PART I

SOME REACTIONS OF STEROIDAL EPOXYKETONES IN ALKALINE MEDIA

PART II

HYDRIODIC ACID REDUCTIONS OF VICINAL OXYGENATED COMPOUNDS

Thesis for the Degree of Ph. D.

MICHIGAN STATE UNIVERSITY

Ronald Andrew LeMahieu

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MICHIGAN STATE UNIVERSITY
[redacted]
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ABSTRACT

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Since α,β-epoxyketones were reported to undergo a Favorskii ring contraction, this rearrangement might provide a convenient route to nor-steroids.

The α- and β-epoxides from cholest-4-en-3-one were converted by methanolic base to 4-methoxycholest-4-en-3-one I. An isomer previously believed to be I was identified as 3-methoxycholest-2-en-4-one II. The ultraviolet spectra of these enol ethers and others are discussed with respect to the increment caused by the α-methoxyl group.

Treatment of 1α,2α-epoxy-5α-cholestan-3-one with methanolic base gave 2-methoxycholest-1-en-3-one. An isomer, 3-methoxycholest-3-en-2-one, was prepared by

methylation of the diosphenols derived from cholestan-2, 3-dione with dimethyl sulfate. The structure and reactivity of the two diosphenols derived from cholestan-2,3-dione and isomerization of the diosphenols to the α-diketone is discussed.

The epoxide from cholest-5-en-4-one was prepared and shown to be the β-oxide. This epoxide was rearranged by methanolic base to A-norcholest-3-en-3-oic acid and 6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-oic acid. The mechanism of formation of these compounds is discussed and is compared with that of the Favorskii reaction.

Oxidation of the α- and β-epoxides from cholest-4-en-3-one with alkaline hydrogen peroxide gave 5β-carboxy-4-oxacholestan-3-one and 5α-carboxy-4-oxacholestan-3-one respectively. Oxidation of the α-epoxide from cholest-1-en-3-one under these conditions gave 1ξ-carboxy-2-oxa-5α-cholestan-3-one. The mechanism of formation of these lactone acids is discussed.

Enol ethers I and II as well as 4-hydroxycholest-4-en-3-one are reduced by hydriodic acid in refluxing acetic acid to 5α-cholestan-4-one. This seems to be a general reaction of alicyclic α-ketols as well as α-diketones and two mechanisms are suggested. Reduction of unsymmetrical benzils

with hydriodic acid proceeds only under more vigorous conditions and probably goes by a different mechanism.

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By

Ronald Andrew LeMahieu

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To Bethene

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation and gratitude to Professor William Reusch for his inspiration, guidance and understanding during the course of this investigation.

Appreciation is also extended to the Dow Chemical Company and E. I. duPont de Nemours and Co., Inc. for summer fellowships.

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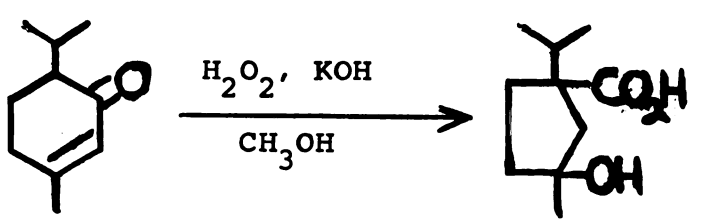
PART I

SOME REACTIONS OF STEROIDAL EPOXYKETONES IN ALKALINE MEDIA

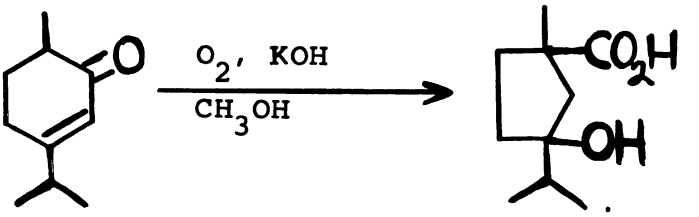
INTRODUCTION

Weitz (1,2) found that hydrogen peroxide reacted with α,β-unsaturated ketones in alkaline alcoholic solution to form epoxyketones, which were quite reactive and on short boiling with alcoholic alkali rearranged to 1,2-diketones or the corresponding enols.

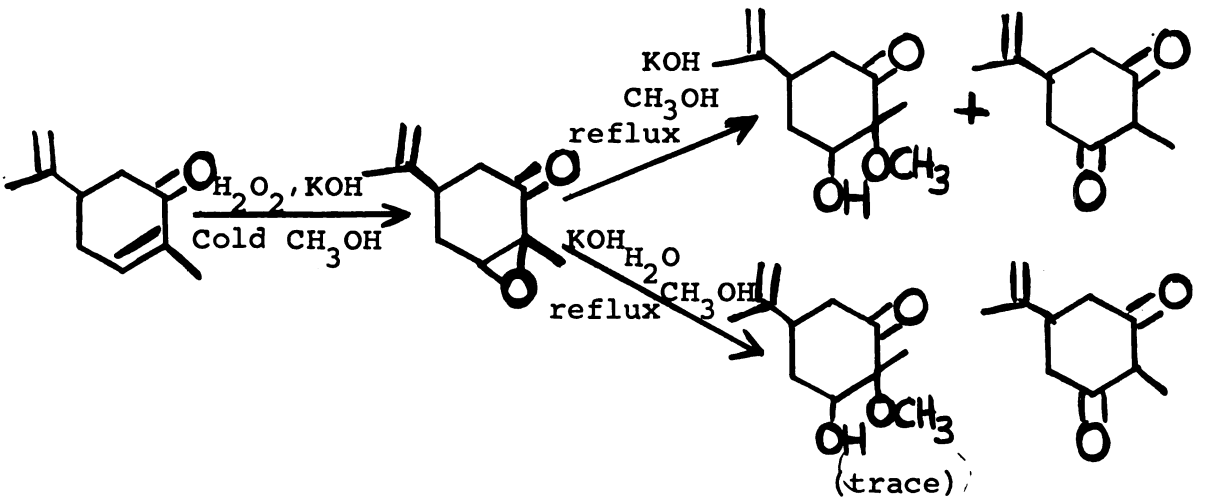
Treibs (3) investigated the products formed on autooxidation of certain α,β-unsaturated ketones and those formed by reaction of these ketones with hydrogen peroxide in alkaline solution. He found that the products were the same in both cases but that in the hydrogen peroxide method conditions could be varied to a greater degree and production of resinous products could be almost completely avoided. Thus, piperitone with hydrogen peroxide, potassium hydroxide and methanol gave a hydroxy acid in 35-45% yield (3).

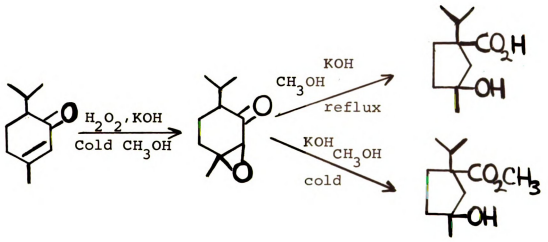


To study the effect of the position of alkyl groups with respect to the active grouping ($\rangle C{=}C{-}\overset{O}{\overset{\|}{C}}-$), Treibs next investigated the products of autooxidation of carvenone in alkaline alcoholic solution (4). Carvenone was found to give a hydroxy acid isomeric with that formed from piperitone.

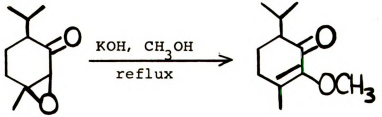


Next Treibs found that α,β-epoxyketones could be isolated by treating α,β-unsaturated ketones with hydrogen peroxide, potassium hydroxide and methanol under mild conditions. The rearrangement products from these epoxyketones could be changed by varying the reaction conditions (3,5,6).

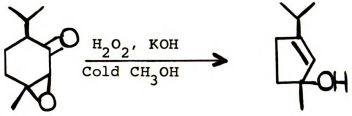




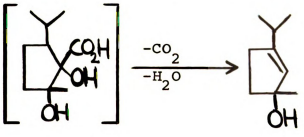
When 30% methanolic potassium hydroxide was added dropwise to a boiling solution of piperitone oxide in methanol, the diosphenol methyl ether was formed.



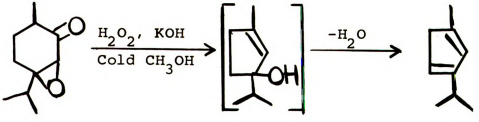
When excess hydrogen peroxide and potassium hydroxide were added to piperitone oxide in cold methanol, a tertiary alcohol was isolated in 45% yield (6).



The mother liquors evolved an equivalent of carbon dioxide when acidified and Treibs suggested that the tertiary alcohol was formed from an unstable carboxylic acid.

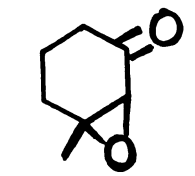


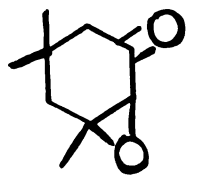
Treibs also found that if excess hydrogen peroxide was used in preparing the oxide of carvenone or if the auto-oxidation was carried out in hot solution, the oxide was further oxidized to a tertiary alcohol (7). This alcohol, unlike that from piperitone, split off water in the alkaline solution to give a yellow C_9H_{14} hydrocarbon.

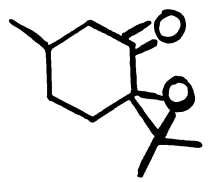


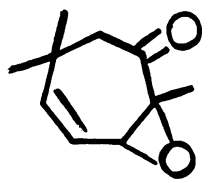
Some of the other epoxyketones which were reacted with refluxing methanolic potassium hydroxide by Treibs (7) are entered in the following table.

Substrate

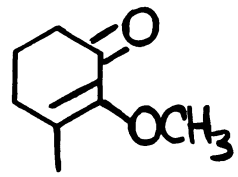


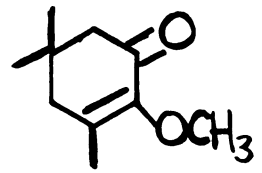


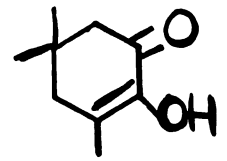




Products

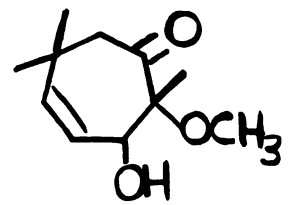




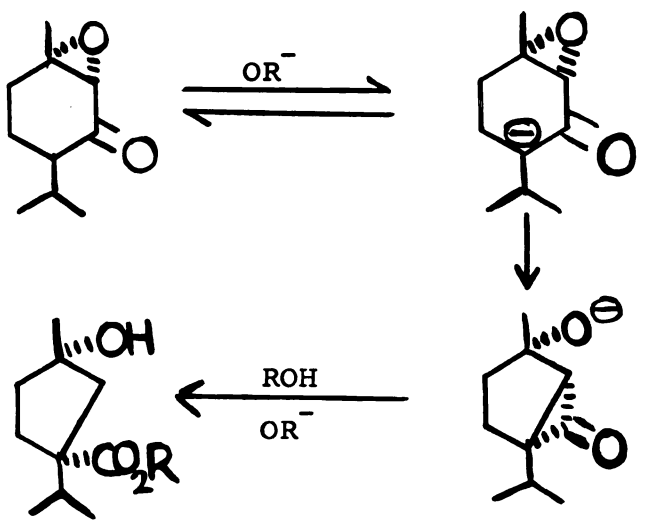


(trace)

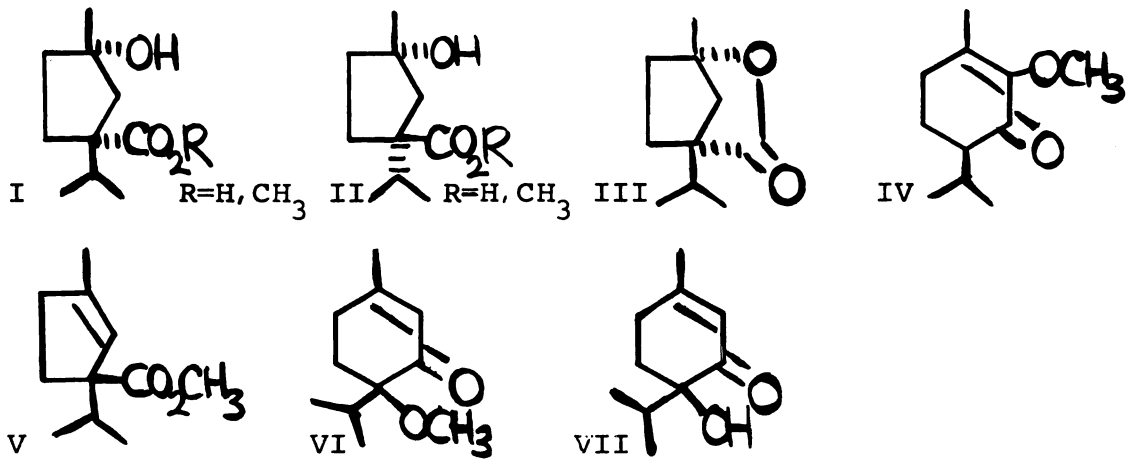
acids



House reported a thorough study of rearrangements of epoxyketones with the purpose of determining the stereochemistry of the Favorskii rearrangement (8). The direct displacement mechanism leading to a cyclopropanone intermediate should produce only cis-hydroxy acid derivatives.

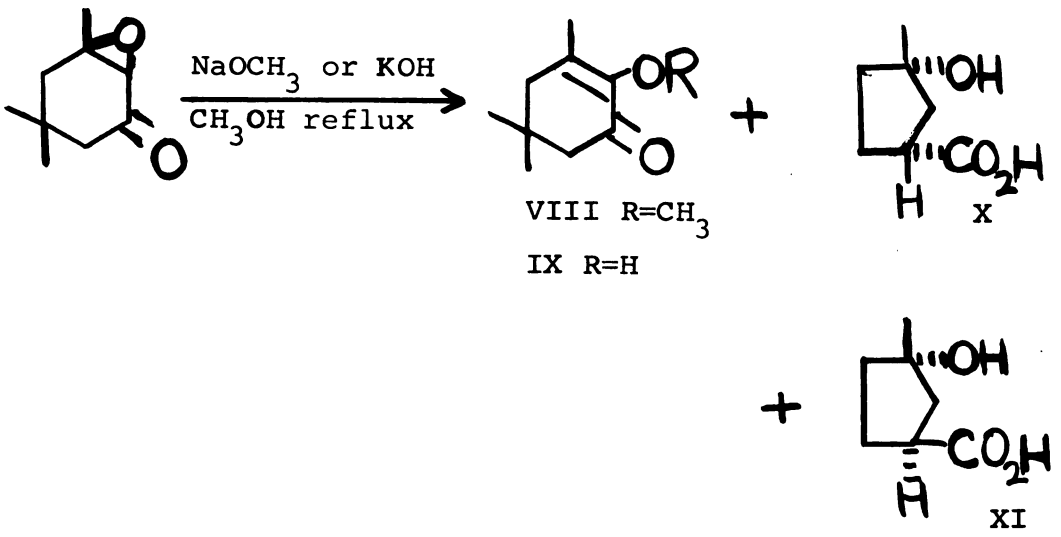


He found that reaction of piperitone oxide with either methanolic potassium hydroxide or methanolic sodium methoxide under a variety of conditions afforded as major products the cis-hydroxy acid derivatives I, the trans-hydroxy acid derivatives II, the lactone III and the enol ether IV as well as small amounts of the unsaturated ester V and the methoxy piperitone VI. The presence of additional water in the reaction mixture favored the formation of the methoxypiperitone VI and a new component, the hydroxy ketone VII.

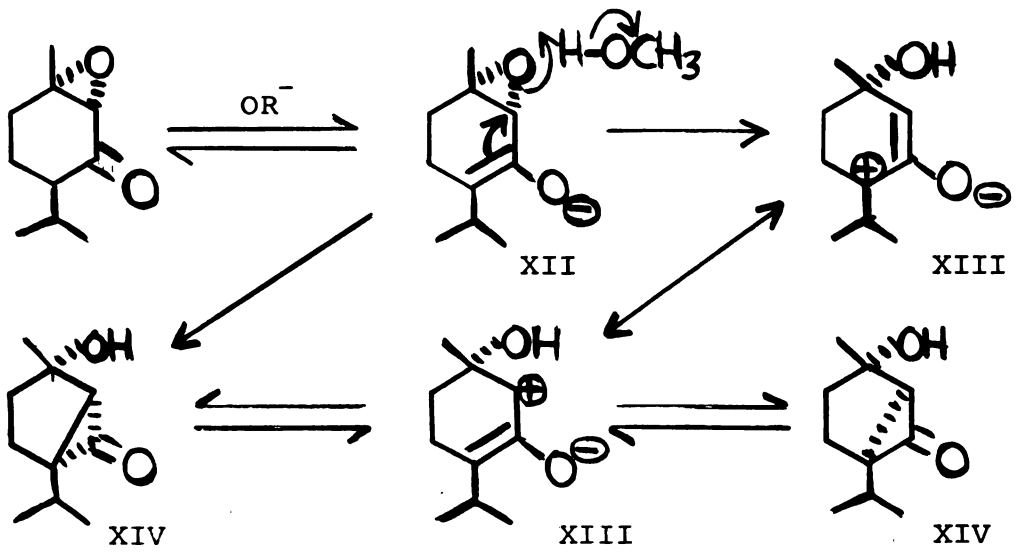


When piperitone oxide was stirred with aqueous potassium hydroxide, the only neutral product was the hydroxy ketone VII formed in 88% yield. The lactone III was formed in 70% yield, as the sole neutral product, when piperitone oxide was stirred with potassium t-butoxide in 1,2-dimethoxy ethane.

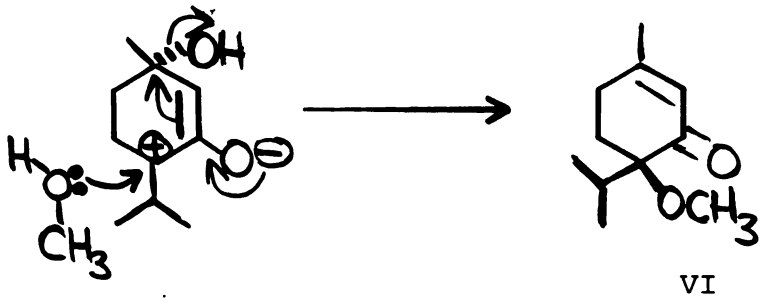
The reaction of isophorone oxide with either sodium methoxide or potassium hydroxide in methanol gave the enol ether VIII as the major product (81-85%) along with smaller amounts of the enolic α-diketone IX. When potassium hydroxide was employed, small amounts of the hydroxy acids X and XI were also detected. Addition of water to the reaction mixture increased the amount of hydroxy acids and that of the enolic α-diketone.



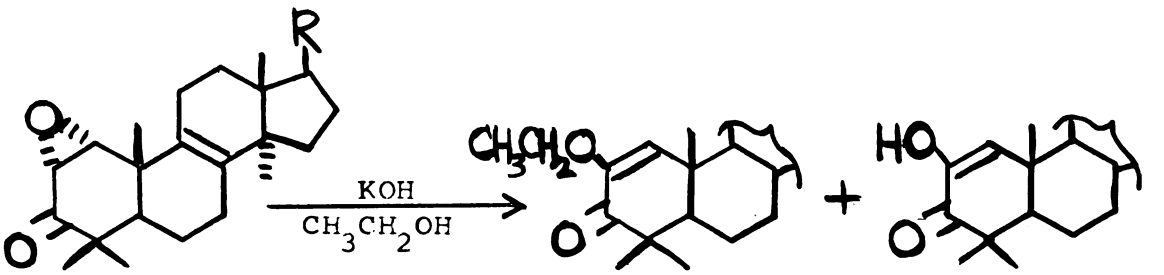
Any proposed mechanism for these reactions has to account for the stereospecific formation of the lactone III from reaction of piperitone oxide with potassium t-butoxide in 1,2-dimethoxy ethane as well as the formation of derivatives of the cis-hydroxy acid I and the trans-hydroxy acid II in methanolic sodium methoxide. House, therefore, favors a mechanism for the non-stereospecific rearrangement in which the enolate anion XII undergoes dissociation to form a planar intermediate XIII rather than direct displacement to give the cyclopropanone XIV. An equilibrium between the diastereomeric forms of the cyclopropanone XIV would also account for the non-stereospecific rearrangement.



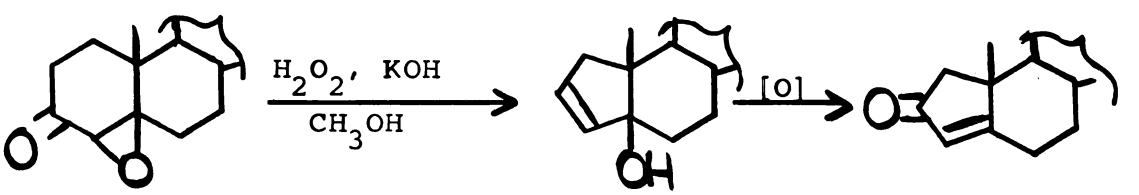
In the nonpolar solvent, 1,2-dimethoxyethane, neither ionic dissociation XII or existence of a species such as XIII is favored and a direct displacement of the epoxide ring may be involved leading to stereospecific products. The above mechanism also accounts for the formation of displacement products.



The reaction of 1α,2α-epoxylanost-8-en-3-one with potassium hydroxide in ethanol has been reported and tentative structural assignments have been made for the products (9).



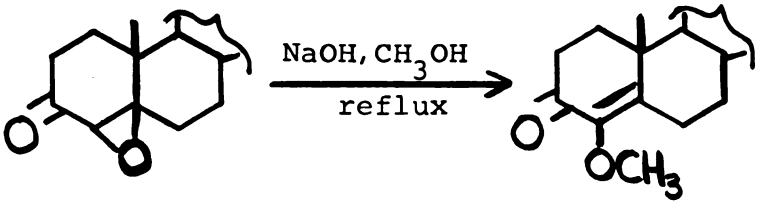
Since piperitone oxide had been observed to undergo a Favorskii type ring contraction, this rearrangement might provide a novel approach to norsteroids. The oxidative modification leading to ring-contracted, allylic alcohols seemed especially appropriate for this purpose.



An investigation of the effect of substitution and stereochemistry of the epoxide ring on the ring contraction would be facilitated in the steroids because of their rigid geometry.

RESULTS AND DISCUSSION

The only isolable product from the reaction of 4β,5-epoxy-5β-cholestan-3-one with methanolic sodium hydroxide or sodium methoxide was 4-methoxycholest-4-en-3-one I. Compound I was also the only product from reaction of 4α,5-epoxy-5α-cholestan-3-one with methanolic sodium hydroxide.*



This structural assignment was based upon the elemental analysis, infrared spectrum ($\lambda_{max}^{CCl_4}$ 5.97, 6.25 μ), ultraviolet spectrum ($\lambda_{max}^{C_2H_5OH}$ 255 mμ, log ε 4.1), nuclear magnetic resonance spectrum (-OCH_3 at 6.48τ, no absorption in the region between 4 and 5τ), hydrolysis to the known diosphenol II and conversion via the ethylenethioketal III to 5α-cholestan-4-one.

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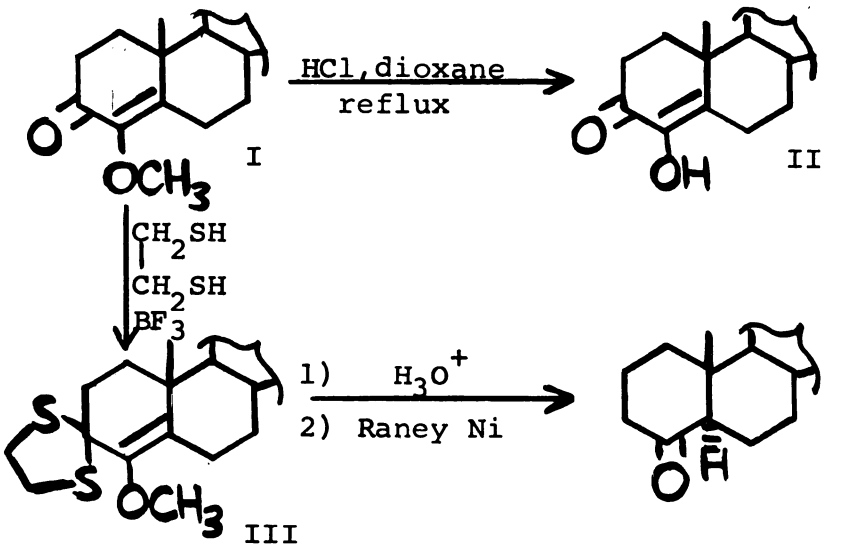
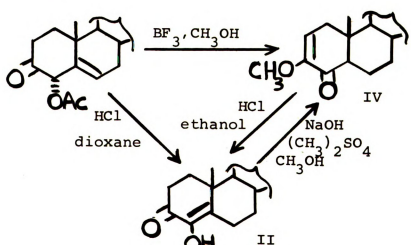
*This experiment was performed by Professor William H. Reusch.

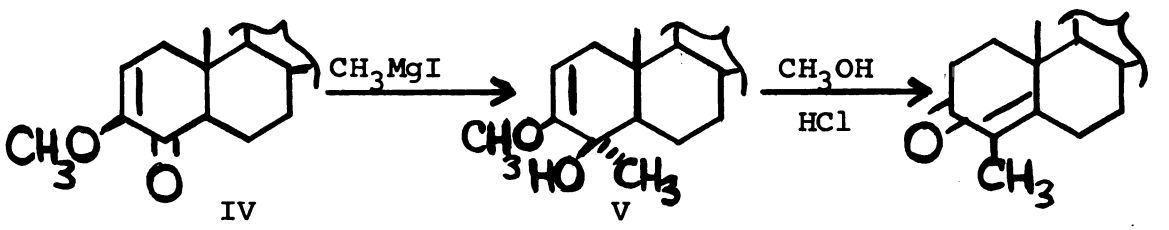


The formation of I probably proceeds by opening of the oxirane ring through methoxide ion attack at C_4 followed by β-elimination of water. Fieser and Stevenson (10) had reported I as the product from the reaction of 4α-acetoxy-cholest-5-en-3-one with boron trifluoride in refluxing methanol. The correct structure was shown to be 3-methoxy-5α-cholest-2-en-4-one IV by hydrolysis to the diosphenol II and especially by the nuclear magnetic resonance spectrum which exhibited a pair of overlapping doublets at 4.55τ (characteristic of $>C=C\underline{H}-CH_2-$) with an area approximately 1/3 that of the methoxyl group resonance at 6.51τ. Assignment of structure IV was supported by the infrared

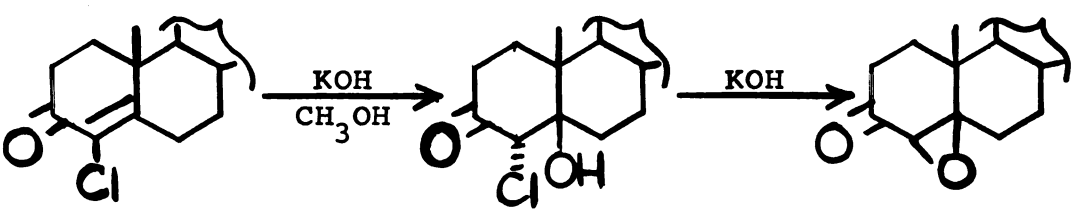
($\lambda_{max}^{CCl_4}$ 5.95, 6.12 μ) and ultraviolet ($\lambda_{max}^{C_2H_5OH}$ 263 mμ, log ε 3.8) spectra. Since I is not changed by treatment with boron trifluoride in refluxing methanol, it cannot be an intermediate in the formation of IV. Diosphenol II does not react with diazomethane, however a refluxing alkaline solution of dimethyl sulfate slowly converted II to the enol ether IV. Enol ether IV was also the major product from reaction of II with boron trifluoride in refluxing methanol (10). Therefore, the reaction of 4α-acetoxy-cholest-5-en-3-one with boron trifluoride in refluxing methanol could proceed through the diosphenol II which is methylated to give IV.



The structure of IV was also demonstrated by Camerino, Patelli and Sciaky (11). Their proof of structure rested on conversion of IV to 4-methylcholest-4-en-3-one via 3-methoxy-4β-hydroxy-4α-methyl-5α-cholest-2-ene V.

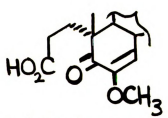


These workers have also prepared the testosterone and progesterone analogs of I and IV. In addition they reported a synthesis of the testosterone analog of I from 4-chlorotestosterone acetate by reaction with potassium hydroxide in methanol at room temperature. This reaction probably proceeds through the epoxyketone which is attacked by methoxide ion as in the formation of I.

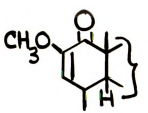


The enhanced bathochromic shift due to the α-methoxyl group in enone IV (+36 mμ) as contrasted with that of enone I (+11 mμ) seemed unprecedented. However, a careful search of the literature revealed reports on several model systems. Stork et al. had reported enol

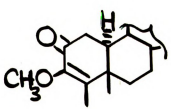
ethers VI a,b in their total synthesis of dl-conessine (12) and enol ether VII from quassin had also been reported (13). The enol ether VIII from friedelane-2,3-dione was reported by Kane and Stevenson (14) and House and Gilmore (8) had reported enol ethers IX and X.



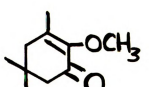
VI a) 8α-isomer $\lambda_{max}^{C_2H_5OH}$ 267.5 mμ
b) 8β-isomer λ_{max} 262 mμ



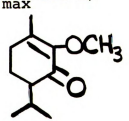
VII λ_{max} 264 mμ



VIII λ_{max} 255 mμ



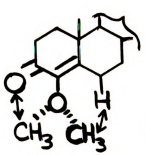
IX $\lambda_{max}^{C_2H_5OH}$ 251 mμ



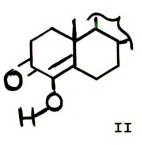
$\lambda_{max}^{C_2H_5OH}$ 250 mμ

These substituted enone chromophores fall into two classes: those with a cis-β-alkyl substituent—I, VIII, IX and X (Δ^{OCH_3} +11, +16, +12 and +11 mμ respectively)—and those without a cis-β-alkyl substituent—IV, VIa,

VIb and VII (Δ^{OCH_3} +36, +40.5, +35 and +37 mμ respectively). It seems that for maximum overlap of the non-bonding electrons of the methoxyl group with the enone chromophore there must not be a cis-β-alkyl substituent on the enone chromophore, a condition met by compounds IV, VIa, VIb and VII. An examination of molecular models shows that coplanarity of the methoxyl group in I is prevented by crowding with either the carbonyl oxygen or the C-6 methylene group and a much smaller substituent effect is observed. Crowding is absent in the diosphenol II ($\lambda_{max}^{C_2H_5OH}$ 278 mμ) and this compound exhibits a bathochromic increment of +35 mμ for the α-hydroxyl.

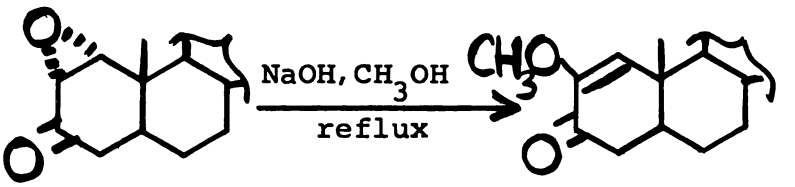


I



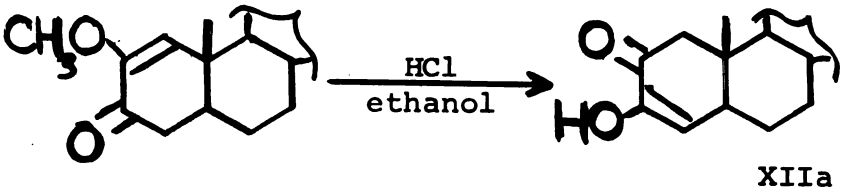
II

Treatment of 1α,2α-epoxy-5α-cholestan-3-one with methanolic sodium hydroxide yielded 2-methoxy-5α-cholest-1-en-3-one XI as the major product.



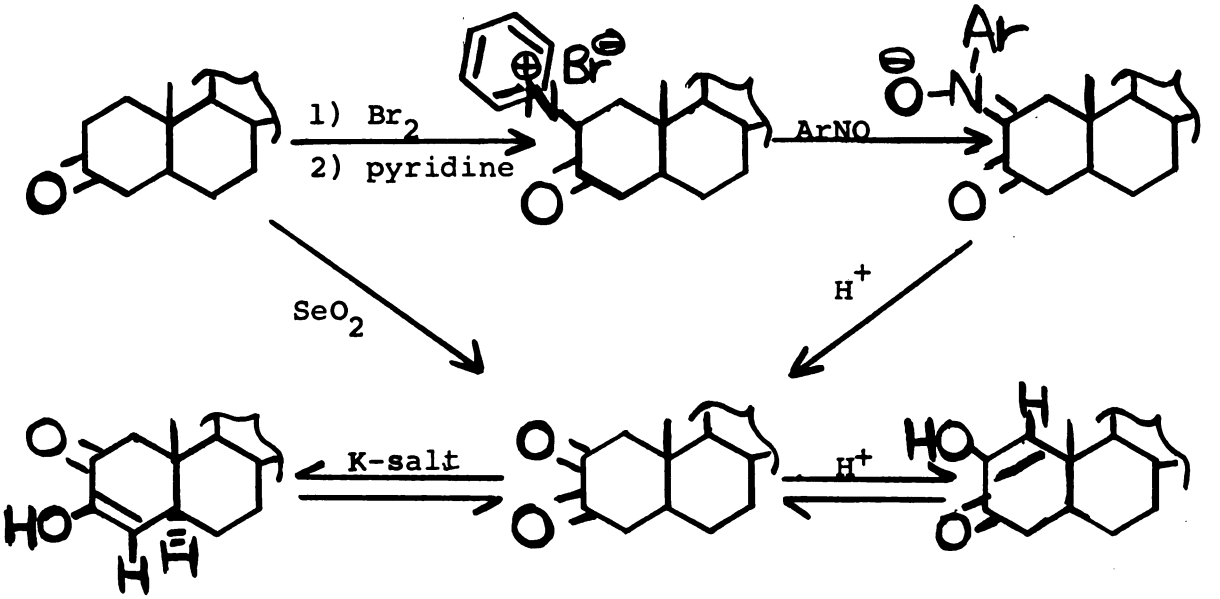
XI

This structural assignment of XI was based on the infrared spectrum, $\lambda_{max}^{CCl_4}$ 5.95 and 6.23 μ, the ultraviolet spectrum, $\lambda_{max}^{C_2H_5OH}$ 265 mμ (log ε 3.9, Δ^{OCH_3} +38 mμ), the nuclear magnetic resonance spectrum, (vinyl hydrogen and methoxyl hydrogen appear as singlets at 4.18 and 6.57τ respectively with an area ratio of 1:3.3) and the elemental analysis. In addition, the methyl ether was hydrolyzed by acid to the diosphenol XIIa.



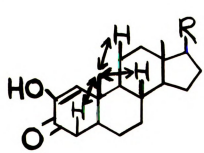
XIIa

The diosphenols XIIa and XIIb and the α-diketone XIIc constitute an interesting tautomeric system which has been prepared using either the procedure of Ruzicka et al. (15) or that of Stiller and Rosenheim (16).



Chemical evidence in support of these structural assignments includes oxidation of either XIIa or XIIb to yield 2,3-seco-5α-cholestan-2,3-dioic acid and reduction of the tosylate from XIIa to 5α-cholestan-2-one (15). Nuclear magnetic resonance measurements of the vinyl hydrogen resonance of XIIa and XIIb in deuterochloroform have been reported (17). These workers report a vinyl doublet centered at 4.32τ for XIIa and a vinyl singlet at 3.63τ for XIIb. The nuclear magnetic resonance spectrum in carbon tetrachloride solution of a carefully purified sample of XIIa exhibited the hydroxyl resonance at 4.31τ, the vinyl doublet at 4.43τ (J = 2.5 cps) and a sharp peak at

3.80τ. This latter peak was attributed to the vinyl hydrogen of XIIb and indicated about 7% of XIIb to be present. The infrared spectrum of this sample exhibited a very weak band at 5.75 μ showing some XIIc also to be present. Acid treatment of XIIa gave XIIb in about 12% yield (18). The nuclear magnetic resonance spectrum of XIIb, vinyl singlet at 3.82τ and hydroxyl at 4.32τ, was in complete agreement with the structure. This apparent isomerization of XIIa to XIIb in acid solution was unexpected since an inspection of molecular models indicated that isomer XIIa had fewer and less severe non-bonded interactions than XIIb. In addition to the C_{19}:C_4 interaction present in XIIb but not in XIIa, the former isomer has the more serious compressions between C_{19}:C_{11} and C_{19}:C_8.



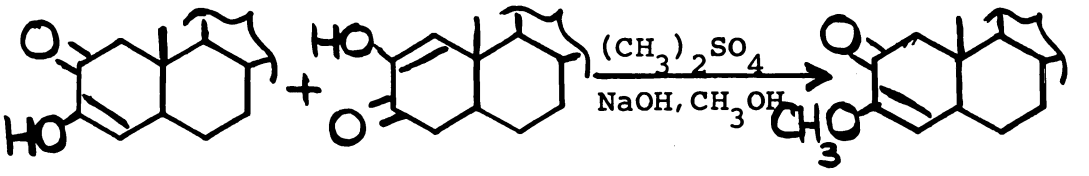
Isomer XIIa would, therefore, be expected to be the more stable and to predominate at equilibrium. An examination of the mother liquors from the acid treatment of XIIa by nuclear magnetic resonance showed three low field resonances

at 3.78τ (vinyl from XIIb), 4.12τ (hydroxyl) and 4.45τ (vinyl doublet from XIIa), the areas of which indicated a mixture of 18% XIIb and 82% XIIa. The fact that XIIb was obtained by acid isomerization of XIIa therefore does not imply that XIIb is the more stable isomer but merely that it is more insoluble than XIIa. The downfield shift of the hydroxyl absorption (4.32τ in either pure isomer to 4.12τ in the mixture) implies intermolecular hydrogen bonding in these diosphenol mixtures. A shift in the carbonyl stretching frequency in the infrared to 6.02 μ agrees with this suggestion.

Diosphenol XIIa was found to be unstable upon standing in the solid state either at room temperature or in the refrigerator. After standing for two weeks the substance had become yellow and the melting point had dropped to 105-125°. The nuclear magnetic resonance spectrum indicated a mixture of 15% XIIb and 85% XIIa. After thirty days the yellow solid melted at 70-75° and strong absorption appeared at 5.78 and 5.89 μ in the infrared while the 2.92 and 5.98 μ bands which characterized XIIa were much diminished in intensity. The areas of the low field resonances in the nuclear magnetic resonance spectrum represented about 13% diosphenols when compared with

the methyl resonance at 8.37τ. Since about 50% of **XIIa** was recovered from this low melting material via the potassium salt, it seems that no deep seated structural changes occurred. Isomerization of **XIIa** to the α-diketone **XIIc** would explain these facts.

Methylation of a mixture of **XIIa** and **XIIb** with dimethyl sulfate in alkaline methanol gave 3-methoxy-5α-cholest-3-en-2-one **XIII**.

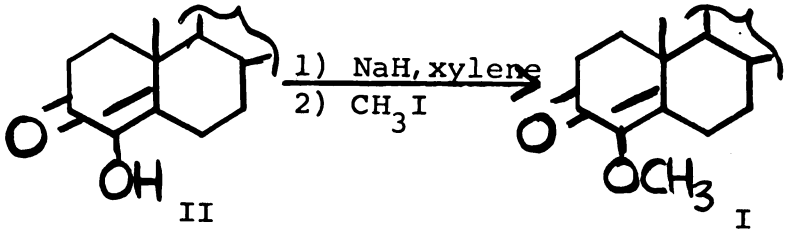


XIIa **XIIb** **XIII**

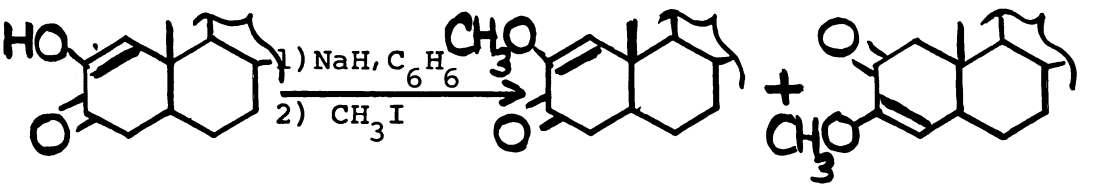
This structural assignment was based on the elemental analysis, the infrared spectrum (5.96 and 6.18 μ), the ultraviolet spectrum ($\lambda_{max}^{C_2H_5OH}$ 266 mμ, log ε 3.9, Δ^{OCH_3} + 39 mμ) and the nuclear magnetic resonance spectrum (vinyl doublet at 4.83τ and methoxyl at 6.49τ). Since there are no obvious steric factors favoring alkylation of one diosphenol over the other, it is surprising that **XIII** is the exclusive product. This selectivity probably indicates a difference in the stability of the diosphenol conjugate bases and/or the corresponding methyl ethers (**XI** and **XIII**). Diosphenol **XIIa** and its conjugate base are

the more stable isomers at equilibrium for reasons discussed earlier; methylation of the conjugate base of XIIa gives XIII.

Camerino, Patelli and Sciaky reported (11) that II could be methylated with sodium hydride in refluxing xylene to give I.

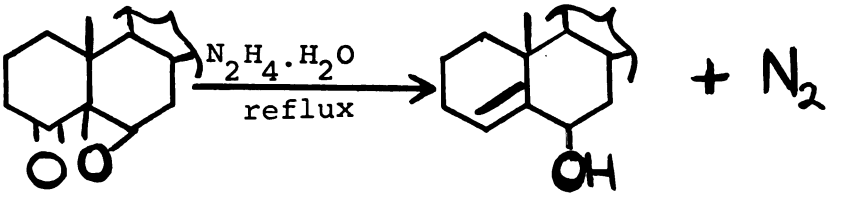


This result must mean irreversible formation of the conjugate base of II followed by methylation of the C_4 oxygen, which is the site of greater negative charge. Methylation of the enolate anion prepared by reaction of XIIa with sodium hydride gave a mixture of 96% XIII and 4% XI. Identical treatment of the enolate anion from XIIb yielded a mixture of 56% XIII and 44% XI. Partial equilibration of the enolate anions must be occurring in the latter case.

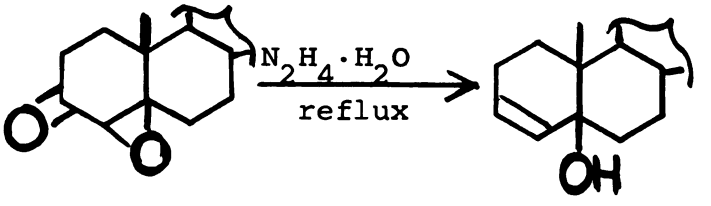


XIIb XI XIII

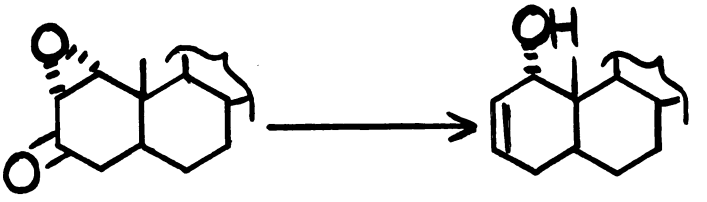
The epoxide from cholest-5-en-4-one was an unknown compound and therefore structural and stereochemical evidence was desired. Utilization of a novel reaction of epoxyketones with hydrazine hydrate to yield allylic alcohols (19) demonstrated that the oxide ring was beta.



Wharton (19) and other workers (20, 21) have shown that the reaction proceeds to the allylic alcohol with retention of stereochemistry at the β-carbon of the oxide.

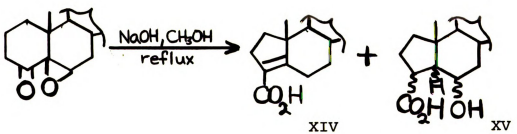


(19)



(20)

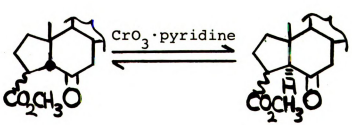
The only characterizable acidic products from the reaction of 5,6β-epoxy-5β-cholestan-4-one with sodium hydroxide in refluxing methanol were A-norcholest-3-en-3-oic acid XIV and 6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-oic acid XV.



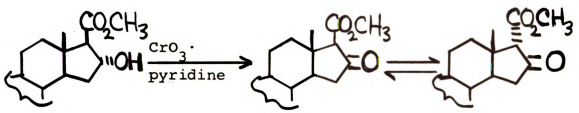
XIV XV

Purification of XIV and XV was accomplished by conversion to their methyl esters and chromatography on alumina. The structural assignment of XIV, as the methyl ester, was based on the infrared spectrum ($\lambda_{max}^{CCl_4}$ 5.87 and 6.07 μ), the ultraviolet spectrum ($\lambda_{max}^{C_2H_5OH}$ 237 mμ, log ε 4.0), the nuclear magnetic resonance spectrum (CO_2CH_3 singlet at 6.41τ, no vinyl hydrogen), the elemental analysis and a mixture melting point of the methyl ester with the authentic compound which was kindly provided by Professor H. J. E. Loewenthal (22). Assignment of structure XV, as the methyl ester, was based on the elemental analysis, the infrared spectrum ($\lambda_{max}^{CCl_4}$ 2.85 and 5.76 μ), the nuclear magnetic resonance spectrum (hydroxyl at 6.12τ, CO_2CH_3 at 6.39τ)

and chemical evidence. The stereochemistry of XV at C_3, C_5 and C_6 has not been elucidated although, for reasons to be discussed later, it seems likely that the carboxyl at C_3 is beta, the hydrogen at C_5 is beta and the hydroxyl at C_6 is also beta. Hydroxy acid XV was oxidized with chromic oxide-pyridine complex to a keto acid which could not be decarboxylated by refluxing in xylene. Therefore, this keto acid is probably not a β-keto acid. Since the hydroxyl group could be oxidized to a ketone, it is probably secondary. The oxidation of either the hydroxy acid XV or the corresponding methyl ester with chromic oxide-pyridine complex gave oily products which could not be crystallized or further purified by chromatography. It seems likely that partial epimerization at C_5, a labile center in the keto ester, has occurred to give an epimeric mixture.



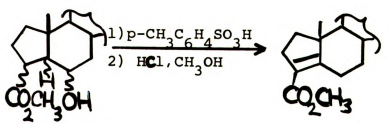
Epimerization in the presence of chromic oxide-pyridine complex is not without precedent (23).



Both of the epimeric keto esters could be isolated by fractional crystallization in the above case.

Attempted conversion of the oily keto ester from XV via the thioketal to methyl-A-nor-5β-cholestan-3β-carboxylate and then by Barbier-Wieland degradation to A-nor-5β-cholestan-3-one was unsuccessful.

Partial dehydration of XV was accomplished with p-toluenesulfonic acid and the double bond was isomerized to yield XIV along with unreacted XV.

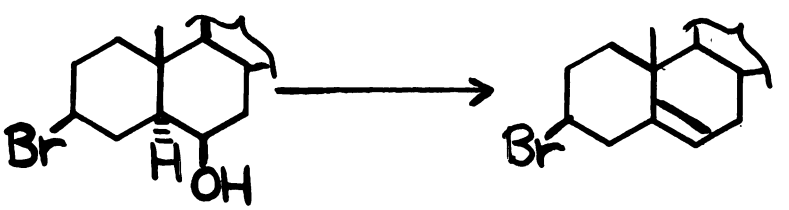


XV XIV

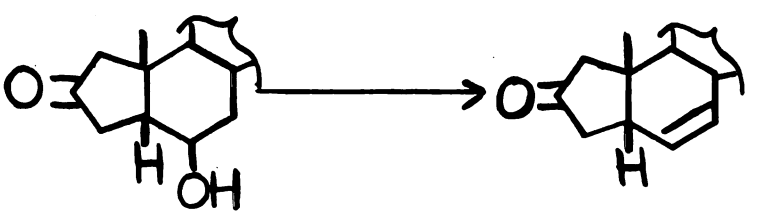
The apparent absence of lactone in the above reaction is significant in regard to the stereochemistry of XV at C_5. If the Favorskii-type ring contraction leading to XV were

stereospecific, the hydroxyl at C_6 would be beta and the carboxyl at C_3 would also be beta. If the C_5 hydrogen were alpha, lactone formation would have occurred during reflux with p-toluenesulfonic acid. If, on the other hand, the C_5 hydrogen were beta, the lactone would be very strained and probably would not form.

Dehydration of XV with phosphorous oxychloride in pyridine followed by isomerization of the double bond in alkaline solution and hydrogenation yielded XIV as well as an unidentified ester. Dehydration of XV would probably occur in a diaxial manner to give XVI; this has been demonstrated in two related cases.



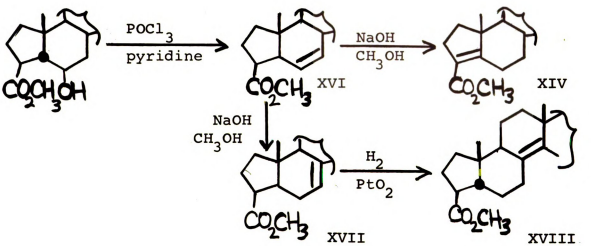
(24)



(25)

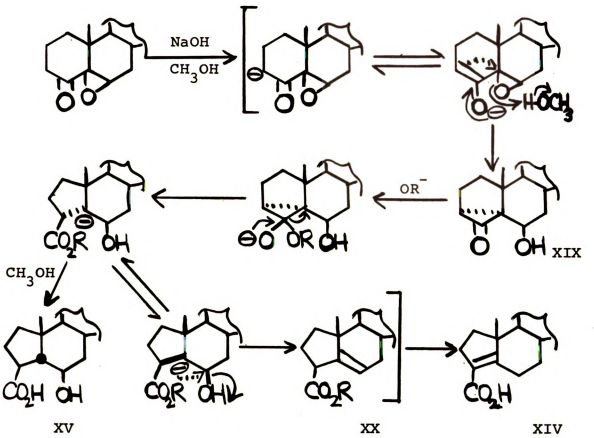
Compound XVI could then be isomerized to XVII as well as XIV by the alkaline solution. Compound XIV is resistant to hydrogenation while a double bond at the 7,8-position,

as in XVII, migrates to the 8,14 position XVIII and is not hydrogenable (26).

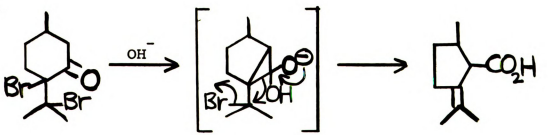


Some support for structure XVII is gained from the infrared absorption at 11.66 μ ($\begin{smallmatrix} R \\ R \end{smallmatrix}\!\!>\!C\!=\!C\!<\!\!\begin{smallmatrix} R \\ H \end{smallmatrix}$) which disappears after the attempted hydrogenation.

The formation of XIV and XV in this reaction can be rationalized by a Favorskii-type mechanism. Opening of the epoxide by back-side attack of the enolate anion gives the cyclopropanone XIX which is then opened to give the β-anion. The β-anion can be protonated immediately from the β-side by methanol to give XV or it can invert to give the α-anion. Diaxial elimination of hydroxyl ion from the α-anion leads to XX which is isomerized to XIV in the alkaline medium.

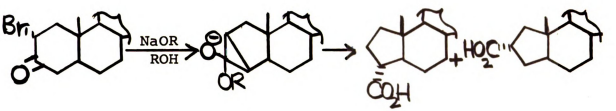


Formation of XIV in this reaction is analogous to the product from the Favorskii reaction of pulegone dibromide (27).

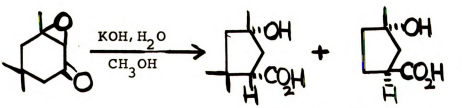


There is, however, an important difference between the ordinary Favorskii reaction and the ring contraction of epoxyketones. When anions of equal stability are involved,

the Favorskii reaction yields products from opening of the cyclopropanone in both possible ways (28).



On the other hand, ring contraction of epoxyketones apparently gives cyclopropanones which only open one way—to give 1,3-substitution in the product.



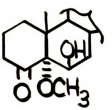
(22)

(low yield)

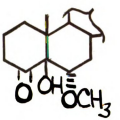
Even when a tertiary and a secondary anion are involved as in the opening of XIX, 1,3-substitution is observed in the product. This manner of opening, in contrast to that observed in the Favorskii itself, must be related to the presence of the hydroxyl group. The hydroxyl can hydrogen bond with the proton donating species and so facilitate protonation at the adjacent carbon or it can stabilize the anion by its inductive effect.

From the neutral products of the reaction of 5,6β-epoxy-5β-cholestan-4-one with methanolic sodium hydroxide

more XIV could be isolated by chromatography. No other pure compounds could be separated, although an oil with spectral characteristics expected for XXI or XXII was obtained.

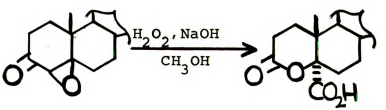


XXI

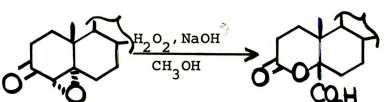


XXII

Oxidation of epoxyketones XXIII and XXIV with alkaline hydrogen peroxide gave the epimeric lactone acids XXV and XXVI respectively rather than the A-nor allylic alcohols anticipated by analogy with piperitone oxide (6, 7).

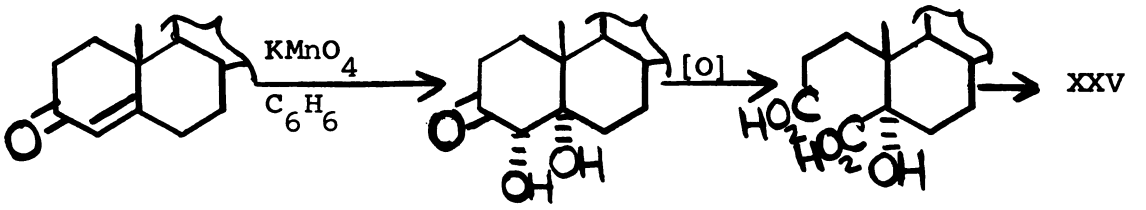


XXIII XXV

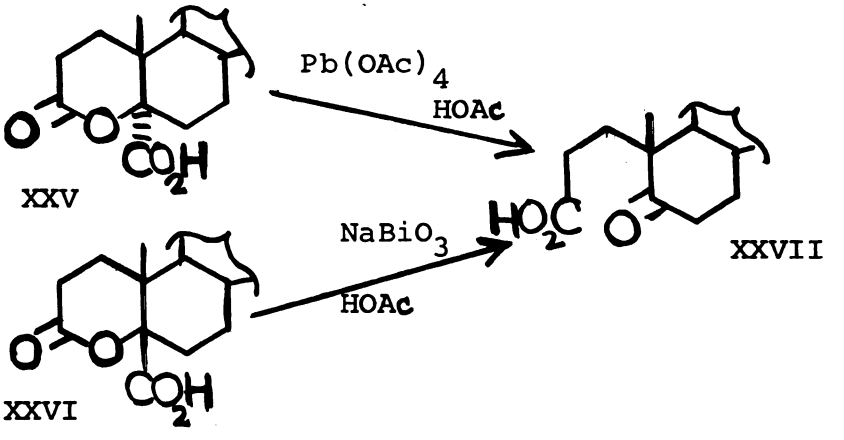


XXIV XXVI

Windaus (29) and Tschesche (30) reported XXV as one of the permanganate oxidation products of cholest-4-en-3-one, but cited little evidence for this formulation. Tschesche (30) suggested a mechanism for the formation of XXV.



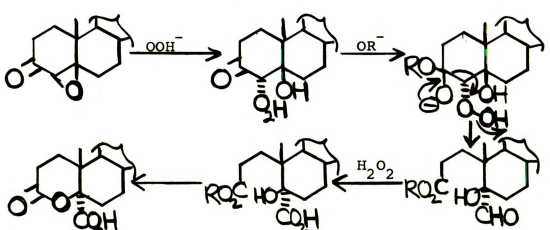
Structural assignments of XXV and XXVI were based on elemental analyses, infrared spectra ($\lambda_{max}^{C_4Cl_6}$ 5.72 and 5.87 μ for XXV, $\lambda_{max}^{CCl_4}$ 5.72 and 5.85 μ for XXVI) and degradation to the known keto acid XXVII by oxidation with lead tetraacetate and sodium bismuthate respectively.



Isomer XXVI was recovered unchanged from treatment with lead tetraacetate under conditions which convert XXV to XXVII. If the first step in the lead tetraacetate cleavage is

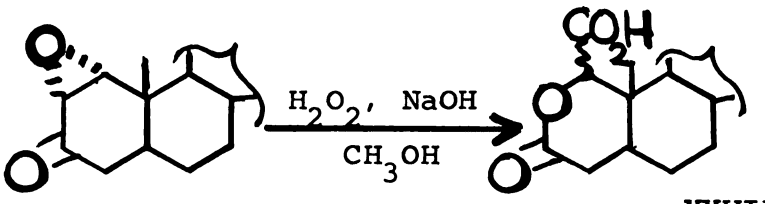
formation of a lead ester with the hydroxyl group from the opened lactone, the fact that XXVI is not cleaved could be due to its hindered axial hydroxy group. The hydroxyl in the hydroxy acid formed on opening of XXV would be equatorial and more accessible to the bulky lead tetraacetate. Sodium bismuthate oxidations are more vigorous than those with lead tetraacetate.

Stereochemistry at C_5 in XXV and XXVI has not been rigorously demonstrated although mechanistic considerations indicate retention at C_5 is probable. Since the lactone acid obtained from the β-oxide is epimeric with that formed from the α-oxide, the reaction must have proceeded with either retention or inversion at C_5. Attack to open the oxide would probably occur at C_4, the less hindered site, as it must in the formation of I. This would lead to retention of configuration at C_5.



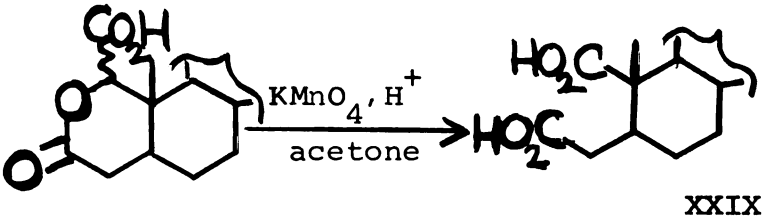
XXV

Lactone acid formation was also observed when 1α, 2α-epoxy-5α-cholestan-3-one was refluxed with hydrogen peroxide in alkaline methanol.



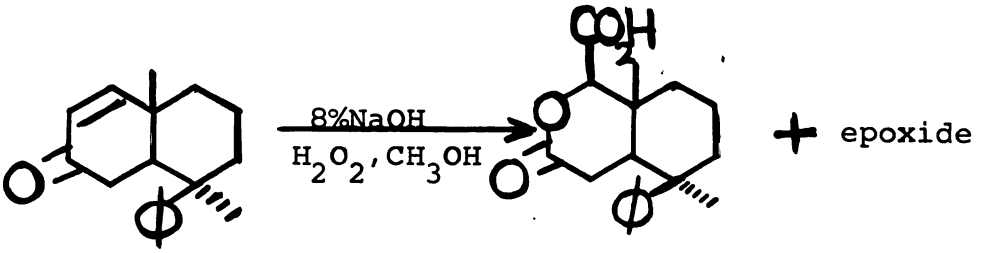
XXVIII

The structure of XXVIII was based on the elemental analysis, the infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.72 and 5.81 μ) and cleavage with potassium permanganate in acidic solution to the known diacid XXIX.

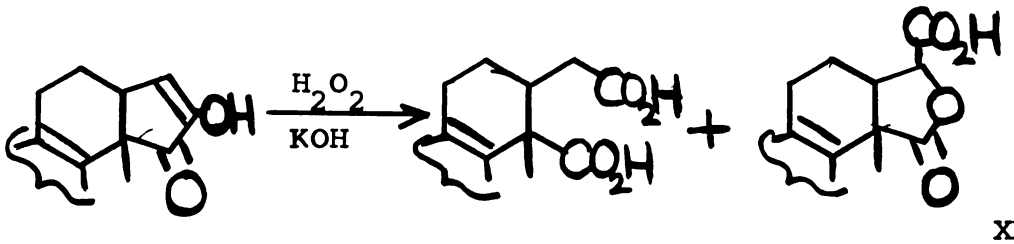


XXIX

A similar rearrangement has been reported to Dr. William H. Reusch in a private communication by Professor R. Ireland.

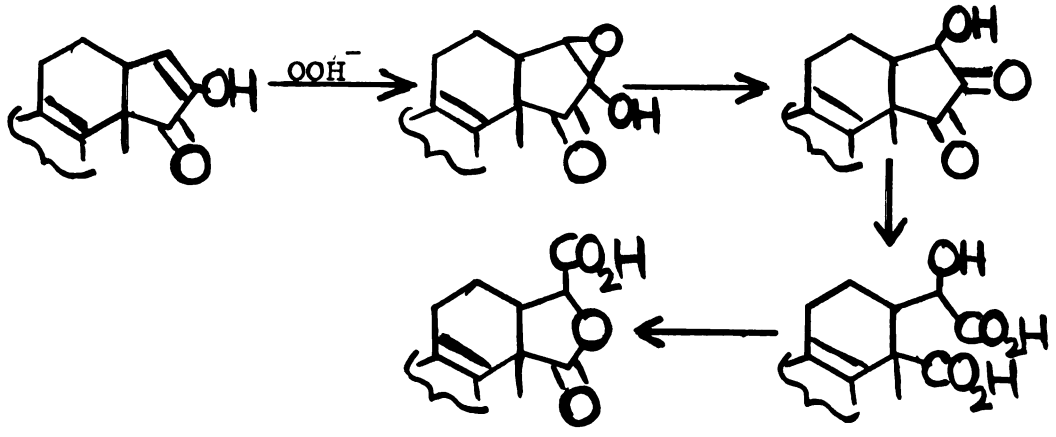


Cleavage of an α-diketone with hydrogen peroxide in alkaline solution has also been reported to yield a lactone acid **XXX** as one of the products (31).



XXX

The following mechanism was suggested for the above reaction.



This mechanism cannot be operative in the formation of **XXV** and **XXVI** since it would not be stereospecific.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. The infrared spectra were obtained with a Perkin-Elmer, model 21, spectrophotometer. The ultraviolet spectra were determined with a Beckman, DK-2, spectrophotometer. The nuclear magnetic resonance spectra were determined in carbon tetrachloride solution using a Varian Associates, A-60, high resolution spectrometer. The microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

4-methoxycholest-4-en-3-one

A. A solution of 200 mg. of 4β,5-epoxy-5β-cholestan-3-one (32), (m.p. 117.5-118.5°) in 25 ml. of methanol was treated with 2 ml. of 4 N sodium hydroxide and refluxed for 24 hours. Dilution with water followed by 24 hours at 5° gave 180 mg. of a solid, m.p. 124-126°. Crystallization from aqueous methanol gave 140 mg. of 4-methoxycholest-4-en-3-one as needles, m.p. 133-135°; $\lambda_{max}^{CCl_4}$ 5.97 and 6.25 μ; $\lambda_{max}^{C_2H_5OH}$ 255 mμ (log ε4.1); $[\alpha]_D^{28}$ + 87.5° (c 0.56 g./100 ml. $CHCl_3$); n.m.r. 6.48τ(OCH_3), no vinyl hydrogen. An analytical

sample, m.p. 136-138°, was prepared by crystallization from petroleum ether.

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 80.54; H, 11.52.
Found: C, 80.52; H, 11.39.

B. A solution of 200 mg. of 4β,5-epoxy-5β-cholestan-3-one in 25 ml. of methanol was treated with 0.43 g. of sodium methoxide and refluxed for 24 hours. Dilution with water followed by 24 hours at 5° gave 160 mg. of a solid; m.p. 95-110°. The infrared spectrum of this crude solid showed it to be a mixture of approximately equal amounts of 4-methoxycholest-4-en-3-one and 4β,5-epoxy-5β-cholestan-3-one.

3-methoxy-5α-cholest-2-en-4-one

A solution of 700 mg. of 4α-acetoxycholest-5-en-3-one (33) (m.p. 155-157°) in 35 ml. of methanol was refluxed for 1 hour with 0.7 ml. of freshly distilled boron trifluoride etherate. Dilution with water followed by cooling at 5° overnight gave 460 mg. of crude product which was crystallized from petroleum ether and twice from methanol to give 120 mg. of 3-methoxy-5α-cholest-2-en-4-one as needles, m.p. 148-149°; $\lambda_{max}^{CCl_4}$ 5.95, 6.12, 9.07 μ; $\lambda_{max}^{C_2H_5OH}$ 263 mμ (log ε 3.7); n.m.r. 4.52, 4.58 (pair of overlapping doublets

due to $C=\underline{CH}-CH_2-$) and 6.51τ(OCH_3)(ratio of peak areas ~ 3:8).

This material is presumed to be identical with the product obtained by Fieser and Stevenson (10); m.p. 150-151°; $\lambda_{max}^{CHCl_3}$ 5.91, 6.06, 9.00 μ; $\lambda_{max}^{C_2H_5OH}$ 263 mμ (log ε 3.7).

4-hydroxycholest-4-en-3-one

A solution of 200 mg. of 4α-acetoxycholest-5-en-3-one (33) in 10 ml. of 95% ethanol containing 1 ml. of boron trifluoride etherate was refluxed for 1 hour. The mixture was diluted with water and cooled to 5° overnight to give a yellowish solid which was crystallized twice from methanol to give 100 mg. of 4-hydroxycholest-4-en-3-one, m.p. 145-147°; n.m.r. 3.8τ(-OH). Reported m.p. 149-150° (10).

Methylation of 4-hydroxycholest-4-en-3-one

A solution of 700 mg. of 4-hydroxycholest-4-en-3-one in 100 ml. of methanol was treated with 200 mg. of sodium hydroxide and 2.7 g. of dimethyl sulfate and refluxed for 24 hours. Water was added until a cloudiness persisted and the reaction mixture was cooled to 0°. The infrared spectrum of the solid product (650 mg.) indicated that a mixture of unreacted 4-hydroxycholest-4-en-3-one and 3-methoxy-

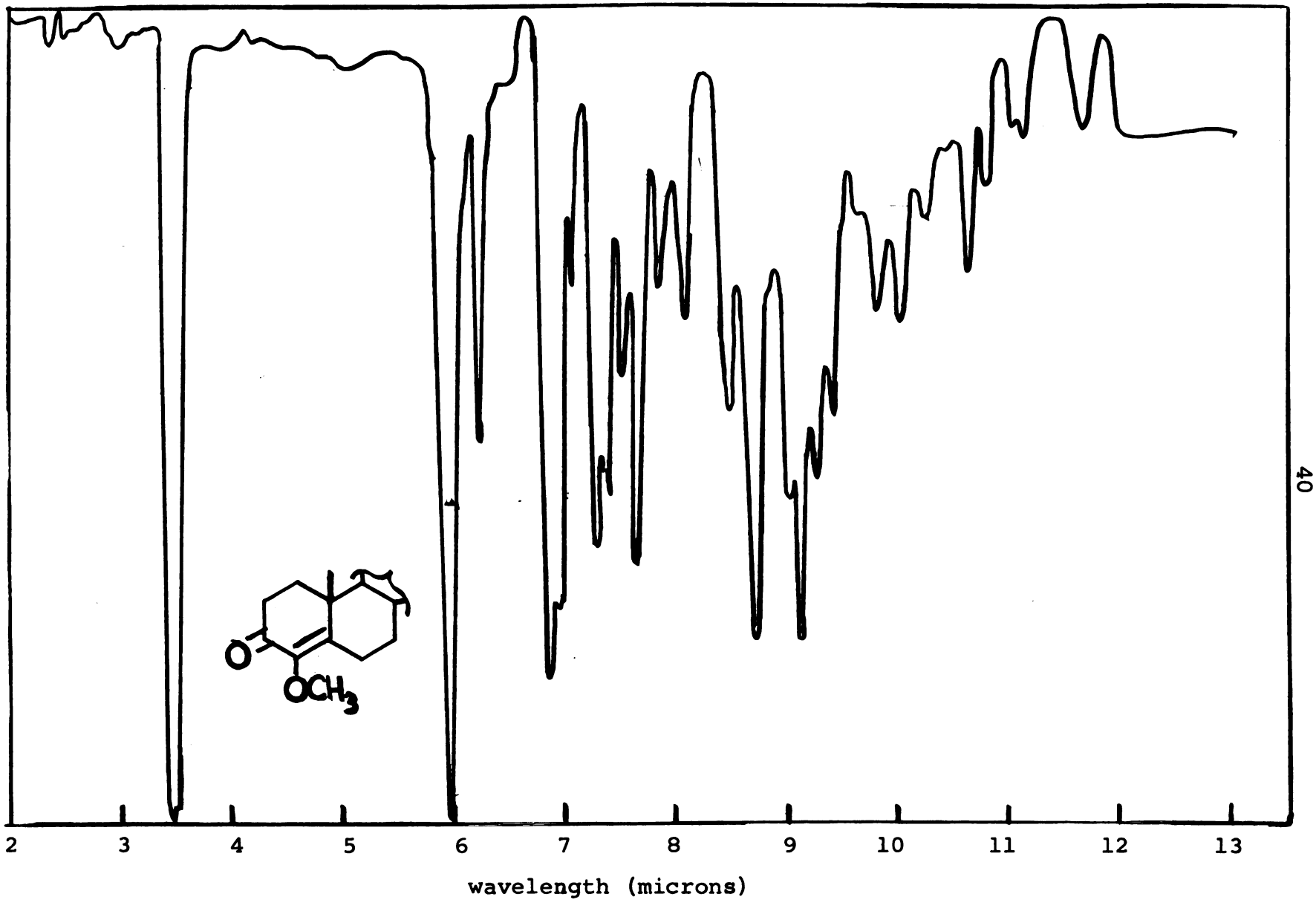


Figure 1. Infrared spectrum of 4-methoxy-cholest-4-en-3-one (in CCl_4).

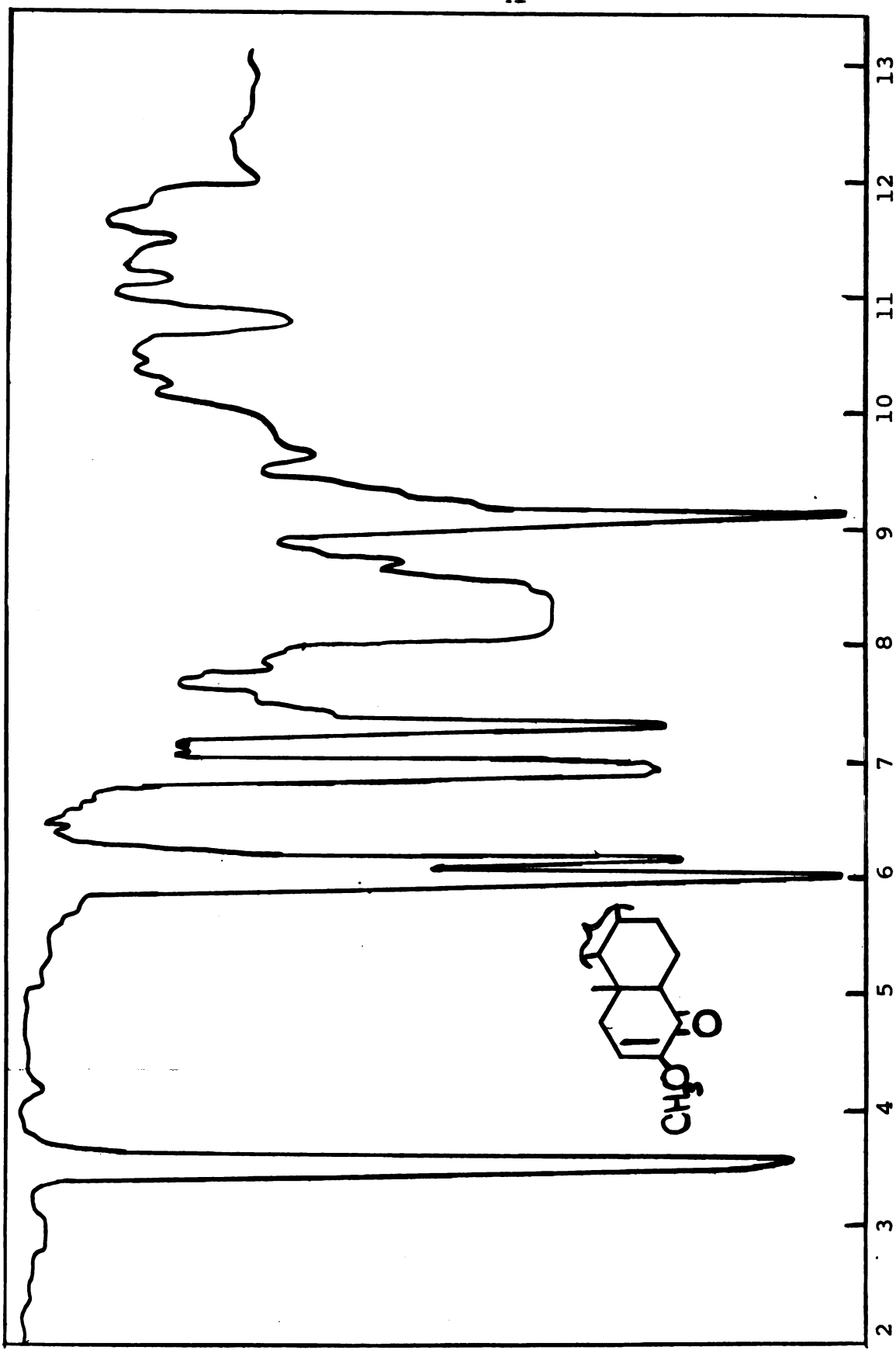


Figure 2. Infrared spectrum of 3-methoxy-5α-cholest-2-en-4-one (in CCl_4).

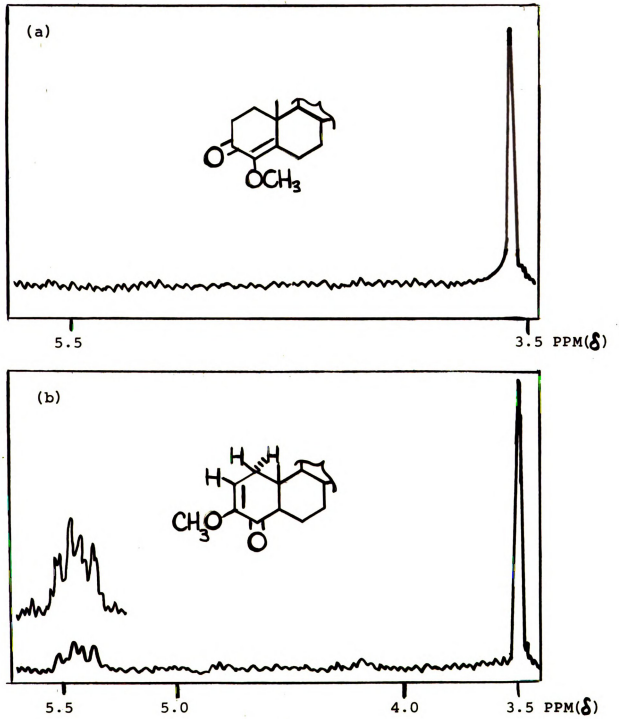


Figure 3. Nuclear magnetic resonance spectra, 60 Mc., reference: internal-tetramethylsilane (in CCl_4).

(a) 4-methoxycholest-4-en-3-one.
(b) 3-methoxy-5α-cholest-2-en-4-one.

cholest-2-en-4-one had been produced. Chromatography of 200 mg. of this mixture on 20 g. of neutral alumina (activity I) gave 80 mg. of 3-methoxy-5α-cholest-2-en-4-one, m.p. 146-147°, eluted with benzene and identified by mixture melting point and infrared spectrum. Elution with ether gave 100 mg. of unreacted 4-hydroxycholest-4-en-3-one.

Hydrolysis of 4-methoxycholest-4-en-3-one

A solution of 200 mg. of 4-methoxycholest-4-en-3-one in 25 ml. of dioxane which contained 2 ml. of conc. hydrochloric acid was refluxed for 24 hours. Water was added and the yellow solid which formed was crystallized from methanol to give 100 mg. of 4-hydroxycholest-4-en-3-one, m.p. 144-146°, identified by mixture melting point and infrared spectrum. These conditions are much more vigorous than those reported (10) and found for the hydrolysis of 3-methoxy-5α-cholest-2-en-4-one.

Attempted rearrangement of 4-methoxycholest-4-en-3-one

A solution of 200 mg. of 4-methoxycholest-4-en-3-one in 20 ml. of methanol was refluxed with 1 ml. of boron trifluoride etherate for 1 hour. The mixture was diluted with water and cooled at 0° to give a solid which was

crystallized from aqueous methanol to yield 170 mg. of unreacted 4-methoxycholest-4-en-3-one, m.p. 134-135°, identified by mixture melting point and infrared spectrum.

Ozonolysis of 4-methoxycholest-4-en-3-one

Ozone was bubbled through a solution of 100 mg. of 4-methoxycholest-4-en-3-one in 15 ml. of chloroform with cooling in a dry ice-isopropyl alcohol bath. The blue color indicated excess ozone after 5 minutes and the ozone flow was continued for an additional 5 minutes. After the mixture warmed to room temperature, it was treated with 50 ml. of water, 2 ml. of 30% hydrogen peroxide and 300 mg. of sodium hydroxide and heated on the steam bath for 5 hours. The mixture was cooled to room temperature and extracted with ether to remove any neutral material. Acidification with cold, dilute hydrochloric acid and extraction with ether gave an oily residue after evaporation of the ether. The acid could not be crystallized and so was converted to its methyl ester with diazomethane. The infrared spectrum was practically identical to that of the known methyl ester of 4,5-secocholestan-5-one-3-oic acid, $\lambda_{max}^{CCl_4}$ 5.80 and 5.89 μ; n.m.r. 6.45τ($-CO_2CH_3$), ratio of the $-CO_2CH_3$ peak area to that of the rest of the hydrogens in the

molecule = 0.089. The calculated ratio for a keto ester is 0.068 but because the n.m.r. tube contained ether, the ratio is slightly high.

Ozonolysis of 3-methoxy-5α-cholest-2-en-4-one

A solution of 100 mg. of 3-methoxy-5α-cholest-2-en-4-one in 15 ml. of chloroform was ozonized and worked up exactly as with 4-methoxycholest-4-en-3-one. The acid could not be crystallized either and so was converted to its methyl ester with diazomethane. The infrared spectrum was consistent with that expected for a diester, $\lambda_{max}^{CCl_4}$ 5.81 μ. n.m.r. 6.51τ(CO_2CH_3), ratio of $-CO_2CH_3$ peak area to that of the rest of the hydrogens in the molecule = 0.125. The calculated ratio for a diester is 0.136.

Ozonolysis of Cholest-4-en-3-one

A solution of 500 mg. of cholest-4-en-3-one in 15 ml. $CHCl_3$ was ozonized as described (34) to give 230 mg. of 3,4-secocholestan-5-one-3-oic acid, m.p. 137-142°, (reported m.p. 150-151°). Conversion of this keto acid to its methyl ester with diazomethane gave an oil, $\lambda_{max}^{CCl_4}$ 5.80, 5.89 μ; n.m.r. 6.44τ(CO_2CH_3), ratio of the $-CO_2CH_3$ peak area to that of the rest of the hydrogens in the molecule = 0.071.

The calculated ratio for the keto ester is 0.068.

Conversion of 4-methoxycholest-4-en-3-one to 5α-cholestan-4-one

A solution of 100 mg. of 4-methoxycholest-4-en-3-one in 0.5 ml. of acetic acid was treated with 0.4 ml. of ethanedithiol and 0.4 ml. of boron trifluoride etherate and allowed to stand at room temperature for 15 hours. The reaction mixture was poured into water and extracted with ether; the ether extract was washed with 5% sodium carbonate, dried and evaporated to give a heavy oil. This oil was taken up in 25 ml. of ethanol containing 1.5 ml. of 20% hydrochloric acid and heated on a steam bath for 10 minutes. Dilution with water followed by extraction with ether gave a semisolid which was dissolved in 15 ml. of absolute ethanol and refluxed with 300 mg. of Raney nickel for 6 hours. The Raney nickel was removed by filtration and the reaction mixture was diluted with water and extracted with ether. After the ether extract was washed with water and decolorized, it was evaporated to dryness to give 70 mg. of a semisolid. Two crystallizations from aqueous methanol gave pure 5α-cholestan-4-one, m.p. 97-98°, identified by mixture melting point and infrared spectrum with authentic material (35).

Attempted conversion of 3-methoxy-5α-cholest-2-en-4-one to 5α-cholestan-3-one

A solution of 100 mg. of 3-methoxy-5α-cholest-2-en-4-one was treated with 0.4 ml. of ethanedithiol and 0.4 ml. of boron trifluoride etherate at room temperature. A solid formed after 2 minutes and the reaction mixture was allowed to stand at room temperature for 30 minutes. The solid was triturated with 5 ml. of methanol, filtered, and washed with methanol. This solid was added to a solution of 30 ml. of dioxane, 3 ml. of water and 1 ml. of conc. hydrochloric acid and the mixture was refluxed for 15 minutes. Addition of water and extraction with ether gave a yellowish solid on evaporation of the ether, $\lambda_{max}^{CCl_4}$ 5.86 μ. This solid was dissolved in 30 ml. of absolute ethanol and refluxed for 6 hours with 0.4 g. of Raney nickel. Removal of the Raney nickel by filtration and dilution with water gave a white solid, m.p. 60-70°. Crystallization from methanol raised the melting point to 75-80°. The infrared spectrum showed no absorption in the carbonyl region and this compound may be 5α-cholestane; (reported m.p. 80°).

5α-carboxy-4-oxacholestan-3-one*

A solution of 200 mg. of 4β,5-epoxy-5β-cholestan-3-one in 25 ml. of methanol was heated at reflux while 1.6 ml. of 30% hydrogen peroxide and 1 ml. of 4 N sodium hydroxide were added simultaneously. After refluxing for 24 hours, the reaction mixture was diluted with water and extracted with ether to give 10 mg. of neutral material. The aqueous portion was acidified and extracted with ether to yield 180 mg. of acidic material which was crystallized from aqueous methanol to give 120 mg. of a white solid, m.p. 213-215°; $\lambda_{max}^{C_4Cl_6}$ 5.72, 5.87 μ. Three crystallizations of this acid from methanol gave material with a melting point of 202-205°. Partial epimerization at C_5 would account for this behavior on crystallization. The methyl ester was prepared with diazomethane and obtained as a solid, m.p. 152-154°; $\lambda_{max}^{CCl_4}$ 5.72, 5.76 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38.

Found: C, 75.11; H, 10.49.

These properties compare favorably with those reported for 5α-carboxy-4-oxacholestan-3-one by Windaus (29) and

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*The stereochemistry at C_5 was not rigorously established although retention at C_5 is preferred from mechanistic considerations.

Tschesche (30), m.p. 217-218°; methyl ester m.p. 148-149°. A by-product from the epoxidation of cholest-4-en-3-one (32) was also shown to be 5α-carboxy-4-oxacholestan-3-one. From 5 g. of cholest-4-en-3-one, 900 mg. of 5α-carboxy-4-oxacholestan-3-one could be obtained by purification as in the above preparation.

5β-carboxy-4-oxacholestan-3-one

A solution of 49 mg. of 4α,5-epoxy-5α-cholestan-3-one* in 6 ml. of methanol was refluxed while 0.4 ml. of 30% hydrogen peroxide and 0.3 ml. of 4 N sodium hydroxide were added quickly. An additional ml. of methanol was added to dissolve a white solid which formed. After refluxing for 24 hours, the mixture was poured into 15 ml. of cold 3% sodium hydroxide. Ether extraction of this basic mixture gave 3 mg. of a neutral oil, while acidification and extraction of the aqueous portion with ether yielded 40 mg. of a white solid. Several crystallizations of this solid from ethyl acetate-cyclohexane and from aqueous methanol gave 11 mg. of material, m.p. 184-192°, which strongly depressed the

*The α-oxide was prepared by photosensitized oxidation of cholest-4-en-3β-ol according to the procedure kindly provided by Professor Alex Nickon. Alex Nickon and Wilford L. Mendelson, J. Am. Chem. Soc., 85, 1894 (1963).

melting point of 5α-carboxy-4-oxacholestan-3-one. The infrared spectrum of 5β-carboxy-4-oxacholestan-3-one, $\lambda_{max}^{CCl_4}$ 5.72 and 5.85 μ, was significantly different from 5α-carboxy-4-oxacholestan-3-one in the fingerprint region. Difficulties in further purification led to the preparation of the methyl ester by reaction with diazomethane. Two crystallizations from aqueous methanol gave lustrous plates, m.p. 116-119°, mixture melting point with 5α-carbomethoxy-4-oxacholestan-3-one, 102-120°, $\lambda_{max}^{CCl_4}$ 5.70-5.78 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38.
Found: C, 74.52; H, 10.89.

Cleavage of 5α-carboxy-4-oxacholestan-3-one

A solution of 500 mg. of 5α-carboxy-4-oxacholestan-3-one in 20 ml. of benzene and 20 ml. of acetic acid was stirred with 1.0 g. of lead tetraacetate for 80 hours at room temperature. Ethylene glycol was added to destroy the excess lead tetraacetate and the reaction mixture was diluted with water and extracted with ether. The yellow oil obtained by evaporation of the dried ether extract was crystallized from petroleum ether to give 320 mg. of solid, m.p. 125-134°. Three crystallizations from petroleum ether-benzene raised the melting point to 149-150°. A

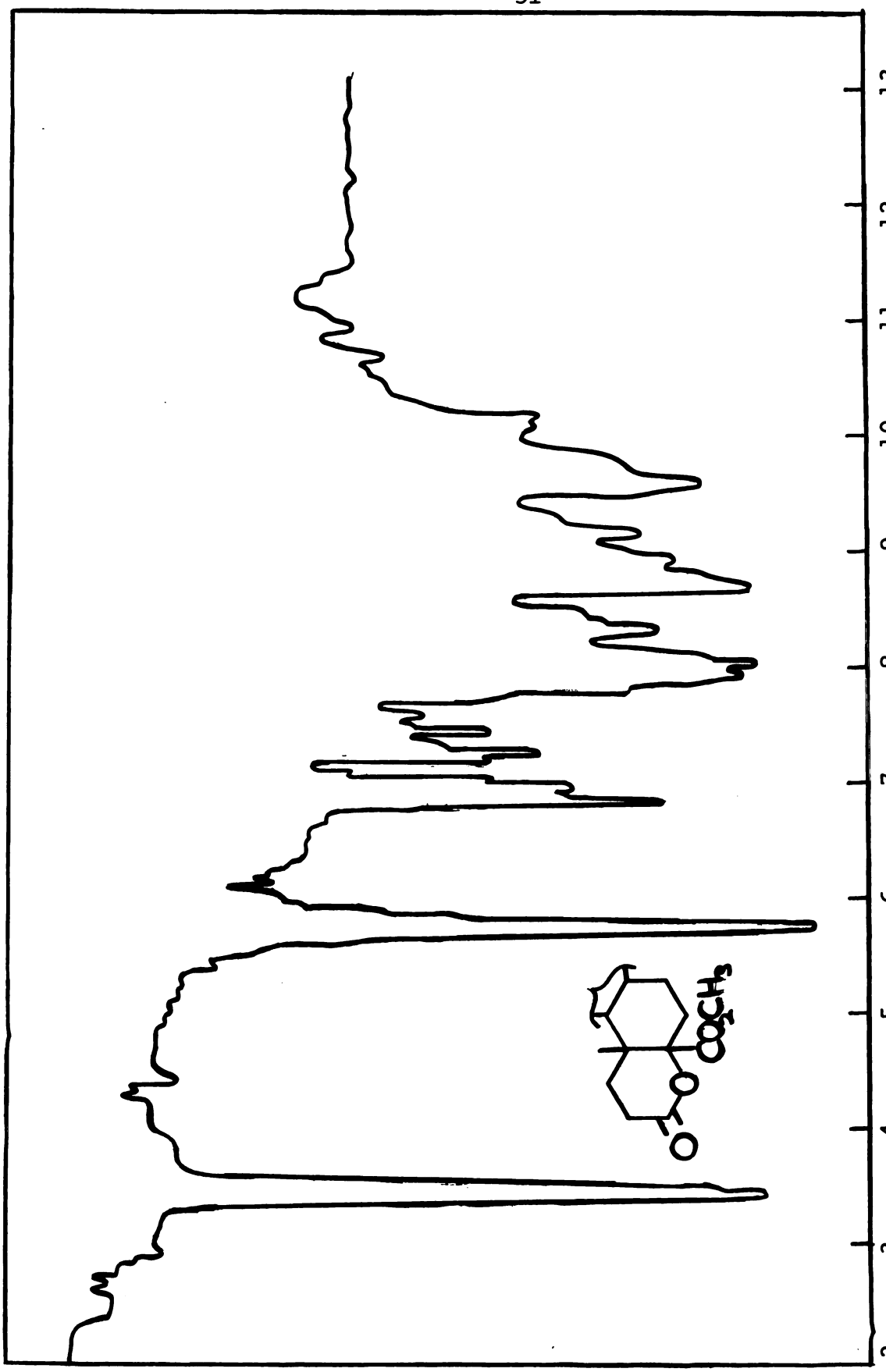


Figure 4. Infrared spectrum of 5β-carbomethoxy-4-oxacholestan-3-one (in CCl_4).

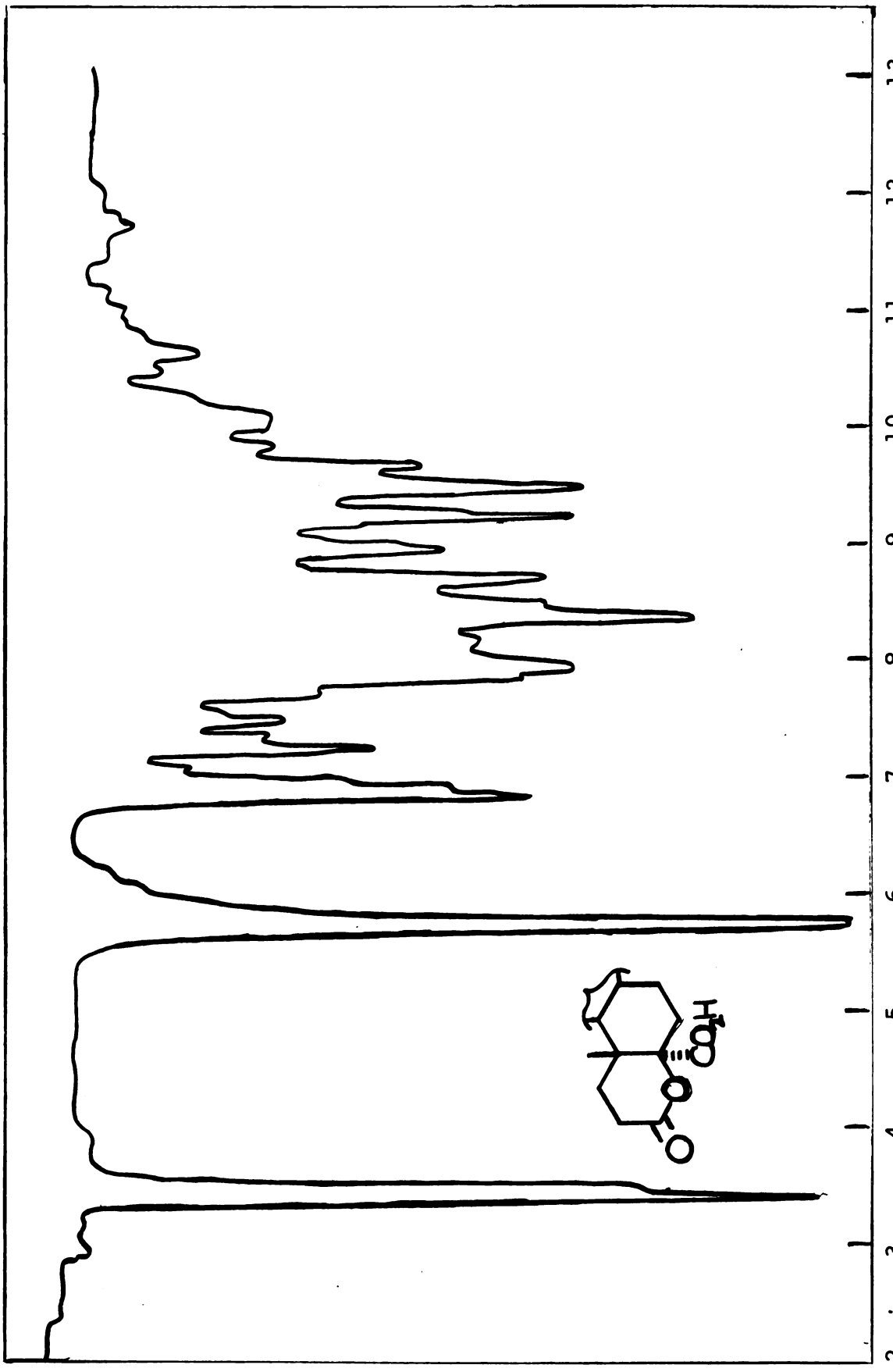


Figure 5. Infrared spectrum of 5α-carbomethoxy-4-oxacholestan-3-one (in CCl_4).

mixture melting point with authentic 3,4-secocholestan-5-one-3-oic acid (m.p. 151.5-152.5°) prepared by ozonolysis of cholest-4-en-3-one (34) was not depressed and the infrared spectra of the corresponding methyl esters were identical.

Attempted cleavage of 5β-carboxy-4-oxacholestan-3-one

A solution of 23 mg. of 5β-carboxy-4-oxacholestan-3-one in 5 ml. of benzene and 5 ml. of acetic acid was treated with 75 mg. of lead tetraacetate and stirred at room temperature for 80 hours. Workup as described in the previous reaction yielded 15 mg. of unreacted 5β-carboxy-4-oxacholestan-3-one, m.p. 185-192°.

Cleavage of 5β-carboxy-4-oxacholestan-3-one

A solution of 15 mg. of 5β-carboxy-4-oxacholestan-3-one in 3 ml. of acetic acid was stirred with 50 mg. of sodium bismuthate for 24 hours at room temperature followed by 3 hours on the steam bath. Phosphoric acid was added to precipitate bismuth phosphate and the reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried and evaporated to yield 14 mg. of an oil which gave 7 mg. of solid, m.p. 125-135°, upon trituration with petroleum ether.

Crystallization from benzene-petroleum ether raised the melting point to 135-140°. The infrared spectrum of the methyl ester prepared with diazomethane showed this to be a mixture of unreacted 5β-carboxy-4-oxacholestan-3-one and 3,4-secocholestan-5-one-3-oic acid. The oily methyl ester mixture was converted to a 2,4-dinitrophenylhydrazone derivative (36) which was obtained as an oil. The derivative was taken up in chloroform, stirred with bentonite, filtered and evaporated to yield an oil which was chromatographed on 5 g. of neutral alumina. Elution with 10% chloroform in petroleum ether gave a yellow semisolid which was crystallized from aqueous ethanol to give a yellow solid, m.p. 90-93°. The 2,4-dinitrophenylhydrazone derivative, m.p. 93-96°, of the authentic keto ester did not depress this melting point.

4-acetoxycholest-4-en-3-one

A solution of 2.3 g. of 4-hydroxycholest-4-en-3-one in 10 ml. of anhydrous pyridine was treated at room temperature with 2.5 g. of acetic anhydride and allowed to stand overnight at room temperature (37). The reaction mixture was poured onto ice and extracted with ether. After the ether extract was washed with water and 5% sodium carbonate solution,

it was dried and evaporated to yield a yellow oil, n.m.r. 3.85 (broad quartet) 7.88τ(CH_3-C(=O)-O-). The area ratio was approximately 1:4. Crystallization from petroleum ether gave 700 mg. of white solid, m.p. 96-98°, (reported m.p. 100-101°). The n.m.r. spectrum showed only a trace resonance at 3.85 and a strong peak at 7.88τ(CH_3-C(=O)-O-). The mother liquor probably contains some 3-acetoxy-5α-cholest-2-en-4-one (3.85 resonance).

Attempted thermal rearrangement of 4β,5-epoxy-5β-cholestan-3-one

A solution of 50 mg. of 4β,5-epoxy-5β-cholestan-3-one in 1 ml. of pure heptane was degassed, sealed in a tube and heated at 280-285° for 12 hours. Removal of the solvent yielded a yellowish semisolid which had an infrared spectrum almost identical to 4β,5-epoxy-5β-cholestan-3-one (trace absorption at 6.00, 6.20 μ).

5α-cholest-1-en-3-one

A solution of 20 g. of 2α-bromo-5α-cholestan-3-one (38) in 200 ml. of dimethylformamide was treated with 8.5 g. of lithium chloride and 4.9 g. of lithium carbonate and refluxed under nitrogen for 5 hours. The mixture was poured into water and extracted with ether. After the

ether extract was washed with dilute hydrochloric acid, dilute sodium hydroxide and water, it was dried, decolorized with Norite and evaporated to dryness. Two crystallizations from 95% ethanol gave 12 g. of 5α-cholest-1-en-3-one, m.p. 90-92°, (reported m.p. 95°).

2-methoxy-5α-cholest-1-en-3-one

A solution of 1.0 g. of 1α,2α-epoxy-5α-cholestan-3-one (39) (m.p. 119-120°) in 90 ml. of methanol was refluxed with 3 ml. of 12 N sodium hydroxide for 5 hours. Dilution with water followed by extraction with ether gave 900 mg. of a neutral oil upon evaporation of the dried ether extract. This material was chromatographed on 40 g. of neutral alumina. Elution with benzene gave 110 mg. of unreacted 1α,2α-epoxy-5α-cholestan-3-one and elution with benzene-ether (1:1) gave 590 mg. of 2-methoxy-5α-cholest-1-en-3-one, m.p. 69-70°; $\lambda_{max}^{CCl_4}$ 5.95, 6.23 μ; $\lambda_{max}^{C_2H_5OH}$ 265 mμ (log ε 3.9); $[\alpha]_D^{25}$ 67° (c 0.38 g./100 ml. C_2H_5OH); n.m.r. 4.18 (vinyl singlet), 6.57τ(OCH_3). An analytical sample was prepared by crystallization from aqueous ethanol, m.p. 70-71°.

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 80.54; H, 11.52.
Found: C, 80.47; H, 11.55.

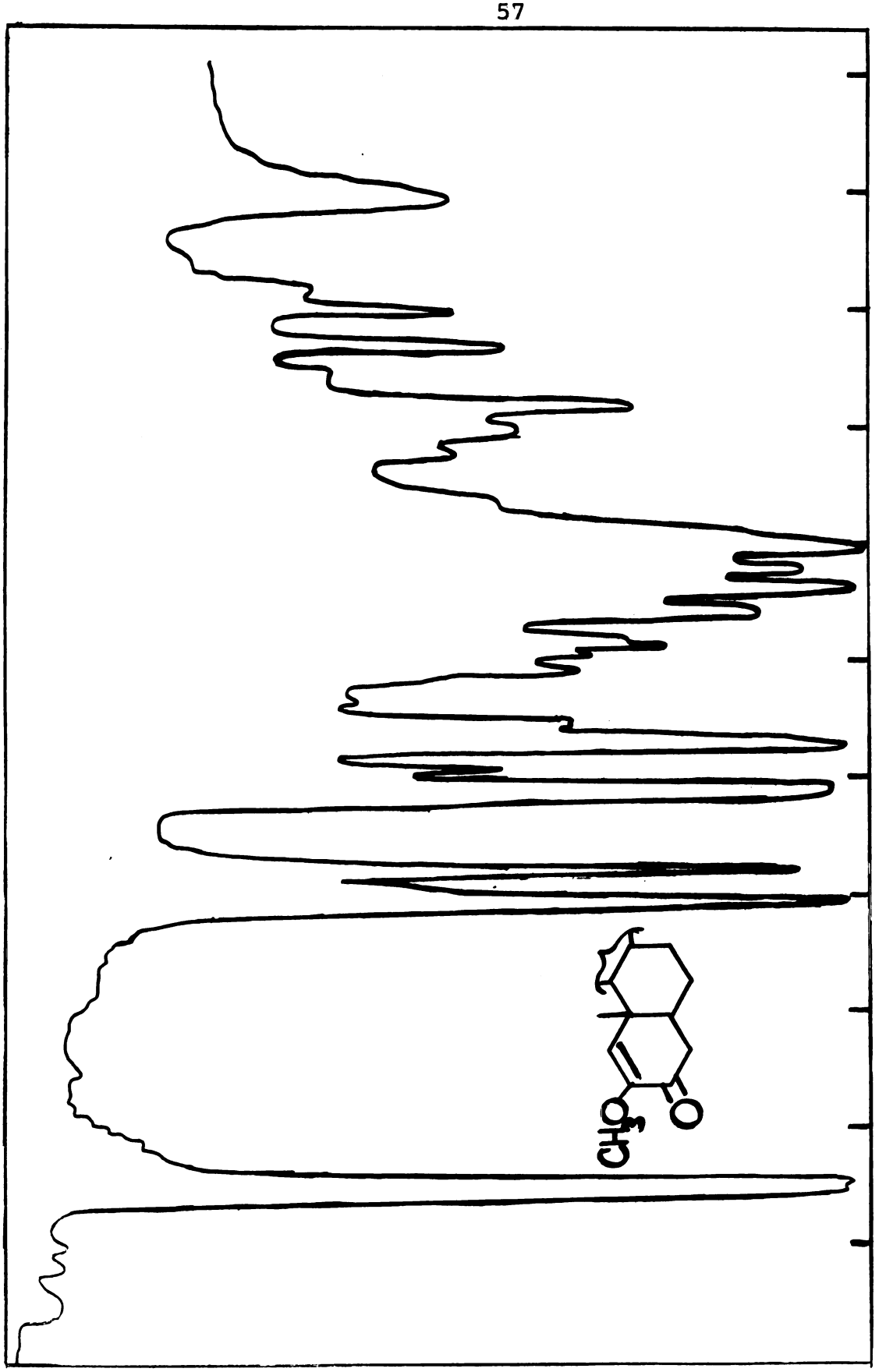


Figure 6. Infrared spectrum of 2-methoxy-5α-cholest-1-en-3-one (in CCl_4).

The aqueous fraction yielded 50 mg. of acidic material.

3-hydroxy-5α-cholest-3-en-2-one

A mixture of diosphenols was prepared by either the procedure of Stiller and Rosenheim (16) or that of Ruzicka et al. (15). When an ether solution of this mixture was shaken with ice-cold 20% potassium hydroxide, the insoluble potassium salt formed in the aqueous layer. After several extractions, the combined aqueous layers were washed with ether and most of the liquid was decanted from the potassium salt. A suspension of the salt in ether was shaken with dilute hydrochloric acid to free the enol. The ether extract was washed with dilute sodium bicarbonate before it was dried and evaporated. Crystallization of the white residue from petroleum ether gave 3-hydroxy-5α-cholest-3-en-2-one, m.p. 143-145°, (reported m.p. 144-145°); $\lambda_{max}^{CCl_4}$ 2.92, 5.75 μ (weak), 5.98, 8.25 μ; n.m.r. 4.31 (hydroxyl), 4.43 (vinyl doublet, J=2.5cps), 3.80τ (vinyl from 2-hydroxy-5α-cholest-1-en-3-one which is present as an impurity in approximately 7%).

2-hydroxy-5α-cholest-1-en-3-one

A 400 mg. sample of 3-hydroxy-5α-cholest-3-en-2-one was

dissolved in 3 ml. of acetic acid containing 0.1 ml. of conc. hydrochloric acid and heated on the steam bath for 10 minutes (18). Upon cooling, a solid precipitated and was crystallized twice from ethyl acetate to give 60 mg. of 2-hydroxy-5α-cholest-1-en-3-one, m.p. 161-162°, (reported m.p. 160-162°); $\lambda_{max}^{CCl_4}$ 2.93, 6.00, 11.65 μ; n.m.r. 3.82 (vinyl singlet), 4.32τ(hydroxyl). The absorptions are of equal area. The mother liquor exhibited resonances at 3.78, 4.12 and 4.45τ, the areas of which indicate a mixture of 18% 2-hydroxy-5α-cholest-1-en-3-one and 82% 3-hydroxy-5α-cholest-3-en-2-one. The downfield shift of the hydroxyl absorption (4.32τ in pure 2-hydroxy-5α-cholest-1-en-3-one and in 3-hydroxy-5α-cholest-3-en-2-one to 4.12τ in mixture) implies intermolecular hydrogen bonding. A shift in the carbonyl stretching frequency in the infrared to 6.02 μ agrees with this suggestion.

Evidence for cholestan-2,3-dione

Upon standing at room temperature or in the refrigerator, 3-hydroxy-5α-cholest-3-en-2-one was unstable in the crystalline state and became yellow. After two weeks the melting point was 105-125° and this substance exhibited n.m.r. absorptions at 3.76, 4.12 and 4.42τ(doublet). The areas of these peaks

indicated a mixture of 15% 2-hydroxy-5α-cholest-1-en-3-one and 85% 3-hydroxy-5α-cholest-3-en-2-one. This mixture gave n.m.r. absorptions at 3.56, 4.15 and 4.39τ(doublet) in methylene bromide and at 3.69 (broad, hydroxyl and vinyl peaks are not resolved) and 4.66τ(doublet) in cyclohexane. After standing for one month, the yellow solid melted at 70-75° and showed weak absorption at 2.94 and 6.02 μ and strong absorption at 5.78 and 5.89 μ in the infrared. Very weak peaks at 3.86, 4.19 and 4.44τ were observed in the n.m.r. spectrum, the areas of which represented about 13% diosphenol. A 50 mg. sample of the low melting yellow substance was taken up in ether and converted to the potassium salt by shaking with 20% potassium hydroxide. The potassium salt was suspended in ether and shaken with dilute hydrochloric acid to free the enol. Upon evaporation of the dried ether extract, 35 mg. of crude solid was obtained and was crystallized from petroleum ether to yield 20 mg. of 3-hydroxy-5α-cholest-3-en-2-one, m.p. 140-142°, identified by mixture melting point and infrared spectrum. The mother liquors showed strong absorption just above 6.00 μ in the infrared. A 38 mg. sample of the low melting yellow substance was dissolved in 1.8 ml. of absolute ethanol and refluxed for 1 hour with 38 mg. of o-phenylene diamine (18).

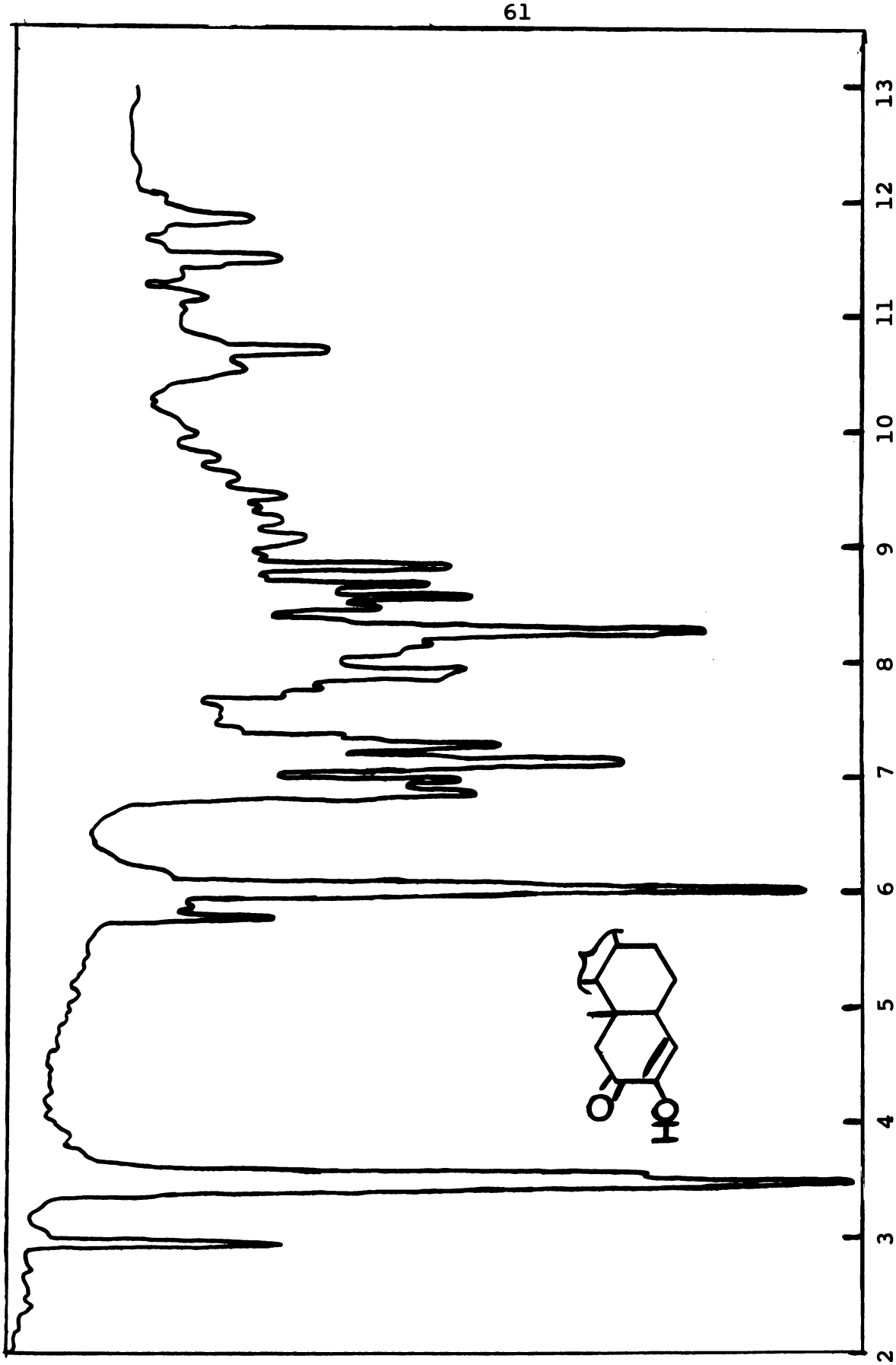


Figure 7. Infrared spectrum of 3-hydroxy-5α-cholest-3-en-2-one (in CCl_4).

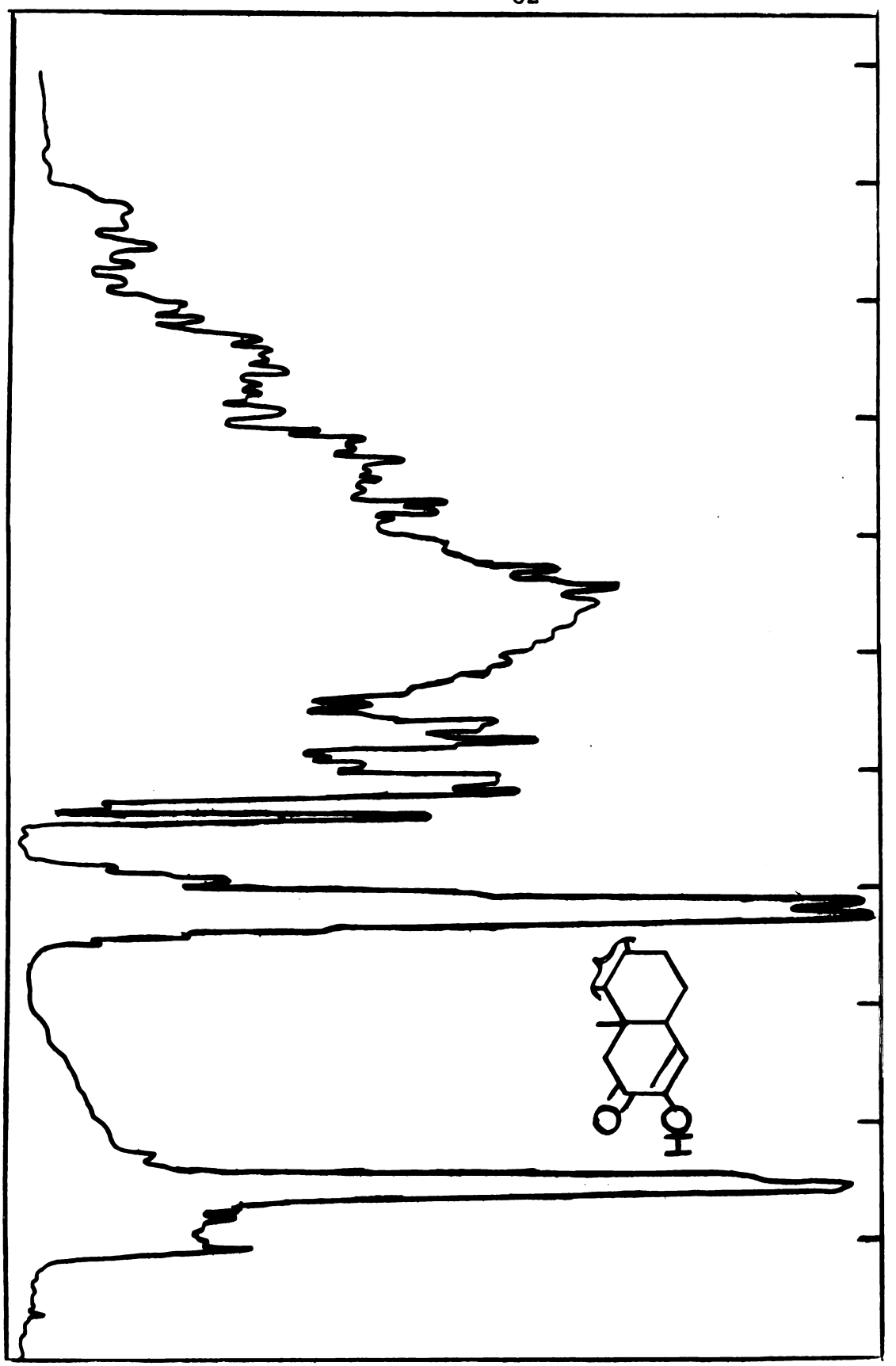


Figure 8. Infrared spectrum of 3-hydroxy-5α-cholest-3-en-2-one after standing for longer than one month (CCl_4 solution).

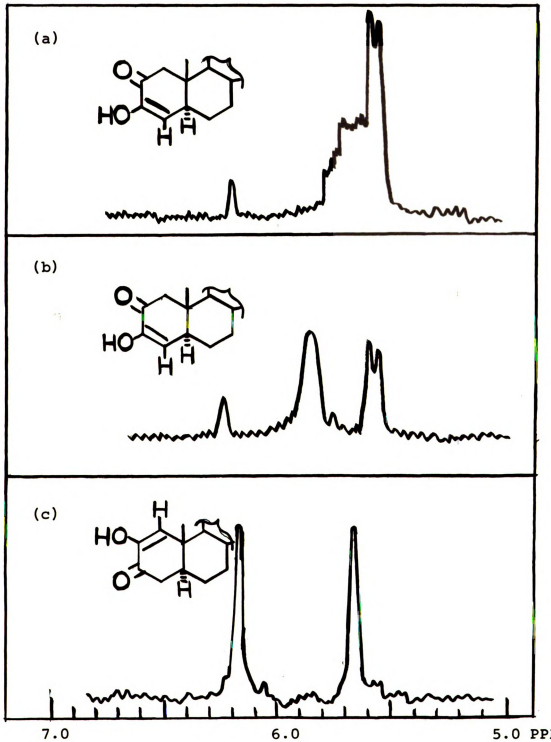


Figure 9. Nuclear magnetic resonance spectra, 60 Mc., reference: internal-tetramethylsilane (in CCl_4).

(a) 3-hydroxy-5α-cholest-3-en-2-one.
(b) 3-hydroxy-5α-cholest-3-en-2-one after standing for 2 weeks.
(c) 2-hydroxy-5α-cholest-1-en-3-one.

On cooling, 10 mg. of the quinoxaline derivative was obtained as light tan plates, m.p. 170-175°, (reported m.p. 179-180°).

Deuterium exchange of 3-hydroxy-5α-cholest-3-en-2-one

A 100 mg. sample of impure 3-hydroxy-5α-cholest-3-en-2-one (containing about 15% 2-hydroxy-5α-cholest-1-en-3-one) was dissolved in 10 ml. of anhydrous tetrahydrofuran and refluxed for 1 hour with 3 ml. of 99.8% deuterium oxide. The reaction mixture was evaporated to dryness under reduced pressure to yield a white solid. This solid exhibited n.m.r. resonances at 3.86, 4.19 and 4.48τ(doublet) with the area of the hydroxyl resonance now only 1/7 that of the total vinyl hydrogen area. After 24 hours of reflux with deuterium oxide in dioxane, the area of the hydroxyl resonance was only 0.06 that of the total vinyl hydrogen area.

Hydrolysis of 2-methoxy-5α-cholest-1-en-3-one

A solution of 250 mg. of 2-methoxy-5α-cholest-1-en-3-one in 40 ml. of 95% ethanol containing 0.5 ml. of conc. hydrochloric acid was refluxed overnight. The reaction mixture was diluted with water and extracted with ether. Upon shaking the ether extract with 20% potassium hydroxide,

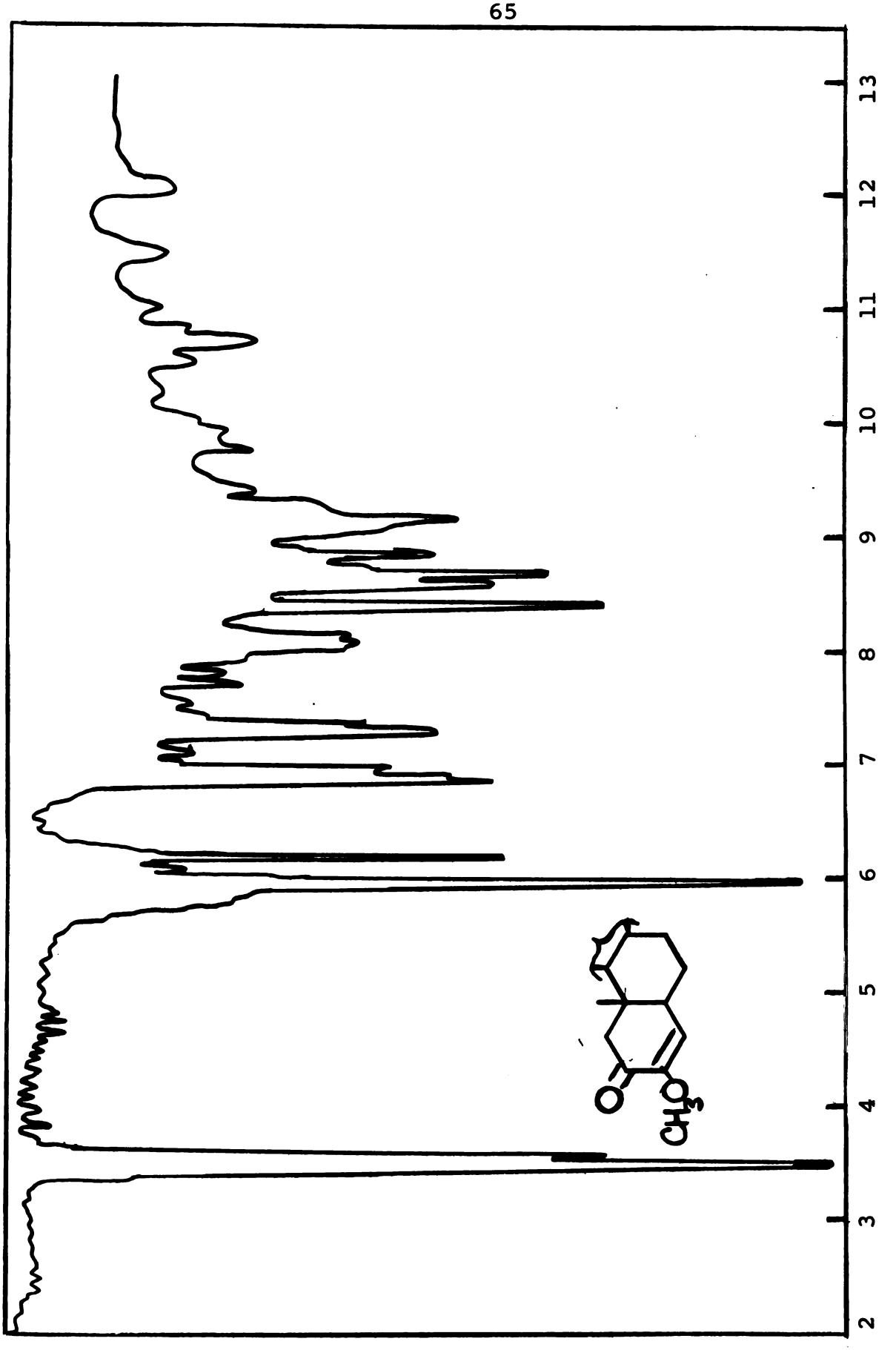


Figure 10. Infrared spectrum of 3-methoxy-5α-cholest-3-en-2-one (in CCl_4).

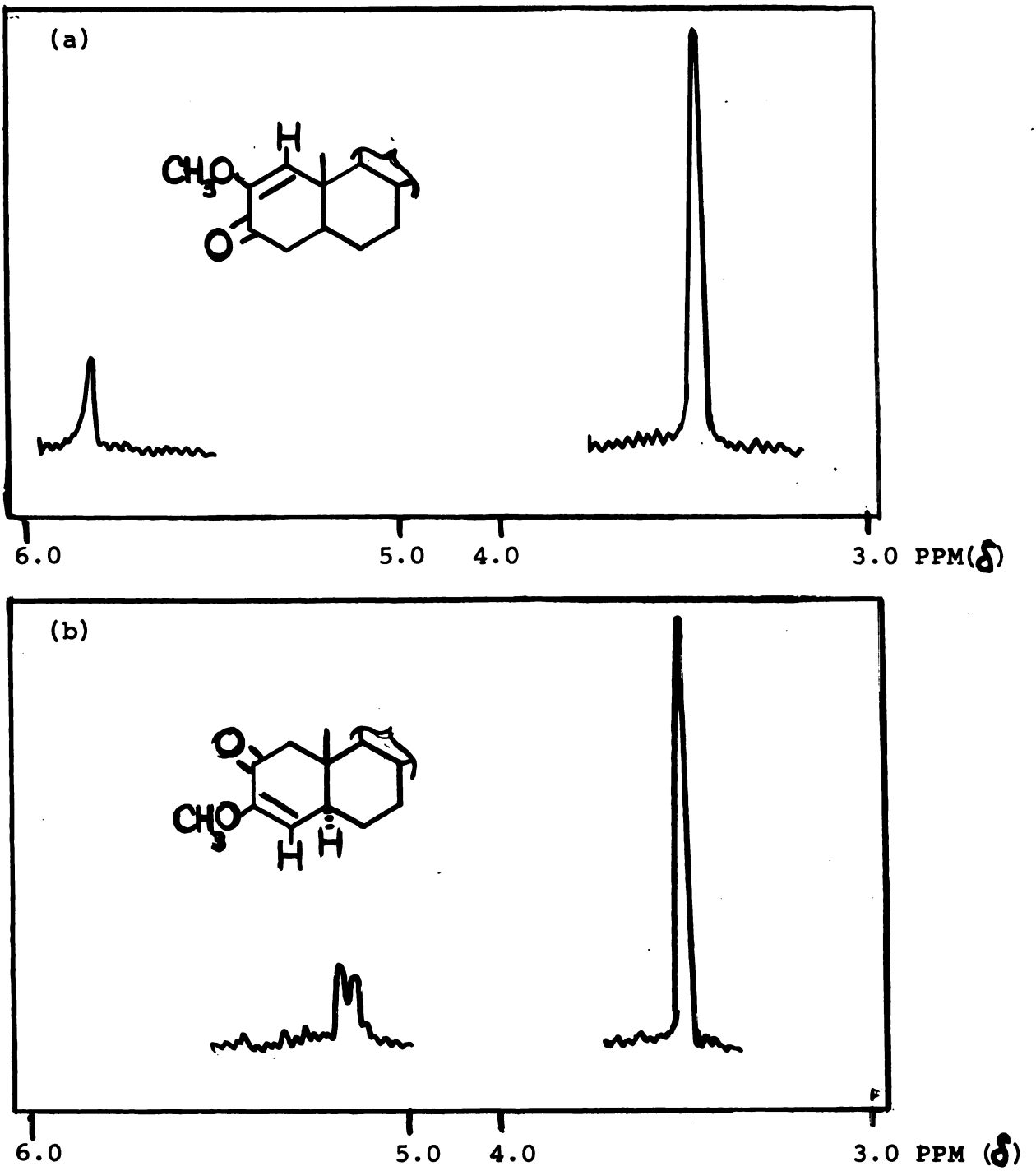


Figure 11. Nuclear magnetic resonance spectra, 60 Mc., reference: internal-tetramethylsilane (in CCl_4).

(a) 2-methoxy-5α-cholest-1-en-3-one.
(b) 3-methoxy-5α-cholest-3-en-2-one.

the potassium salt formed. After washing the aqueous layer with ether, the combined ether layers were dried and evaporated to yield 160 mg. of unreacted 2-methoxy-5α-cholest-1-en-3-one. Acidification and ether extraction of the aqueous fractions containing the suspended potassium salt gave 90 mg. of 3-hydroxy-5α-cholest-3-en-2-one, m.p. 137-139°. The identification was confirmed by mixture melting point and identity of the infrared spectrum with authentic 3-hydroxy-5α-cholest-3-en-2-one.

3-methoxy-5α-cholest-3-en-2-one

A solution containing 560 mg. of a mixture of 3-hydroxy-5α-cholest-3-en-2-one and 2-hydroxy-5α-cholest-1-en-3-one in 40 ml. of methanol was refluxed for 20 hours with 200 mg. of sodium hydroxide and 2.5 g. of dimethyl sulfate. The reaction mixture was diluted with water and extracted with ether. Upon evaporation of the dried ether extract, 550 mg. of a yellow oil was obtained. The oil was chromatographed on 30 g. of neutral alumina and elution with petroleum ether gave 150 mg. of an oil, $\lambda_{max}^{CCl_4}$ 5.82 μ. Elution with benzene gave 230 mg. of 3-methoxy-5α-cholest-3-en-2-one, m.p. 153-155°; $\lambda_{max}^{CCl_4}$ 5.96, 6.18 and 8.40 μ; $\lambda_{max}^{C_2H_5OH}$ 266 mμ (log ε3.9) n.m.r. 4.83 (doublet) and 6.49τ(OCH_3) with an

area ratio of 1:2.9. An analytical sample, m.p. 157-158°, was prepared by crystallization from aqueous ethanol.

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 80.54; H, 11.52.

Found: C, 80.71; H, 11.33.

Elution with ether gave 60 mg. of an oily mixture of 3-methoxy-5α-cholest-3-en-2-one and unreacted diosphenols, $\lambda_{max}^{CCl_4}$ 2.95, 5.81, 5.95, 6.03, 6.21 μ.

Methylation of 3-hydroxy-5α-cholest-3-en-2-one using sodium hydride and methyl iodide

A freshly prepared sample of 200 mg. of 3-hydroxy-5α-cholest-3-en-2-one was dissolved in 20 ml. of dry benzene and treated with 50 mg. of sodium hydride (52.8% dispersion in mineral oil) at reflux for 45 minutes. When the hydride was added, a flocculent solid formed and a gas was evolved. After cooling to room temperature, 2 ml. of methyl iodide was added and the mixture was refluxed for 20 hours. The excess sodium hydride was decomposed with a few drops of ethanol and the reaction mixture was diluted with water and extracted with ether. By shaking the ether extract with 20% potassium hydroxide, 70 mg. of unreacted 3-hydroxy-5α-cholest-3-en-2-one was obtained as the potassium salt. The residue obtained by evaporation of the ether extract

was chromatographed on 15 g. of neutral alumina and yielded 88 mg. of a solid on elution with ether. Crystallization from aqueous ethanol gave 60 mg. as needles, m.p. 121-131°, having an infrared spectrum identical with that of 3-methoxy-5α-cholest-3-en-2-one. The n.m.r. spectrum showed a very weak resonance at 4.20 and stronger absorptions at 4.90 (doublet) and 6.48τ(OCH_3). The ratio of the areas of the vinyl hydrogen doublet to the methoxyl singlet indicated that this material contained 94% 3-methoxy-5α-cholest-3-en-2-one and 6% 2-methoxy-5α-cholest-1-en-3-one. Although some purification was achieved by further chromatography and crystallization, the melting point could only be raised to 133-135° (pure 3-methoxy-5α-cholest-3-en-2-one melts at 157-158°). A fraction melting at 75-95°, apparently enriched in 2-methoxy-5α-cholest-1-en-3-one, was also obtained by this further chromatography.

Methylation of 2-hydroxy-5α-cholest-1-en-3-one using sodium hydride and methyl iodide

A solution of 54 mg. of freshly prepared 2-hydroxy-5α-cholest-1-en-3-one in 15 ml. of dry benzene was refluxed for 50 minutes with 7 mg. of the sodium hydride dispersion. After the addition of 1 ml. of methyl iodide to the reaction

mixture, reflux was continued for 20 hours. Workup as in the previous procedure gave 5 mg. of 3-hydroxy-5α-cholest-3-en-2-one. Chromatography of the dried ether extract on 5 g. of neutral alumina gave 52 mg. in two crystalline fractions on elution with ether, m.p. 105-140° and m.p. 50-105°; $\lambda_{max}^{CCl_4}$ 5.96, 6.20 μ; n.m.r. 4.14 (singlet), 4.81 (doublet) and 6.52τ(OCH_3). A comparison of the areas of the vinyl hydrogen resonances from the two combined fractions indicated this material was a mixture of 44% 2-methoxy-5α-cholest-1-en-3-one and 56% 3-methoxy-5α-cholest-3-en-2-one.

1α-carboxy-2-oxa-5α-cholestan-3-one

A solution of 1 g. of 1α,2α-epoxy-5α-cholestan-3-one (39) in 125 ml. of methanol was heated at reflux while 8 ml. of 30% hydrogen peroxide and 8 ml. of 4 N sodium hydroxide were added simultaneously. After fifteen minutes at reflux, 75 ml. of methanol was added to dissolve a white solid which had formed and the reaction mixture was then refluxed for 4 hours. After cooling, the reaction mixture was diluted with 300 ml. of cold 5% sodium hydroxide and extracted with ether. Evaporation of the dried ether extract gave 50 mg. of an oil. Acidification of the aqueous portion with cold dilute hydrochloric acid followed by ether

extraction yielded 850 mg. of an oil. Trituration with cold petroleum ether gave 270 mg. of white solid, m.p. 215-225°, which was crystallized from ether-hexane to give plates, m.p. 240-242°; $\lambda_{max}^{CHCl_3}$ 5.72, 5.81 μ. An analytical sample, m.p. 241-243°, was crystallized from ether-hexane.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.94; H, 10.25.

Found: C, 75.00; H, 10.36.

The acidic mother liquors from the trituration could not be crystallized from ether-hexane or methanol although the infrared spectrum was quite similar to that of pure 1ε-carboxy-2-oxa-5α-cholestan-3-one. The methyl ester was prepared using diazomethane and was crystallized twice from aqueous methanol to give crystals, m.p. 85-87°; $\lambda_{max}^{CCl_4}$ 5.68, 5.72 μ.

Cleavage of 1ε-carboxy-2-oxa-5α-cholestan-3-one

A 50 mg. sample of 1ε-carboxy-2-oxa-5α-cholestan-3-one was dissolved in 10 ml. of acetone containing 3.5 ml. of 14% sulfuric acid and treated with 50 mg. of potassium permanganate at room temperature. The reaction mixture was stirred vigorously at room temperature for 1/2 hour and filtered to remove the manganese dioxide. Dilution with water followed by ether extraction and evaporation of the dried ether extract gave an oil. Trituration with petroleum

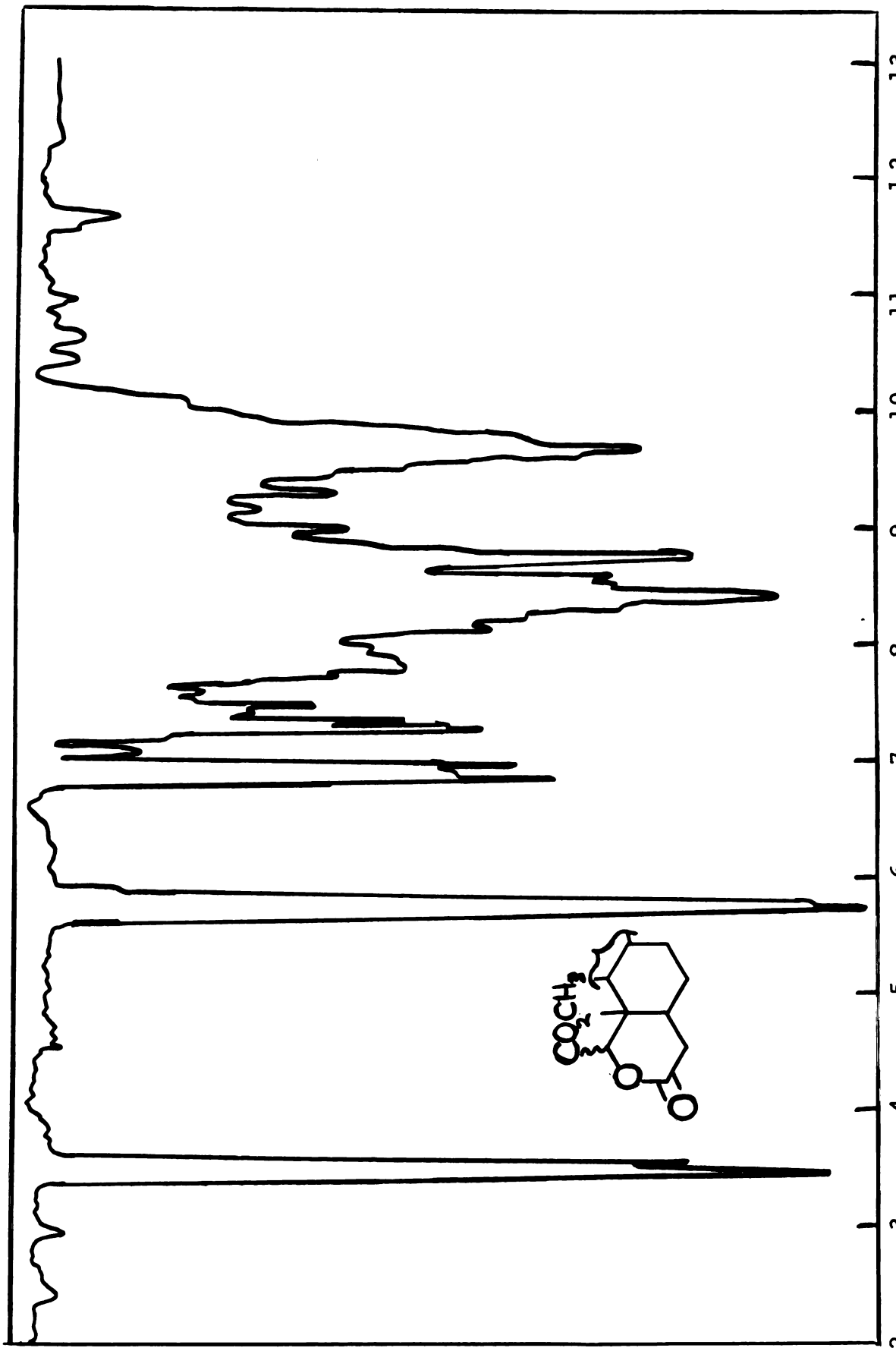


Figure 12. Infrared spectrum of 12-carbomethoxy-2-oxa-5α-cholestan-3-one (in CCl_4).

ether gave 30 mg. of a white solid, m.p. 215-220°, which was recrystallized from ether-hexane to give material with m.p. 224-226°. The reported melting point for 1,2-seco-5α-cholestan-1,3-dioic acid is 227-230°. A mixture melting point with authentic 1,2-seco-5α-cholestan-1,3-dioic acid (22) was not depressed.

5,6β-epoxy-5β-cholestan-4-one

To a stirred solution of 5 g. of cholest-5-en-4-one (35) in 600 ml. of methanol at room temperature, 20 ml. of 30% hydrogen peroxide and 20 ml. of 4 N sodium hydroxide were added dropwise and simultaneously over a one hour period. The reaction mixture was stirred at room temperature for two hours, diluted with water and left overnight at 7°. After filtration of the white solid, it was taken up in ether, dried and evaporated to yield 3.63 g. of solid which was crystallized twice from methanol, to yield a solid m.p. 98-100°; $\lambda_{max}^{CCl_4}$ 5.83 μ.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07.

Found: C, 79,36; H, 10.70; ash, 1.05.

The percentage of ash should, in a pure sample, be composed of 81% carbon and 11% hydrogen. When these values are added the percentages are: C, 80.20; H, 10.82. The

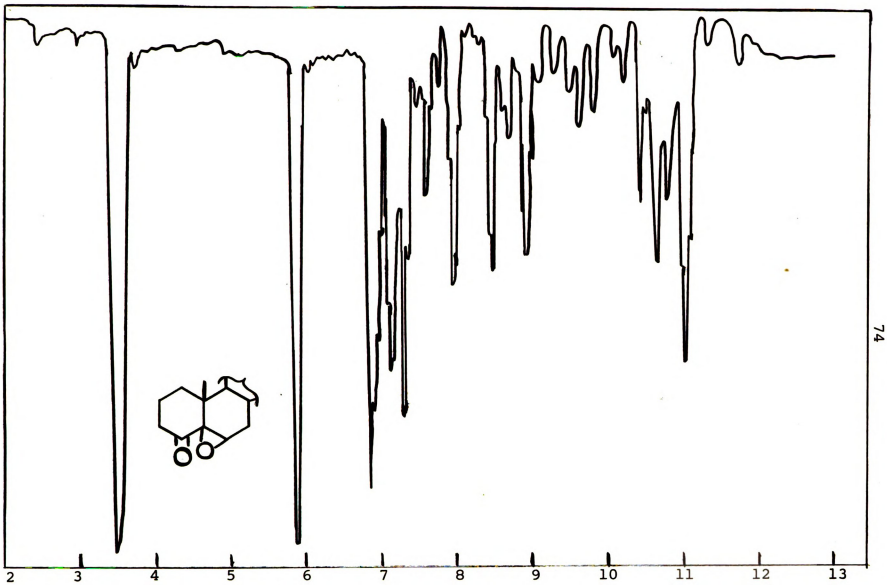


Figure 13. Infrared spectrum of 5,6β-epoxy-5β-cholestan-4-one (in CCl_4).

aqueous portion from the epoxidation was acidified and extracted with ether to yield 680 mg. of an oil.

Stereochemistry of 5,6β-epoxy-5β-cholestan-4-one

A suspension of 250 mg. of 5,6β-epoxy-5β-cholestan-4-one in 25 ml. of 85% hydrazine hydrate was heated at 90° for ten minutes (19). Nitrogen was evolved and the solid became slightly yellow. The reaction mixture was then refluxed for 15 minutes, poured into water and extracted with ether to yield 230 mg. of a semisolid. Passage of this material in benzene solution through a column of 10 g. of silica gel gave 200 mg. of solid on elution with benzene. Two crystallizations from acetone gave 150 mg., m.p. 86-87°, (reported for 6β-hydroxycholest-4-ene, m.p. 86-87°, [40]); $\lambda_{max}^{CCl_4}$ 3.00, 6.15, 11.37 μ. The melting point reported for 6α-hydroxycholest-4-ene is 139-140° (40).

Rearrangement of 5,6β-epoxy-5β-cholestan-4-one

A solution of 500 mg. of 5,6β -epoxy-5β-cholestan-4-one in 45 ml. of methanol was refluxed for 24 hours with 1.5 ml. of 12 N sodium hydroxide. After dilution with water and acidification, the reaction mixture was extracted with ether. The ether extract was shaken with 10% sodium hydroxide

to separate the acidic material which partially precipitated in the aqueous layer. Acidification and ether extraction gave 300 mg. of acidic semisolid material. The methyl ester of this material, which was prepared using diazomethane, exhibited $\lambda_{max}^{CCl_4}$ 2.90, 5.78, 5.86, 6.08 μ and was chromatographed on 30 g. of neutral alumina. Elution with benzene-ether (4:1) gave 66 mg. of a solid, m.p. 58-62°. After two crystallizations from aqueous ethanol, the melting point was raised to 78-79°; $\lambda_{max}^{CCl_4}$ 5.87, 6.07 μ; $\lambda_{max}^{C_2H_5OH}$ 237 mμ (log ε 4.0); $[\alpha]_D^{28}$ + 83° (c 0.151 g./100 ml. $CHCl_3$). An analytical sample, m.p. 83-84°, was crystallized from aqueous ethanol.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 80.54; H, 11.52.

Found: C, 80.64; H, 11.40.

This compound was shown by mixture melting point and infrared spectrum to be methyl-A-norcholest-3-en-3-carboxylate (22). An authentic sample of this compound was kindly provided by Professor Loewenthal. The reported physical properties of the authentic compound agree well: m.p. 84-84.5°, $\lambda_{max}^{CCl_4}$ 5.90, 6.09 μ, $\lambda_{max}^{C_2H_5OH}$ 237 mμ (log ε 4.1); $[\alpha]_D$ + 66° (c 1. 79). Elution with benzene-ether (3:2) gave 182 mg. of an oil which was crystallized from petroleum ether to yield 150 mg. of methyl-6β-hydroxy-A-nor-5β-

cholestan-3ε-carboxylate, m.p. 94-97°; $\lambda_{max}^{CCl_4}$ 2.84, 5.76, 10.02 μ; n.m.r. 6.12 (broad), 6.39τ (CO_2CH_3). The peaks have area ratios of 1:3.5. The resonance of the carbinyl hydrogen at C_6 may also appear in this region and cause the error in the integration. $[\alpha]_D^{28}$ +69° (c 0.182 g./100 ml. of $CHCl_3$). An analytical sample, m.p. 100-100.5°, was crystallized from aqueous ethanol.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 77.73; H, 11.18.

Found: C, 77.56, H, 11.35.

The ether solution containing the neutral material was washed with water, dried and evaporated to yield 160 mg. of an oil, which was chromatographed on 10 g. of neutral alumina. Elution with benzene-petroleum ether (1:1) gave 40 mg. of solid which was identified as methyl-A-norcholest-3-en-3-carboxylate by mixture melting point and by its infrared spectrum. Further elution with benzene-ether (4:1) gave 37 mg. of a yellow oil $\lambda_{max}^{CCl_4}$ 2.87(m), 5.87(s), 6.02(s), 6.14(w) μ. This oil probably contains methyl-A-norcholest-3-en-3-carboxylate as well as a substance with $\lambda_{max}^{CCl_4}$ 2.87, 6.02 and 6.17 μ. Finally elution with benzene-ether (3:2) gave 63 mg. of a yellow oil, $\lambda_{max}^{CCl_4}$ 2.85(m), 5.76(m), 5.85(s) μ. This probably contains methyl-6ε-hydroxy-A-nor-5ε-cholestan-3ε-carboxylate and a compound with

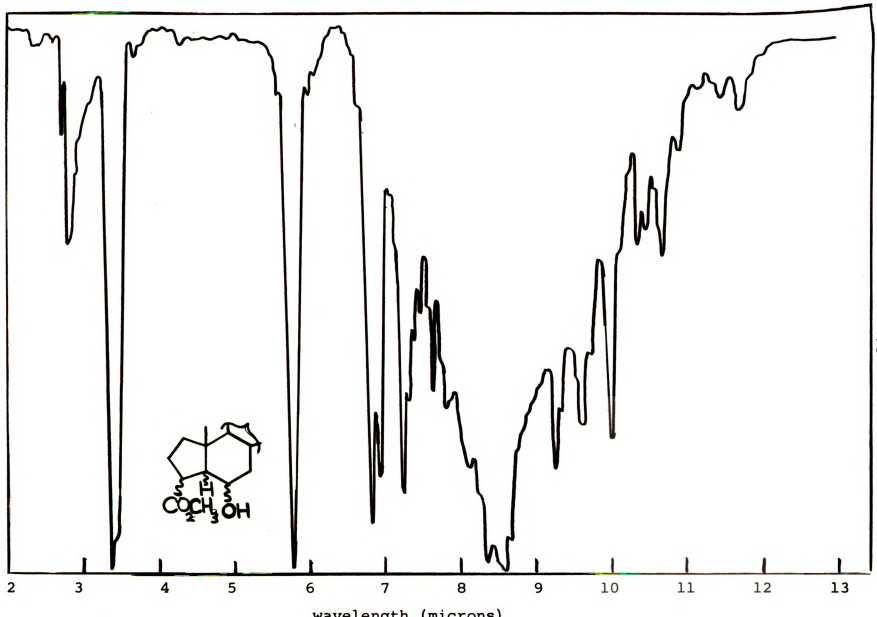


Figure 14. Infrared spectrum of methyl 6β-hydroxy-A-nor-5β-cholestan-3β-carboxylate (in CCl_4).

$\lambda_{max}^{CCl_4}$ 2.85, 5.85 μ. Possibilities for this latter compound are 5-methoxy-6β-hydroxy-5α-cholestan-4-one or 6α-methoxy-5-hydroxy-5β-cholestan-4-one. Neither of the two last fractions could be crystallized and further purification was not achieved by rechromatography.

Attempted hydrogenation of methyl-A-norcholest-3-en-3-carboxylate

A 50 mg. sample of methyl-A-norcholest-3-en-3-carboxylate was dissolved in 20 ml. of absolute ethanol and stirred with 20 mg. of rhodium on alumina in a hydrogen atmosphere at 60° for 72 hours. No hydrogen uptake was observed and after filtration of the catalyst the reaction mixture was evaporated to dryness to yield a white solid, $\lambda_{max}^{CCl_4}$ 5.78(w), 5.86, 6.06 μ. Except for the weak band for a saturated ester at 5.78 μ, the spectrum was identical to pure methyl-A-norcholest-3-en-3-carboxylate. Chromatography to separate the saturated ester was not attempted.

Oxidation of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate

Chromium trioxide-pyridine complex was prepared by adding 100 mg. of chromium trioxide in small portions to 3 ml. of pyridine with stirring (41). The temperature was kept at

15-20° during the addition. A solution of 100 mg. of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate in 2 ml. of pyridine was treated with the yellow chromium trioxide-pyridine complex prepared above and allowed to stand overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. After the ether extract was washed with 10% hydrochloric acid and dried, it was evaporated to yield 96 mg. of an oil, $\lambda_{max}^{CCl_4}$ 5.74, 5.83, 7.93 μ. Chromatography of this oil on 30 g. of neutral alumina and elution with benzene-ether (1:4) yielded 70 mg. of a clear oil, $\lambda_{max}^{CCl_4}$ 5.74, 5.83 μ. This oil resisted repeated crystallization attempts.

Hydrolysis of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate and oxidation to A-nor-5ξ-cholestan-6-one-3ξ-oic acid

A solution of 150 mg. of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate in 20 ml. of 95% ethanol was refluxed for 5 hours with 1.5 ml. of 2 N sodium hydroxide. After dilution with water and extraction to separate neutral products, the aqueous layer was acidified and extracted with ether. Evaporation of the dried ether extract gave 140 mg. of a semisolid, $\lambda_{max}^{CCl_4}$ 3.00 (broad) 5.86, and 7.96 μ. This semisolid was oxidized with the chromium trioxide-

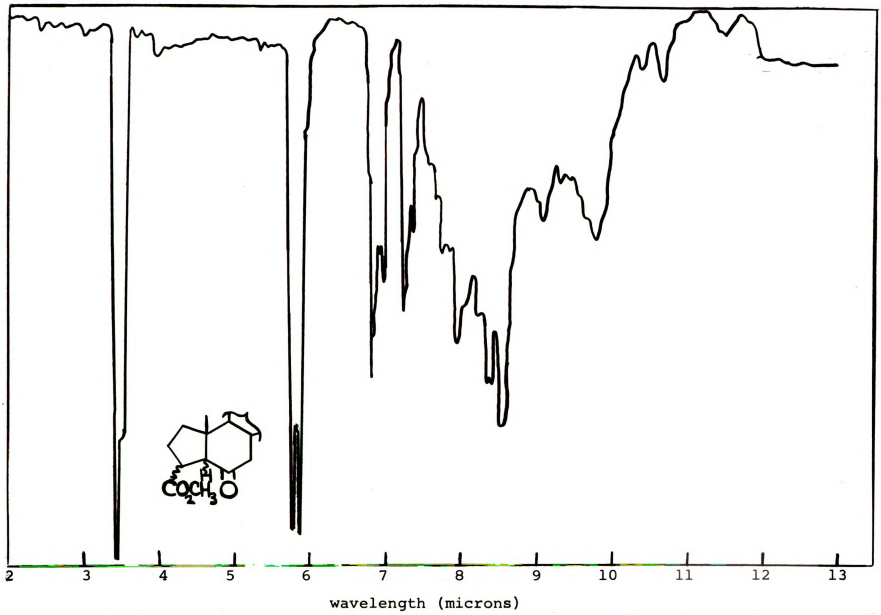


Figure 15. Infrared spectrum of methyl-A-nor-5ξ-cholestan-6-one-3ξ-carboxylate (in CCl_4).

pyridine complex from 150 mg. of chromium trioxide and 5 ml. of pyridine using the same procedure used with methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate and gave 100 mg. of semisolid, $\lambda_{max}^{CCl_4}$ 5.86 and 7.95 μ. An attempted crystallization from aqueous ethanol was unsuccessful.

Attempted decarboxylation of A-nor-5ξ-cholestan-6-one-3ξ-oic acid

A solution of 100 mg. of oily A-nor-5ξ-cholestan-6-one-3ξ-oic acid in 10 ml. of xylene was refluxed for 5 hours. Evaporation of the solvent under reduced pressure yielded 98 mg. of an oil. The methyl ester of this material was prepared with diazomethane and exhibited $\lambda_{max}^{CCl_4}$ 5.75 and 5.84 μ. No decarboxylation had occurred since the infrared spectrum was identical to that of methyl-A-nor-5ξ-cholestan-6-one-3ξ-carboxylate.

Attempted conversion of methyl-A-nor-5ξ-cholestan-6-one-3ξ-carboxylate to methyl-A-nor-5ξ-cholestan-3ξ-carboxylate

A solution of 50 mg. of chromatographed methyl-A-nor-5ξ-cholestan-6-one-3ξ-carboxylate in 1.5 ml. of acetic acid was treated at room temperature with 0.5 g. of ethanedithiol and 0.5 g. of boron trifluoride etherate and allowed to stand overnight. The reaction mixture was diluted with

water and extracted with ether. After the ether extract was washed with 10% sodium hydroxide and with water, it was dried and evaporated to give an oil, $\lambda_{max}^{CCl_4}$ 5.77 and 7.94 μ. The crude thioketal was dissolved in 5 ml. of dioxane and 5 ml. of ethanol and refluxed with 1 g. of Raney nickel W-2 for 4 hours. Filtration of the Raney nickel and evaporation to dryness yielded an oil, $\lambda_{max}^{CCl_4}$ 5.78 and 7.95 μ, which was chromatographed on 5 g. of neutral alumina. Elution with ether gave 30 mg. of a clear oil which could not be crystallized. When this material was taken up in petroleum ether and cooled to -60°, a white solid was obtained but on warming to room temperature it redissolved.

Attempted degradation to A-nor-5β-cholestan-3-one

A solution of 100 mg. of the oily ester mixture from above in 7 ml. of dry benzene was added dropwise at room temperature to a solution of phenylmagnesium bromide prepared from 141 mg. of magnesium and 0.8 ml. of bromobenzene in 15 ml. of dry ether (42). The reaction mixture was refluxed overnight and poured onto a mixture of ice and dilute hydrochloric acid. After separation of the organic layer, it was dried and evaporated; $\lambda_{max}^{CCl_4}$ 2.95 μ and no carbonyl absorption. The residue was taken up in a mixture of 10 ml. of acetic

acid and 5 ml. of acetic anhydride and refluxed for 2 hours. After cooling, the reaction mixture was poured into ice water and extracted with ether. The ether extract was washed with water and 10% sodium hydroxide, dried and evaporated to yield 90 mg. of an oil which showed no hydroxyl absorption in the infrared. This oil was dissolved in 15 ml. of ethyl acetate and cooled to -40° while a steam of ozone was bubbled through for 25 minutes. After evaporation of the solvent under reduced pressure, 1 g. of zinc dust and 15 ml. of acetic acid were added and the mixture was refluxed for 2 hours. The reaction mixture was diluted with water and extracted with ether. Chromatography of the oil obtained on evaporation of the dried ether extract on 5 g. of neutral alumina and elution with pentane gave 70 mg. of diphenyl which was carried through from the Grignard reaction. Elution with benzene-ether (4:1) gave a few mg. of an oil, $\lambda_{max}^{CCl_4}$ 5.77 μ. Reported for A-nor-5β-cholestan-3-one, 5.77 μ. The dinitrophenylhydrazone of this oil could only be obtained as a semisolid which could not be purified by chromatography.

Dehydration of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate with p-toluenesulfonic acid

A 50 mg. sample of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate was dissolved in 10 ml. of benzene and refluxed for 15 hours with 20 mg. of p-toluenesulfonic acid. After dilution with water, the reaction mixture was extracted with ether. The ether extract was washed with 5% sodium carbonate, dried and evaporated to give an oil, $\lambda_{max}^{CCl_4}$ 2.90 (very weak), 5.78 and 7.93 μ. This oil was dissolved in 15 ml. of methanol and refluxed 5 hours with 0.6 ml. of 50% hydrochloric acid. After dilution with water, the reaction mixture was extracted with ether. The ether extract was reesterified with diazomethane and evaporated to yield an oil, $\lambda_{max}^{CCl_4}$ 2.90 (weak), 5.76, 5.87 and 6.09 μ. Chromatography of the oil on 10 g. of neutral alumina and elution with benzene-ether (4:1) gave 8 mg. of methyl-A-norcholest-3-en-3-carboxylate which was identified by mixture melting point and infrared spectrum. Elution with ether gave 30 mg. of a semisolid with an infrared spectrum almost identical to that of methyl-6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-carboxylate. No lactone seemed to form under these conditions.

Dehydration of methyl-6β-hydroxy-A-nor-5β-cholestan-3β-carboxylate with phosphorous oxychloride

A solution of 50 mg. of methyl-6β-hydroxy-A-nor-5β-cholestan-3β-carboxylate in 5 ml. of anhydrous pyridine was allowed to stand overnight at room temperature with 100 mg. of phosphorous oxychloride and then diluted cautiously with water. The reaction mixture was extracted with ether and evaporated to yield 47 mg. of a semisolid, $\lambda_{max}^{CCl_4}$ 5.76, 5.88 (weak), 6.08 and 11.55 μ. The product from above was refluxed overnight in 10 ml. of methanol with 1.5 ml. of 2 N sodium hydroxide. Acidification and extraction with ether gave a solid on evaporation of the ether extract. The acid was reesterified with diazomethane to yield 40 mg. of an oil, $\lambda_{max}^{CCl_4}$ 5.78, 5.87 (weak), 6.08 and 11.66 μ (weak). A solution of this oil in 10 ml. of absolute ethanol was stirred overnight at room temperature in a hydrogen atmosphere with 10 mg. of platinum oxide. No accurate volume of hydrogen uptake could be obtained. Filtration of the catalyst and evaporation of the ethanol yielded a semisolid, $\lambda_{max}^{CCl_4}$ 5.78, 5.87 (medium), 6.08 and no absorption at 11.66 μ. Chromatography of this material on 10 g. of neutral alumina and elution with benzene-petroleum ether (4:1) gave 30 mg. of a clear oil, 5.78 μ,

no double bond stretch absorption. Elution with benzene-ether (4:1) gave 5 mg. of solid methyl-A-norcholest-3-en-3-carboxylate identified by mixture melting point and infrared spectrum.

SUMMARY

Treatment of either 4β,5-epoxy-5β-cholestan-3-one or 4α,5-epoxy-5α-cholestan-3-one with methanolic base yielded 4-methoxycholest-4-en-3-one I. An isomer previously believed to be I was identified as 3-methoxy-5α-cholest-2-en-4-one IV. The structures of these compounds were established by spectral data, elemental analysis, hydrolysis to the known diosphenol II and conversion of I via its ethylene-thioketal to 5α-cholestan-4-one. The bathochromic influence of the α-methoxyl group in IV is +36 mμ as contrasted with +11 mμ for I. In order for the α-methoxyl group on an enone to attain coplanarity and exhibit its maximum bathochromic increment the enone chromophore must not bear a cis-β-alkyl substituent.

Treatment of 1α,2α-epoxy-5α-cholestan-3-one with methanolic base gave 2-methoxy-5α-cholest-1-en-3-one which was identified by spectral data, elemental analysis and hydrolysis to the known diosphenol XIIa. Methylation of a mixture of the 2,3-diosphenols with dimethyl sulfate gave an isomeric compound, 3-methoxy-5α-cholest-3-en-2-one. The nuclear magnetic resonance spectrum shows that

diosphenol XIIa, the more stable isomer, predominates at equilibrium. Isomer XIIa was found to be unstable in the solid state and to isomerize to a compound with properties expected for the α-diketone XIIc.

Epoxidation of cholest-5-en-4-one gave 5,6β-epoxy-5β-cholestan-4-one; the stereochemistry was demonstrated by reaction with hydrazine to yield 6β-hydroxycholest-4-ene. Reaction of 5,6β-epoxy-5β-cholestan-4-one with methanolic base gave A-norcholest-3-en-3-oic acid XIV and 6ξ-hydroxy-A-nor-5ξ-cholestan-3ξ-oic acid XV. Compound XIV was identified as its methyl ester by mixture melting point with the authentic material and XV was identified by spectral data and elemental analysis as well as dehydration and isomerization to XIV. The formation of XIV and XV can be rationalized by a Favorskii type mechanism.

Oxidation of the β- and α-epoxides from cholest-4-en-3-one with alkaline hydrogen peroxide gave 5α-carboxy-4-oxacholestan-3-one XXV and 5β-carboxy-4-oxacholestan-3-one XXVI respectively. These structures were established by spectral data, elemental analysis and oxidation of both XXV and XXVI to the known keto acid XXVII.

PART II

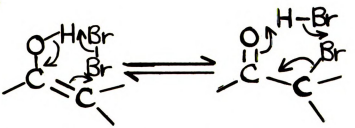
HYDRIODIC ACID REDUCTIONS OF VICINAL OXYGENATED COMPOUNDS

INTRODUCTION

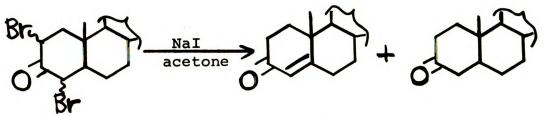
Many examples of hydriodic acid reduction of organic functional groups have been reported in the literature. For example, arylolefins, arylalkanols, arylketones, highly conjugated olefins, benzils, and 1,2-glycols are all reduced. Some of these reactions may be considered as hydride transfers to carbonium ions. These carbonium ions must be unstable enough to react and yet not so unstable that significant concentrations cannot be produced. It has been shown that log k for a hydride transfer reaction is directly proportional to the difference in pK_R+ of the two carbonium ions which exchange the hydride (43). The direction of hydride transfer will be a function of the stability (pK_R+) of the carbonium ions. When the reduction of carbonium ions in equilibrium with either alcohols or olefins was studied, it was found that carbonium ions with pK_R+ more negative than -11 were instantly reduced by sodium bromide in sulfuric acid (44). Carbonium ions with pK_R+ more positive than -11 were inert. The limit for reductions of carbonium ions with potassium iodide in 60% sulfuric acid was found to be a pK_R+ of about -5. While the

triphenylmethyl cation was rapidly reduced, the 4-methoxy-triphenylmethyl cation was inert to potassium iodide in 60% sulfuric acid.

Rates of debromination of some α-bromoketones by hydrobromic acid in acetic acid have been measured and this reaction has been suggested to the exact reverse of bromination of a ketone through the enol in a polar solvent (45). A common cyclic activated state has been proposed for reduction of bromoketones by hydrobromic acid and bromination of ketones (46).

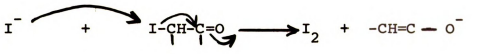


The reaction of a 2,4-dibromo-3-ketosteroid with sodium iodide in refluxing acetone was studied as a means of introducing the Δ^4-double bond in the cortisone series (47).

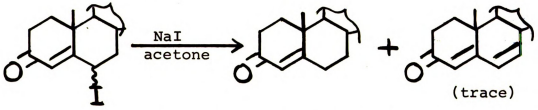


These workers found that the saturated ketone was formed even when iodoacetone was added to react competitively with any hydriodic acid and concluded that iodide ion must be

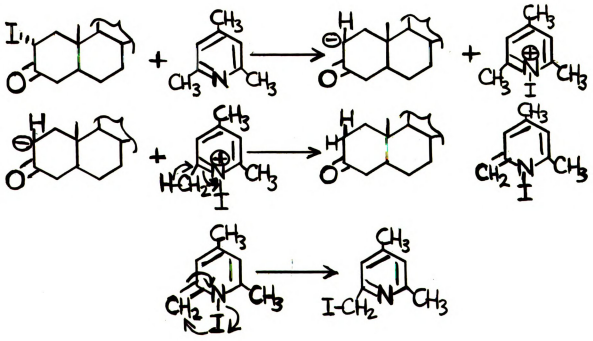
responsible for the reduction. A possible mechanism was suggested.



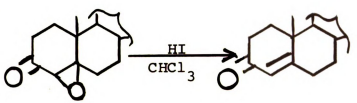
Compounds having an iodine atom vinylogously alpha to a carbonyl group also undergo facile reduction (48).



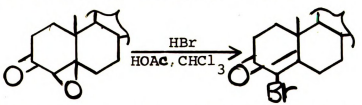
In contrast to the usual dehydrohalogenation of α-haloketones by collidine, α-iodoketones are reduced under these conditions (49). Collidine acts as an electron source in the suggested mechanism.



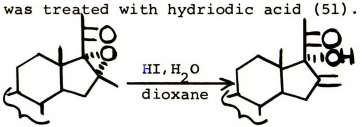
Epoxyketones have been reduced with hydriodic acid in chloroform or with potassium iodide in acetic acid (32, 50).



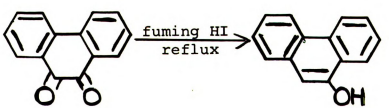
When these epoxyketones are treated with hydrobromic or hydrochloric acid under the same conditions, 4-halo-α,β-unsaturated ketones are formed (32, 50).



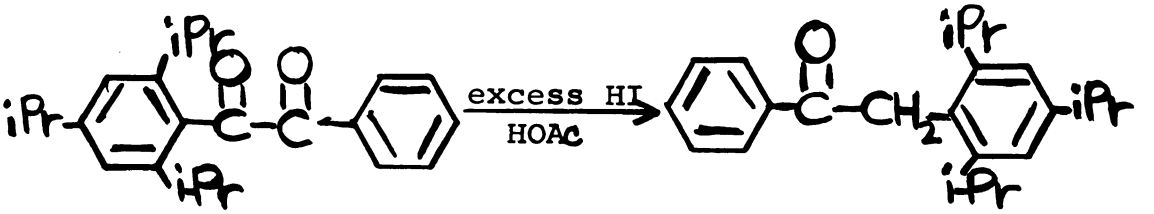
Reduction was not observed when a 16,17-epoxy-20-ketosteroid was treated with hydriodic acid (51).



Reduction of some aromatic diketones under very drastic conditions, heating with excess fuming hydriodic acid in a free flame, was reported in the early literature (52).

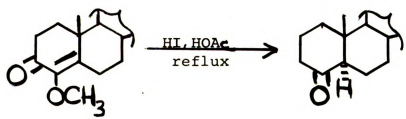


A study of the reduction of several unsymmetrical benzils has also been made; the hindered carbonyl was always found to be the one which was reduced (53).



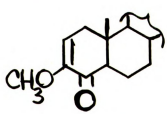
RESULTS AND DISCUSSION

Since initial attempts to effect the hydrolysis of 4-methoxycholest-4-en-3-one I under mild conditions were unsuccessful, I was treated with a refluxing acetic acid solution of hydriodic acid. The product of this reaction was not the expected diosphenol but was 5α-cholestan-4-one II. Identification of II was based on the infrared spectrum and a mixture melting point with the authentic compound (35).

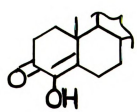


I II

5α-cholestan-4-one II was also obtained when the above reaction was applied to either enol ether III or diosphenol IV. Diosphenol IV undoubtedly is a common intermediate in all of these reductions.

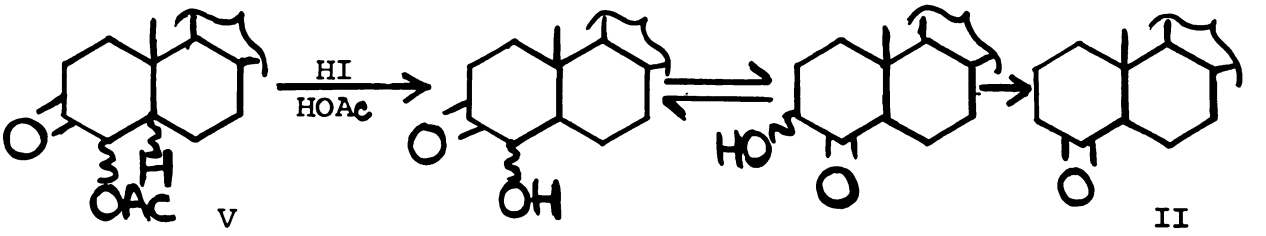


III



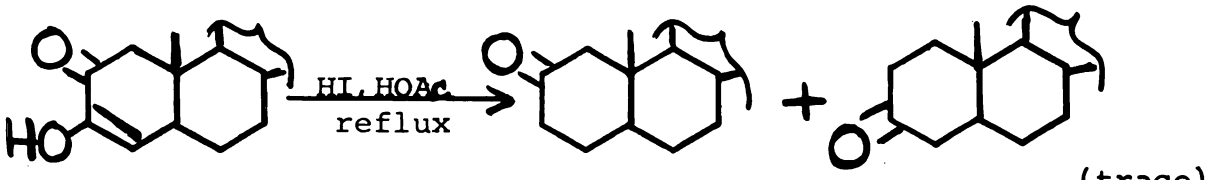
IV

Support for the suggestion that the reduction proceeds via a tautomeric mixture of α-hydroxyketones was obtained by reduction of 4α-acetoxy-5α-cholestan-3-one V to 5α-cholestan-4-one.*



V II

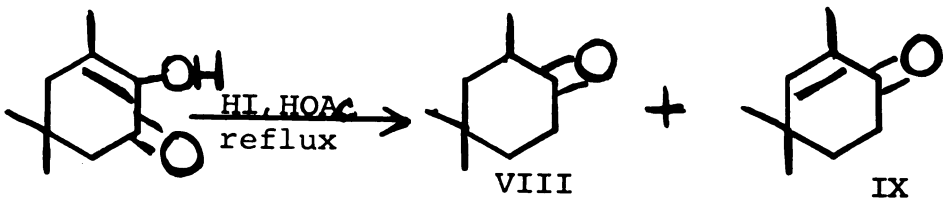
Extension of the hydriodic acid reduction to the 2,3-enolic diketone gave a mixture containing mainly 5α-cholestan-2-one VI contaminated by a small amount of 5α-cholestan-3-one VII. Chromatography on alumina served to separate pure VI which was identified by a mixture melting point with the known compound (15). 5α-cholestan-3-one was not obtained in pure form but its presence was indicated by the infrared spectrum.



VI VII (trace)

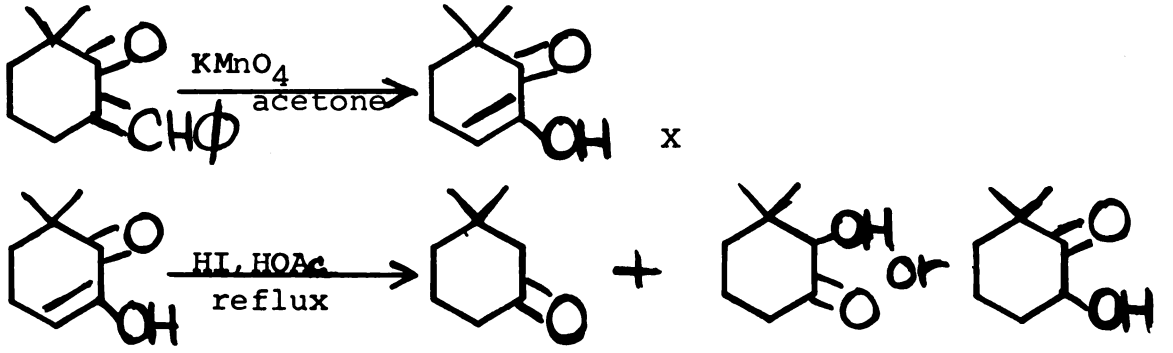
*This experiment was done by Bob Guynn, an NSF undergraduate research participant.

To test the generality of the reduction it was extended to other alicyclic α-diketones. Reduction of 3,5,5-trimethylcyclohexan-1,2-dione gave 2,4,4-trimethylcyclohexanone VIII and 2,4,4-trimethyl-2-cyclohexen-1-one IX in 54% and 13% yield respectively.



Identification of VIII was based on the infrared spectrum which was identical with that of the authentic compound and the melting point of the dinitrophenylhydrazone derivative which was identical with that reported for VIII (54). A comparison of the infrared spectrum and the retention time in vapor phase chromatography of VIII demonstrated that it was definitely different from 3,5,5-trimethylcyclohexanone. Identification of IX was based on the identity of its infrared spectrum with that reported for the authentic compound, its ultraviolet spectrum ($\lambda_{max}^{C_2H_5OH}$ 233.5 mμ, log ε 4.0; reported $\lambda_{max}^{C_2H_5OH}$ 235 mμ [55]), its nuclear magnetic resonance spectrum (vinyl singlet at 3.73τ) and the identity of the melting point of its dinitrophenylhydrazone, m.p. 163-165°, with the melting point reported for the authentic compound, 163-164° (55).

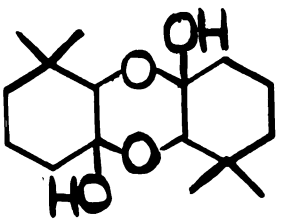
Oxidation of 2-benzal-6,6-dimethylcyclohexanone with potassium permanganate gave 3,3-dimethylcyclohexan-1,2-dione X in 16% yield. Hydriodic acid reduction of X gave 3,3-dimethylcyclohexanone XI and 2-hydroxy-3,3-dimethylcyclohexanone XII (or 2-hydroxy-6,6-dimethylcyclohexanone) in 58% and 16% yield respectively.



XI XII

Identification of XI was based on comparison of its infrared spectrum and retention time with an authentic sample in addition to a mixture melting point of its dinitrophenylhydrazone derivative with the authentic derivative. The tautomeric ketol mixture XII was identified by its infrared spectrum, ($\lambda_{max}^{CCl_4}$ 2.90, 5.83 and 9.03 μ) and by conversion to the scarlet dinitrophenylhydrazone derivative of 3,3-dimethylcyclohexan-1,2-dione, m.p. 235-237°, reported m.p. 237-238° (56). Ketols are known to give dinitrophenylhydrazones of α-diketones (57). The slower reduction of X as well as isolation of the tautomeric ketol mixture XII appears to be due to steric hindrance by the geminal dimethyl

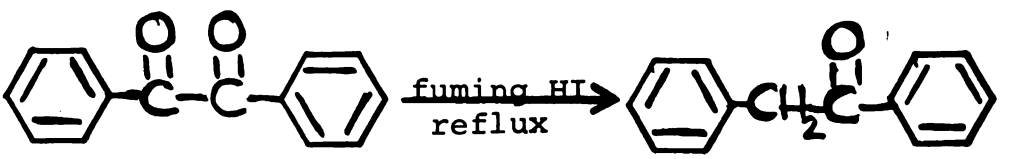
group in X. Further reduction of the ketol could be achieved by longer reflux, however, this gave rise to another compound as well. The physical properties of this compound: $\lambda_{max}^{C_4Cl_6}$ 2.90 and 7.94 μ and insolubility in common organic solvents indicate that this compound may be a dimer XIII of 2-hydroxy-3,3-dimethylcyclohexanone.



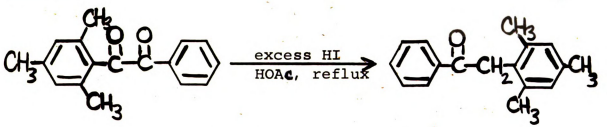
XIII

Reduction of alicyclic α-diketones can also be effected by prolonged refluxing with potassium iodide in acetic acid. Cholestan-3,4-6-trione gave approximately 50% conversion to 5α-cholestan-3,6-dione after overnight reflux.

Seemingly analogous reductions of aromatic α-diketones have been reported in the early literature, however, much more vigorous conditions are required for these reductions (52).

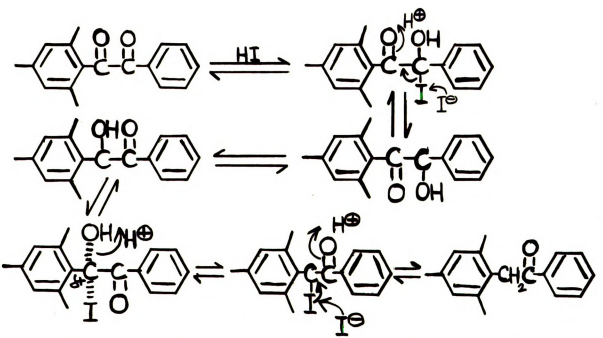


Several unsymmetrical benzils have also been reduced under vigorous conditions (53). The hindered carbonyl was found to be reduced in all of the cases studied, and therefore electrical effects must be much more important than steric effects.



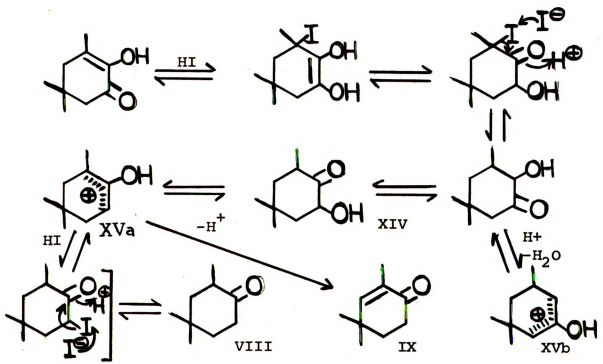
That these α-diketones, which cannot exist in an enolic form, are reduced by a mechanism different from the alicyclic cases was demonstrated by submitting benzil to reaction conditions under which alicyclic α-diketones are reduced. Benzil was reduced to benzoin but benzoin could not be further reduced to deoxybenzoin. Benzil, however, was reduced to deoxybenzoin when 12 molar equivalents of hydriodic acid were employed as in the procedure of Fuson and Hoch (53). The reduction of unsymmetrical benzils can be rationalized by addition of hydriodic acid to one of the carbonyl groups followed by reductive removal of the iodine atom to yield benzoin. Reduction of benzoin can be viewed as S_N2 displacement of the protonated hydroxyl group by iodide ion with some positive charge development on the central carbon

atom in the transition state and the ortho- and para-methyl groups stabilizing the positive charge by electron release. Steric effects of the ortho-methyls are unimportant since attack can occur perpendicular to the plane of the substituted benzene ring. Reduction of the resulting α-iodoketone with hydriodic acid yields deoxybenzoin.

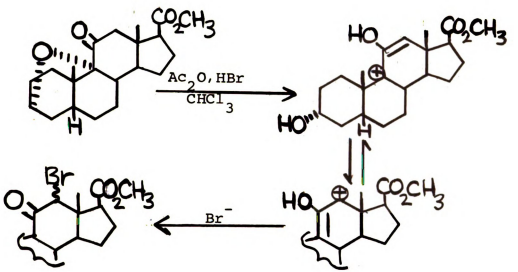


A proposed mechanism for the reduction of alicyclic α-diketones with hydriodic acid should predict the correct product, require 4 equivalents of hydriodic acid and explain the apparent acid catalysis. A ketol intermediate seems likely since α-ketols and the corresponding α-diketones give identical products. Several mechanisms can be written for the reduction but only two seem to predict the correct product in all cases. The first mechanism is initiated

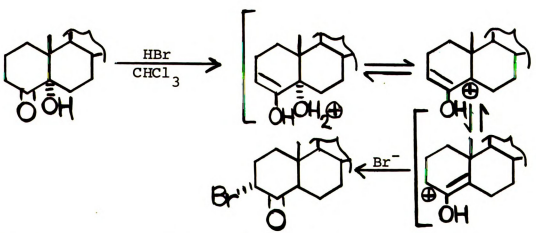
by Michael addition of hydriodic acid to the enone system followed by reduction of the α-iodoketone to a tautomeric ketol mixture XIV. Loss of the protonated hydroxyl from the enol form of XIV could give two different allylic carbonium ions, XVa,b of which XVa is more stable. Attack of iodide ion on XVa and reduction of the resulting α-iodoketone yields the reduced product VIII. Loss of a proton from XVa leads to the α,β-unsaturated ketone product IX.



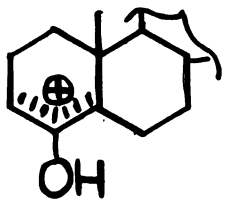
Allylic carbonium ions of type XVa have been postulated in an interesting reaction of a 3α,9α-epoxyketone (58).



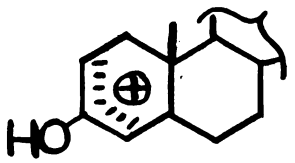
The reaction of a 4,5-ketol with hydrobromic acid (59) can also be viewed as proceeding through an allylic carbonium ion.



In reduction of the enolic α-diketone IV the allylic ions involved are XVIa and XVIb of which XVIa is more stable. One of the resonance contributors to XVIa is a tertiary carbonium ion while both contributors to XVIb are secondary ions.

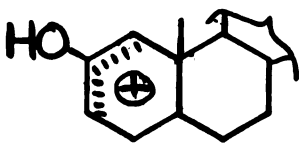


XVIa

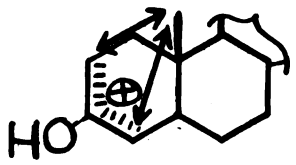


XVIb

Steric hindrance by the axial C_{19} methyl group to solvation of the allylic ion XVIIb favors XVIIa and this ion again leads to the observed product in the case of 2,3-diketone.

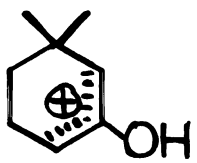


XVIIa



XVIIb

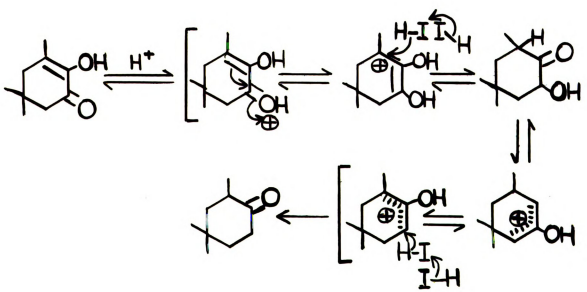
Only one allylic ion XVIII is possible from α-diketone X.



XVIII

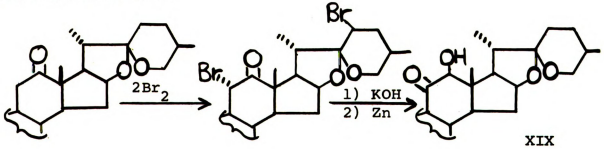
It is not surprising that no methyl migration was observed in XVIII giving a tertiary carbonium ion because the allylic ion probably is more stable than the tertiary ion. The solvolysis of α,γ-dimethylallyl chloride, with two secondary carbon atoms, in 75% aqueous acetone is 630 times faster than t-butylchloride (60).

An alternate mechanism was brought to light by some recent work on reduction of triaryl carbonium ions by hydriodic acid acting as a hydride transfer agent (44). The direction of hydride transfer is a function of the stability of the carbonium ions involved. If the carbonium ions involved in the hydriodic acid reduction of α-diketones are less stable than iodonium ion (I^+), they would be reduced. Several experiments to test this mechanism by attempting the reduction of α-diketones with triphenylmethane and an acid catalyst were inconclusive. A possible mechanism for hydride reduction is much like that suggested earlier.



As an example of the synthetic utility of this reduction it was applied to a problem which arose in one of

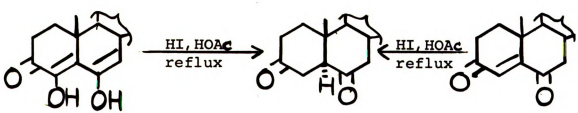
the syntheses of cortisone from abundant steroids. Hecogenin was an obvious raw material for cortisone production since it seemed likely that the C_{12} carbonyl group could be moved to C_{11}. An efficient process for conversion of the 11,12-ketol diacetate into the 11-ketone was found in direct reduction with calcium in liquid ammonia. Since 11-ketotigogenin is convertible into cortisone by well developed processes, its preparation from hecogenin made commercial production of cortisone possible. The 11,12-ketol XIX was prepared from hecogenin by bromination followed by equilibration with alkali to hydrolyze the C_{11} bromide and isomerize to the more stable ketol which was debrominated with zinc dust (61).



XIX

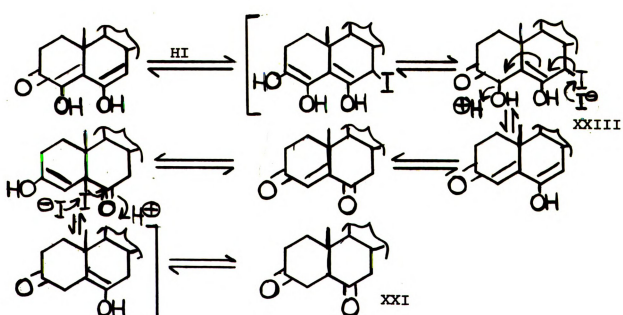
Reduction of the 11,12-ketol XIX was effected by refluxing with potassium iodide in acetic acid to yield a substance with a melting point identical with that reported for 11-ketotigogenin. A mixed melting point with authentic 11-ketotigogenin was depressed and the reduction product may be a stereoisomer.

Several modifications of the original 3,4-enolic diketone IV were made by Bob Guynn, NSF undergraduate research participant. Cholestan-3,4-6-trione XX was reduced by hydriodic acid to 5α-cholestan-3,6-dione XXI. It was subsequently shown that cholest-4-en-3,6-dione XXII was also reduced to XXI under these conditions and XXII may be an intermediate in the reduction of XX.

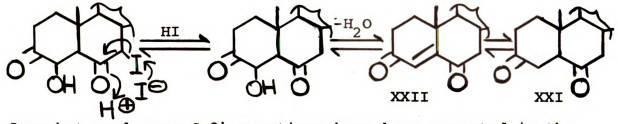


XX XXI XXII

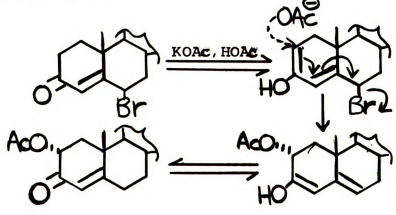
The formation of XXI can be rationalized by a S_N2' type mechanism.



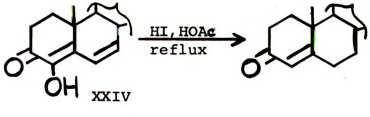
Another possibility for this mechanism would be reduction of the keto form of XXIII followed by elimination of water to give XXII which is further reduced.



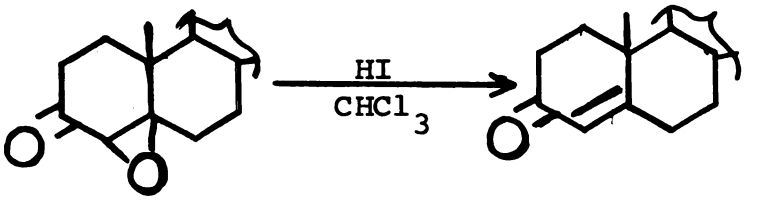
Somewhat analogous S_N2' reactions have been reported in the literature (62).



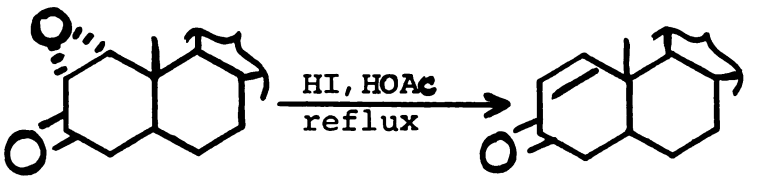
Reduction of 4-hydroxycholest-4,6-diene-3-one XXIV with hydriodic acid gave cholest-4-en-3-one. This reaction cannot be explained by any of the mechanisms discussed thus far and its mechanism is still obscure.



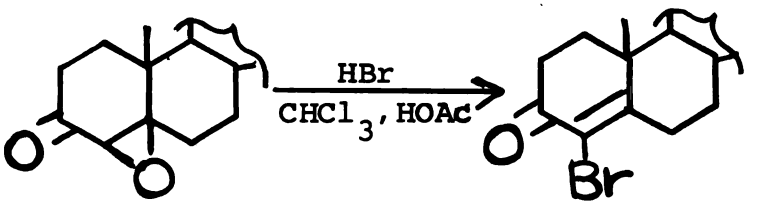
Epoxyketones are reduced by hydriodic acid to α,β-unsaturated ketones.



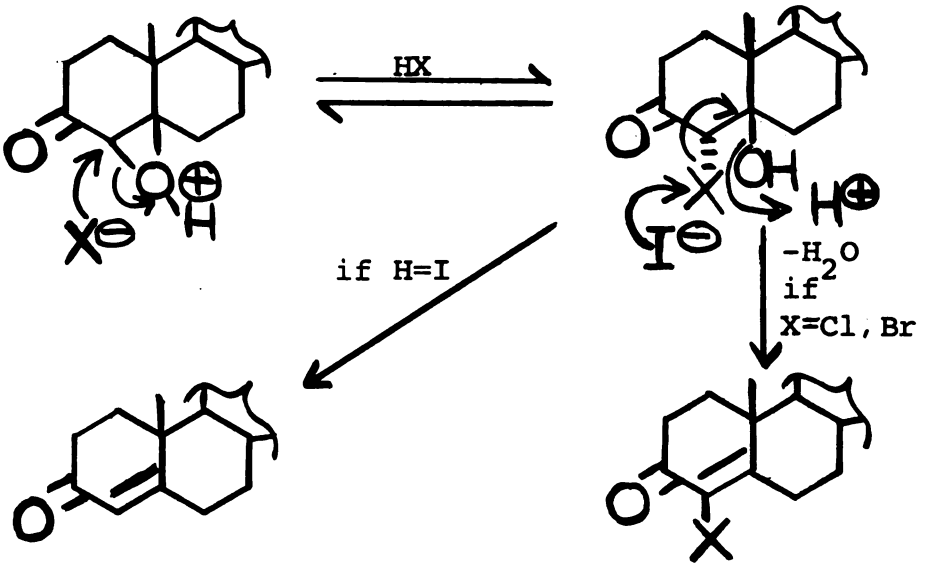
(32)



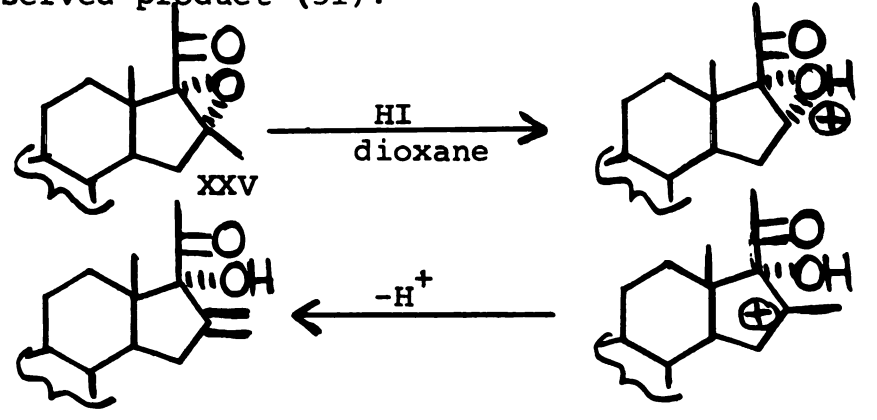
On the other hand, when epoxyketones are treated with hydrobromic or hydrochloric acid, α-haloenones are formed (32).



These results can be explained by an opening of the protonated oxide ring by halide ion to give α-halo-β-hydroxyketones. When the halogen is iodine, reduction followed by elimination of water occurs. Only elimination of water occurs when the halogen is bromine or chlorine.



When both the α- and the β-carbons of the epoxide ring are tetrasubstituted as in XXV, displacement by halide ion does not occur. Ionization of the protonated oxide followed by the loss of a proton from the resulting carbonium ion gives the observed product (51).



EXPERIMENTAL

Reduction of 4-methoxycholest-4-en-3-one

A solution of 200 mg. of 4-methoxycholest-4-en-3-one in 15 ml. of acetic acid containing 0.5 ml. of 47% hydriodic acid was refluxed for 1 hour. The reaction mixture was diluted with water and extracted with ether. After the ether extract was washed with 10% sodium hydroxide, decolorized and dried, it was evaporated to yield 180 mg. of a solid. Crystallization from aqueous methanol gave 100 mg. of 5α-cholestan-4-one, m.p. 96-97°, (reported m.p. 99-100°) identified by mixture melting point and comparison of the infrared spectrum with authentic material (35).

Reduction of 3-methoxy-5α-cholest-2-en-4-one

A solution of 100 mg. of 3-methoxy-5α-cholest-2-en-4-one in 15 ml. of acetic acid was treated with 0.5 ml. of 47% hydriodic acid and refluxed for 30 minutes. A workup similar to that described in the preceding preparation gave 85 mg. of solid which was crystallized from aqueous methanol to give 55 mg. of 5α-cholestan-4-one, m.p. 95-97°, identified by mixture melting point.

Reduction of 4-hydroxycholest-4-en-3-one

A solution of 200 mg. of 4-hydroxycholest-4-en-3-one in 15 ml. of acetic acid was treated with 0.5 ml. of 47% hydriodic acid and refluxed for 30 minutes. The usual workup gave 160 mg. of solid which was crystallized from aqueous methanol to yield 80 mg. of 5α-cholestan-4-one, m.p. 95-96°, identified by mixture melting point.

Reduction of 3-hydroxy-5α-cholest-3-en-2-one

A solution of 400 mg. of 3-hydroxy-5α-cholest-3-en-2-one in 30 ml. of acetic acid was treated with 2 ml. of 47% hydriodic acid and refluxed for 30 minutes. The usual work-up gave 370 mg. of semisolid material. This material was chromatographed on 15 g. of neutral alumina and eluted with benzene-ether (1:1) to yield 310 mg. of solid, m.p. 95-102°. Further crystallization did not raise the melting point. However, rechromatography on 20 g. of neutral alumina and elution with benzene-ether (1:1) gave two crystalline fractions. The first was crystallized from aqueous ethanol to yield 140 mg. of 5α-cholestan-2-one, m.p. 127-128° (reported m.p. 130.5-131.5° [15]); $\lambda_{max}^{CCl_4}$ 5.86, 10.35, 10.46 μ, identified by mixture melting point and comparison of the infrared spectrum with authentic 5α-cholestan-2-one

(15). The second fraction, m.p. 103-110°; $\lambda_{max}^{CCl_4}$ 5.86, 5.88, 9.74 and 10.46 μ, probably was a mixture of 5α-cholestan-3-one and 5α-cholestan-2-one has $\lambda_{max}^{CCl_4}$ 5.88, 9.74 and 10.48 μ.

Preparation of 3,5,5-trimethylcyclohexan-1,2-dione

A solution of 10 g. of isophorone oxide in 200 ml. of benzene was refluxed with 11 g. of p-toluenesulfonic acid monohydrate for 80 minutes. After dilution with water, 200 ml. of ether was added and the organic layer was separated and washed with three 50 ml. portions of 5% sodium bicarbonate. The organic layer was then extracted with three 30 ml. portions of 20% potassium hydroxide. Acidification of the combined aqueous layers followed by extraction with ether and evaporation gave a solid which was crystallized from petroleum ether to give 1.5 g. of 3,5,5-trimethylcyclohexan-1,2-dione as needles. Recrystallization from petroleum ether raised the melting point to 91-92°, (reported m.p. 92-93°, [63]).

Reduction of 3,5,5-trimethylcyclohexan-1,2-dione

A. A solution of 1.79 g. of 3,5,5-trimethylcyclohexan-1,2-dione in 35 ml. of acetic acid was treated with 13 g. of 47%

hydriodic acid and refluxed for 2 hours. After the reaction mixture was diluted with water and extracted with ether, the ether extract was washed with 50% sodium thiosulfate, 5% sodium bicarbonate and 20% potassium hydroxide to recover unreacted diosphenol. Acidification of the aqueous extract and extraction with ether yielded 500 mg. of unreacted 3,5,5-trimethylcyclohexan-1,2-dione. The neutral material was obtained as 1.18 g. of an oil on evaporation of the dried ether extract, $\lambda_{max}^{CCl_4}$ 5.83 and 5.94 μ. Vapor phase chromatographic analysis on a 15% neopentyl glycol succinate column at 123° showed two peaks which were collected by preparative chromatography on the same column. The first peak, which comprised 81% of the neutral product, was identified as 2,4,4-trimethylcyclohexanone, $\lambda_{max}^{CCl_4}$ 5.84. The infrared spectrum was identical with that given for 2,4,4-trimethylcyclohexanone (64). The dinitrophenylhydrazone was crystallized from ethanol as needles, m.p. 149-150° (reported m.p. 150-151° [54]). The second peak was identified as 2,4,4-trimethyl-2-cyclohexen-1-one, $\lambda_{max}^{CCl_4}$ 5.95, 6.08 μ. The infrared spectrum was identical with that reported for 2,4,4-trimethyl-2-cyclohexen-1-one (65). $\lambda_{max}^{C_2H_5OH}$ 233.5 mμ (log ε 4.0); n.m.r. 3.73 (singlet), 7.63 (broad triplet), 8.19 (broad triplet),

8.19 (broad triplet), 8.32 (singlet) and 8.86τ(singlet). The red dinitrophenylhydrazone was crystallized from ethanol, as needles, m.p. 163-165°, (reported m.p. 163-164° [55]).

B. A solution of 70 mg. of 3,5,5-trimethylcyclohexan-1,2-dione in 10 ml. of acetic acid was treated with 300 mg. of potassium iodide and refluxed for 6 hours. The reaction mixture was worked up as before and yielded 43 mg. of light yellow crystals, m.p. 109-111°; $\lambda_{max}^{CCl_4}$ 2.80 (weak and broad) and 7.95 μ. No saturated ketone was obtained and 20 mg. of unreacted diosphenol was recovered in the usual manner.

Preparation of 3,3-dimethylcyclohexan-1,2-dione

A solution of 7 g. of 2-benzal-6,6-dimethylcyclohexanone (66) in 140 ml. of acetone was treated dropwise at ice bath temperature with a solution of 5.2 g. of potassium permanganate and 3.9 g. of anhydrous magnesium sulfate in 105 ml. of water with stirring. The addition took 1 hour and the reaction mixture was stirred at room temperature for an additional 30 minutes. Filtration removed the manganese dioxide and the filtrate was poured into water and extracted with ether. Acidic material was removed by extraction with 20% sodium hydroxide. After acidification and ether extraction, the carboxylic acids (probably dimethyladipic

and benzoic acid) were removed by extraction with 5% sodium bicarbonate. The ether solution was dried and evaporated to yield 800 mg. of a thick oil; $\lambda_{max}^{CCl_4}$ 2.95, 6.00 and 11.89 μ; $\lambda_{max}^{C_2H_5OH}$ 265 mμ (log ε 3.8). The oil gave a deep green ferric chloride test and the di-DNP was prepared by refluxing in ethanol with excess Brady reagent for 30 minutes, scarlet plates with m.p. 239-240°, (reported m.p. 237-238° [56]); $\lambda_{max}^{CHCl_3}$ 352 mμ (log ε 4.4) and 388 mμ (log ε 4.3), (reported [56] $\lambda_{max}^{CHCl_3}$ 351 mμ (log ε 4.5) and 388 mμ (log ε 4.4). The diketone was also shown to be homogeneous by vapor phase chromatography on a 20% silicone column at 165°. Evaporation of the ether solution from the neutral portion gave 2 g. of starting material and 900 mg. of benzaldehyde.

Reduction of 3,3-dimethylcyclohexan-1,2-dione

A solution of 620 mg. of 3,3-dimethylcyclohexan-1,2-dione in 30 ml. of acetic acid was treated with 6 g. of 47% hydriodic acid and refluxed for two hours. Workup as with 3,5,5-trimethylcyclohexan-1,2-dione gave 460 mg. of neutral oil. Vapor phase chromatography on a 15% neopentyl glycol succinate column at 119° gave two peaks. The first peak, 78% of the neutral material, was shown to be 3,3-dimethylcyclohexanone by comparison of its infrared spectrum, $\lambda_{max}^{CCl_4}$ 5.86 μ, and

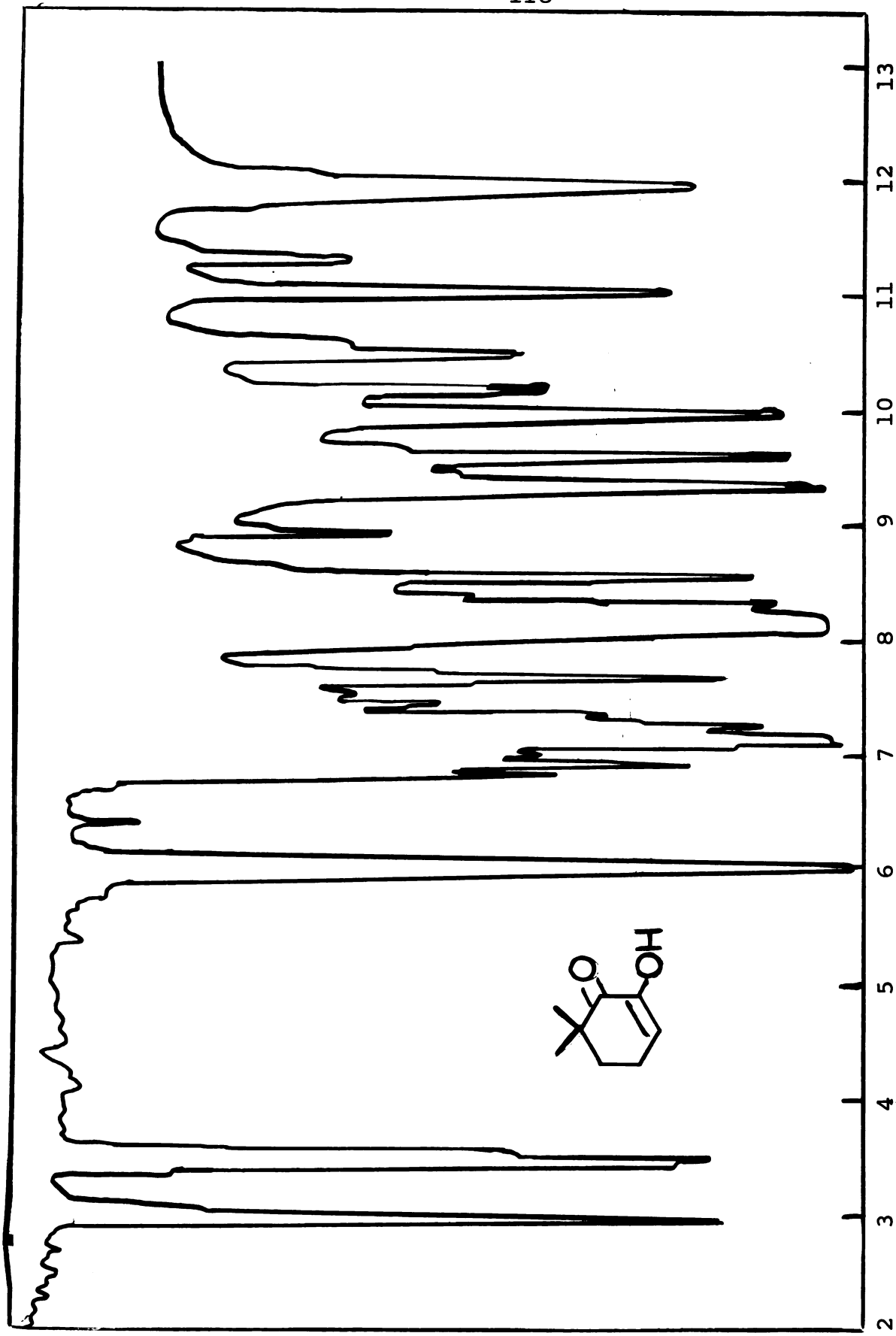


Figure 16. Infrared spectrum of 3,3-dimethylcyclohexane-1,2-dione (in CCl_4).

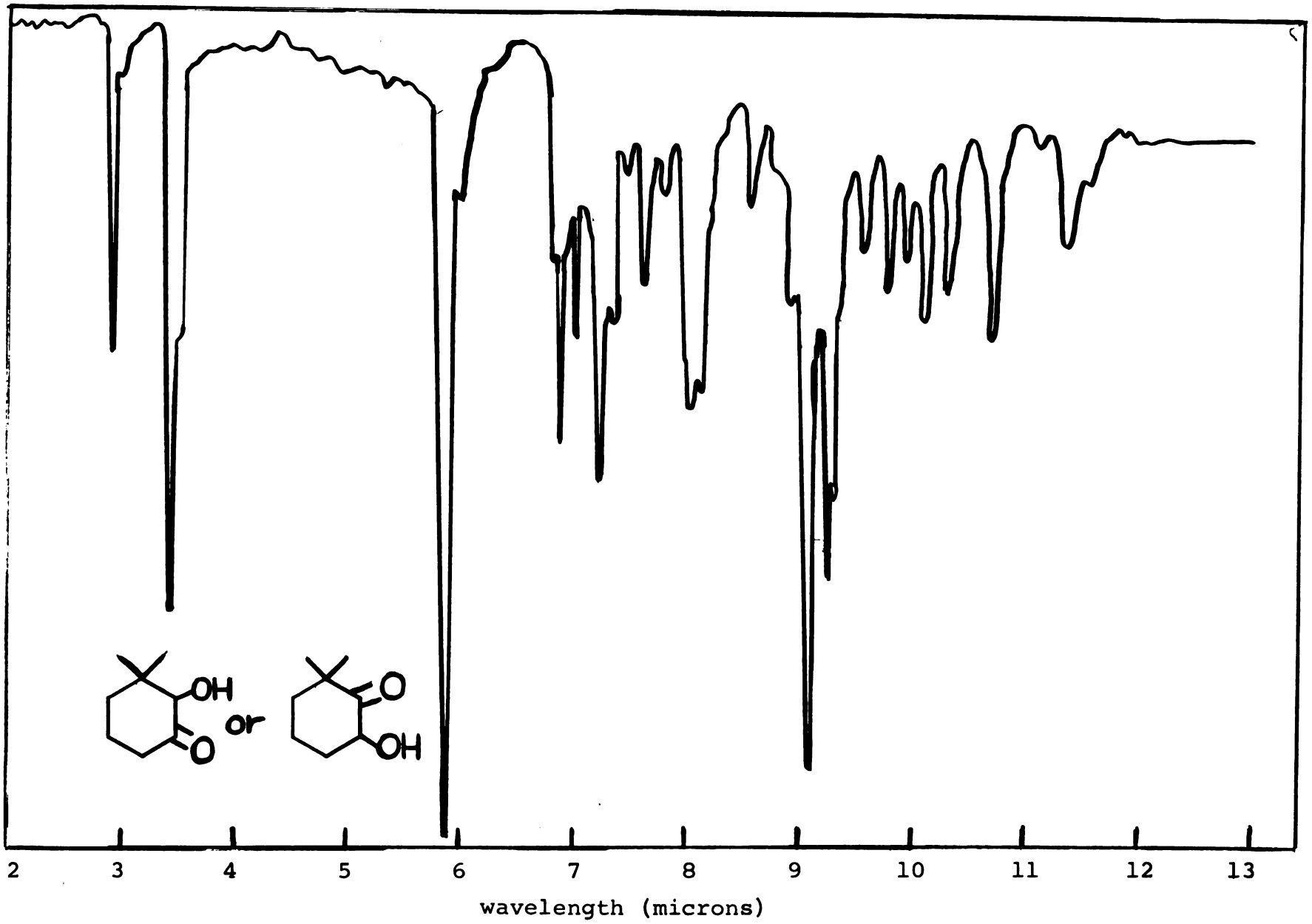


Figure 17. Infrared spectrum of 2-hydroxy-3,3-dimethylcyclohexanone or 2-hydroxy-6,6-dimethylcyclohexanone (in CCl_4).

its retention time with an authentic sample.* The crude DNP was chromatographed on alumina and repeatedly crystallized from ethanol to give needles, m.p. 105-120°. Authentic 3,3-dimethylcyclohexanone gave a DNP, m.p. 105-118°, (reported m.p. 140.5° [67]). The mixture melting point was not depressed. The second peak was shown to be 2-hydroxy-3,3-dimethylcyclohexanone (or 2-hydroxy-6,6-dimethylcyclohexanone), $\lambda_{max}^{CCl_4}$ 2.90, 5.83 and 9.03 μ, by conversion to the scarlet di-DNP, m.p. 235-237°, of 3,3-dimethylcyclohexan-1,2-dione which was identified by mixture melting point. A solution of 100 mg. of the product mixture from above in 10 ml. of acetic acid was treated with 1 g. of 47% hydriodic acid and refluxed for 4 hours. Evaporation of the ether after the usual workup gave an oil which also contained some white crystals. The oil was shown to contain 90% 3,3-dimethylcyclohexanone and 10% hydroxyketone by vapor phase chromatography. The crystals, which were almost insoluble in ether, were filtered to give 8 mg. of needles, m.p. 114-115°; $\lambda_{max}^{C_4Cl_6}$ 2.90 (broad) and 7.95 μ. This compound is almost insoluble in carbon tetrachloride,

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*3,3-dimethylcyclohexanone was prepared by oxidation of 3,3-dimethylcyclohexanol, which was prepared by high pressure reduction of 5,5-dimethylcyclohexan-1,3-dione.

chloroform and ether and may be a dimer of 2-hydroxy-3,3-dimethylcyclohexanone.

Reduction of 2-hydroxycyclohexanone

A sample of 1 g. of 2-hydroxycyclohexanone (Aldrich Chemical Company) was dissolved in 40 ml. of acetic acid and refluxed for 1 hour with 2 g. of 47% hydriodic acid. The reaction mixture was diluted with water and the neutral products were extracted with ether. After the ether extract was washed with 20% sodium hydroxide and water, it was dried and evaporated to yield 420 mg. of a light yellow oil. This material was identified as cyclohexanone by its infrared spectrum (traces of cyclohexenone were also present), retention time on a 6 foot 20% silicone column at 100° and preparation of a dinitrophenylhydrazone, m.p. 158-159°, (after chromatography on alumina), which was identical with an authentic sample.

Reduction of cholestan-3,4-6-trione

A solution of 150 mg. of cholestan-3,4,6-trione in 40 ml. of acetic acid was treated with 3 g. of potassium iodide and refluxed for 23 hours. The reaction mixture was worked up as usual to yield 120 mg. of a semisolid, $\lambda_{max}^{CCl_4}$ 5.84, 6.15 and 6.40 μ. Authentic 5α-cholestan-3,6-dione absorbs

in the infrared at 5.84 μ and cholestan-3,4,6-trione absorbs at 6.15 and 6.40 μ. The relative intensities of these peaks indicated a mixture of approximately 60% of the 3,6-diketone and 40% starting material.

Reduction of 22-isoallospirostan-3β,12β-diol-11-one

A solution of 200 mg. of 22-isoallospirostan-3β-12β-diol-11-one (61) in 40 ml. of acetic acid was treated with 3 g. of potassium iodide and refluxed for 17 hours. The reaction mixture was diluted with water and extracted with ether. After the ether extract was washed with sodium thiosulfate solution, 10% sodium hydroxide and water, it was dried, decolorized and evaporated to yield 170 mg. of solid, m.p. 210-217°. After hydrolysis with refluxing ethanolic sodium hydroxide, the solid obtained on dilution with water was chromatographed on 5 g. of alumina. Elution with chloroform gave a white solid, m.p. 208-210°, which was crystallized from acetone-hexane to raise the melting point to 221-224° (reported for 22-isoallospirostan-3β-ol-11-one, m.p. 223-226° [68]). The mixture melting point was depressed to 208-210°. Refluxing with zinc dust in acetic acid did not change this material.

Reduction of benzil

A. A sample of 2 g. (0.01 m.) of benzil was dissolved in 30 ml. of acetic acid and refluxed for 1 hour with 12 g. (0.044 m.) of 47% hydriodic acid. The usual workup gave 1.25 g. of white solid, which was crystallized twice from ethanol to yield pure benzoin as needles, m.p. 133-134°. Identification was by mixture melting point and comparison of the infrared spectrum with that of authentic benzoin.

B. A sample of 500 mg. (0.0025 m.) of benzil was dissolved in 17 ml. of acetic acid and refluxed for 2 hours with 10.3 g. (0.038 m.) of 47% hydriodic acid (53). Dilution with water gave a solid which was filtered and washed well with water to yield 390 mg. of white solid. Crystallization from ethanol gave deoxybenzoin, m.p. 53-54°, identified by a mixture melting point with authentic material.

C. A sample of 300 mg. of benzil was dissolved in 45 ml. of acetic acid and refluxed for 24 hours with 1.1 g. of potassium iodide. Dilution with water and filtration gave 270 mg. of a yellow solid which was crystallized from ethanol to give long yellow needles of unreacted benzil, m.p. 92-93°, (reported m.p. 95°). The infrared spectrum was identical to that of authentic benzil.

Attempted reduction of benzoin

A. A solution of 1 g. (0.0048 m.) of benzoin in 30 ml. of acetic acid was treated with 5.4 g. (0.0195 m.) of 47% hydriodic acid and refluxed for 1 hour. Dilution with water followed by ether extraction and the usual workup gave 960 mg. of solid. Fractional crystallization from aqueous ethanol gave 780 mg. of unreacted benzoin, identified by mixture melting point and infrared spectrum. A second fraction of 130 mg. was obtained on dilution of the filtrate with water, m.p. 65-72°; $\lambda_{max}^{CCl_4}$ 5.77 and 5.93 μ. The infrared spectrum was identical with that recorded for acetylbenzoin (69). Crystallization from methylcyclohexane raised the melting point to 75-78° (reported m.p. 81-82°).

B. A solution of 300 mg. of benzoin in 45 ml. of acetic acid was refluxed for 24 hours with 1.1 g. of potassium iodide. Dilution with water followed by ether extraction and the usual workup gave 250 mg. of solid. The infrared spectrum of this solid indicated that it was a mixture of unreacted benzoin and acetylbenzoin.

Reduction of 4β,5-epoxy-5β-cholestan-3-one

A sample of 200 mg. of 4β,5-epoxy-5β-cholestan-3-one dissolved in 20 ml. of acetic acid was treated with 1 ml. of 47%

hydriodic acid and refluxed for 30 minutes. The usual work-up gave 170 mg. of solid which was crystallized from aqueous methanol to yield 140 mg. of cholest-4-en-3-one as needles, m.p. 78-79°, identified by mixture melting point and infrared spectrum.

Reduction of 1α,2α-epoxy-5α-cholestan-3-one

A solution of 200 mg. of 1α,2α-epoxy-5α-cholestan-3-one in 20 ml. of glacial acetic acid was treated with 1 ml. of 47% hydriodic acid and refluxed for 30 minutes. Workup as usual gave 180 mg. of solid which was crystallized from aqueous ethanol to yield 130 mg. of cholest-1-en-3-one, m.p. 94-95°, (reported m.p. 95° [70]), identified by mixture melting point and infrared spectrum.

Attempted hydride reduction of 3,5,5-trimethylcyclohexan-1,2-dione

A solution of 90 mg. of 3,5,5-trimethylcyclohexan-1,2-dione in 30 ml. of acetic acid and 4 drops of conc. sulfuric acid was refluxed for 2 hours with 200 mg. of triphenylmethane. After dilution with water, the reaction mixture was extracted with ether. Unreacted 3,5,5-trimethylcyclohexan-1,2-dione (70 mg.) was recovered by shaking the ether extract with 20% sodium hydroxide solution. The neutral

material was obtained as 190 mg. of a white solid on evaporation of the ether. A sample of this material on vapor phase chromatography gave no peaks corresponding to those obtained in the hydriodic acid reduction of 3,5,5-trimethylcyclohexan-1,2-dione.

SUMMARY

Enol ethers I and IV as well as diosphenol II were reduced by hydrogen iodide in refluxing acetic acid to 5α-cholestan-4-one. Diosphenol XIIa was reduced to 5α-cholestan-2-one under these conditions; other alicyclic α-diketones and α-ketols were also reduced and the products identified. Two mechanisms involving an allylic carbonium ion correctly predict all of the products obtained. Reduction of benzils requires more vigorous conditions and apparently proceeds by a different mechanism. The synthetic utility of this reduction was discussed.

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