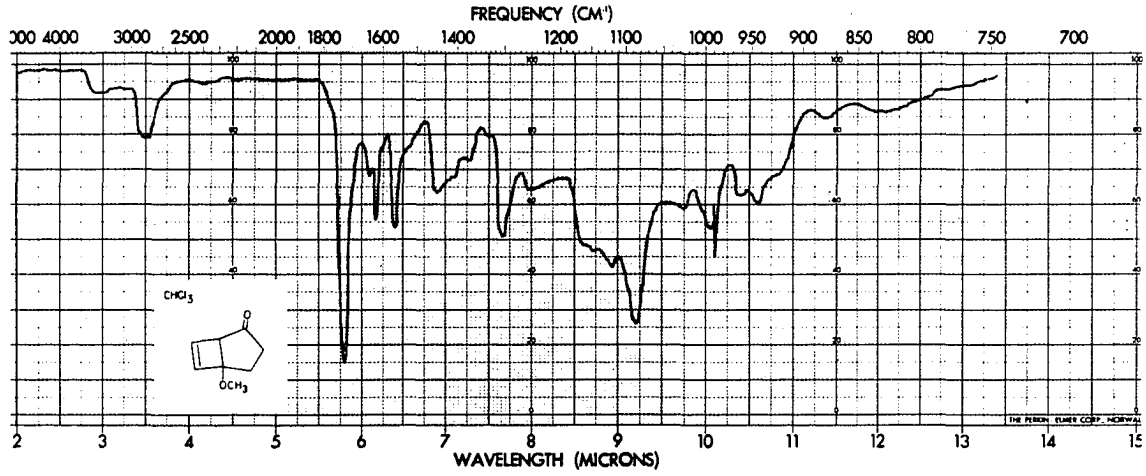
Figure 29. Infrared spectra

Top - 5-Methoxy-2,4-cycloheptadienone CXX

Middle - 5-Methoxybicyclo[3.2.0]hept-6-en-2-one CXXV

Bottom - 5-Methoxy-2,4-cycloheptadienol CXXIII


FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CAPILLARY FILM
O
OCH3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CHCl3
O
OCH3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

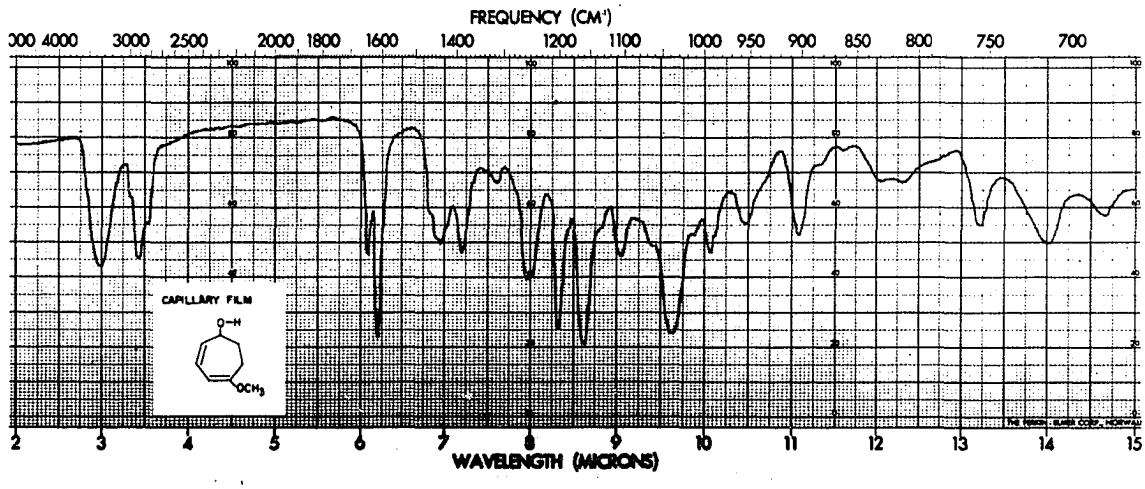
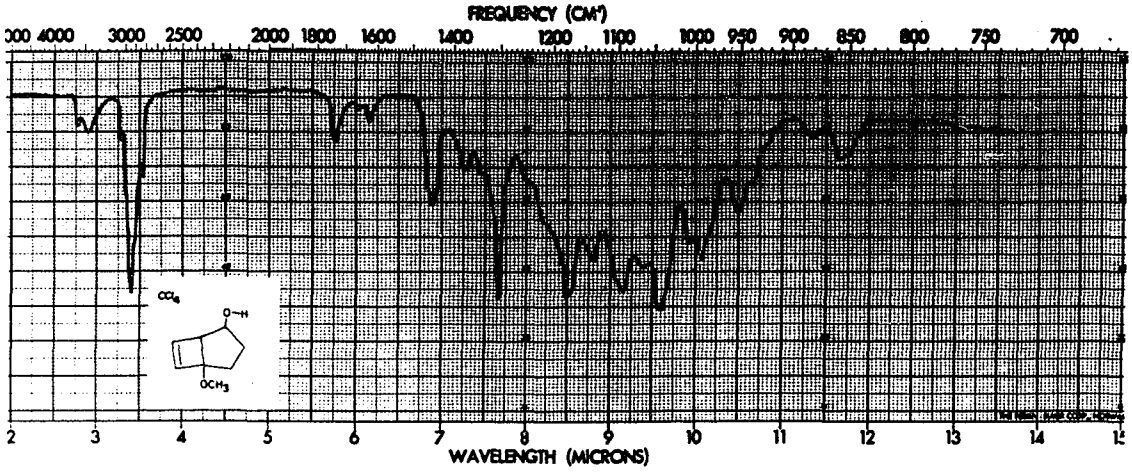

FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CAPILLARY FILM
O–H
OCH3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

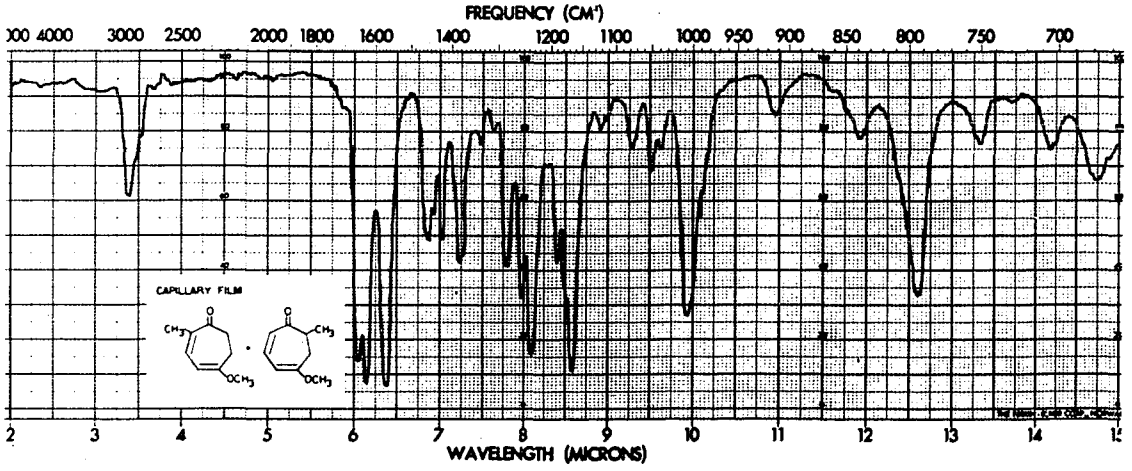
Figure 30. Infrared spectra

Top - 5-Methoxybicyclo[3.2.0]hept-6-en-2-ol CXXIV

Middle - Mixture of 5-methoxy-2-methyl-2,4-cycloheptadienone CXXIX and 4-methoxy-2-methyl-4,6-cycloheptadienone CXXXVIII

Bottom - 2-Methyl-3,5-cycloheptadienone CXLIV


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CAPILLARY FILM
WAVELENGTH (MICRONS)

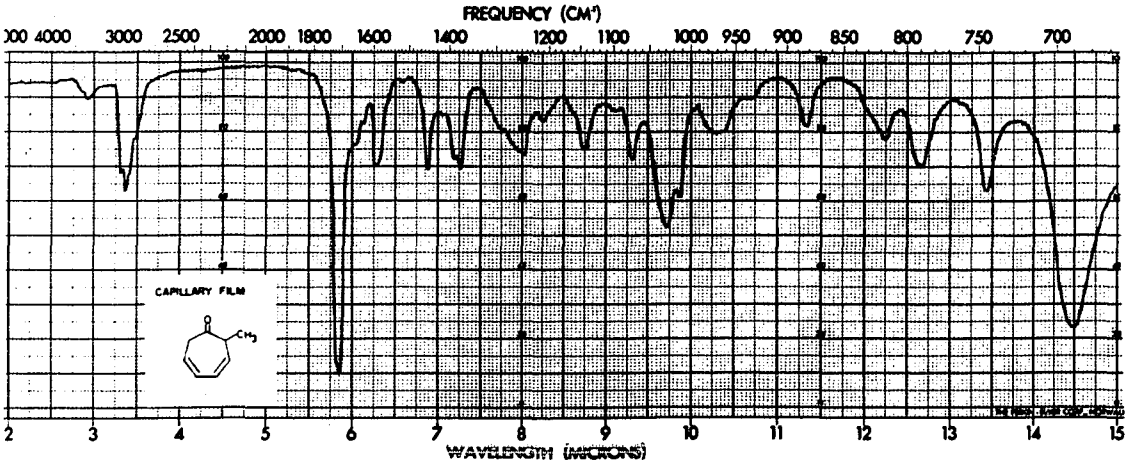
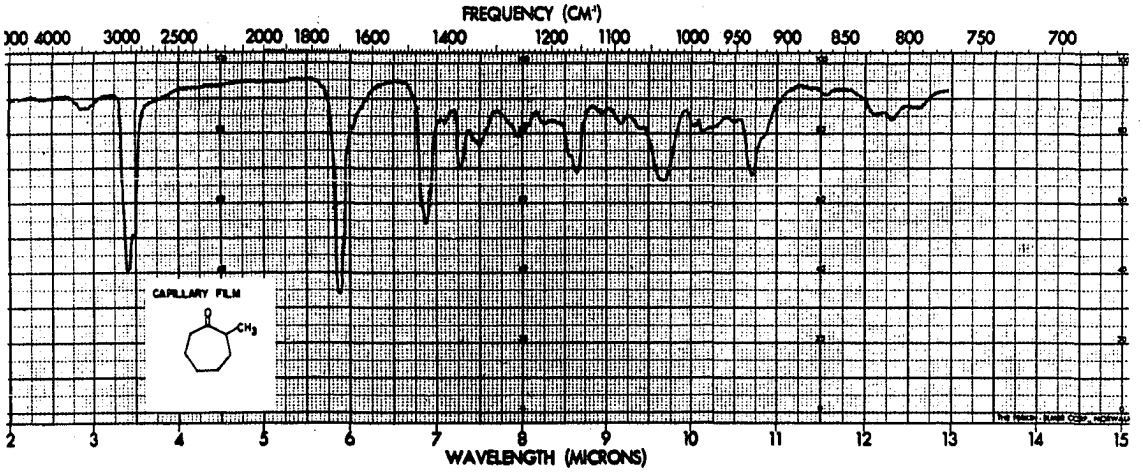

FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CAPILLARY FILM
WAVELENGTH (MICRONS)

Figure 31. Infrared spectra

Top - 2-Methylcycloheptanone CXLVI

Bottom - 2-Methyl-3,5-cycloheptadienol CXLVIII


FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CAPILLARY FILM
CH3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

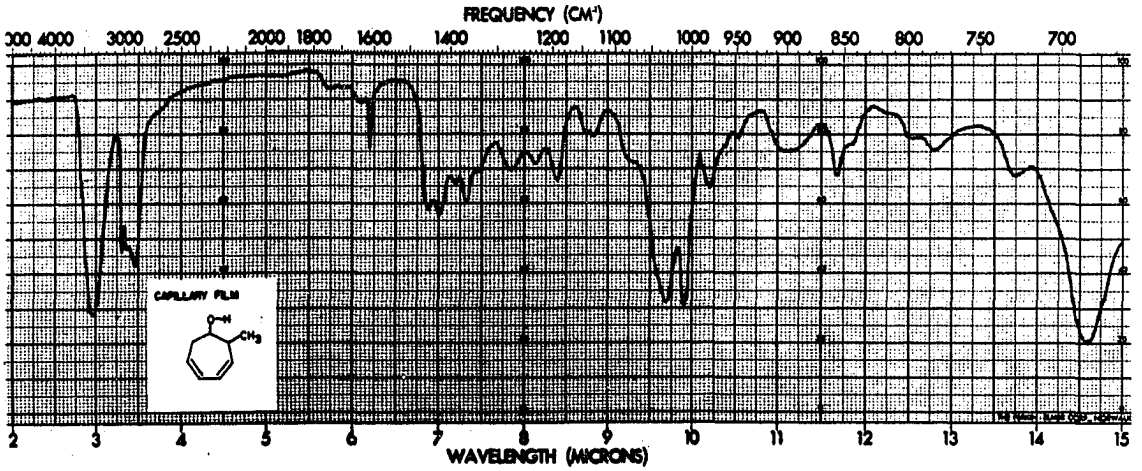
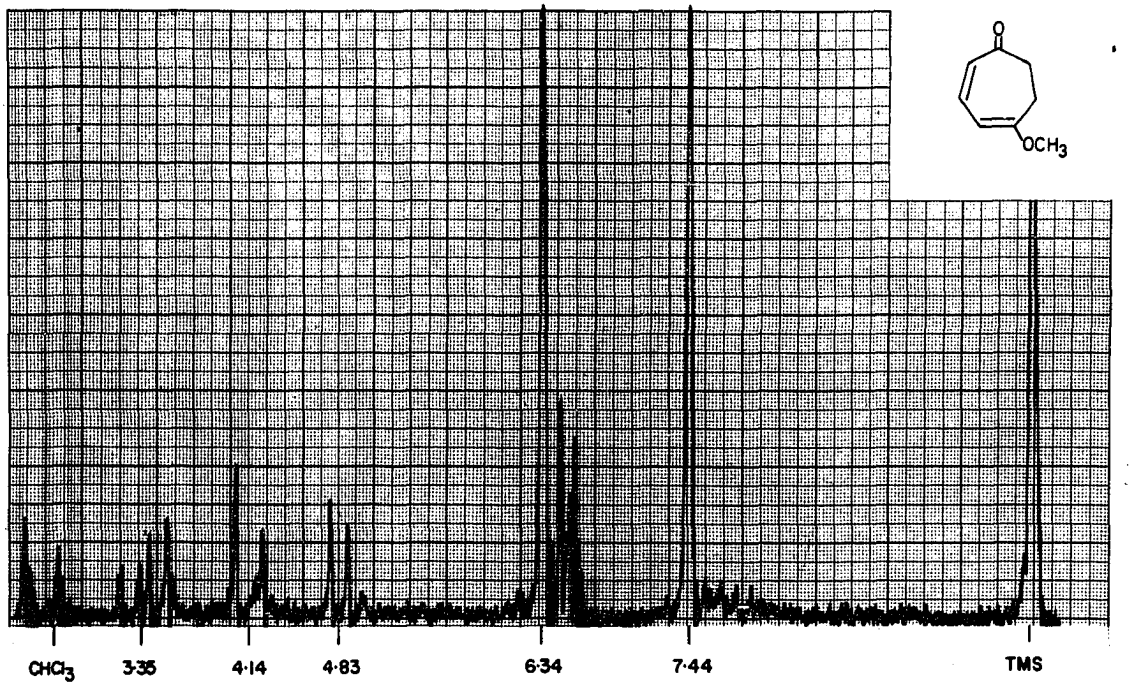

FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
CAPILLARY FILM
O-H
CH3
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Figure 32. Nuclear magnetic resonance spectra

Top - 5-Methoxy-2,4-cycloheptadienone CXX

Bottom - 5-Methoxybicyclo[3.2.0]hept-6-en-2-one CXXV


O
OCH3
CHCl3
3·35
4·14
4·83
6·34
7·44
TMS
TAU

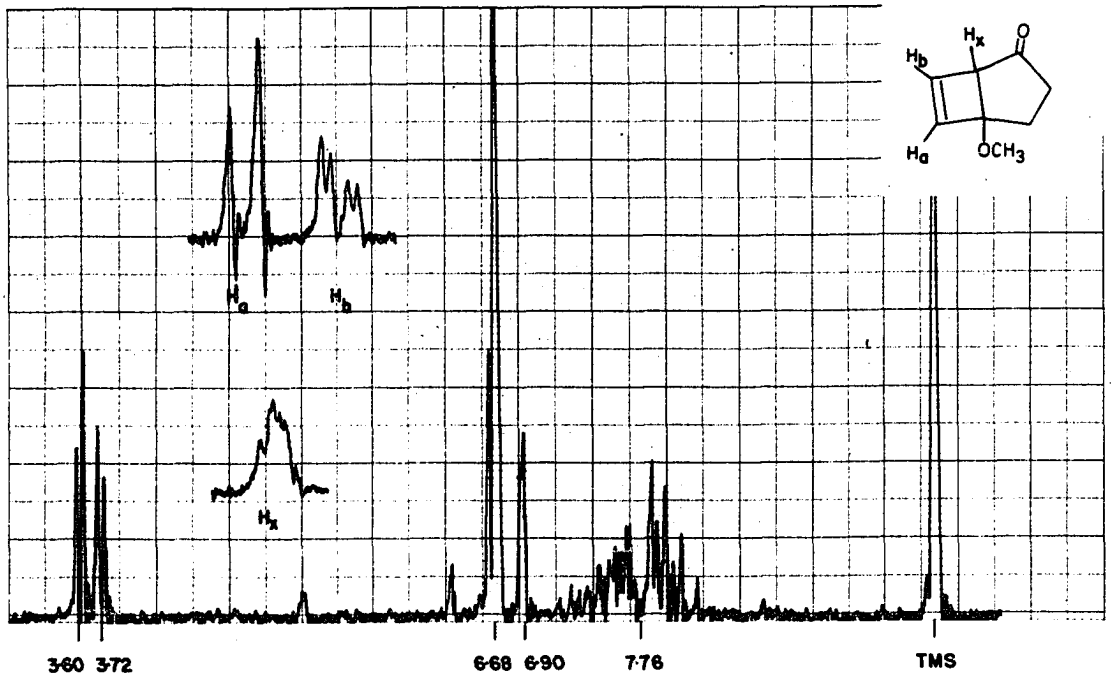
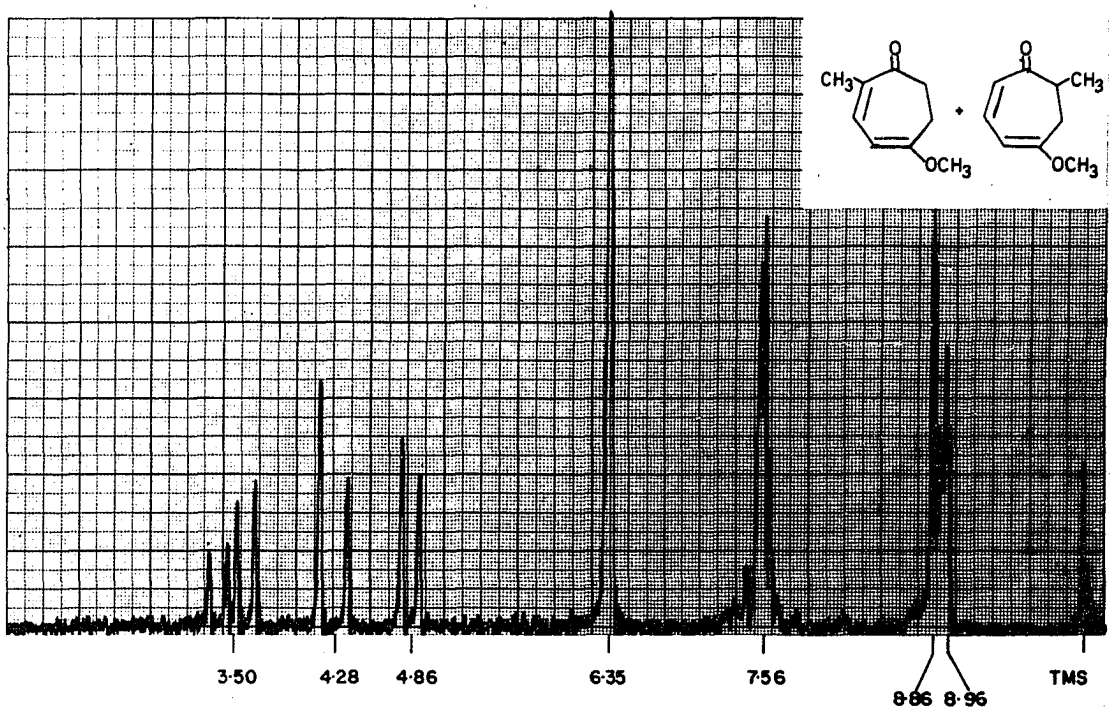
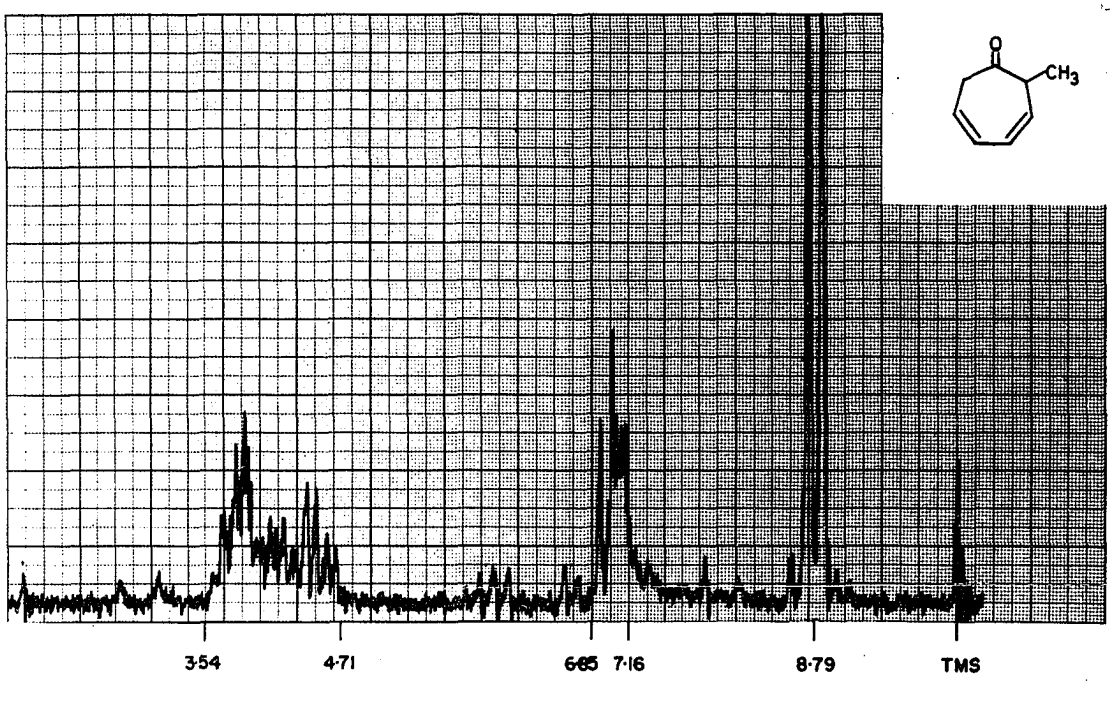

Hx
O
Hb
Ha
OCH3
Ha
Hb
Hx
3·60
3·72
6·68
6·90
7·76
TMS
TAU

Figure 33. Nuclear magnetic resonance spectra

Top - Mixture of 5-methoxy-2-methyl-2,4-cycloheptadienone CXXXIX and 4-methoxy-2-methyl-4,6-cycloheptadienone CXXXVIII

Bottom - 2-Methyl-3,5-cycloheptadienone CXLIV


CH3
OCH3
CH3
OCH3
3·50
4·28
4·86
6·35
7·56
8·86
8·96
TMS
TAU


CH3
3·54
4·71
6·65
7·16
8·79
TMS
TAU

Fractions 8-11 (16%, Dimer I) were combined and recrystallized from absolute methanol. In an evacuated capillary, the crystals melted at 211-213°C. For the infrared spectrum of Dimer I see Figure 5, page 37. The proton magnetic resonance spectrum is shown in Figure 7, page 41. The molecular weight (Rast in camphor) of Dimer I was 294 (theoretical 276.4).
Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.17; H, 10.03.

Fractions 15-36 (80%, Dimer II) were combined and recrystallized from absolute methanol. In an evacuated capillary, the crystals melted at 187.5-190°C. For the infrared spectrum see Figure 5, page 37. The n.m.r. spectrum is shown by Figure 7, page 41. The molecular weight (Rast in camphor) of Dimer II was found to be 264 (theoretical 276.4). The molecular weight determined by vapor osmometry (in benzene) was 274.*
Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.12; H, 10.15.

B. Freshly distilled isophorone (250 ml., b.p. 94-5° at 15 mm.) was irradiated as the neat liquid using a Pyrex immersion well that was cooled internally by tapwater. The source was a Hanovia Type A, high-pressure mercury arc lamp. After three days, 43 g. of solid was filtered off. Chromatography

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*The author expresses his appreciation to Mr. T. A. Rettig for obtaining this molecular weight.

on basic alumina of 0.5 g. of the crude dimer gave 0.32 g. (64%) of Dimer I and 0.18 g. (36%) of Dimer II.

Attempted reaction of isophorone dimer with phenyl magnesium bromide

A 7.2×10^{-3} molar solution (5 ml.) of phenyl magnesium bromide in ether was prepared in the usual way. An ether-tetrahydrofuran (1:1) solution containing 2 g. (7.2×10^{-3} m.) of isophorone dimer was added over a fifteen minute period to the Grignard solution. No reaction was seen to have occurred. After one hour of stirring at room temperature, the reaction mixture was quenched by the careful addition of water. The salts were filtered off, and the ether filtrate was dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the crystalline solid was checked in the infrared for hydroxyl absorption. The carbonyl band was very strong and no hydroxyl absorption was present. Only the dimer isomers could be obtained by column chromatography on basic alumina.

Attempted reaction of isophorone dimer with methyl magnesium iodide

A 7.2×10^{-3} molar solution (5 ml.) of methyl magnesium iodide in ether was prepared in the usual way. The Grignard solution was added over thirty minutes to a stirred solution of 2 g. (7.2×10^{-3} m.) of isophorone dimer mixture in 80 ml. of ether-tetrahydrofuran (5:3). After stirring for one hour

at room temperature, the reaction mixture was hydrolyzed by the careful addition of water. The salts were filtered off and the filtrate was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave a crystalline solid (1.86 g.). Chromatography on basic alumina gave only pure dimer isomers and no addition products.

Lithium aluminum hydride reduction of isophorone dimer

A slurry of 1 g. (0.0036 m.) of the isophorone dimer mixture in 40 ml. of anhydrous ether was quickly added to 0.06 g. (0.0063 m.) of lithium aluminum hydride in 20 ml. of ether. A small volume of tetrahydrofuran was added to take the dimer into solution. The reaction mixture was stirred at room temperature for 24 hours after which it was hydrolyzed by the addition of water. The salts were filtered off, and the ether filtrate was dried over anhydrous magnesium sulfate. After filtration of the salts and removal of the ether under reduced pressure, the resulting solid showed a 2.97 u hydroxyl absorption as well as a 5.94 u carbonyl absorption in the infrared. The solid was chromatographed on basic alumina. The only compounds isolated were diol (m.p. 166-7°) and unreacted dimers.

Attempted reduction of isophorone Dimer II with lithium aluminum tri-tertiary-butoxyhydride

Isophorone Dimer II (0.5 g., 0.0018 m.) was dissolved in 50 ml. of diglyme (freshly distilled from lithium aluminum

hydride); 0.44 g. (0.0018 m.) of the hydride reagent was added to the stirred solution, and the solution was heated at 90° (bath temperature) for twenty hours. Distilled water was added to the hot reaction mixture until no visible reaction occurred. The solution was filtered, and the filtrate was dried over anhydrous sodium sulfate. After reduction in volume (under reduced pressure) by one-half, the diglyme solution was diluted with an equal volume of water that immediately precipitated a solid. After filtration and drying, the solid was found to weigh 0.4 g. and to melt at 187-9°C. (Dimer II m.p. 187.5-189°C).

Reaction of isophorone Dimer II with isopropenyl acetate

Isophorone Dimer II (0.52 g., 0.0019 m.) was dissolved in 7 ml. of isopropenyl acetate. Three drops of concentrated sulfuric acid were added to the solution. The reaction mixture was slowly distilled over a two-hour period until the volume of the reactants was three milliliters. Water (15 ml.) was added to the cooled reaction mixture, and the resulting solution was allowed to stand overnight at room temperature. The crystals that precipitated were filtered off and recrystallized twice from Skelly D. The m.p. was found to be 95-7°C. For the infrared spectrum of Dimer II di-enol acetate (LXXXI), see Figure 5, page 37. The n.m.r. spectrum is reproduced in Figure 8, page 43.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.60; H, 9.36.

Acid catalyzed reaction of isophorone dimer with ethylene glycol

A. One-half gram (0.0018 m.) of isophorone dimer mixture, 0.11 g. (0.0018 m.) of ethylene glycol and 0.1 g. of p-toluene sulfonic acid were dissolved in 250 ml. of toluene. The small volume of water formed in the reaction was azeotroped from the reaction mixture by means of a Dean-Stark reflux head. After all the water had been removed, toluene was slowly distilled until the volume of the reaction mixture was 50 ml. This solution, after cooling, was washed with 2 x 25 ml. portions of 5% potassium carbonate solution. After drying over anhydrous magnesium sulfate, the toluene was removed under reduced pressure leaving a gummy solid (0.58 g.). The residue was chromatographed on a 10 x 260 mm. column of basic alumina. The first fraction, 0.16 g. (m.p. 209-212°, from benzene) corresponded to Dimer I by infrared comparison. The second solid fraction obtained from the column weighed 0.25 g. (m.p. 121.5-123°, from 20% ether in benzene) and corresponded to the mono-ketal of one of the dimer isomers. The last fraction (0.15 g., m.p. 180-3°, from 40% benzene in ether) corresponded to Dimer II by infrared comparison. For the infrared spectrum of the Dimer II mono-ketal (LXXXII), see Figure 6, page 39. The n.m.r. spectrum is shown in

Figure 8, page 43.

B. Four separate attempts were made, using the previous technique, to form the mono-ketal derivative of pure isophorone Dimer I. In two attempts, concentrated sulfuric acid was used as the catalyst while in the other two attempts, p-toluene sulfonic acid was used. In all cases, some isophorone was formed as well as obtention of unreacted Dimer I. The mono-ketal previously formed must have been that of isophorone Dimer II. Later preparation using pure Dimer II gave the mono-ketal derivative in good yields.

Treatment of isophorone Dimer I with concentrated sulfuric acid

A solution of 0.29 g. (0.001 m.) of isophorone Dimer I in 20 ml. of concentrated sulfuric acid was heated at 85-90° for 15 minutes on the hotplate and allowed to sit overnight at room temperature. The acid solution was poured onto 150 ml. of chipped ice, after which it was extracted with 2 x 75 ml. portions of ether. The yellow ether fractions were combined and dried over anhydrous sodium sulfate. After reduction in volume to 5 ml., the ether solution smelled strongly of isophorone. Vapor phase chromatographic analysis on a Perkin Elmer R column showed isophorone to be the only product. The retention time was identical to that of a known sample of isophorone in ether. The aqueous, acidic fraction was brought to neutrality by the addition of solid sodium bicarbonate.

The neutral solution was extracted with ether and analyzed as previously. The only compound found was a slight trace of isophorone.

Treatment of isophorone Dimer II with concentrated sulfuric acid

A solution of 0.24 g. (0.009 m.) of isophorone Dimer II in 20 ml. of concentrated sulfuric acid was heated at 85-90° for 15 minutes on the hotplate and allowed to sit overnight at room temperature. The brown acid solution was poured onto 150 ml. of chipped ice. An immediate precipitate appeared. After filtration and vacuum drying, the solid weighed 0.18 g. The solid was recrystallized from Skelly D giving 0.15 g. (62.5%) of off-white needles melting at 185-8° (isophorone Dimer II m.p. 187.5-189°). The infrared spectrum was identical with that of Dimer II. The aqueous, acidic fraction was extracted with ether, dried and evaporated; giving no residue. The acidic solution was neutralized with solid sodium bicarbonate and extracted with ether. The ether after evaporation left no residue. No isophorone could be detected in the reaction.

Irradiation of 3-methylcyclohexenone

Freshly distilled 3-methylcyclohexenone (15 g., b.p. 78-9° at 13 mm.) in 100 ml. of a 3:1 water-ethanol solution was irradiated for three days with three General Electric

sunlamps (275 watts). A thick oil had settled out which readily crystallized. The solid was filtered and dried. Chromatography of the crude dimer on basic alumina gave one isomer, m.p. 145° (reported (13) 144-5°). For the infrared spectrum of the dimer see Figure 6, page 39.

Experimental for the Photochemistry of Testosterone Acetate

Irradiation of testosterone acetate (LXXXIII)

Testosterone acetate (LXXXIII, 8 g., 0.024 m.) in 2 liters of tertiary-butyl alcohol was irradiated in a Pyrex immersion well for approximately 40 hours with a Hanovia Type A high-pressure mercury arc lamp. The solution was magnetically stirred, and a slow stream of nitrogen was continually bubbled through the solution. The water flowing through the immersion well was so adjusted that the temperature of the solution was just above the freezing point of the solvent (25-6°C). The course of the reaction was followed by vapor phase chromatography using a six-foot analytical column with 1 or 3% General Electric SE-30 on acid-washed, siliconized Chromosorb P (100-120 mesh) as packing. Irradiation was continued until 60% of the starting material had been converted to photoproducts. It was found that complete conversion of starting material caused formation of small quantities of side-products that made separation difficult. After stopping

the reaction, the solvent was removed under reduced pressure by means of a rotary-film evaporator. The gummy residue was immediately chromatographed on a 50 x 200 mm. column of Woelm alumina previously prepared by the addition of 8 ml. of water to each 100 g. of Woelm grade I neutral alumina. The following is a typical example of the chromatography.

The residue was dissolved in a minimum volume of benzene with warming. Skelly B was added to the benzene solution until the concentration of benzene in Skelly B was approximately 25%. The solution was pipetted onto the column, and the chromatography proceeded as follows.

Eluent system	Fraction number	Weight (grams)	Total weight (grams)
5% benzene in Skelly B	1 and 2	--	--
	3	1.47	1.47
	4	1.13	2.60
	5	0.88	3.48
	6	0.64	4.12
	7	0.39	4.51
10% benzene in Skelly B	8	0.36	4.87
	9	0.22	5.09
	10	0.20	5.29
	11	0.11	5.40
	12	0.20	5.60
	13	0.16	5.76
	14	0.09	5.85

	15	0.03	5.88
20% benzene in Skelly B	16	trace	5.88
	17	0.06	5.94
	18	0.07	6.01
	19	0.06	6.07
	20 and 21	0.07	6.14
40% benzene in Skelly B	22 and 23	0.09	6.23
	24 and 25	0.07	6.30
	26	trace	6.30
	27	0.34	6.64
	28 through 36	0.89	7.53
	37 through 43	0.40	7.93

The volume of each fraction collected was 200 ml., and the fractions were checked by vapor phase chromatography for content.

Fractions 3 and 4 (2.6 g., 32.5%) were combined and recrystallized twice from ether/pentane. After drying, the melting point was 167-9°C and $[\alpha]_D^{31} = 32.2^\circ$ (c. = 0.906, $CHCl_3$). For the infrared spectrum and n.m.r. spectrum see Figures 11 and 17, pages 63 and 75. The compound showed $\lambda_{max}^{95\% \text{ ethanol}}$ 209 mu (5,200). The physical constants and spectral data indicated that this compound (10α-methyl-1β, 5β-cycloandrostan-17β-ol-2-one 17-acetate) was identical with Jeger's (26) dihydro-ketone-A_3 obtained from the irradiation of 1-dehydrotestosterone after acetylation and cata-

lytic hydrogenation. This compound was found to be identical to the ketone obtained by Kropp (28) through the same route as Jeger. A mixed melting point of photo-testosterone acetate and an authentic sample from Kropp showed no depression (mixed m.p. 167-9°). The infrared spectra were superimposable in every respect. For the infrared spectrum of Kropp's compound see Figure 11, page 63.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.14. Found: C, 76.48; H, 9.09.

Fractions 5 through 18 (3.4 g., 42.5%) were identified as testosterone acetate by infrared and vapor phase analysis. These fractions were usually added to another irradiation for further conversion to photoproducts.

Fractions 19 through 43 (1.9-2.0 g., 25%) were combined and recrystallized twice from ether/pentane. After drying, the melting point was 109-109.5° and $[\alpha]_D^{31} = 39.3^\circ$ (c. = 1.43, $CHCl_3$). The lumi-testosterone acetate (LXXXV, 3α-(3-keto-1-cyclopenten-1-yl)-3β,5aβ-dimethyl-6β-acetoxy-as-hydrindacene) showed $\lambda_{max}^{95\% \text{ ethanol}}$ 232 mu (18,600). For the infrared spectrum see Figure 13, page 67, and for the n.m.r. spectrum (52 mg. in 400 ul $CDCl_3$) see Figure 19, page 79.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.14. Found: C, 76.48; H, 9.16.

(LXXXVIII) showed m.p. 204-5° and $[\alpha]_D^{31}$ = 66.2° (c. = 1.63, $CHCl_3$). The yield of pure product was 331 mg. (67%). For the infrared ($CHCl_3$) and n.m.r. spectra see Figures 12 and 18, pages 65 and 77. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ ethanol}$ 208.8 mu (6,470).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.20; H, 9.85. Found: C, 79.01; H, 10.10.

10α-Methyl-1β,5β-cycloandrostan-2,17-dione (LXXXIX)

The chromium trioxide-pyridine complex was prepared in the usual way using 250 mg. of chromium trioxide and 2 ml. of pyridine (61); 210 mg. of LXXXVIII in 3 ml. of pyridine were added to the oxidation mixture with cooling. After thorough swirling, the reaction mixture was allowed to sit at room temperature for six hours. Water (100 ml.) was added to the black solution, after which it was extracted with 4 x 30 ml. portions of ether. The ether fractions were combined and washed with 5 x 50 ml. portions of ice-cold 0.1N hydrochloric acid followed by 2 x 50 ml. portions of water. After drying over anhydrous magnesium sulfate, the ether was removed under reduced pressure leaving 187 mg. of crystalling, white residue (90%). The solid was recrystallized from methanol/water giving colorless needles which after drying at 56° at 0.1 mm. melted at 153-4° and showed $[\alpha]_D^{31}$ = 133° (c. = 1.11, $CHCl_3$). The ultraviolet spectrum showed $\lambda_{max}^{95\%\ ethanol}$ 208.7 mu (6,720)

and 283.5 mu (111). The infrared and n.m.r. spectra are shown in Figures 12 and 21, pages 65 and 83.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.67; H, 9.42.

3α-(3-Ketocyclopentyl)-3β,5aβ-dimethyl-6β-acetoxy-as-hydrindacene (XC)

A solution of 104.3 mg. (315 um) of lumi-testosterone acetate in absolute ethanol was hydrogenated over 5% palladium on charcoal. The sample was allowed to absorb one molar equivalent of hydrogen. After removal of the solvent under reduced pressure, the residual viscous oil was recrystallized three times from methanol/water giving 57 mg. (54%) of colorless needles that melted at 84-6°C after vacuum drying. For the infrared spectrum of dihydro-lumi-testosterone acetate (XC) see Figure 14, page 69. The n.m.r. spectrum is reproduced by Figure 21, page 83.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.70. Found: C, 75.93; H, 9.64.

3α-(2,4-Dibenzylidene-3-ketocyclopentyl)-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (XCI)

A solution of 50 mg. (150 um) of XC and 0.5 ml. of freshly distilled benzaldehyde in 10 ml. of 1N methanolic potassium hydroxide was shaken well and allowed to sit at room temperature for three days. Water (10 ml.) was added to the reaction mixture, and after sitting for three hours a yellow

solid precipitated. The solid was collected by centrifugation and recrystallized from methanol/water. After two more recrystallizations from acetone/water, 17 mg. (10%) of yellow needles melting at 190-2°C were obtained. The dibenzal derivative (XCI) showed $\lambda_{max}^{95\% \text{ ethanol}}$ 231 mu (16,800) and 348 mu (32,100) in the ultraviolet. The infrared spectrum is shown in Figure 14, page 69.

Anal. Calcd. for $C_{33}H_{38}O_2$: C, 84.94; H, 8.21. Found: C, 85.13; H, 8.16.

3α-(3,5-Dibenzylidene-4-keto-1-cyclopenten-1-yl)-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (XCII)

A solution of lumi-testosterone acetate (LXXXV, 200 mg.), 1 ml. of freshly distilled benzaldehyde and 20 ml. of 1N methanolic potassium hydroxide was refluxed for 12 hours. Water (20 ml.) was added, and the yellow oil was extracted with ether. After drying over anhydrous sodium sulfate and removal of the ether under reduced pressure, the residual, viscous oil was chromatographed on Woelm grade III neutral alumina. The benzaldehyde eluted quickly in 25% benzene in Skelly B. The dibenzal derivative came off the column in 10% Skelly B in benzene. After one recrystallization, the m.p. of the yellow, crystalline solid was 183-6°C. One further recrystallization from ether gave a melting point of 186-187.5°C. The ultraviolet spectrum showed $\lambda_{max}^{95\% \text{ ethanol}}$ 317 mu (31,300) and 225.3 mu (shoulder, 15,000). The infra-

red spectrum of the dibenzal derivative XCII is shown in Figure 13, page 67. The n.m.r. spectrum is shown in Figure 20, page 81.

Anal. Calcd. for $C_{33}H_{36}O_2$: C, 85.30; H, 7.81. Found: C, 85.30; H, 7.79.

3α-(3-Keto-1-cyclopenten-1-yl)-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (XCIV)

A solution of 0.5 g. (0.0015 m.) of LXXXV in 25 ml. of 5% methanolic potassium hydroxide was refluxed for one hour after which the reaction mixture was cooled and diluted with 200 ml. of water. After cooling in an ice bath, the solid was filtered, washed with water and recrystallized from methanol-water. The resulting pale-yellow platelets showed m.p. 148.5-150° and $[\alpha]_D^{31} = 54.5°$ (c. = 1.09, $CHCl_3$). The yield of pure lumi-testosterone (XCIV) was 255 mg. (50%). The infrared spectrum (in $CHCl_3$) is shown in Figure 14, page 69, and the n.m.r. spectrum is shown in Figure 19, page 79. The ultraviolet spectrum showed $\lambda_{max}^{95\% \text{ ethanol}}$ 232.3 mu (18,900) and 297.7 mu (87).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.20; H, 9.85. Found: C, 79.47; H, 10.00.

3α-Carboxy-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (XCIIIb)

LXXXV (1 g.) was converted to its dibenzal derivative by the method described on page 143; 0.78 g. of crude XCII was

obtained after the chromatography. In order to acetylate the 17-hydroxy group the residue was dissolved in a 1:1 mixture of acetic anhydride-pyridine and allowed to sit overnight at room temperature. The pyridine and acetic anhydride were removed under reduced pressure leaving a viscous brown liquid. The residue was dissolved in 100 ml. of ethyl acetate and ozonized at -10°. A large excess of ozone was fed through the solution. The ozonolysis caused the brilliant yellow color of the dibenzal derivative to disappear. Three ml. of 30% hydrogen peroxide was added to the ozonolysis mixture, and the resulting solution was magnetically stirred for 12 hours at room temperature. Fifteen ml. of water were added to the solution, and the ethyl acetate was removed under reduced pressure. The insoluble (in water) organic solids were extracted with 2 x 50 ml. portions of ether. The ether solution was extracted with 2 x 20 ml. portions of 5% potassium hydroxide. The basic extracts were combined and warmed on the hotplate for 1 hour. The solution was cooled and brought to the acid side by addition of cold, 6N hydrochloric acid. The acidic solution was extracted with 3 x 50 ml. portions of ether to remove the gummy solid that had precipitated upon acidification. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure leaving 160 mg. of solid residue. The residue was chromatographed on a 15 x 170 mm. column of Unisil

(silicic acid, 100-120 mesh). The first solid to elute from the column in benzene was benzoic acid (76 mg.). It was identified by comparison of the infrared spectra. Another acid (21 mg., very smelly) came off the column in 1:9 ether/benzene. This acid was not identified. The third acid to elute from the column showed characteristic steroid absorption in the infrared. The fraction (48 mg.) was dissolved in a small volume (15 ml.) of 5% potassium hydroxide and precipitated in the cold by addition of cold, dilute hydrochloric acid. The resulting solid was filtered and washed with water. After air drying, the acid was recrystallized from ethyl acetate and dried at 56° (0.1 mm.) for 2 hours. The melting point was taken, but variable results were obtained. With a very small sample and slow heating, the melting point was 180-181.5° while a small sample with fast heating melted at 185-7°. A large sample and slow heating showed a melting point of 191-3°. The acid was recrystallized twice from methanol/water and dried for two hours at 56° and 0.1 mm. The melting point was 189.5-191°. The structure of the acid was formulated as 3α-carboxy-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (XCIIIb). The acid showed $[\alpha]_D^{27} = 11°$ (c. = 0.575, $CHCl_3$).

An infrared spectrum of this acid (XCIIIa, prepared by a different route) was obtained from Caspi (52). The infrared spectrum of the authentic acid was identical to that of the ozonolysis product (for the comparison see Figure 15, page 71). The melting point of Caspi's acid was 189-190°.

Caspi quoted peaks in the n.m.r. at 6.34, 8.88 and 9.28 τ for the acid. The n.m.r. of XCIIIb is reproduced in Figure 20, page 81.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.58. Found: C, 71.56; H, 9.58.

Preparation of 3α-carboxy-3β,5aβ-dimethyl-6β-propionoxy-as-hydrindacene (XCVII)

A solution of 15 mg. of 3α-carboxy-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (XCIIIb) in 2 ml. of a 1:1 mixture of pyridine and propionic anhydride was allowed to sit at room temperature for two days after which the propionic anhydride and pyridine were removed under reduced pressure leaving a tan solid. The residue was dissolved in methanol and with cooling (0°) a small amount (2 mg.) of crystals precipitated. These were isolated and found to melt at 189.5-191° indicating starting material (XCIIIb). The mother liquor, after addition of water, produced a crop (10 mg.) of fine needles after cooling. The solid was isolated and washed by centrifugation. After drying at 56° and 0.1 mm. for 1 hour, XCVII was found to melt at 151-2° (literature (52) 151-2°). The infrared spectrum of XCVII is shown in Figure 13, page 67. A reproduction of the infrared spectrum obtained from Caspi (52) is shown by Figure 16, page 73.

Experimental for the Photochemistry of Spiro-(4,5)-deca-1,4-diene-3-one

Spiro-(4,5)-deca-1,4-diene-3-one (CVII)

A. The procedure of Baird and Winstein (56) was used to prepare the spiro-dienone. The only modification made in their procedure involved the purification of the crude product. Instead of distillation, the crude spiro-dienone was dissolved in a small (approximately 50 ml.) volume of ether and percolated through a 10 cm. column of basic alumina. This procedure served to remove all phenolic and polymeric impurities. The dienone from this procedure was used in the irradiation of CVII in ether.

B. To obtain pure spiro-dienone, the crude product was carefully chromatographed on basic alumina. Only two fractions were obtained. The first fraction (see the following experiment) was later shown to be a cyclic ether. The second fraction was the pure spiro-dienone. After removal of the solvent, the dienone was molecularly distilled from glass apparatus previously soaked in 1% sodium hydroxide. The dienone thus obtained was crystalline at room temperature. For the infrared spectrum and n.m.r. spectrum see Figures 22 and 24, pages 93 and 97. The spiro-dienone showed absorption at $\lambda_{max}^{95\% \text{ ethanol}}$ 242 mu (14,500).

Irradiation of spiro-(4,5)-deca-1,4-diene-3-one (CVII) in ether

The spiro-dienone (CVII, 3.37 g., 0.023 m.) in 1 l. of anhydrous ether was irradiated in a Pyrex flask. The flask contained internal glass cooling coils through which tapwater was rapidly circulated. The flask was mounted approximately 20 cm. from a General Electric UA-3 high-pressure mercury arc lamp. The progress of the irradiation was followed in the ultraviolet by observing the decay of the 242 mu absorption of the spiro-dienone. The reaction was stopped after 18.3 hours of irradiation. After completion of the irradiation, the reaction mixture showed absorptions at 278 and 305 mu in the ultraviolet. The ether solution was dried over anhydrous sodium sulfate and after filtration, the ether was removed under reduced pressure giving 3.34 g. of dark yellow residue. One gram of the residue was chromatographed on a silica gel column (25 x 200 mm.). The silica gel was applied to the column in a slurry with Skelly B. The total volume of each eluent was 70 ml., and the volume of each collected sample was 20 ml. The following fractions were collected:

Eluent	Fraction no.	Weight	Form
3:4 benzene in Skelly B	10-12 (A)	0.12 g.	solid, m.p. 123-6°
3:4 Skelly B in benzene	14-15 (B)	small	semi-solid
2:5 Skelly B in benzene	16-19 (C)	0.3 g.	liquid
1:6 Skelly B in benzene	21-23 (D)	0.15 g.	liquid

benzene	24-27 (E)	0.16 g.	solid, m.p. 131-4°
2:5 ether in benzene	30-32 (F)	0.2 g.	solid

Fraction A (0.12 g., 12% of sample weight) was recrystallized from cyclohexane and dried in a vacuum desiccator (15 mm.). After drying, the melting point was 132-132.5°. The infrared spectrum is shown in Figure 23, page 95. The n.m.r. spectrum is shown in Figure 25, page 99. The ultraviolet spectrum showed $\lambda_{max}^{95\% \text{ ethanol}}$ 277 mu (1,160) and 285 mu (855). The osmometric molecular weight in benzene was 294. The molecular weight and spectral data indicated that the compound was a cyclic dimer (CXIX) of 4-p-hydroxyphenyl-1-butanol. Anal. Calcd. for $C_{20}H_{24}O_2$: C, 80.97; H, 8.16. Found: C, 80.99; H, 8.21.

Fraction B, by infrared analysis, was found to be a mixture of fractions A and C. No further separation was attempted.

Fraction C (0.3 g., 30% of sample weight) was sublimed at 0.3 mm. and 90°. The white crystals (m.p. 66-8°) showed $\lambda_{max}^{95\% \text{ ethanol}}$ 273 mu (1,340) and 279 mu (1,340) (57). The n.m.r. spectrum of CVIII is shown in Figure 25, page 99. Equal amounts of CVIII and authentic 5,6,7,8-tetrahydro-1-naphthol (m.p. 65-7°) when admixed melted at 66.5-67.5°. Both compounds were identical in the infrared. For the infrared comparison see Figure 22, page 93.

Fraction D (0.15 g., 15% of sample weight) was recrystallized from hexane giving colorless crystals (m.p. 57.5-59°).

The compound showed $\lambda_{max}^{95\% \text{ ethanol}}$ 281.3 mu (2,250) (57) in the ultraviolet. The n.m.r. spectrum of CIX is reproduced in Figure 24, page 97. Equal amounts of CIX and authentic 5,6,7,8-tetrahydro-2-naphthol (m.p. 58-9°) when admixed melted at 58-9°. The infrared spectra of both compounds were identical. For the infrared comparison see Figure 22, page 93.

Fraction E (0.16 g.) was recrystallized from n-hexane. The colorless solid melted at 140-1° after drying in a vacuum desiccator. The infrared spectrum (titled as Unknown) is shown in Figure 23, page 95. The ultraviolet spectrum showed absorption at 230 mu. The molecular weight (ebullioscopic in benzene) was found to be 160. The structure of the compound was not elucidated.

Anal. Found: C, 80.90; H, 7.93.

Attempted acid-catalyzed rearrangement of spiro-(4,5)-deca-1,4-diene-3-one on silicic acid

The spiro-dienone (0.26 g.) in benzene was eluted onto a column of silicic acid. The sample was allowed to remain on the column for 30 hours. The column was then eluted with benzene giving a fraction of the cyclic ether. Further elution with ether-benzene gave 0.15 g. of spiro-dienone identified by infrared comparison with pure dienone. No 5,6,7,8-tetrahydro-2-naphthol (CIX) was obtained after elution with methanol.

Purification of Aldrich technical grade 5,6,7,8-tetrahydro-1-naphthol and 5,6,7,8-tetrahydro-2-naphthol

The naphthols obtained from the Aldrich Chemical Company were technical grade and very impure. An extremely convenient method of purification was found that worked very well on most phenolic compounds. The crude naphthol was dissolved in Skelly B and percolated through a 10 cm. column of silicic acid. The eluate was slightly yellow while the column retained all of the colored impurities. After removal of the Skelly B under reduced pressure the naphthol was recrystallized in the usual way. The 5,6,7,8-tetrahydro-1-naphthol after this treatment and recrystallization from Skelly B melted at 65-7°. The 5,6,7,8-tetrahydro-2-naphthol, after the same treatment, melted at 58-9°.

Irradiation of spiro-(4,5)-deca-1,4-diene-3-one (CVII) in tertiary-butyl alcohol

A solution containing 0.84 g. (0.005 m.) of the spirodienone in 500 ml. of tertiary-butyl alcohol was irradiated in a Pyrex flask. The flask was constructed with internal glass cooling coils through which tapwater was circulated. The water was circulated at a rate slow enough to prevent the solvent from freezing. The flask was mounted 15 cm. from a General Electric UA-3 medium-pressure mercury arc lamp. The progress of the irradiation was followed in the ultraviolet by observing the decay of the 242 mu absorption of the spiro-

dienone. The irradiation was stopped after 10 hours, and the solvent was removed under reduced pressure. The entire residue was chromatographed on a silicic acid column. The first fraction (0.25 g., 27.5%, from dilute benzene in Skelly B) was tentatively identified in the infrared as 5,6,7,8-tetrahydro-1-naphthol (CVIII). One recrystallization from hexane gave a crystalline solid (m.p. 67-68.5°) which admixed with authentic 5,6,7,8-tetrahydro-1-naphthol showed no depression (m.p. 67-8°). The second fraction (0.1 g.) was found to be a mixture of naphthols by infrared analysis. The third fraction (0.16 g., 20%) to elute from the column was tentatively identified as 5,6,7,8-tetrahydro-2-naphthol (CIX) from its infrared spectrum. The compound, crude from the column, melted at 50-55°. One recrystallization from n-hexane gave a white solid (m.p. 58-9°). When the solid was admixed with authentic 5,6,7,8-tetrahydro-2-naphthol (m.p. 58-9°), there was no depression (m.p. 58-9°). All infrared spectra of the naphthols were superimposable with their authentic counterparts. The column was finally eluted with 5% methanol in chloroform. A viscous liquid was eluted, but the fraction was so small it was not investigated.

Irradiation of spiro-(4,5)-deca-1,4-diene-3-one (CVII) in glacial acetic acid

The spiro-dienone (CVII, 0.81 g., 0.0055 m.) in 300 ml. of glacial acetic acid was irradiated in a Pyrex flask for 10

hours. The flask was constructed with internal glass cooling coils through which tapwater was rapidly circulated. The acetic acid was removed under reduced pressure by means of a rotary evaporator. The residual red-brown residue was chromatographed on a 25 x 300 mm. column of silicic acid. The first fraction (0.156 g., 19%, 1:3 Skelly B-benzene) to elute from the column was identified in the infrared as being 5,6,7,8-tetrahydro-1-naphthol (CVIII). Crystallization of the oil from hexane gave pure CVIII, m.p. 67-68.5°. The mixed m.p. of CVIII with authentic 5,6,7,8-tetrahydro-1-naphthol showed no depression (m.p. 67-8°). The second fraction to elute weighed 0.041 g. (5.1%) and was a mixture of the two naphthols (based on infrared absorption). The third fraction (0.335 g., 41%, from benzene) was shown to be 5,6,7,8-tetrahydro-2-naphthol (CIX) by infrared analysis. The solid was recrystallized from hexane and dried under vacuum. The m.p. was found to be 58.5-59.5°. The mixed melting point of CIX with authentic 5,6,7,8-tetrahydro-2-naphthol showed no depression (m.p. 58.5-59°). The infrared spectra of both CVIII and CIX were entirely superimposable with their authentic counterparts.

Stability check on spiro-(4,5)-deca-1,4-diene-3-one (CVII) in glacial acetic acid

A solution of 0.56 g. of CVII in 3 ml. of glacial acetic acid was allowed to stand in the dark at room temperature

(29-30°) for 10.5 hours. The ultraviolet absorption spectrum of the solution was recorded at zero time and at the end of the waiting period. No decrease in absorption was observed at 242 mu (c. = 1.26×10^{-5} m.), and no increase in absorption was observed at 281 mu (c. = 1.26×10^{-3} m.). CVII shows $\lambda_{max}^{95\% \text{ ethanol}}$ 242 mu (14,500), and 5,6,7,8-tetrahydro-2-naphthol shows $\lambda_{max}^{95\% \text{ ethanol}}$ 281.3 mu (2,250) in the ultraviolet. All dilutions were made with 95% ethanol.

Experimental for the Reactions of gamma-Tropolone Methyl Ether and Tropone with Grignard and Hydride Reagents

Lithium aluminum hydride reduction of gamma-tropolone methyl ether (LVIII)

A solution of 3.1 g. (0.023 mole) of gamma-tropolone methyl ether (LVIII) in 30 ml. of anhydrous ether was added to a magnetically stirred solution of 1.6 g. (0.046 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether. The addition took 5 minutes during which time the reaction mixture was continually flushed with dry nitrogen. After a 10 minute stirring period, the reaction mixture was cautiously quenched with water (approximately 15 ml.). After separation of the layers, the ether layer was dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure left a yellow, oily residue. Chromatography of this residue on basic alumina gave a ketonic fraction (from Skelly B: benzene, 4:1,

0.61 g., 20%) and an alcoholic fraction (from $CHCl_3$, 1.21 g., 40%) as evidenced by their infrared spectra. The ketonic fraction was molecularly distilled with the oil bath at 70-5°C and the pressure 0.12 mm. For the infrared spectrum of 5-methoxy-2,4-cycloheptadienone (CXX), see Figure 29, page 119. The ultraviolet spectrum of CXX showed $\lambda_{max}^{95\% \text{ ethanol}}$ 328 mu (8,500). The n.m.r. spectrum is shown in Figure 32, page 125. Anal. Calcd. for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.36, H, 7.41.

Pasto (35) reported that the alcoholic fraction obtained from the chromatography consisted of a mixture of 4-methoxy-3,5-cycloheptadienol (CXXII) and 5-methoxy-2,4-cycloheptadienol (CXXI). Although Pasto reported partial separation of these alcohols by gas phase chromatography, all further attempts at separation were unsuccessful.

Hydrolysis of 5-methoxy-2,4-cycloheptadienone (CXX) in 95% ethanol at room temperature

A solution of 31.5 mg. (0.000228 m.) of CXX in 10 ml. of 95% ethanol was successively diluted to a concentration of 4.56×10^{-5} molar with 95% ethanol. The temperature of the solution was maintained constant at 23 ± 0.5°. Periodically a sample was removed and checked in the ultraviolet for change. The following data were recorded:

Time (minutes)	Absorbance (332 mu)	% Reaction
16.6	.386	0.35
95.0	.381	1.6
177.0	.378	2.5

Basic hydrolysis of 5-methoxy-2,4-cycloheptadienone (CXX)

A solution of 31.5 mg. (0.000228 m.) of CXX in 10 ml. of 95% ethanol was successively diluted to a concentration of 2.28×10^{-4} molar with 95% ethanol. A 1 ml. aliquot of this solution was diluted to a concentration of 4.56×10^{-5} molar with 0.1054N sodium hydroxide. The final concentration of base was 0.0842N. The solution was maintained at a constant temperature of $23 \pm 0.5^{\circ}$, and the following data were obtained from its ultraviolet spectrum at various intervals of time.

Time (minutes)	Absorbance (342 mu)	% Reaction
2.1	.377	2.7
5.2	.372	4.0
10.2	.369	4.8
15.2	.365	5.6
32.2	.354	8.6
46.2	.339	12.6
60.0	.328	15.5

The percent reaction column was obtained by subtracting the observed molar extinction coefficient from the theoretical

coefficient and dividing the result by the theoretical molar extinction coefficient. The theoretical molar extinction coefficient of 5-methoxy-2,4-cycloheptadienone (CXX) in basic solution was assumed to be the same as in neutral solution.

Acid hydrolysis of 5-methoxy-2,4-cycloheptadienone (CXX)

A solution of 31.5 mg. (0.000228 m.) of CXX in 10 ml. of 95% ethanol was successively diluted to a concentration of 2.28×10^{-4} molar with 95% ethanol. A 1 ml. aliquot of this solution was diluted to a concentration of 4.65×10^{-5} molar with 0.1194N sulfuric acid. The final acid concentration was 0.0955N. The solution was maintained at a constant temperature of $23 \pm 0.5^{\circ}$, and the following data were obtained from its ultraviolet spectrum at various time intervals.

Time (minutes)	Absorbancy (342 mu)	Absorbancy (235 mu)	% of CXXIX
2	0.310	0.104	42.2
4	0.260	0.130	52.8
6	0.220	0.153	62.2
8.5	0.177	0.175	71.0
10	0.154	0.185	75.5
12	0.129	0.194	78.9
14	0.108	0.205	83.3
16	0.090	0.214	86.8
18	0.077	0.219	88.8

20	0.064	0.226	91.8
30	0.030	0.240	97.6
40	0.020	0.244	98.3
50	0.016	0.246	99.9

The percent yield of 2-cyclohepten-1,4-dione was based upon $\lambda_{max}^{95\% \text{ ethanol}}$ 233 mu (5,400) (35).

5-Methoxy-2,4-cycloheptadienol (CXXIII)

A solution of 170 mg. (0.0012 mole) of 5-methoxy-2,4-cycloheptadienone (CXX) in 5 ml. of anhydrous ether was added over a 5 minute period to a stirred solution of 100 mg. (0.0026 mole) of lithium aluminum hydride in 20 ml. of anhydrous ether. After 5 minutes stirring, the reaction mixture was hydrolyzed by careful addition of water. The solids were filtered off, and the ether filtrate was dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure leaving 140 mg. of a pale yellow liquid. The residue was molecularly distilled giving 120 mg. of 5-methoxy-2,4-cycloheptadienol (CXXIII) which showed $\lambda_{max}^{95\% \text{ ethanol}}$ 256 mu (7,590) in the ultraviolet. For an infrared spectrum see Figure 29, page 119. Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.69; H, 8.99.

Acid hydrolysis of 5-methoxy-2,4-cycloheptadienol (CXXIII)

A standard solution of 16 mg. of CXXIII in 5 ml. of 95% ethanol was prepared. This provided a 0.0228 molar solution of CXXIII. Further dilutions were made using 0.1194N sulfuric acid until the concentration of CXXIII in acid became 4.56×10^{-5} molar. The ultraviolet spectrum of this solution showed λmax 299 mu (4,890). This corresponds to a 79% yield of the expected 2,4-cycloheptadienone (CXXVI) (59).

Reaction of gamma-tropolone methyl ether (LVIII) with methyl magnesium iodide

A 0.033 molar solution of methyl magnesium iodide in ether was prepared as usual. Three grams (0.022 m.) of LVIII in 20 ml. of ether were added gradually over a 10 minute period to the Grignard reagent. The reaction mixture was continually stirred (magnetically) and cooled (ice bath) throughout the addition. During the addition, a yellow solid was seen to form. After the addition the reaction mixture was stirred at room temperature for two hours. The excess Grignard reagent and the addition compound were hydrolyzed by the cautious addition of 50 ml. of water. The layers were separated, and water (125 ml.) was added to the water layer after which this layer was extracted several times with fresh ether. The ether fractions were combined and dried over anhydrous sodium sulfate. The ether was removed under

reduced pressure (rotary evaporator) leaving 1.8 g. of viscous residue. Column chromatography of the residue on basic alumina gave 1.25 g. (38%) of a ketonic fraction (6.01 u). Vapor phase chromatography showed two components in a 9:1 ratio. The spectral data indicated that the ketone mixture was 10% 4-methoxy-2-methyl-4,6-cycloheptadienone (CXXXVIII) and 90% 5-methoxy-2-methyl-2,4-cycloheptadienone (CXXXIX). The infrared spectrum of the ketone mixture is shown in Figure 30, page 121, and the nuclear magnetic resonance spectrum is shown in Figure 33, page 127. The ultraviolet spectrum showed $\lambda_{max}^{95\% \text{ ethanol}}$ 201 mu (8,430) and 331 mu (7,160).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.03; H, 7.95. Found: C, 71.30; H, 8.00.

Reaction of tropone (CXL) with methyl magnesium iodide

A 0.042 molar solution of methyl magnesium iodide in ether was prepared as usual. A solution of 3 g. (0.028 m.) of freshly distilled tropone (b.p. 75-8° at 0.1 mm.) in 30 ml. of ether was added slowly (15 minutes) to the Grignard reagent with continuous stirring. Each drop of the tropone solution caused a bright yellow solid to form in the reaction flask. The solid then rapidly dissolved. After the addition the clear yellow solution was allowed to stir for ten minutes. Water (4 ml.) was added very slowly to hydrolyze excess Grignard reagent and the addition compound. The ether layer was

decanted from the thick solids. After drying (over anhydrous Na_2SO_4) and filtering the ether was removed under reduced pressure (rotary evaporator) leaving 2.01 g. of brown residue. The residue was molecularly distilled very slowly and carefully. The oil bath temperature was maintained at 60-5° at 0.1 mm. giving 1.3 g. (38%) of a pale yellow oil which showed a carbonyl band in the infrared at 5.86 u, see Figure 30, page 121. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ ethanol}$ 246 mu (5,170) and 291 mu (806). Vapor phase chromatography showed two peaks with the larger peak representing somewhat more than 95% of the sample. The nuclear magnetic resonance spectrum, see Figure 33, page 127, supported the assignment of structure of the major isomer as 2-methyl-3,5-cycloheptadienone (CXLIV).

Anal. Calcd. for $C_8H_{10}O$: C, 78.63; H, 8.25. Found: C, 78.87; H, 8.39.

Lithium aluminum hydride reduction of 2-methyl-3,5-cycloheptadienone (CXLIV)

A solution of 200 mg. (0.0016 m.) of CXLIV and CXLV in 5 ml. of ether was added over a five minute period to a stirred solution of 0.1 g. (0.0026 m.) of lithium aluminum hydride in 20 ml. of ether. After stirring for five minutes, the reaction mixture was hydrolyzed carefully with water, and the resultant solids were filtered off. After drying the ethereal solution over anhydrous magnesium sulfate, the ether

was removed under reduced pressure (rotary evaporator) leaving 170 mg. of a yellow oil. The oil was molecularly distilled (oil bath temperature 39-41° at 0.15 mm.) giving 145 mg. (72%) of pale, yellow product which was shown to be a mixture of CXLVII and CXLVIII by vapor phase chromatography. For the infrared spectrum see Figure 31, page 123. The ultraviolet spectrum of CXLVII and CXLVIII showed $\lambda_{max}^{95\%\ ethanol}$ 241 mu (10,420) and 247 mu (10,040).

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.32; H, 10.00.

Catalytic reduction of 2-methyl-3,5-cycloheptadienone (CXLIV)

65.4 mg. (0.000535 m.) of CXLIV in 15 ml. of n-pentane containing pre-reduced palladium (10%) on charcoal were found to absorb 26.0 ml. of hydrogen. The theoretical volume of hydrogen was 26.5 ml. The n-pentane was removed under reduced pressure leaving a residue that was purified by molecular distillation. The infrared spectrum, Figure 31, page 123, showed peaks at 3.42, 3.49, 5.90 and 6.89 u as expected for 2-methylcycloheptanone (CXLVI). The 2,4-dinitrophenyl hydrazone of CXLVI was prepared as usual. After percolation through an alumina column and three recrystallizations, the compound still melted low at 116-7° (lit. (60) 121-2°). However, upon admixture with known 2-methylcycloheptanone 2,4-dinitrophenylhydrazone, no depression was observed upon

melting (m.p. 120-121.3°).

Complete lithium aluminum hydride reduction of tropone (CXL)

A solution of 4.4 g. (0.0414 m.) of tropone in 10 ml. of anhydrous ether was added with stirring to 0.59 g. (0.0621 m.) of lithium aluminum hydride in 40 ml. of ether. The rate of addition was such, that the addition required ten minutes. Stirring was continued for ten minutes. The reaction mixture was then hydrolyzed with moist sodium sulfate in such a way as to form no water layer. The solids were filtered off, and the ether filtrate was dried over anhydrous magnesium sulfate. The dry ether solution was reduced in volume to approximately 35 ml. This solution was added over a ten minute period to a stirred solution of 0.59 g. (0.0621 m.) of lithium aluminum hydride in 40 ml. of ether. After stirring for 30 minutes the reaction mixture was worked up as before except that the ether was completely removed leaving 3.27 g. of crude product. A small portion of this residue was molecularly distilled (oil bath temperature 60-65° at 0.3 mm.) to obtain a sample for spectral data. The infrared spectrum showed maxima at 3.00, 3.32, 3.45, 6.21, 6.95 and 9.56 u. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ ethanol}$ 243 mu (4,440). Vapor phase chromatography showed three compounds with one major peak (approximately 60%). The spectral data indicated that the major component was 3,5-cycloheptadienol (CXLII).

Hydrogenation of 3,5-cycloheptadienol (CXLII)

A solution of 118 mg. of crude 3,5-cycloheptadienol in 10 ml. of cyclohexane containing 25 mg. of pre-reduced 10% palladium-on-carbon catalyst was permitted to absorb hydrogen. Hydrogen uptake ceased after absorption of 45 ml. (85% of theoretical). Evaporation of the solvent after removal of the catalyst by filtration gave cycloheptanol (CXLIII) which showed the same retention on a diethylene glycol succinate vapor phase chromatography column alone and mixed with authentic cycloheptanol obtained by lithium aluminum hydride reduction of cycloheptanone. The product on treatment with 3,5-dinitrobenzoyl chloride gave cycloheptyl 3,5-dinitrobenzoate, m.p. 80° (reported (59) 79°).

Experimental for the Photochemistry of 5-Methoxy-2,4-Cycloheptadienone

Irradiation of 5-methoxy-2,4-cycloheptadienone (CXX)

A solution of 330 mg. (0.00239 m.) of CXX in 75 ml. of anhydrous ether in a quartz vessel fitted with a reflux condenser was irradiated with a General Electric UA-3 mercury arc lamp for seventy minutes at a distance of 15 cm. The ether solution was concentrated under reduced pressure, and the yellow residue was molecularly distilled giving 290 mg. (88%) of 5-methoxy-bicyclo[3.2.0]hept-6-en-2-one (CXXV), as

a very pale yellow liquid. The ultraviolet absorption spectrum of CXXV showed $\lambda_{max}^{95\% \text{ ethanol}}$ 332 mu (1,120) and end absorption. For the infrared spectrum see Figure 29, page 119. The n.m.r. spectrum (CCl_4) is reproduced in Figure 32, page 125.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.50; H, 7.51.

Ring-opening of 5-methoxybicyclo[3.2.0]hept-6-en-2-one (CXXV) in 95% ethanol

31.3 mg. (0.0226 m.) of CXXV was diluted to 10 ml. Further dilutions were made until the concentration of CXXV in 95% ethanol was 2.26×10^{-4} molar. This solution was maintained at 23 ± 0.5° throughout the experiment. The reaction mixture was periodically checked in the ultraviolet. 5-Methoxy-2,4-cycloheptadienone showed $\lambda_{max}^{95\% \text{ ethanol}}$ 328 mu (8,500). The following data were recorded.

Time (minutes)	Absorbance (331 mu)	% reaction
8.8	0.515	26.9
19.0	0.620	32.2
32.6	0.700	36.4
42.1	0.761	39.6
51.9	0.822	42.8
55.2	0.851	44.3
65.9	0.919	47.9
76.2	0.982	51.1

Base catalyzed ring-opening of 5-methoxybicyclo[3.2.0]hept-6-en-2-one (CXXV)

12.0 mg. (0.00868 m.) of CXXV were diluted to 10 ml. with 95% ethanol. A further dilution using 95% ethanol was made to 8.68×10^{-4} molar. A 1 ml. aliquot of this solution was diluted to 10 ml. using 0.1054N sodium hydroxide. This made the final concentration of base 0.0948N with a concentration of 8.68×10^{-5} m. for CXXV. The basic solution was checked periodically in the ultraviolet providing the following data:

Time (minutes)	Absorbance (342 mu)	% reaction
2.3	0.270	36.6
4.2	0.339	46.0
6.2	0.395	53.5
8.2	0.438	59.4
10.2	0.472	64.0
12.2	0.500	67.8
14.2	0.524	71.0
16.2	0.541	73.4
18.2	0.556	75.4
24.2	0.580	78.6
30.2	0.589	79.9

The percent reaction column was based upon a molar extinction coefficient of 8,500 for 5-methoxy-2,4-cycloheptadienone in basic solution, as in neutral solution.

Acid catalyzed ring-opening of 5-methoxybicyclo[3.2.0]hept-6-en-2-one (CXXV) at room temperature

A 1 ml. aliquot of the 95% ethanol solution 8.68×10^{-4} molar in CXXV (from the previous experiment) was diluted to 10 ml. with 0.1194N sulfuric acid. This made the final concentration of acid 0.1074N with a concentration of 8.68×10^{-5} molar for CXXV. The acidic solution was checked periodically in the ultraviolet, providing the following data:

Time (minutes)	Absorbancy (342 mu)	Absorbancy (234 mu)	% yield of CXXIX
1.5	0.362	0.135	29
3.5	0.390	0.196	42
6.5	0.334	0.272	58
8.6	0.277	0.311	67
10.5	0.229	0.343	73
12.5	0.186	0.368	78
14.5	0.149	0.390	83
16.5	0.121	0.406	87
18.5	0.100	0.419	89.4
20.5	0.084	0.429	91.6
48.5	0.048	0.465	99

The percent yield of 2-cyclohepten-1,4-dione was based upon $\lambda_{max}^{95\% \text{ ethanol}}$ 233 mu (5,400) (35). This assumed the molar extinction coefficient to be the same in acidic solution as in neutral solution.

5-Methoxybicyclo[3.2.0]heptan-2-one (CXXV)

A solution of 0.1016 g. (0.000735 m.) of CXX in 25 ml. of absolute methanol was hydrogenated over pre-reduced Adam's catalyst. The sample absorbed 98% of the theoretical amount of hydrogen. After removal of the solvent under reduced pressure, the residue was molecularly distilled. Care had to be taken as the compound was very volatile. The infrared of the distilled compound was identical to that obtained by Pasto (34) from the complete hydrogenation of photo-gamma-tropolone methyl ether.

5-Methoxybicyclo[3.2.0]hept-6-ene-2-ol (CXXIV)

A solution of 46 mg. of 5-methoxy-2,4-cycloheptadienol (CXXIII) in 60 ml. of anhydrous ether in a quartz vessel with a reflux condenser was irradiated for sixty minutes with a General Electric UA-3 mercury arc lamp. The ether was removed under reduced pressure, and the residue was molecularly distilled. For the infrared spectrum of CXXIV see Figure 30, page 121.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.84.

SUMMARY

It has been known for many years that cyclic, α,β-unsaturated ketones form dimeric cyclobutane derivatives in the presence of light. Irradiation of isophorone (I) gives two crystalline dimers, Dimer I and Dimer II. The syn (Dimer II) and anti (Dimer I) relationship of the carbonyl groups was determined from their reaction in concentrated sulfuric acid. Dimer I is cleaved to isophorone (I) by sulfuric acid, while Dimer II is isolated unchanged. An example of long-range coupling is found in the n.m.r. spectrum of Dimer II. The stereochemistry around the cyclobutane ring was not elucidated. The mono-ketal and the di-enol acetate derivatives of Dimer II were prepared. The n.m.r. and infrared spectra of all products are presented.

10α-Methyl-1β,5β-cycloandrostan-17β-ol-2-one 17-acetate (II) and 3α-(3-keto-1-cyclopenten-1-yl)-3β,5aβ-dimethyl-6β-acetoxy-as-hydrindacene (III) are isolated from the irradiation of testosterone acetate (IV) in tert-butyl alcohol. The structure of II was determined by comparison with an authentic sample. The structure of III was elucidated by ozonolysis of 3α-(3,5-dibenzylidene-4-keto-1-cyclopenten-1-yl)-3β,5aβ-dimethyl-6β-acetoxy-as-hydrindacene (V) to the known 3α-carboxy-3β,5aβ-dimethyl-6β-hydroxy-as-hydrindacene (VI). The proof of structure, chemistry and the spectra of these compounds are fully discussed.

The photochemistry of spiro-(4,5)-deca-1,4-diene-3-one (VII) was studied. Irradiation of VII in ether, tert-butyl alcohol and glacial acetic acid gives varying yields of 5,6,7,8-tetrahydro-1-naphthol (VIII) and 5,6,7,8-tetrahydro-2-naphthol (IX). Yields of IX are found to increase with increasing acidity of the solvent. Photochemical mechanisms are presented for the formation of VIII and IX. The structures of VIII and IX were determined by comparison with authentic samples.

The reaction of Grignard and hydride reagents on gamma-tropolone methyl ether (X) and tropone (XI) was studied. This work was supplementary to that of D. J. Pasto (Ph.D., 1960). The reaction of methyl Grignard on X gives mainly 2-methyl-4-methoxy-4,6-cycloheptadienone (XII). Methyl Grignard with XI gives 2-methyl-3,5-cycloheptadienone (XIII). The reaction of lithium aluminum hydride and X gives 5-methoxy-2,4-cycloheptadienone (XIV) and a mixture of two isomeric alcohols. The reaction of hydride with XI gives 3,5-cycloheptadienone (XV) and 3,5-cycloheptadienol (XVI). XIV was converted photochemically to 5-methoxybicyclo[3.2.0]hept-6-en-2-one (XVII). The hydrolysis and ring-opening reactions of XIV and XVII were studied.

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