PART I
AN ATTEMPTED WOLFF-KISHNER INITIATED FRAGMENTATION REACTION

PART II
LITHIUM ALUMINUM HYDRIDE REDUCTION OF A STEROID TOSYLATE. A NOVEL REARRANGEMENT

Thesis for the Degree of Ph.D.
MICHIGAN STATE UNIVERSITY
Ronald H. Starkey

1968

This is to certify that the

thesis entitled

Part I: AN ATTEMPTED WOLFF-KISHNER INITIATED FRAGMENTATION REACTION

Part II: LITHIUM ALUMINUM HYDRIDE REDUCTION OF A STEROID TOSYLATE. A NOVEL REARRANGEMENT

presented by

Ronald H. Starkey

has been accepted towards fulfillment
of the requirements for

Ph. D. degree in Chemistry

William H. Rausch

Major professor

Date September 4, 1968

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ABSTRACT

PART I

AN ATTEMPTED WOLFF-KISHNER INITIATED FRAGMENTATION REACTION

PART II

LITHIUM ALUMINUM HYDRIDE REDUCTION OF A STEROID TOSYLATE. A NOVEL REARRANGEMENT

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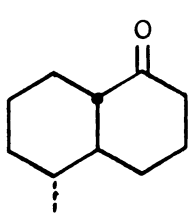
Attempts to effect a fragmentation reaction[1] by means of a number of modifications of the Wolff-Kishner reaction on trans-5-p-toluenesulfonoxy-1-decalone (I) have failed. Reasons for expecting the fragmentation to give trans,trans-1,6-cyclodecadiene are presented.

The failure of the fragmentation to occur is due to a facile competing 1,3-elimination yielding tricyclic cyclopropyl compounds (II). An explanation for the facility of the elimination compared to the desired fragmentation is discussed.



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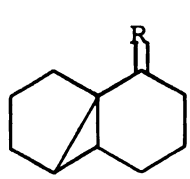
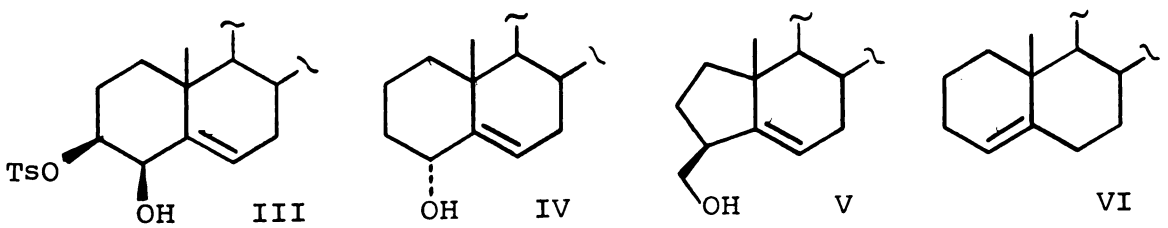


II

Lithium aluminum hydride reduction of 3β-p-toluenesulfonoxycholest-5-en-4β-ol (III) has been reported to give three products; A, B, and C.[2] Product A was subsequently identified correctly by another research group[3] as cholest-5-en-4α-ol (IV), B was not identified, and C was shown to be cholest-4-ene (VI).

The present investigation confirms the formation of IV and VI; and identifies product B as 3β-hydroxymethyl-A-norcholest-5-ene (V).

A possible mechanism for the observed rearrangements is proposed and substantiated by the reaction of III with lithium aluminum deuteride, and preparation of a proposed intermediate cholest-5-en-4-one.



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2. P. Karrer, H. Asmis, K. Sareen, and R. Schwyzer, Helv. Chim. Acta., 34, 1022 (1951).

3. D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. Summers, J. Chem. Soc., 2876 (1955).

PART I

AN ATTEMPTED WOLFF-KISHNER INITIATED FRAGMENTATION REACTION

PART II

LITHIUM ALUMINUM HYDRIDE REDUCTION OF A STEROID TOSYLATE. A NOVEL REARRANGEMENT

By

Ronald H. Starkey

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PART I

AN ATTEMPTED WOLFF-KISHNER INITIATED FRAGMENTATION REACTION

HISTORICAL AND INTRODUCTION

Recently there has been widespread interest in medium-size ring compounds.[1] Many new methods for the synthesis of these interesting and synthetically challenging structures have been developed. Among the most promising synthetic approaches to medium-ring compounds are fragmentation reactions.

Fragmentation reactions have been known for quite some time, but only recently have been recognized as a distinct class of reactions.[2] Recent reviews by Grob[2,3] illustrate and classify the various types of fragmentations and show the great diversity of the reaction.

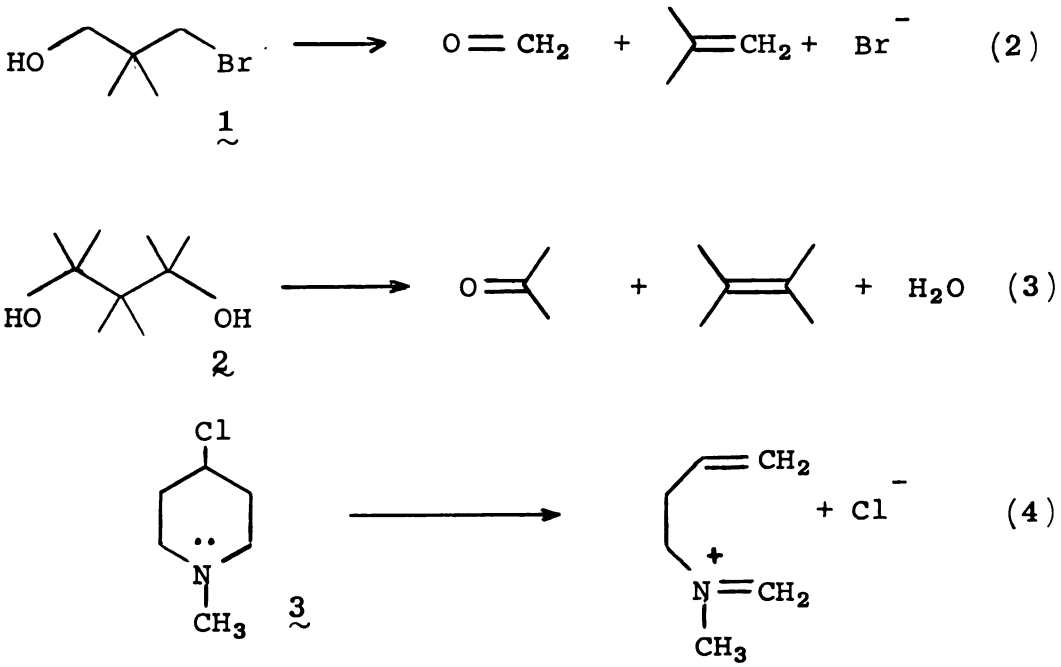
In this context fragmentation refers to the cleavage of a molecule, symbolized by a-b-c-d-X, in the manner shown by equation 1.

$$\underline{a}\text{-}\underline{b}\text{-}\underline{c}\text{-}\underline{d}\text{-}\underline{X} \longrightarrow \underline{a} = \underline{b} + \underline{c} = \underline{d} + \underline{X}^{-} \qquad (1)$$

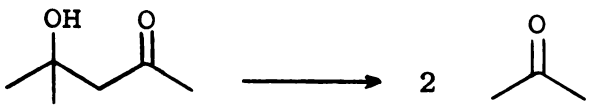
In a heterolytic fragmentation reaction, which is the most common type, a,b,c, and d represent atoms, such as carbon, oxygen, and nitrogen, which are capable of forming multiple bonds. X represents a leaving group such as halogen or tosylate, a-b is the portion of the molecule which is

able to supply electrons, and in most systems c and d are carbon atoms.

Fragmentation reactions occur under a variety of conditions on a multitude of substrates. The fragmentation of 3-bromoalcohol 1 (equation 2), where the leaving group X is bromide and the a-b portions are the hydroxyl and carbinol methylene, takes place in 15% potassium hydroxide solution.[4] Equation 3 illustrates an acid catalyzed fragmentation[5] of



a 1,3-diol. Grob[6] has shown that γ-halo amines, such as 3 undergo thermal fragmentations. A commonly encountered fragmentation reaction, which is not generally thought of as such, is the retro-aldol reaction (equation 5)[7]



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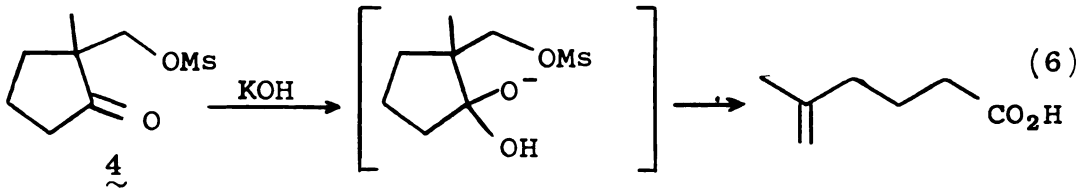

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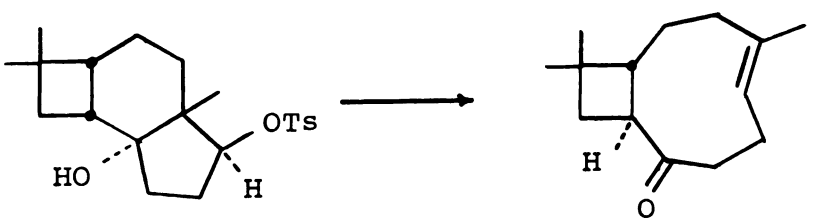
(6)

Fragmentation reactions have been used to open the rings of cyclic compounds[8] (equation 6). When the ring opening is performed on a properly substituted bicyclic system the fragmentation effects a ring expansion. This technique has been applied to substituted hydrindane systems by Corey[9] in the synthesis of Carophyllene (6) (equation 7), and by Tanabe[10] for the preparation of a 13,14-secosteroid (equation 8). Decalin derivatives have been used by



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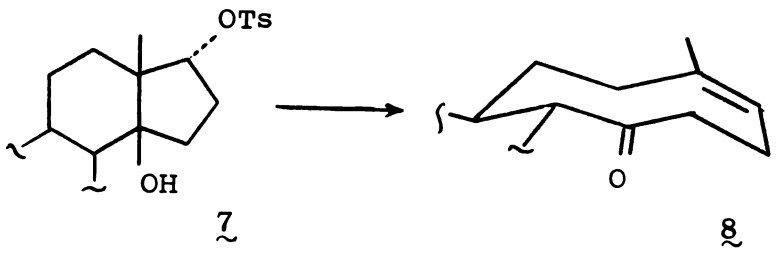
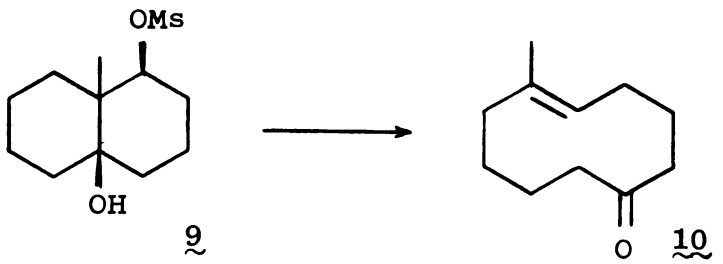


7 8 (8)

Weston[11] (equation 9) and Wharton[12] (equation 10) to prepare unsaturated ten-membered rings.



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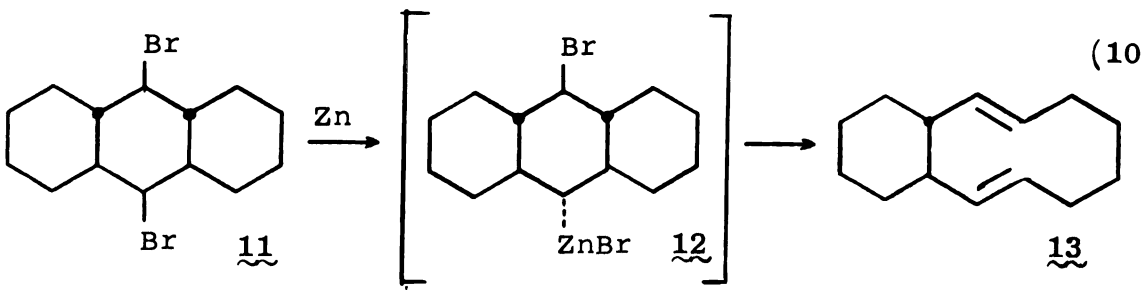
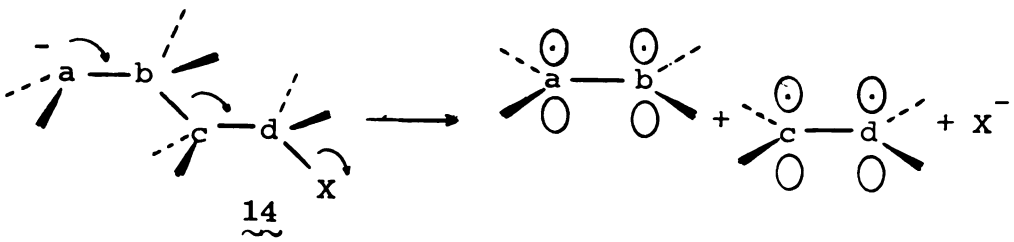


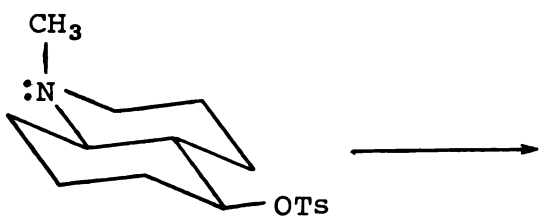
11 12 13 (10)

The preferred geometry for effecting a fragmentation reaction is dependent on stereoelectronic factors[3]. The bonds participating in the fragmentation should be arranged so that overlap of the developing p-orbitals will be at a maximum in the transition state. This geometry is attained in the anti conformation[13] as shown in structure 14.



14 (11)

Thus Grob[14] asserts that the reason the 5-equatorial tosylate of N-methyl decahydroquinoline (15) fragments readily to give 16, while the corresponding axial tosylate 17 only undergoes elimination (equations 12 and 13), is due to the preferred anti geometry of 15. This argument is weakened since the different mode of reaction of 17 may be due only to the fact that a more rapid trans-diaxial β-elimination of the tosylate is now competing with the fragmentation process.



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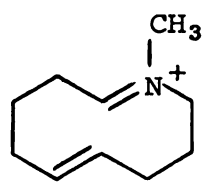

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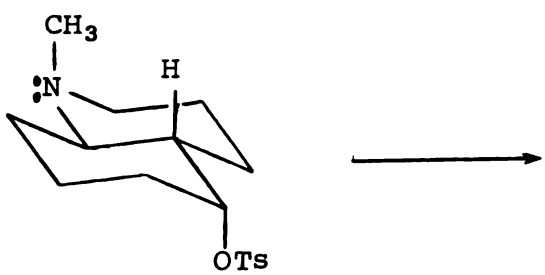

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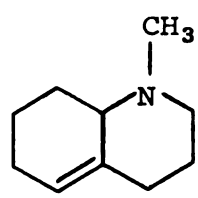
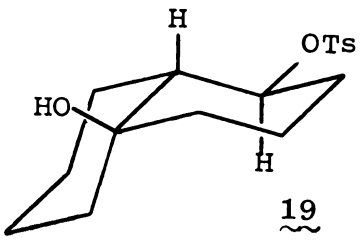


18 (13)

Wharton[15] found that hydroxy tosylate 19 gave the fragmentation product 21 in greater than 90% yield, while under the same conditions the isomer 20, which cannot attain the preferred anti geometry, could be recovered unchanged. Even erythro-dibromohydrocinnamic acid (22), which



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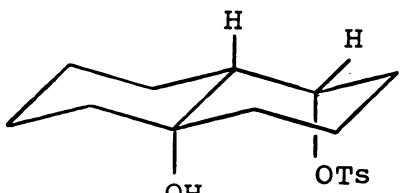

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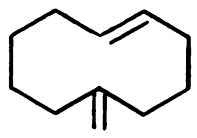
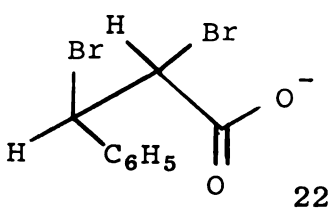


21

does not have a fixed conformation, undergoes fragmentation in acetone exclusively via the anti transition state to give cis-bromostyrene (23).[16]



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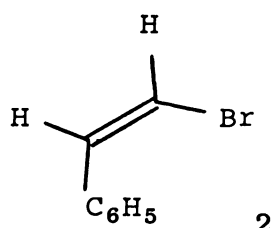
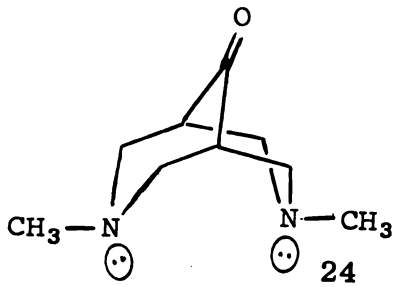


23

(14)

Support for the maximum overlap principle comes from a study of the ultraviolet spectra of piperidones by Cookson.[17] Piperidone 24, which probably has the nitrogen n-electron pairs oriented in the axial (endo) position, shows no intense absorption in the accessible ultraviolet region. A similar structure (25), in which the electron pairs are forced to be equatorial and therefore anti to

the 1,2-bond, has a strong absorption band at 262 mμ (ϵ = 3600) which disappears in acid solution.



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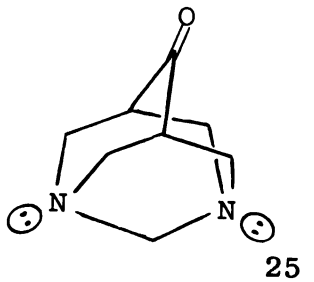

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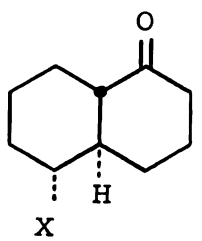
The 5-substituted-1-decalone 26 was chosen as a model for the synthesis of ten membered diene rings via a fragmentation reaction.



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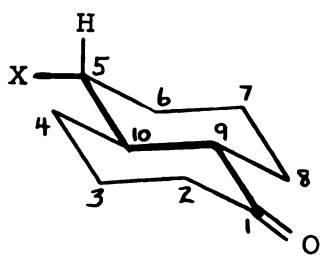
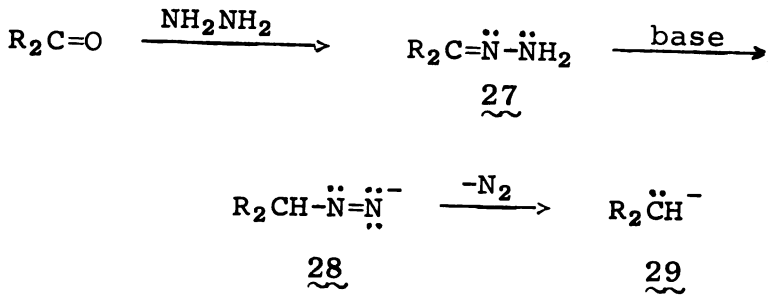


In this rigid decalin ring system the leaving group X occupies an equatorial position and is fixed in the preferred anti-orientation to the 9-10 bond. The equatorial orientation is also advantageous since the preferred trans-diaxial geometry for β-elimination of H-X cannot be attained; thus, any competitive elimination reactions would be minimized. A nucleophilic displacement of X^- would also be quite unfavorable since the axial hydrogens on carbons 7 and 9 would make back-side attack on carbon 5 quite hindered.

The 1,5 arrangement requires that an anion be generated on carbon 1 to effect a fragmentation. This electron pair preferably should be in an equatorial orientation, as this would also make it anti to the 9-10 bond.

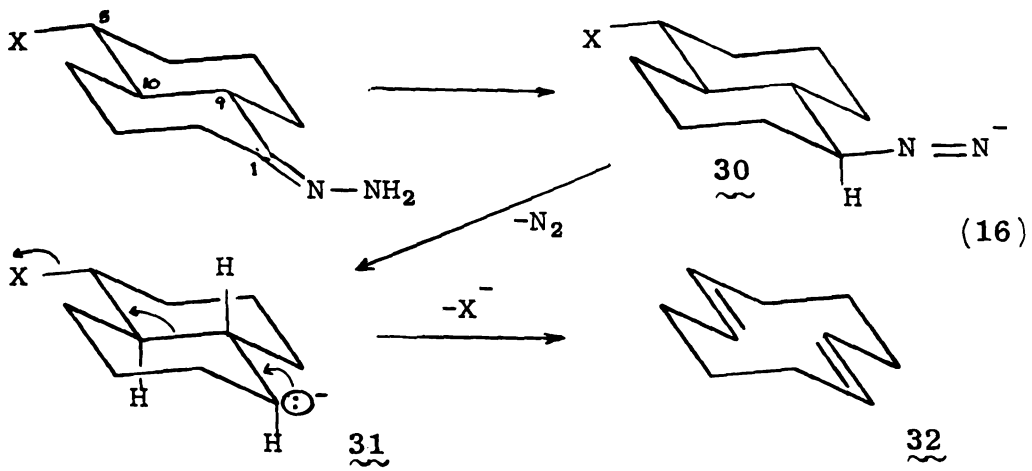
The 1-ketone was chosen because ketones are usually easily prepared and a method for generating an anion on the carbonyl carbon appeared to be at hand. Wolff-Kishner reductions[18] of ketones, according to the accepted mechanism,[19] proceed via a hydrazone (27) which rearranges to a diimide anion structure (28) and then loses nitrogen to leave a carbanion (29) on the original carbonyl carbon (equation 15).



(15)

Under normal Wolff-Kishner conditions this intermediate anion would pick up a proton from the reaction medium and form the hydrocarbon.

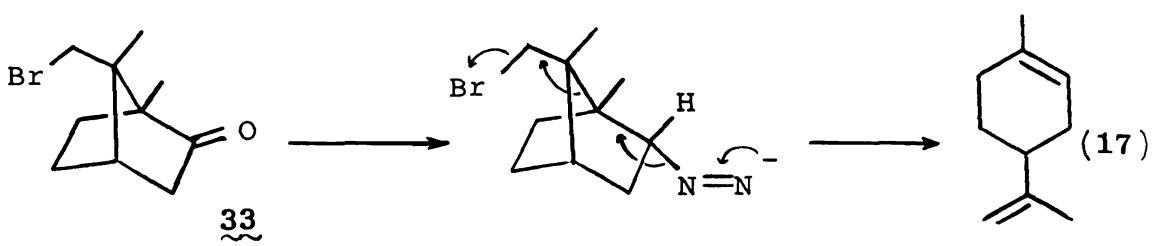
The anion formed from a Wolff-Kishner reaction on a ketone such as 26 has another alternative available to it—it can initiate a fragmentation reaction (equation 16). The hydrogen transfer (27 ⟶ 28) would probably yield 30 since this places the diimide anion in the sterically less



(16)

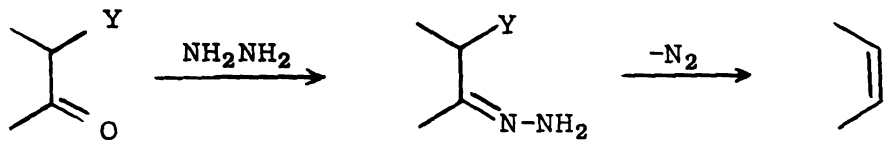
hindered equatorial position. Regardless of whether loss of nitrogen and fragmentation is concerted, the equatorial diimide anion would assure that the electron pair would be anti to the 9-10 bond, and thus all steric requirements for fragmentation would be met.

A fragmentation reaction in the course of a Wolff-Kishner reduction of π-bromo camphor (33) has been observed[20] (equation 17).



(17)

In effect the Wolff-Kishner initiated fragmentation reaction is an "ethylagous" analog of the well known Kishner elimination[21] (equation 18).

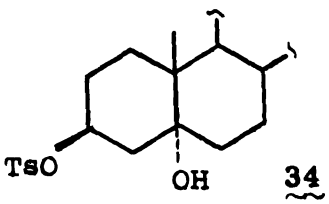


(18)

Leonard and Galfand[22] have found that the greater the ability of the leaving group Y to accommodate a negative charge, the better the yield of Kishner elimination product. In a study of α-halo ketones Wharton, Dunny and Krebs[23] found that the Kishner elimination product yields were in the order F > Cl > Br > I > OTs—the reverse of the normal order based on leaving group ability. This was attributed to a more facile competing β-elimination in these non-rigid systems. Consequently the α-fluoro-compounds did not undergo β-elimination, but remained intact until they could be eliminated by the Kishner route. In addition, the poorer leaving fluoro-compounds required higher temperatures to effect Kishner elimination.

Generalizing from the Kishner elimination to its ethylog, the fragmentation reaction, it appears the best leaving group (X) would be a sulfonate derivative, e.g. tosylate, mesylate, or a reactive halide such as iodide or bromide.

This is borne out by a comparison of the rates of fragmentation of a steroidal tosylate (34) and a chloride (35).[24] The chloride reacted much slower in the fragmentation reaction with potassium t-butoxide than did the tosylate. Thus



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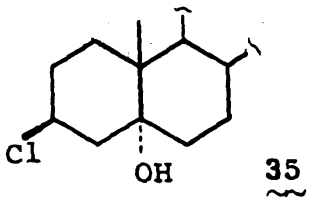

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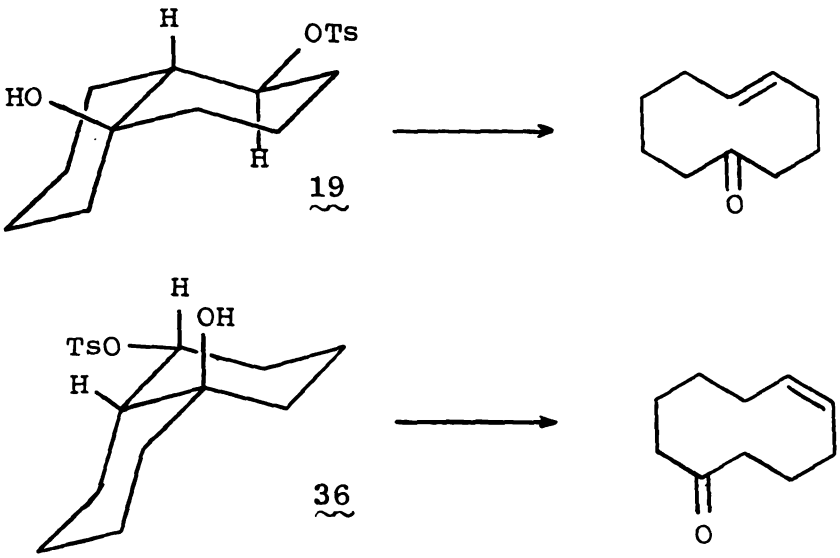
leaving group ability for fragmentation reactions seems to parallel that found for nucleophilic displacement reactions.

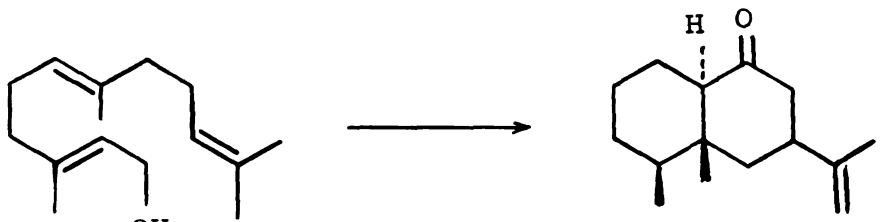
The geometry of the double bonds formed in fragmentation reactions can be deduced by mechanistic considerations. In the trans,trans-1,5-diequatorial substituted system (30), the geometry of the ring system demands that a concerted fragmentation lead to trans,trans-1,6-cyclodecadiene (32). This geometrical stereospecificity is evident from the fragmentation of 19 and 36.[15] Compound 19, in which the hydrogens on carbons 5 and 6 are trans, gives the trans-olefin, whereas when the same hydrogens are cis (36), the cis-olefin results.

In our model system both sets of hydrogens which would become the vinyl hydrogens (hydrogens on carbons 1, 9, 10 and 5 of structure 31) are trans and therefore the expected product would have two trans double bonds in a ten membered ring. Models indicated that 1,6-trans,trans double bonds can be accommodated in a cyclodecane ring and that it can attain an essentially strain free conformation, and therefore should be quite stable. In fact a trans,trans-1,6-cyclodecadiene is postulated[25] as an intermediate in the



19 36

biogenesis of eremophilone (38) from trans-farnesol (37).

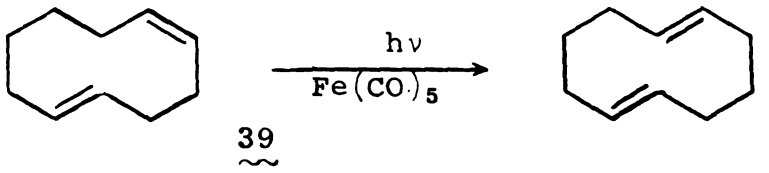


37 38

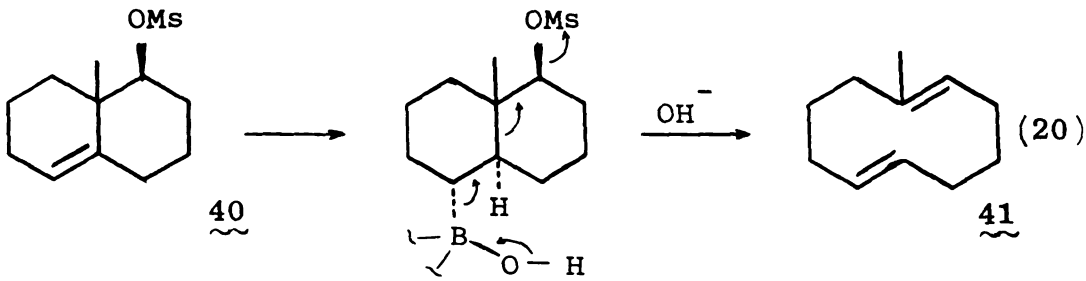
A substituted trans,trans-1,5-cyclodecadiene structure occurs in nature[1a,c] and has recently been synthesized by Corey[26] and Marshall.[27] Cis,cis-1,6-cyclodecadiene has been prepared and is quite stable.[28,29,30]

During the course of the present investigation trans, trans-1,6-cyclodecadiene itself was prepared by Heinback[31] using a photolytic isomerization (equation 19) of cis,trans-1,5-cyclodecadiene (39), and Marshall and Bundy[30] prepared

a methyl substituted trans,trans-1,6-cyclodecadiene (41) by means of a fragmentation reaction (equation 20).



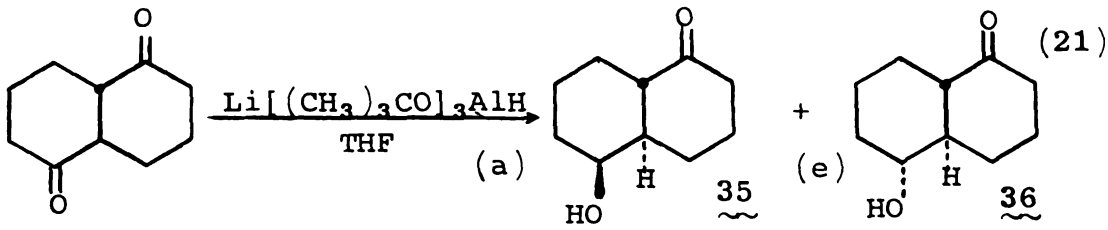
39 32 (19)



40 41 (20)

RESULTS AND DISCUSSION

Reduction of trans-decalin-1,5-dione[32] with one equivalent of lithium tri(t-butoxy)aluminum hydride[33] in tetrahydrofuran (THF), gave a mixture of ketoalcohols 35 and 36. Preparative thin layer chromatography[34] (prep-tlc) afforded pure 35 in 23% yield and pure 36 in 52% yield.

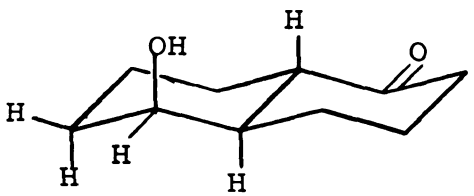


(21)

These two epimeric alcohols were differentiated by their infrared and nuclear magnetic resonance (nmr) spectra. The hydroxyl group of 35 displayed an oxygen-hydrogen (O-H) stretch at 3620 cm^{-1} and a carbon-oxygen (C-O) stretch at 985 cm^{-1}, while epimer 36 showed O-H and C-O stretches at 3600 and 1045 cm^{-1} respectively. The hydroxyl group of 35 was assigned an axial configuration and that of 36 an equatorial, since the O-H stretch of axial alcohols in six-membered rings is known to occur at higher frequencies than that of corresponding equatorial alcohols, and C-O stretching

frequencies are observed at 1040 cm^{-1} for equatorial alcohols and around 1000 cm^{-1} for their axial epimers.[35]

The nmr spectrum of 35 shows a fairly sharp singlet for the carbinol hydrogen (line width[36] 6 cps) at δ 3.97, while the carbinol hydrogen of 36 is a broad unresolved multiplet (line width 22 cps) at δ 3.40. This supports the assignment of trans-5-anti*-hydroxy-1-decalone to 35 and trans-5-syn*-hydroxy-1-decalone to 36, because a carbinol hydrogen that is axial is known[36] to absorb at higher field than the corresponding epimeric equatorial hydrogen. It is also well established[38] that vicinal axial-equatorial



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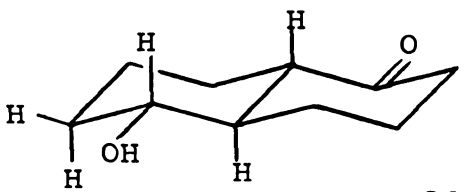

36

hydrogen splitting is much less (J = 1-5 cps) than the splitting between axial-axial hydrogens (J = 8-14 cps). Thus the line width of the axial carbinol hydrogen signal of 36, which is subject to vicinal axial-axial splitting, is broader than the signal from the corresponding equatorial hydrogen of 35.

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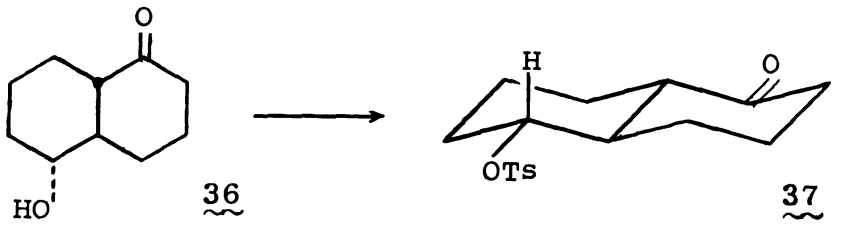
*The configuration of the hydroxyl is described as syn or anti with respect to the nearest bridgehead hydrogen.[37]

Tosylation of ketol 36 with p-toluenesulfonyl chloride in pyridine gave the equatorial tosylate 37 (trans-5-syn*-p-toluenesulfonoxy-1-decalone) in 83% yield. The nmr spectrum confirmed the equatorial orientation of the tosylate

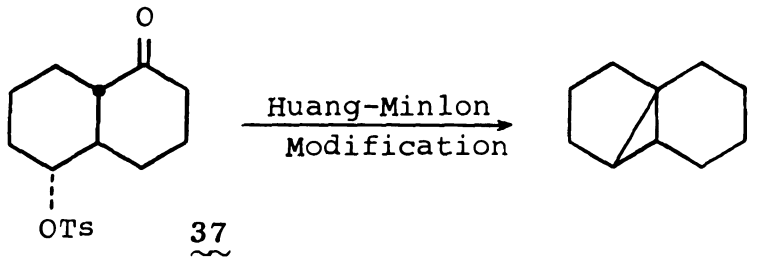


36 37 (22)

by the presence of a one hydrogen multiplet at δ 4.4 (line width 22 cps) due to the axial carbinol hydrogen.

Mild conditions were employed in the first attempt to effect a fragmentation reaction. The Wharton reaction,[39] a special type of Kishner elimination, where the leaving group is epoxide oxygen, proceeds using hydrazine hydrate and potassium acetate in boiling ethanol with no added strong base. Under the conditions of the Wharton reaction[39] ketotosylate 37 was recovered unchanged.

The next attempt to produce fragmentation was by the more vigorous conditions of the Huang-Minlon modification of the Wolff-Kishner reduction. A solution of tosylate 37 in diethylene glycol (DEG) containing hydrazine hydrate and potassium hydroxide was heated to a temperature of 200°. A volatile material isolated from the reaction in 30% yield and purified by glc was identified as tricyclo[4.4.0.$0^{1,5}$]-decane (38).



37 38 (23)

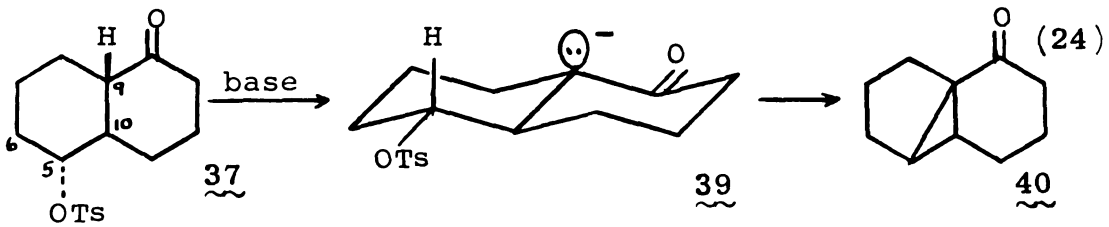
The structure proof of 38 is based on chemical and spectroscopic evidence. A positive tetranitromethane test[40] indicated 38 contained either olefinic unsaturation or a cyclopropane ring. The infrared spectrum showed a cyclopropyl C-H stretch at 3000 cm^{-1} and cyclopropyl skeletal vibration[41] at 1020 cm^{-1}. Nmr revealed two cyclopropyl hydrogens at high field (δ 0.69-0.77), a methylene envelope (δ 1.0-2.0) containing fourteen hydrogens, but no vinyl hydrogen signals.

The mass spectrum confirmed the molecular weight as 136, and examination of the intensity of the M + 1 (molecular ion + 1) and M + 2 peaks relative to the molecular ion peak (Table 1) indicated[42] a molecular formula of $C_{10}H_{16}$.

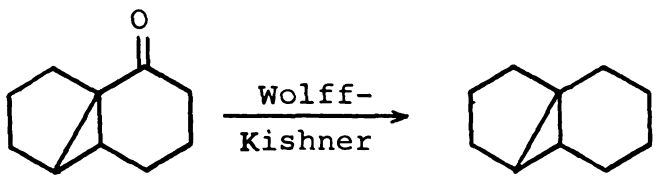
Table 1. Mass spectrum of tricyclo[4.4.0.$0^{1,5}$]decane (38)

	m/e	Experimental % of M	Calculated[43] % of M
M	136	100.0	100.0
M + 1	137	11.4	11.06
M + 2	138	1.0	0.55

Apparently under the basic conditions used, formation of a carbanion on carbon 9 and displacement of the tosylate by this carbanion occurs much faster than the Wolff-Kishner reduction of the ketone (equation 24). Because of its proximity to carbon 5, an electron pair on C-9 is able to displace the tosylate group and give the cyclopropyl-ketone 40.



37 39 40

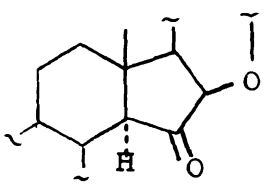


(25)

40 38

Since hydrazine is present in excess, ketone 40 could subsequently undergo reduction by way of the normal Wolff-Kishner reaction (equation 25) to give the hydrocarbon (38).

Abstraction of an α-hydrogen under Huang-Minlon conditions has been documented by Djerassi, Grossnickle and High[44] in the reduction of epimeric digitonins. Both 41 and 42 gave a single reduction product 43.



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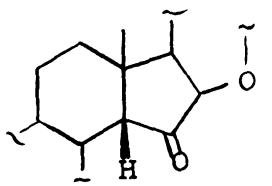

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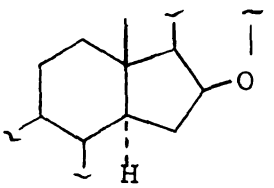


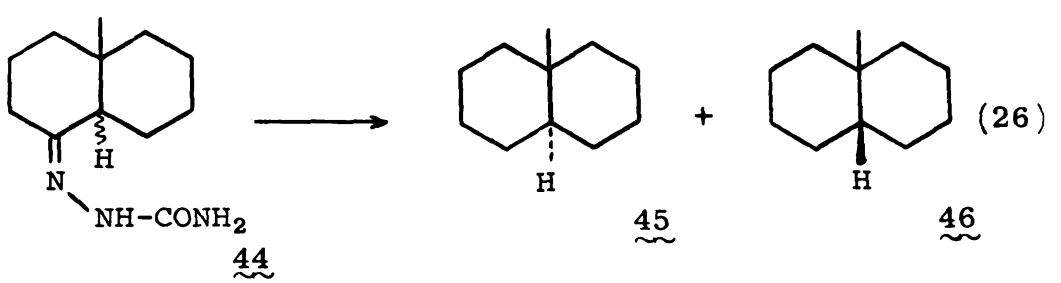
43

Support for the intermediacy of tricyclo[4.4.0.$0^{1,5}$]-decane-2-one (40) during the reduction of 37 was provided by its synthesis from 37 on treatment with potassium hydroxide in refluxing DEG (equation 24). Compound 40 showed infrared cyclopropyl absorption at 3000 cm^{-1}, a cyclopropyl conjugated carbonyl at 1660 cm^{-1}, and an ultraviolet absorption maximum at 219 mμ ($\epsilon = 10^3$). This maximum is typical of cyclopropyl ketones[45] and is reasonably close to the value of 212 mμ calculated for 40 by the method of Dauben and Berezin.[46] The mass spectrum of 40 indicated a molecular weight of 150 and the molecular formula[42] $C_{10}H_{14}O$.

The Lock modification of the Wolff-Kishner reduction is reported to be useful for base sensitive carbonyl compounds.[47] In this method the hydrazone is first prepared in the absence of strong base. The Wolff-Kishner reduction is then effected by heating with base. This method appeared promising for the system under investigation, since it should retard 1,3-elimination of tosylate. This conclusion is based on the assumption that hydrogens α to a hydrazone function are less acidic than those α to a carbonyl group,

since nitrogen is less electronegative than oxygen. Also, the two N-hydrogens of the hydrazone should be quite acidic and would probably be abstracted in preference to the α-hydrogens, decreasing even further the hydrazone function's ability to stabilize an α-negative charge. The N-hydrogen abstraction is also necessary in the first step of the Wolff-Kishner reduction.[19]

In contrast to these arguments, there is a report of epimerization during Wolff-Kishner reduction of a similar system.[48] When semicarbazone 44 was reduced under Huang-Minlon conditions, it gave a mixture of 45 and 46 in a 45:55 ratio. However, the possibility that 44 was a

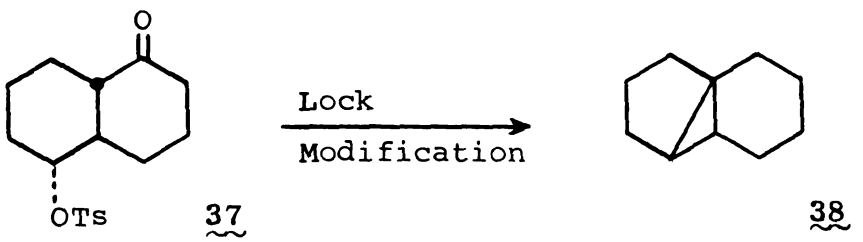


44 45 46 (26)

molecular compound composed of both the cis and trans epimers cannot be ruled out, since the only criterion given for its purity was a melting point which did not change on recrystallization. The equilibrium composition of the ketone from which 44 is derived is 40% cis and 60% trans.

The Lock modification was performed by warming 37 with 95% hydrazine in DEG, followed by addition of potassium hydroxide in DEG and slow heating to 240° (equation 27). The tricyclic hydrocarbon 38 was the only material which

could be isolated from the distillate. The product was isolated by means of gas chromatography and identified by a comparison of its infrared spectrum with tricyclo-[4.4.0.$0^{1,5}$]decane from the Huang-Minlon modification of the Wolff-Kishner reduction.



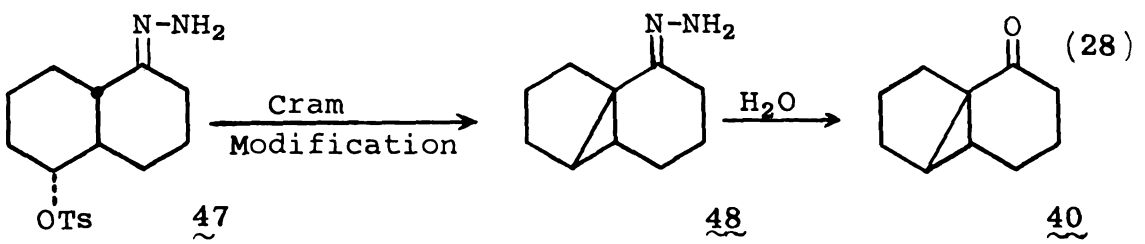
37 38 (27)

Again α-hydrogen abstraction and 1,3-elimination is the mode of reaction. Thus it appears that the rate of abstraction and subsequent displacement, even in the hydrazone, is much greater than the rate of Wolff-Kishner reduction.

The low temperature Cram modification[49] of the Wolff-Kishner reduction was attempted next. The dimethyl sulfoxide (DMSO) used as the solvent in this modification increases the reactivity of the base and therefore should facilitate both the Wolff-Kishner and hydrogen abstraction reactions. However, the use of t-butoxide, since it is a bulkier base than hydroxide, should make abstraction of the tertiary α-hydrogen more difficult. A fragmentation initiated by the Cram modification has been reported[20] (equation 17).

The product from slow addition of the crude hydrazone (47) in DMSO, to a DMSO solution of potassium t-butoxide was isolated and purified by distillation and gas chromatography and identified as tricyclo[4.4.0.$0^{1,5}$]decan-2-one (40) by comparison of its infrared and ultraviolet spectra with that of 40 obtained from base treatment of ketotosylate 37.

The reaction apparently proceeds via 1,3-elimination



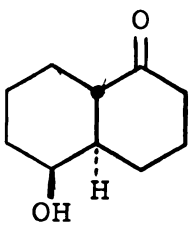
(28)

of tosylate from hydrazone 47 to give the tricyclic hydrazone 48, which is then transformed to 40 during the work-up.

Finally, an attempt was made to prepare trans-5-syn-bromo-1-decalone, since bromide is a poorer leaving group than tosylate and might therefore be less reactive in the 1,3-elimination, but still adequate as a leaving group in the fragmentation. The example of Gustafson and Erman[20] shows that bromide can serve as the leaving group in a Wolff-Kishner initiated fragmentation reaction (equation 17).

Preparation of alkyl bromides by treatment of alcohols with phosphorous tribromide in pyridine proceeds mainly with inversion of configuration at the carbinol carbon.[50] On this basis a bromide prepared from trans-5-anti-hydroxy-1-decalone (35) should yield a decalone with a bromine in

the equatorial position (49). Since the intermediate phos-



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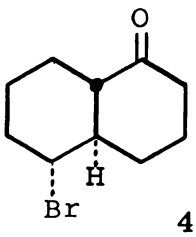
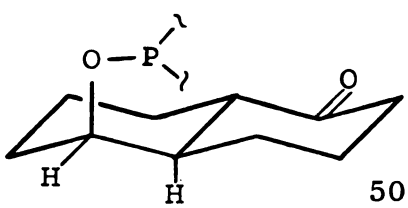


49

phite ester (50) is in the axial position and is well oriented for an anti elimination, attempts to prepare the bromide have led only to 1,2-elimination.



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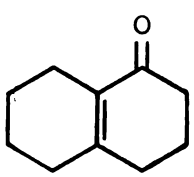
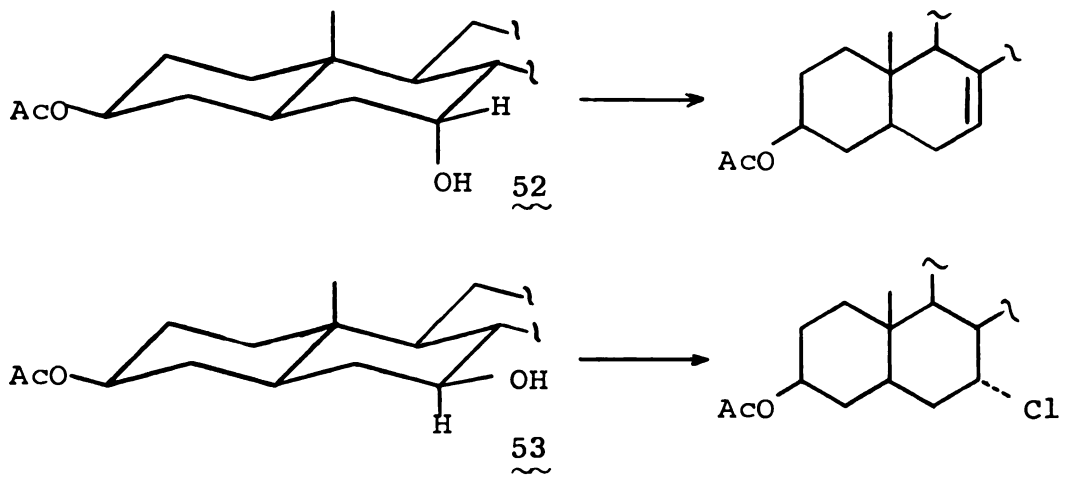


51

Treatment of 35 with phosphorous tribromide in pyridine gave Δ^9-octalone-1 (51) in good yield. The assignment of structure 51 to this product is based on its infrared spectrum.[51] A 1,2-diaxial elimination of the phosphite ester and isomerization of the double bond to a position conjugated with the carbonyl would give rise to the observed product.

The tendency of axial alcohols to undergo elimination rather than substitution is nicely illustrated by an attempt to prepare the 7-chlorides from the corresponding sterols.[52] The reaction of phosphorus oxychloride with the axial alcohol (52) gave only elimination, whereas the

equatorial alcohol (53) gave predominantly substitution.



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53

Attempts to effect a fragmentation reaction by means of a number of modifications of the Wolff-Kishner reaction on trans-5-p-toluenesulphonoxy-1-decalone (37) have failed. The failure of the fragmentation to occur is due to a facile competing 1,3-elimination yielding tricyclic cyclopropyl compounds.

EXPERIMENTAL

General. Infrared spectra were recorded on a Perkin-Elmer 237 B grating spectrophotometer, using sodium chloride cells. A Unicam Sp.800 spectrophotometer was used for ultraviolet spectra. Nuclear magnetic resonance spectra were taken on Varian A-60 and HA-100 high resolution spectrometers, using tetramethylsilane as an internal standard. A Consolidated Electrodynamics Corp. Type 21-103c and an LKB Type 9000 mass spectrometer were used to obtain the mass spectra.

Gas chromatography was performed on an Aerograph A-90-P3 with a thermal conductivity detector, using helium as the carrier gas. A 6% carbowax 20M on 80/100 Aeropack 30 column was employed. Preparative thin layer chromatography was done on 1.5 mm layers of silica gel PF_{254} on 20 × 20 cm glass plates.

Melting points were determined on a Koefler hot stage, and are uncorrected.

Analyses were performed by Spang Microanalytical Labs, Ann Arbor, Michigan.

Brine refers to a saturated sodium chloride solution. All materials were checked for purity by analytical thin layer chromatography on silica gel G.

In all runs of the Wolff-Kishner reduction no isolable product could be obtained by extraction of the residue from the distillation of the crude products.

trans-Decalin-1,5-dione. A 20 g sample of decalin-1,5-diol[53] was oxidized according to the procedure of Johnson, Gutsche and Banerjee[32] yielding 12 g (60%) of trans-decalin-1,5-dione: mp 165-166° [lit[32] mp 166°]; ir ($CHCl_3$) 1715 cm^{-1} (C=O).

Reduction of trans-Decalin-1,5-dione. To a stirred solution of 12.0 g (72.5 mM) of trans-decalin-1,5-dione in 1.2 l of tetrahydrofuran (distilled from $LiAlH_4$), which was maintained at 0° under a nitrogen atmosphere, 23.0 g (90 mM) of lithium tri(t-butoxy) aluminum hydride (Alfa Inorganics) in dry tetrahydrofuran (THF) was added dropwise. After the addition was completed, the solution was allowed to stand at room temperature for 12 hours. Addition of one equivalent of water and evaporation of the THF gave a light yellow solid, which was dissolved in a mixture of ether and 5% aqueous hydrochloric acid. The separated ether layer was washed with water and brine, and then dried over sodium sulfate. Evaporation of the ether gave 9.0 g (75%) of tan crystalline crude product.

Separation of the two alcohols from a 2.0 g sample of the crude product was accomplished by preparative thin layer chromatography[34] (prep-tlc) on two 20 × 20 cm glass plates coated with 1.5 mm layer of silica gel PF_{254} (E. Merck).

Development with anhydrous ether and ultraviolet visualization showed the two alcohols as bands of R_f 0.5 and R_f 0.4.

Elution of the R_f 0.5 band with ether gave 45.6 mg (23% of crude) of the axial ketol 35. Crystallization from hexane-benzene gave white crystals: mp 94-95°; ir ($CHCl_3$) 3620 (O-H), 1710 (C=O), and 985 cm^{-1} (C-OH). [Figure 1]; nmr ($CDCl_3$) δ 3.97 (s, 1H, line width[36] 6 cps, carbinol hydrogen), 2.7-1.2 (m, 15H, methylene and methine hydrogens with hydroxyl at δ 2.2), [Figure 6].

Elution of the R_f 0.4 band with ether gave 103.8 mg (52% of crude) of the equatorial ketol 36. Crystallization from benzene gave white crystals: mp 118-119°; ir ($CHCl_3$) 3600 (O-H), 1710 (C=O) and 1045 cm^{-1} (C-OH) [Figure 2]; nmr ($CDCl_3$) δ 3.4 (m, 1H, line width 22 cps, carbinol hydrogen), 2.8 (s, 1H, O-H), 2.6-1.0 (m, 14, methylene and methine hydrogens) [Figure 7].

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.39; H, 9.44.

Tosylation of trans-5-syn-hydroxy-1-decalone (36).

To a stirred and cooled (0°) solution of 1.0 g (6.0 mM) of 36 in 5 ml of pyridine, 1.6 g (8.4 mM) of solid p-toluenesulfonyl chloride was added in small portions. After the solution was stirred for 12 hrs at 25°, the pyridine was evaporated on a rotary evaporator and the resulting amorphous solid was dissolved in ether. The ether solution was washed twice with water, twice with 5% hydrochloric acid,

and then with brine, followed by drying over sodium sulfate. Evaporation of the ether and crystallization of the crude solid from ether, gave 1.6 g (83%) of the equatorial ketotosylate 37: mp 94-95°; ir ($CHCl_3$) 1715 (C=O), and 1175 cm^{-1} (tosylate) [Figure 3]; nmr ($CDCl_3$) δ 2.45 (s, 3H, CH_3Ar), 4.4 (m, 1H, line width 22 cps, CH-OTs), 7.6 (AB-quartet, 4H, H-Ar).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88; S, 9.95. Found: C, 63.58; H, 6.93; S, 9.90.

Wolff-Kishner Reduction (Huang-Minlon Modification) of Ketotosylate 37. To a solution of 400 mg (7.1 mM) of potassium hydroxide dissolved[54] in 5 ml of diethylene glycol (DEG), 0.3 ml (6.2 mM) of hydrazine hydrate (99%) and 388 mg (1.2 mM) of ketotosylate 37 were added. The distillate, collected while the mixture was heated from 25° to 220° (over a 2 hr period) and then maintained at 220° for 4 hrs, was dissolved in ether and washed with water and with brine. Evaporation of the ether gave 50 mg (30%) of tricyclo[4.4.0.$0^{1,5}$]decane (38), which was collected by and shown to be nearly pure (> 98%) by glc (6% carbowax at 125°). The glc-collected product gave a positive tetranitromethane reaction[40] (bright yellow) and was characterized spectroscopically: ir (neat) 3000 (cyclopropyl C-H), 2975, 2925, 2850, 1445 and 1020 cm^{-1} (cyclopropyl) [Figure 4]; nmr, 100Mc ($CDCl_3$) δ0.69 (m, J = 2 cps), 0.77 (s) combined relative area of 0.69 and 0.77 signals = 1, 1.0-2.0 (many

signals) combined relative area = 7 [Figure 8]; mass spectrum (70 eV) m/e (rel. intensity) 138 (1.0), 137 (11.4), 136 (100) [Figure 9].

Reaction of Ketotosylate 37 with Base. Ketotosylate (37) (200 mg, 0.62 mM) was added slowly to a solution of 200 mg (3.5 mM) of potassium hydroxide in 3 ml of DEG at 25°. The resulting mixture was warmed slowly to reflux temperature and then allowed to reflux for 2 hrs. The solution was cooled and poured into an equal volume of water and extracted twice with ether. The ether extract was washed with water, brine and then dried. Evaporation of the ether gave 77 mg of a yellow oil, from which could be isolated by prep-tlc (silica gel PF_{254}, developed with ether-chloroform [3:2], R_f 0.67) pure tricyclo[4.4.0.$0^{1,5}$]decan-2-one[40]: ir ($CHCl_3$) 3000, 2950, 2875, 1660, 1450 and 1370 cm^{-1} [Figure 5]; uv max (cyclohexane) 219 mμ ($\epsilon = 10^3$); nmr ($CDCl_3$) δ 1.0-2.5 (m); mass spectrum (70 eV) m/e (rel. intensity) 152 (0.78), 151 (11.8), 150 (100).

Wolff-Kishner Reduction (Lock Modification)[47] of Ketotosylate 37. Ketotosylate 37 (322 mg, 1.0 mM) was dissolved in 6 ml of DEG. After 1.0 ml (30 mM) of 95% hydrazine was added the solution was warmed slowly to 170°. The solution was cooled and 500 mg (9 mM) of potassium hydroxide in 4 ml of DEG was added. The volatile material was distilled as the solution was heated slowly to 240° (required

2 hrs). The distillate was poured into water and the water was extracted with pentane. The pentane solution was washed with water, brine, dried over sodium sulfate and the pentane evaporated. A substance which had the same glc retention time and an almost identical infrared spectrum as that of tricyclo[4.4.0.$0^{1,5}$]decane (38) was the only material which could be isolated from the residue by gas chromatography.

Wolff-Kishner Reduction (Cram Modification)[49] of Ketotosylate 37. Preparation of the hydrazone of 37 was accomplished by the procedure of Gustafson and Erman[20] Its infrared spectrum confirmed the crude product as a hydrazone:[55] ir ($CHCl_3$) 3300 and 1665 cm^{-1}. Tlc showed that no 37 was present in the product.

The crude hydrazone of 37 (500 mg, 1.5 mM) in 4 ml of dimethyl sulfoxide (DMSO), was added dropwise over a 6 hr period to a solution of 336 mg (3 mM) of sublimed potassium t-butoxide in 3 ml of dry DMSO. The solutions were protected from moisture and the reaction mixture was continuously swept with nitrogen. After being stirred overnight at room temperature and then heated at 90^0 for 4 hrs the mixture was cooled, poured into 75 ml of ice water, acidified with 5% hydrochloric acid, water, brine and dried over sodium sulfate. Evaporation of the ether and distillation of the resulting brown oil up to a temperature of 130^0 (1.5 mm Hg) gave 80 mg of a yellow liquid (38%). Gas chromatography on 6% carbowax at 180^0 showed a nearly pure major product,

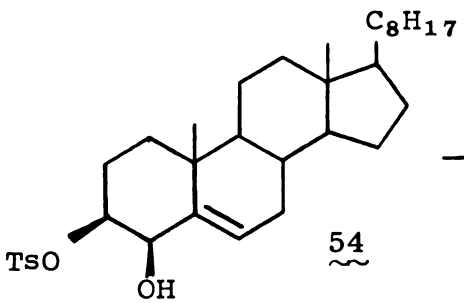
which was identified as tricyclo[4.4.0.$0^{1,5}$]decane-2-one (40), by comparison of its infrared and ultraviolet spectrum with that of 40 from base treatment of the ketotosylate 37.

Reaction of trans-5-anti*-hydroxy-1-decalone (35) with Phosphorous Tribromide. To a flask fitted with a drying tube and containing 0.2 ml (2 mM) of pohsphorous tribromide in 7 ml of dry pyridine, 500 mg (3 mM) of 35 was added. The solution was stirred for 4 hrs at 0^0, 1 hr at 25^0 and then maintained at 100^0 for 0.5 hrs. After standing for 12 hrs at room temperature, water was added and the reaction mixture extracted with ether. The ether extract was washed twice with water, twice with 5% hydrochloric acid, once with brine and dried with sodium sulfate. Glc of the residue from evaporation of the ether, on 6% carbowax at 165^0 afforded 220 mg (52%) of Δ^9-octal-1-one[51] (51): ir (CCl_4) 1665 and 1625 cm^{-1}.

PART II

LITHIUM ALUMINUM HYDRIDE REDUCTION OF A STEROID TOSYLATE. A NOVEL REARRANGEMENT

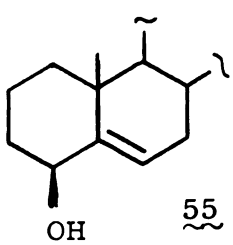
In 1951 Karrer, et al[56] reported the results of a lithium aluminum hydride reduction of tosylate 54. Three compounds, denoted by A, B, and C, were obtained after numerous column chromatographic separations.



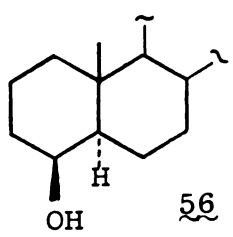
54

A + B + C (29)

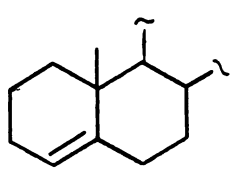
Compound A, obtained in about 20% yield, was assigned the structure cholest-5-en-4β-ol (55) on the basis of catalytic hydrogenation to a saturated alcohol, melting point 189°, which was thought to be 5α-cholestan-4β-ol (56).



55



56

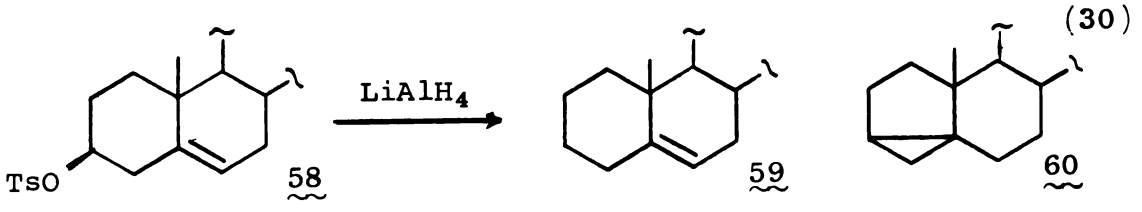


57

Compound C, obtained in only 2% yield, was identified as cholest-4-ene (57) by a mixture melting point with authentic material.

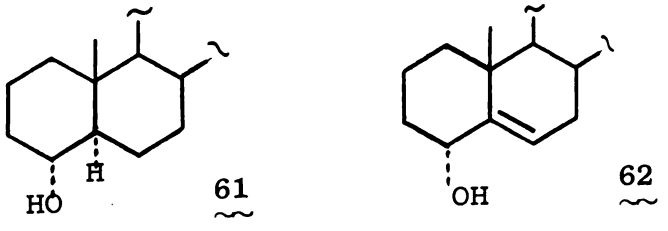
Compound B (ca. 4% yield) was not identified, but was characterized by a melting point of 98° and a specific rotation ($[\alpha]_D^{18}$) of -27.1°.

Karrer apparently assumed that simple displacement of the tosylate group by hydride was responsible for the major product, 55 . In an earlier study Schmidt and Karrer[57] found simple displacement accompanied by i-steroid (60) formation in the reaction of lithium aluminum hydride with cholesterol tosylate (58) (equation 30).



(30)

In 1951 Barton and Rosenfelder[58] reported the preparation of both cholestan-4β-ol (56) and cholestan-4α-ol (61). They found that the physical properties of the compound assumed to be cholestan-4β-ol by Karrer, et al.[56] actually corresponded to the 4α-hydroxy epimer 61.



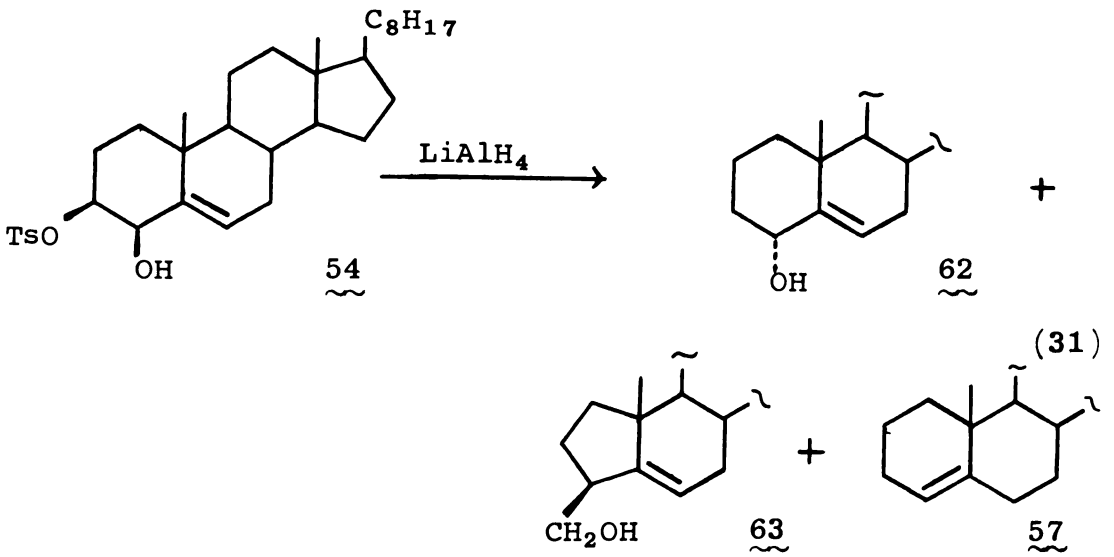
Shoppee and co-workers[59] in 1955 prepared both the α(62) and β(55) epimers of 4-hydroxycholest-5-ene, and demonstrated that the α epimer (62) was identical with the product of the lithium aluminum hydride reduction of tosylate 54. The structural assignments of 61 and 55 were later confirmed by Becker and Wallis.[60] Thus, it appears that the 4α-hydroxy group of tosylate 54 has been epimerized during the reaction with the metal hydride.

A structure for Karrer's compound B has never been proposed and it is difficult, on mechanistic grounds, to see how olefin 57 (Karrer's compound C) can be formed in the reaction.

A reinvestigation of the reaction of 3β-p-toluenesulfonoxycholest-5-en-4 β-ol (54) with lithium aluminum hydride was undertaken because: a) the structure of Karrer's compound B remained unknown; b) the epimerization of an alcohol by lithium aluminum hydride is unprecedented and, therefore the mechanism of the formation of A (62) is not obvious; c) the formation of compound C (57) is unusual and should be confirmed.

RESULTS AND DISCUSSION

Reduction of 3β-p-toluenesulfonoxycholest-5- en-4β-ol (54) by lithium aluminum hydride (LAH) in refluxing ether gave three products which could be separated very effectively by ascending dry column (ADC) chromatography on neutral alumina.



The major product, isolated in 48% yield, was cholest-5-en-4α-ol (62). The assignment of structure 62 to this product is consistent with the infrared and nmr spectra and the physical properties reported for the authentic material. Compound 62, mp (hexane) 141-142°, exhibited a specific rotation of $[\alpha]_D^{25}$ -53°, and appears to be identical to Karrer's compound A (mp 144°, $[\alpha]_D^{17.5}$ -55°) and authentic

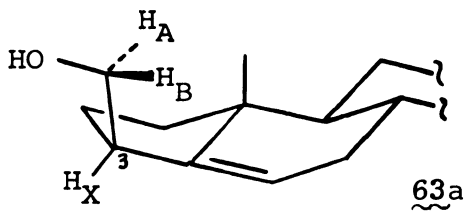
62 prepared by Shoppee, et al.[59] (mp 144°, $[\alpha]_D$ -50°) and Becker and Wallis[60] (mp 143°, $[\alpha]_D$ -54°). The nmr spectrum of 62 displayed a carbinol hydrogen signal of line width 21 cps[36] at δ 4.25. This hydrogen should be axial and thus a fairly broad signal is expected, since the dihedral angle favors a large spin-spin coupling.[38] The infrared spectrum showed hydroxyl O-H stretching at 3600 cm^{-1} and C-O stretching at 1070 cm^{-1}. This C-O stretching frequency is characteristic of an equatorial hydroxyl group.[35] The mass spectrum of 62 displayed a molecular ion at m/e 386 and was consistent with a molecular formula[42] of $C_{27}H_{46}O$. As expected, abundant fragments were observed at m/e 371 ($M-CH_3$) and 368 ($M-H_2O$).

Karrer's compound C, obtained in 3% yield by preparative thin layer chromatography of the least polar fraction from ADC chromatography, was identified as cholest-4-ene (57) by comparison of its physical properties, melting point 80-81°, $[\alpha]_D$ +67° with reported values. (Broome and coworkers[61] report a melting point of 80-81° and $[\alpha]_D$ +67° for cholest-4-ene). The nmr spectrum shows a vinyl hydrogen signal at δ 5.25 and the C-19 methyl at δ 1.00. The value calculated[62] for the C-19 methyl of a Δ^4-steroid is δ 1.025. The mass spectrum exhibited[42] a molecular ion at m/e 370, and indicated a molecular formula $C_{27}H_{46}$.

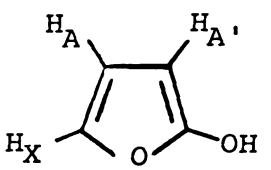
The third product, obtained directly from the ADC chromatography in 33% yield, was crystallized from methanol, mp 99°, $[\alpha]_D^{25}$ -24.4°. These physical constants are

essentially identical to those reported by Karrer[56] for compound B. The structure 3β-hydroxymethyl-A-norcholest-5-ene (63) was assigned to this compound on the basis of its spectral properties and a comparison with authentic 63. The ir spectrum of 63 displayed hydroxyl O-H stretching at 3600 cm^{-1} and C-O stretching at 1020 cm^{-1}, as expected for a primary alcohol. The mass spectrum, molecular ion at m/e 386 and prominent fragments at m/e 371 ($M-CH_3$) and 355 ($M-CH_2OH$), supported the molecular formula $C_{27}H_{46}O$. The nmr spectrum [Figures 17 and 19] showed a vinyl hydrogen of relative area 1 at δ 5.5, a multiplet of area 1 at δ 2.7, and a "doublet" with an area corresponding to two hydrogens centered at δ 3.62 (J = 7.2 cps).

This is a deceptively simple pattern for the carbinol hydrogens, which should be the AB portion of an ABX system, since they are adjacent to an asymmetric center (carbon-3, 63a) and are therefore magnetically non-equivalent. Evidently the chemical shifts of H_A and H_B are nearly equal



63a



64

and the system is essentially of the AA'X type. An AA'X system[63] would account for the observed carbinol hydrogen

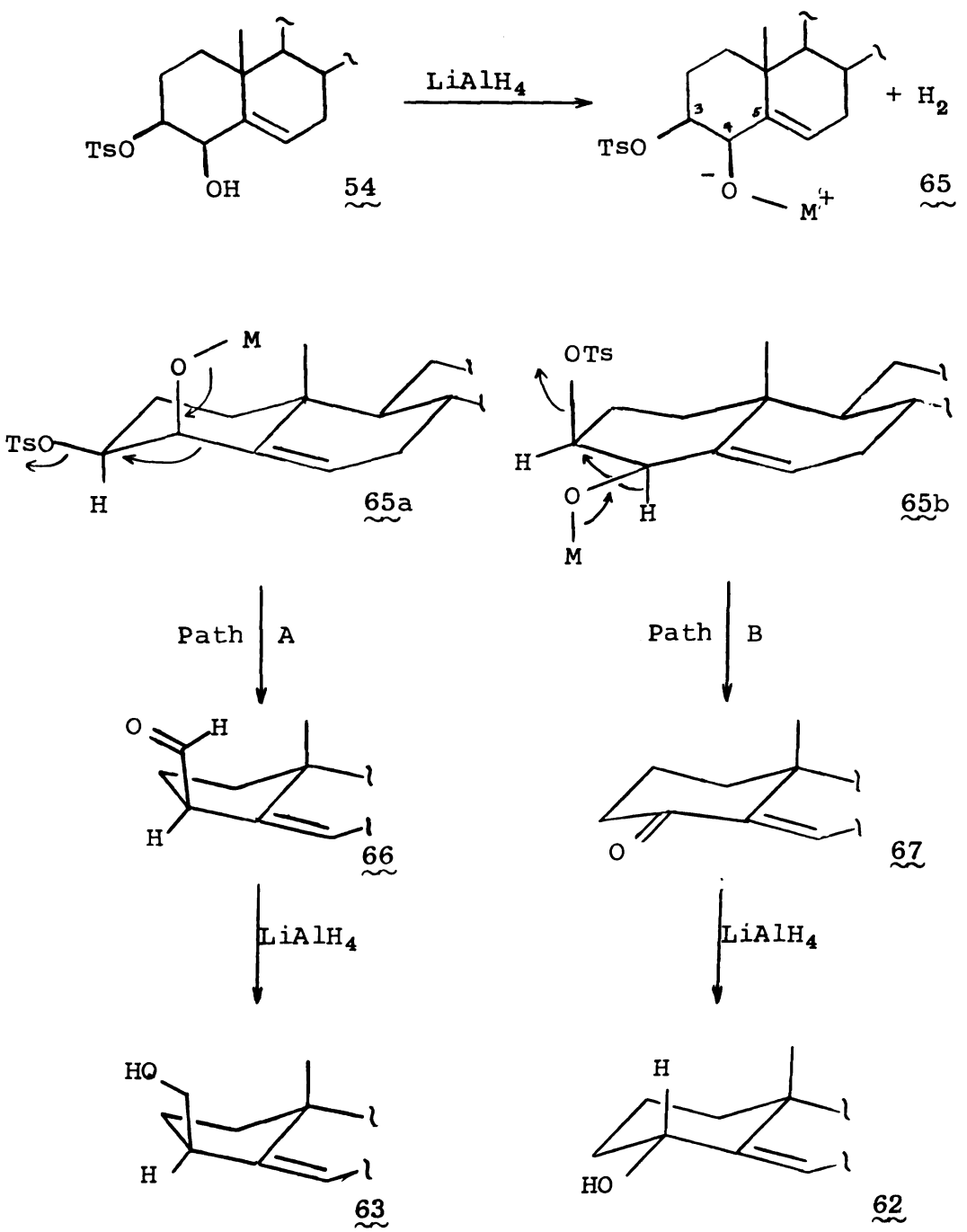
doublet and the broad multiplet for the hydrogen on C-3 at δ 2.7. An example of an AA'X system is found in the nmr spectrum of 2-furfurol (64), which displays a doublet for hydrogens H_A and $H_{A'}$, and a triplet for H_X.[64]

Finally Whitham and Wickramasinghe[65] have prepared 63, by an independent route and report a melting point of 99-101° and $[\alpha]_D$ -26° (c 1.56, $CHCl_3$). Comparison of an infrared spectrum of 63 obtained from the reduction of 54 with that of a sample of 3β-hydroxymethyl-A-norcholest-5-ene, kindly supplied by Prof. G. Whitham, shows the two to be identical. It should also be mentioned that the 3α-hydroxymethyl epimer of 63 has been prepared by Dauben and Ross[66]; this epimer is reported to have a melting point of 102-103° and $[\alpha]_D^{25}$ -45°.

Direct crystallization of the crude lithium aluminum hydride reduction product from benzene affords a crystalline molecular-compound of 62 and 63 with a sharp melting point of 123-124°, which does not change on recrystallization from acetone-hexane. This molecular-compound exhibits an $[\alpha]_D^{25}$ -38.6°, indicating it is a 1:1 complex of 62 and 63. Interestingly, this molecular compound showed only one spot by tlc on silica gel, however, tlc on alumina gave two spots of R_f 0.43 and 0.32.

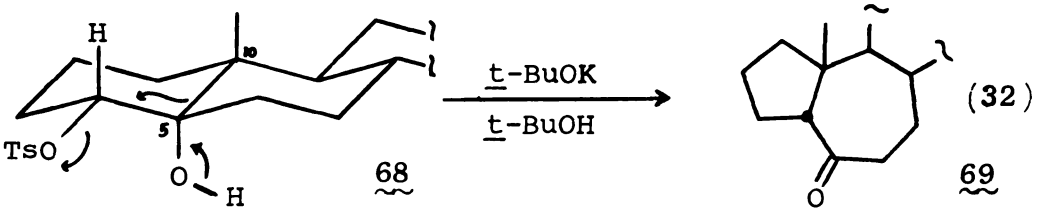
A possible mechanism for the transformation of tosylate 54 to alcohols 62 and 63 is depicted in Scheme 1. The common intermediate for formation of both products is the metal

Scheme 1

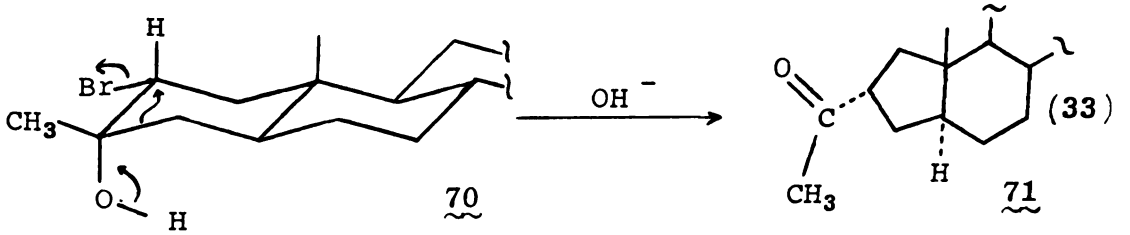

LiAlH4
+ H2
TsO
OH
54
65
M
65a
OTs
65b
Path A
Path B
66
67
LiAlH4
LiAlH4
HO
63
62

alkoxide 65 (M represents either aluminum or lithium). In the chair conformation of this intermediate (65a) the anti orientation of the tosylate and the 4-5 bond is favorable for a semi-benzilic type rearrangement (path A) giving aldehyde 66. This aldehyde would be reduced immediately by the excess hydride present to give the observed product (63). In a twist-boat conformation (65b) the tosylate can attain an orientation anti to the C-4 hydrogen, and a semi-benzylic rearrangement of hydride (path B) would lead to ketone 67. This ketone would then have to be reduced by lithium aluminum hydride from the β side of the molecule to give the equatorial alcohol 62.

Examples[67,68] of this type rearrangement, that ilustrate a geometrical preference in bond migration, are shown in equations 32 and 33. Barton has pointed out that the



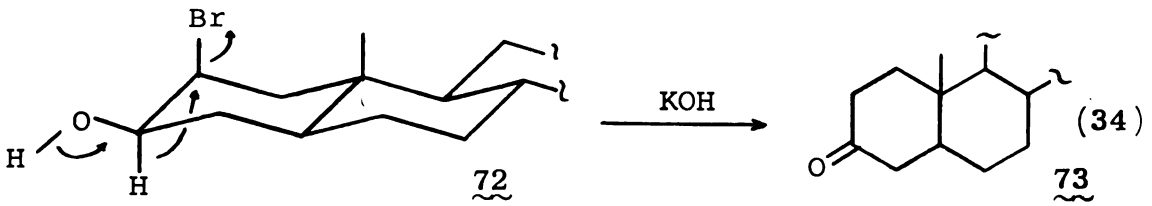
68 69



70 71

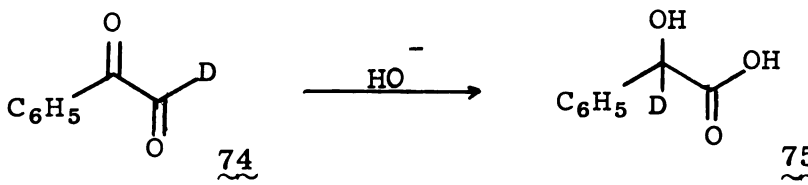
bond which migrates is always the one anti to the leaving group.[69]

1,2-Hydride shifts are less prevalent than 1,2-alkyl shifts. The elimination of HBr from compound 72 can be viewed either as an E_2 elimination or as a hydride shift, as shown in equation 34.[70] The proposal of a hydride shift

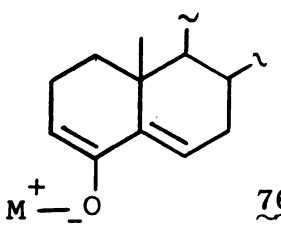


72 73 (34)

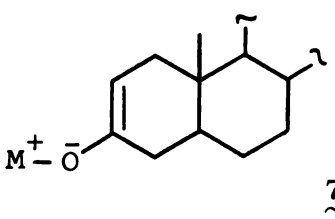
is not unreasonable since it has been demonstrated in the benzylic acid type rearrangement of keto-aldehyde 74 (equation 35).[71]



74 75 (35)



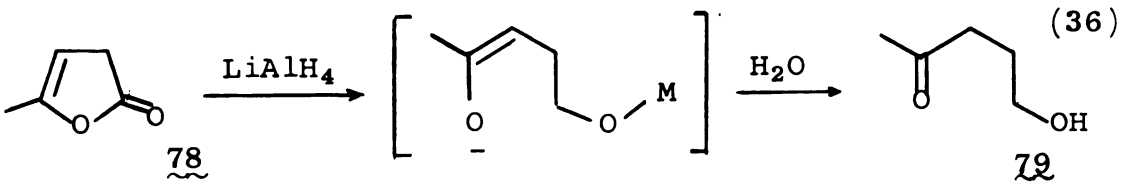
76



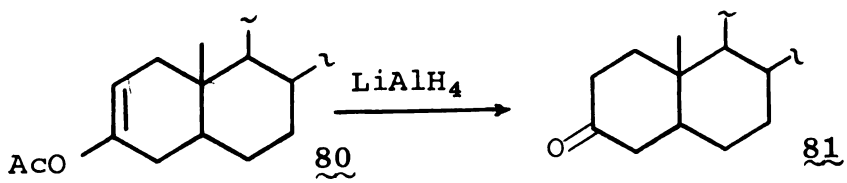
77

The only reasonable alternative to the hydride shift of path B (Scheme 1) is a simple E_2 elimination of HOTs to give enolate anion 76. This alternative is unlikely since there is evidence that enolate anions are not readily reduced by lithium aluminum hydride. Thus LAH reduction of enol

lactone 78 affords ketone 79 in 65% yield. Presumably the enolate anion shown in equation 36 is the product of the hydride reduction and upon work-up gives the ketone.[72] Dauben and Eastham report that ketone 81 can be obtained in 34% yield from the LAH reduction of enol acetate 80, and that the pre-formed lithium enolate of cholestan-4-one (77, M = Li) is quite resistant to hydride reduction.[73] If the enolate anion 76 is an intermediate in the reduction of tosylate 54 one would expect to recover some cholest-5-en-4-one (67), but no ketonic product is observed.



78 79 (36)

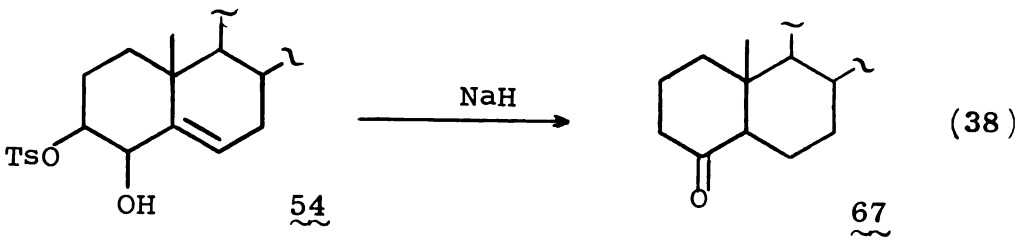


80 81 (37)

Since in the first step of the proposed mechanism LAH is functioning only as a base, reaction of the starting tosylate 54 with a base that is not a carbonyl reducing agent, should afford the proposed intermediates 66 and 67.

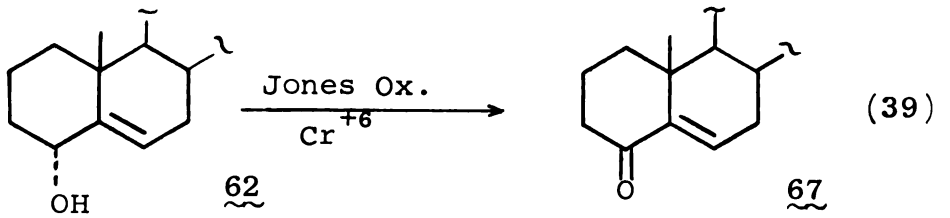
Treatment of tosylate 54 with sodium hydride in THF afforded cholest-5-en-4-one (67) in 48% yield (equation 38). Enone 67 was identified by a comparison of its physical properties (mp 111-112°, λ_{max}^{EtOH} 241 mμ) with reported

values[74], and is identical with the product obtained by



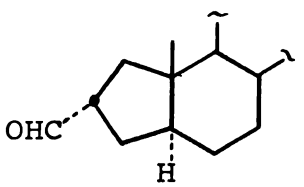
54 67 (38)

Jones oxidation[75] of cholest-5-en-4α-ol (62) (equation 39).



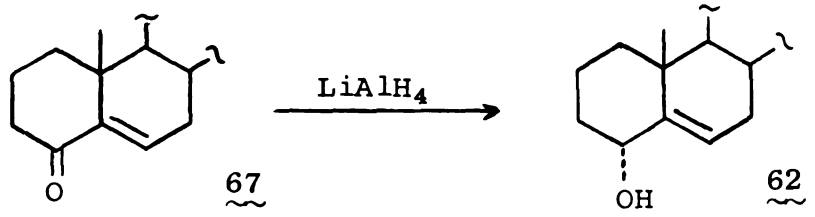
62 67 (39)

It is not surprising that the intermediate aldehyde 66 could not be isolated, since under the strongly basic conditions employed the aldehyde could easily undergo further reactions. A similar aldehyde (82) has been prepared[76] and is found to be quite unstable.



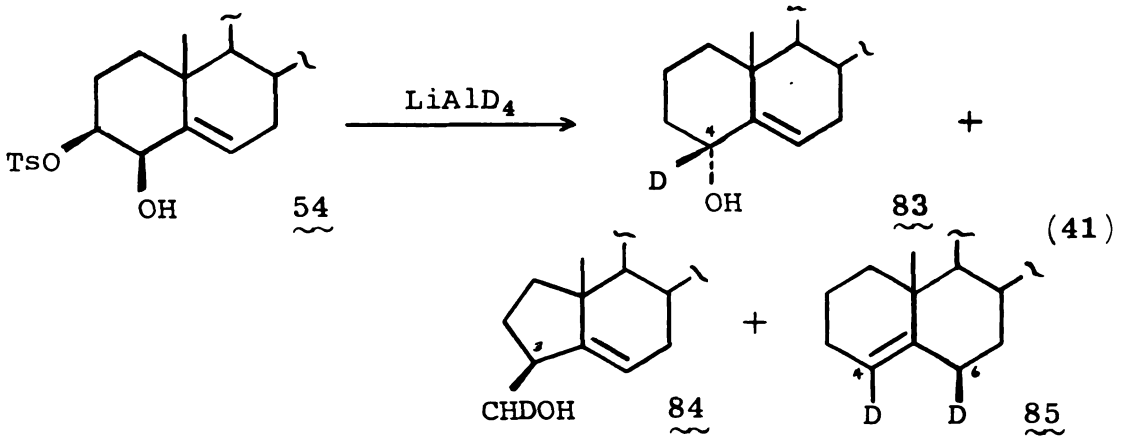
82

If enone 67 is an intermediate in the formation of 62 from 54 it must lead to the α alcohol (62) when reduced with LAH under similar conditions. This reduction of enone 67 afforded 62 in 95% yield, thus confirming reports that enone 67 is reduced by LAH almost exclusively from the β side of the molecule.[59,60]



67 62 (40)

The results of lithium aluminum deuteride (LAD) reduction of tosylate 54 also support the proposed mechanism. The products, obtained in yields comparable to those of the LAH reduction, are shown in equation 41.

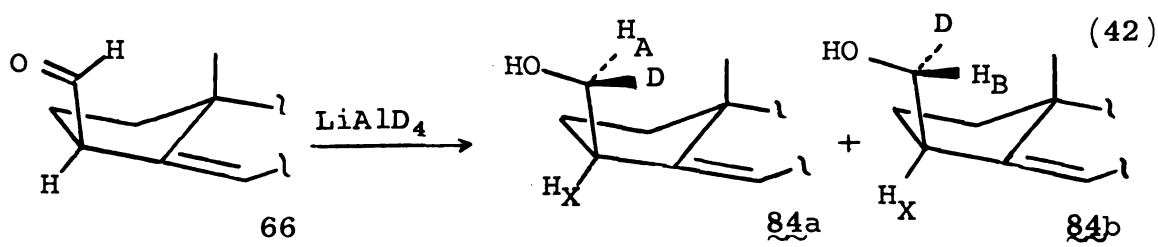


54 83 84 85 (41)

The major product 4β-deuterocholest-5-en-4α-ol (83) was identified by its melting point (141°), and infrared spectrum (2110 cm^{-1}, ν C-D). The incorporation of one deuterium was shown by mass spectrometry. The molecular ion appeared at m/e 387, the largest fragment was at m/e 369 ($M-H_2O$) and a prominent fragment was apparent at m/e 372 ($M-CH_3$) [Figure 24]. The absence of the carbinol hydrogen signal in the nmr spectrum of 83 indicated the deuterium was in the 4β position. This product would result from the LAD reduction of the proposed enone intermediate 67.

The second product, 3β-hydroxydeuteromethyl-A-nor-cholest-5-ene (84), mp 99°, showed C-D stretching in the infrared spectrum at 2140 cm^{-1}. Mass spectrometry showed a molecular ion at m/e 387 indicating a deuterium content of one atom per molecule [Figure 25]. In addition the mass spectrum showed fragments at m/e 372 ($M-CH_3$) and 355 (M-CHDOH). The m/e 355 fragment, which is also present in the corresponding undeuterated alcohol 63, indicates the deuterium is on the carbinol carbon, since it is lost with the hydroxymethylene fragment (CHDOH). The nmr spectrum of 84 shows two doublets at δ 3.56 and 3.62 (J = 7.2 and 7.2 cps) with a combined relative area corresponding to one hydrogen [Figure 20].

Since LAD reduction of the proposed intermediate aldehyde 66 can occur from either side of the carbonyl group, two epimeric alcohols (84a and 84b) should result. The presence of the deuterium changes the magnetic environment of the



66 84a 84b (42)

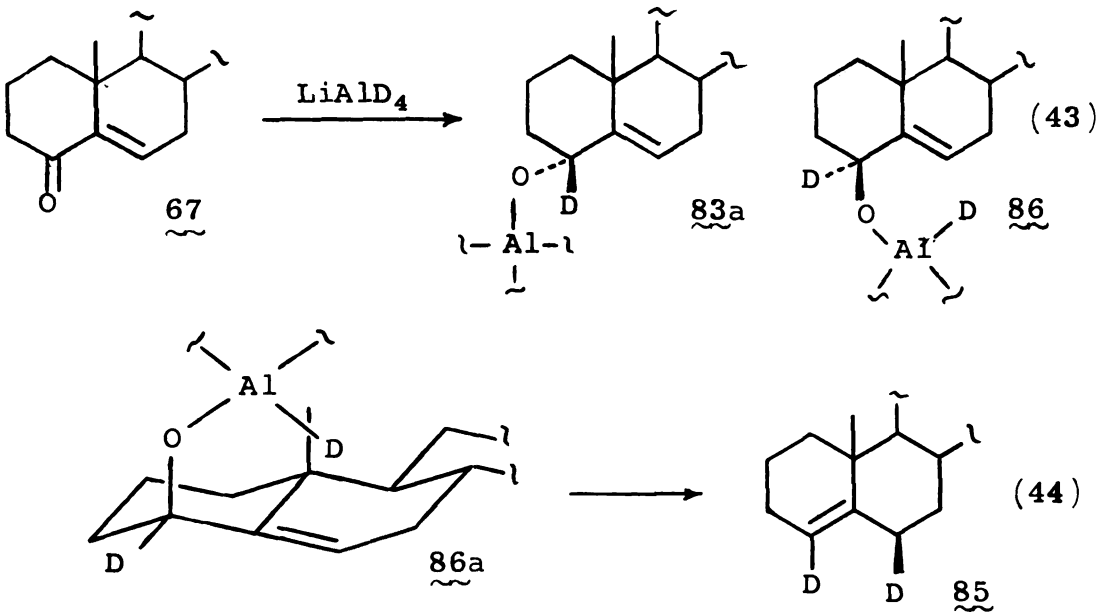
carbinol hydrogen and causes the difference in chemical shifts of hydrogens H_A and H_B to be slightly greater in 84a and 84b than in the corresponding undeuterated alcohol (63). Since the product of the reduction is a mixture

consisting of two epimeric alcohols having carbinol hydrogens with different chemical shifts and each being of the AX type, the resulting signal is two doublets with J = 7.2 cps, one due to epimer 84a (J_{AX}) and the other from 84b (J_{BX}). The doublets are separated by the difference in chemical shifts (3.75 cps) between H_A and H_B. This product is consistent with the proposed intermediacy of aldehyde 66.

The third product, 4,6β-dideuterocholest-4-ene (85), was found to have two deuterium atoms. The mass spectrum revealed a molecular ion at m/e 372 and an $M-CH_3$ fragment at 357 [Figure 26]. Two carbon-deuterium stretching frequencies, at 2220 and 2100 cm^{-1}, were apparent in the infrared spectrum. The nmr spectrum indicated that one of the deuteriums is on carbon 4, since a vinyl hydrogen signal is not present. On the basis of mechanistic considerations the second deuterium is believed to be in the 6β position.

As mentioned previously, LAH reduction of cholest-5-en-4-one (67) gave almost exclusively the 4α-alcohol. If attack of hydride (or deuteride) was predominantly, but not exclusively, from the β side of the molecule some 4β-alkoxide 86 should also be formed in the reduction (equation 43). The 4β-alcohol can actually be isolated from the sodium borohydride reduction of enone 67.[77]

The 4β-aluminumalkoxide (86), since it is axial, is oriented favorably for an allylic rearrangement. The cyclic transition state necessary for this S_Ni' type mechanism[78], illustrated in structure 86a, leads to a compound which has

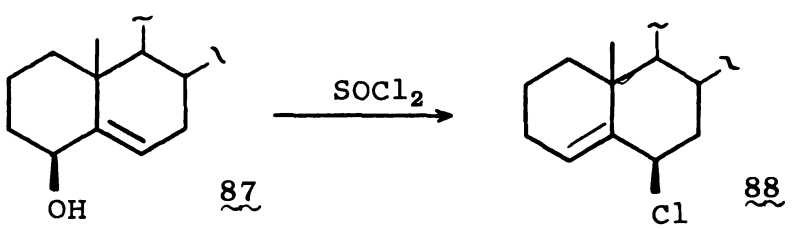


(43)

(44)

the double bond in the observed 4-5 position. In the case of the LAD reduction this mechanism predicts the position of the second deuterium.

A similar allylic rearrangement on the same system has been observed by Young and co-workers.[79] The reaction of thionylchloride with alcohol 87 proceeds exclusively by way of an S_Ni' mechanism, the sole product being 6β-chloro-cholest-4-ene (88).

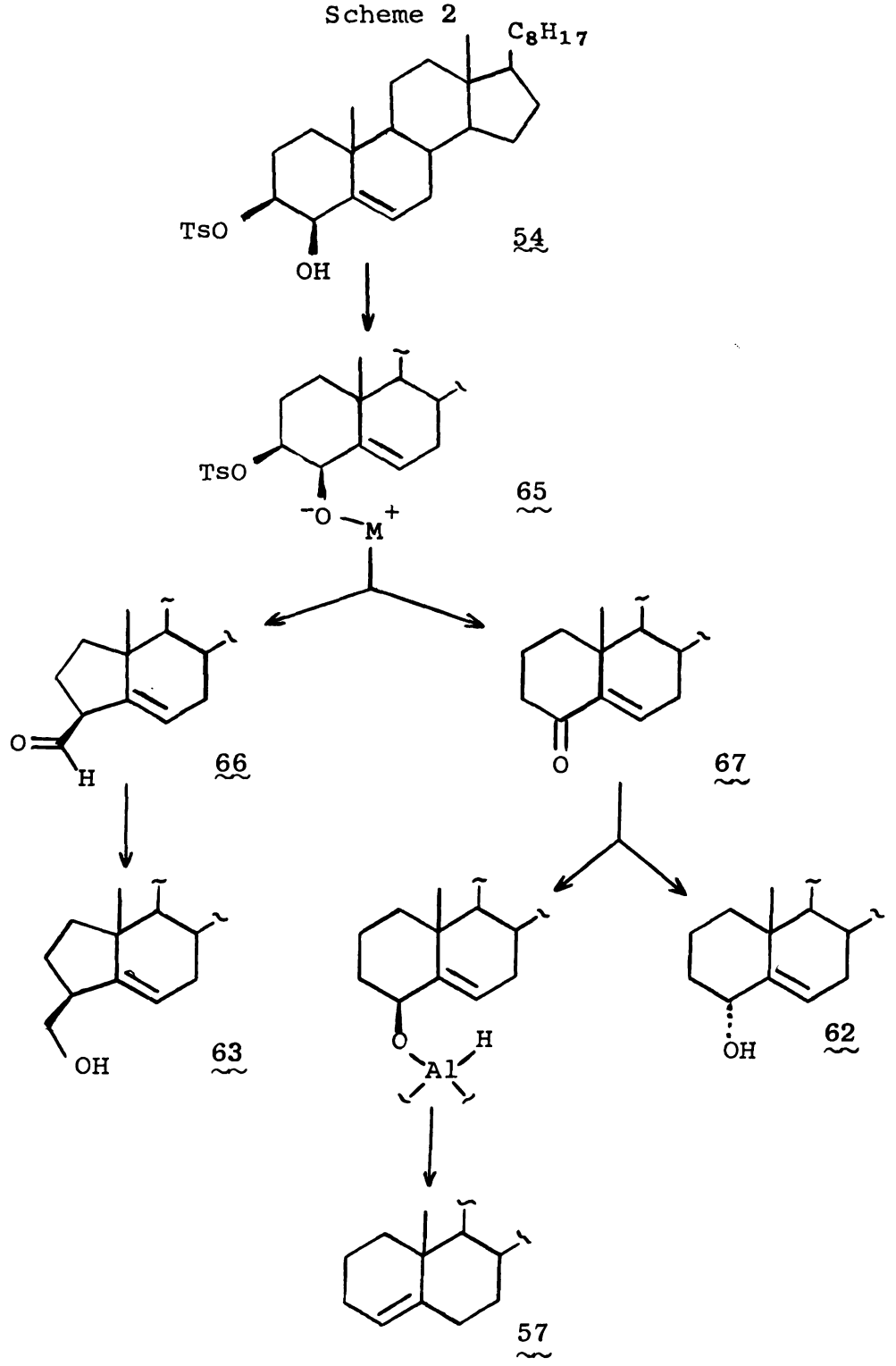


(45)

The proposed mechanism for the formation of cholest-4-ene (57) asserts that enone 67 is a common intermediate for the formation of both olefin 57 and cholest-5-en-4α-ol (62). Lithium aluminum hydride reduction of 67 did not afford any detectable olefin but gave only the 4α-alcohol (62). This may be because the exact conditions under which the tosylate reduction occurs cannot be duplicated in a simple LAH reduction.

The products of the lithium aluminum deuteride reduction and the formation of a proposed intermediate (67), from the reaction of sodium hydride with the starting tosylate (54), clearly substantiate the proposed mechanism. The over-all scheme for the formation of the three products of the lithium aluminum hydride reduction of 54 is shown in Scheme 2.

Scheme 2



EXPERIMENTAL

General. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer, using sodium chloride cells. A Unicam SP. 800 spectrophotometer was used for ultraviolet spectra. Nuclear magnetic resonance spectra were taken on a JEOL Co. C-60H high resolution spectrometer, in deuterochloroform using tetramethylsilane as an internal standard. Mass spectra* were determined on an LKB type 9000 mass spectrometer with an ionizing voltage of 70 eV and an ion source temperature of 230°. Glc inlet was via a 1% SE-30 column at 235°.

Melting points were determined on a Koefler hot stage, and are uncorrected. Specific rotations were obtained on a Perkin-Elmer Model 141 Polarimeter.

Brine refers to an aqueous saturated sodium chloride solution.

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*Mass spectra were obtained thru the courtesy of Dr. C. C. Sweeley, Biochemistry Department, Michigan State University.

3β-p-Toluenesulfonoxycholest-5-en-4β-ol (54). Tosylate 54 was prepared according to the method of Karrer[56]: mp 102-104° (d) [lit[56] mp 111° (d)]; ir ($CHCl_3$) 3580, 2950, 2860, 1175 cm^{-1}; nmr ($CDCl_3$) δ 0.65 (s, 18-CH_3), 0.80 (s, CH_3), 0.90 (s, CH_3), 1.25 (s, 19-CH_3), 2.16 (s, OH), 2.43 (s, Ar-CH_3), 4.24 (m, C-4 H), 4.45 (m, C-3 H), 5.65 (m, C-6 H), 7.6 (AB-q, Ar-H); one spot on tlc (silica gel G, $CHCl_3$).

Lithium Aluminum Hydride Reduction of 3β-p-Toluenesulfonoxycholest-5-en-4β-ol (54). To a flask equipped with reflux condenser and a magnetic stirrer, and containing 1.2 g (31 mM) of lithium aluminum hydride (Ventron) in 200 ml of anhydrous ether, 10.0 g (17.9 mM) of 54 in 100 ml of dry benzene was added in portions. The mixture was stirred for 1 hr at room temperature and then heated at reflux temperature for 20 hrs. The mixture was cooled and 6.1 ml of ethyl acetate was added followed by slow dropwise addition of water until a precipitate formed. After stirring overnight the mixture was filtered and the filter cake washed with ether. The filtrate was washed twice with water, once with 5% sodium bicarbonate and once with brine, then dried over sodium sulfate. Evaporation of the solvent gave 6.6 g of crude product.

Crystallization of the crude product from benzene afforded a crystalline material of mp 123-124°, $[\alpha]_D^{25}$ -38.6° (c 0.5, $CHCl_3$); tlc (silica gel G, $CHCl_3$) one spot, R_f 0.36. Recrystallization from acetone-hexane did not change the melting point.

Ascending Dry Column (ADC) Chromatography of the LAH Reduction Product. ADC chromatography is a modification of methods described by Loev and Goodman,[80] and Dev, et al.[81] A 0.5 g portion of the crude product, which had been pre-absorbed on 2.5 g of alumina, was added to the top of 110 g neutral alumina (Woelm, activity II, Brockman scale) which had been dry packed in a 2.5 x 45 cm glass column. An additional 2.5 g of alumina was placed on top of the pre-adsorbed sample and the empty portion of the column was filled with cotton. The column was inverted into anhydrous ether and allowed to develop by the ascending solvent. The solvent front was kept just above the level of the solvent outside the column to insure a fairly slow development by capillary action. When the solvent had reached the top of the alumina packing, the column was righted and after removal of the cotton, was eluted with anhydrous ether in a normal fashion. Collection of 20 ml fractions gave the results shown in Table 2.

Table 2. ADC chromatography of the LAH reduction product.

Fract.	Wt. (mp) mg	Fract.	Wt. (mp) mg	Fract.	Wt. (mp) mg
1.	48	5.	8	10.	4
2.	2	6.	13	11.	1
3.	90 (142^0)	7.	53 (99^0)	12.	1
4.	160 (142^0)	8.	63 (99^0)	13.	0
		9.	55 (99^0)	Total	498 mg

Compound A. Recrystallization of fractions 3 and 4 (250 mg, 48% yield) from hexane gave cholest-5-en-4α-ol (62): mp 141-142° $[\alpha]_D^{25}$ -53° (c 0.45, $CHCl_3$); [lit[59,60] mp 144°, 143°, $[\alpha]_D^{17.5}$ -55.0 (c 1.49, $CHCl_3$), $[\alpha]_D$ -54° (c 1.0, $CHCl_3$)]; R_f 0.43 (neutral alumina act. II, ether); ir ($CHCl_3$) 3600, 2940, 2860, 1470, 1375, and 1070 cm^{-1} [Figure 10]; nmr ($CDCl_3$) δ 0.68 (s, 18-CH_3), 0.80 (s, CH_3), 0.91 (s, CH_3), 0.98 (s, 19-CH_3), 1.05-2.5 (methylene envelope) 2.05 (s, O-H), 4.25 (m, 1H, line width 21 cps, CH-OH), 5.8 (m, 1H, vinyl H) [Figure 13]; mass spectrum (70 eV, direct probe, ion source 230°) m/e (rel intensity) 388 (1.4), 387 (8.4), 386 (27), 371 (22), 368 (100), 353 (20), [Figure 21].

Compound B. Recrystallization of fractions 7-10 (175 mg, 33% yield) from methanol gave 3β-hydroxymethyl-A-nor-cholest-5-ene (63): mp 99°; $[\alpha]_D^{25}$ -24.4° (c 0.5, $CHCl_3$), [lit[65] mp 99-101°; $[\alpha]_D$ -26° (c 1.56, $CHCl_3$)]; R_f 0.32 (neutral alumina act. II, ether); ir ($CHCl_3$) 3600, 2950, 2860, 1465, 1380, and 1020 cm^{-1} [Figure 11]; nmr ($CDCl_3$) δ 0.70 (s, 18-CH_3), 0.82 (s, CH_3), 0.90 (s, 2CH_3), 1.0-2.4 (methylene envelope) 2.05 (s, OH), 2.7 (m, 1H, C-3 H), 3.62 (d, 2H, J = 7.2 cps, carbinol-H), 5.5 (m, 1H, vinyl H) [Figures 14 and 19]; mass spectrum (70 eV, direct probe, ion source 230°) m/e (rel intensity) 389 (5), 387 (30), 388 (100), 372 (9), 371 (30), 355 (45), [Figure 22].

Compound C. Preparative thin layer chromatography of ADC chromatography fraction 1 (48 mg) on one 20 × 20 cm glass plate with a 1.5 mm layer of silica gel PF_{254}, using hexane as the developing solvent, showed a band of R_f 0.80. Elution of this band with ether and crystallization from acetone gave 15 mg (3% yield) of cholest-4-ene (57): mp 80-81°; $[\alpha]_D^{27}$ +67° (c 0.6, $CHCl_3$), [lit[61] mp 81°, $[\alpha]_D^{18}$ +67° ($CHCl_3$)]; ir ($CHCl_3$) 2940, 2860, 1470, and 1375 cm^{-1} [Figure 12]; nmr ($CDCl_3$) δ 0.67 (s, 18-CH_3), 0.80 (s, CH_3), 0.90 (s, CH_3), 1.00 (s, 19-CH_3), 1.05-2.4 (methylene envelope), 5.25 (m, vinyl-H) [Figure 15]; mass spectrum (70 eV, glc inlet, ion source 230°) m/e (rel intensity) 372 (4.6), 371 (30), 370 (100), 355 (25) [Figure 23].

Lithium Aluminum Deuteride Reduction of 3β-p-Toluenesulfonoxycholest-5-en-4β-ol (54). The same procedure and work-up used in the lithium aluminum hydride reduction was employed for the lithium aluminum deuteride reduction of 54. Separation by ADC chromatography afforded the three products in yields similar to those obtained in the lithium aluminum hydride reduction of 54.

A) 4β-Deuterocholest-5-en-4α-ol (83): mp 141-142° (from hexane); ir ($CHCl_3$) 2110 cm^{-1} (C-D); nmr ($CDCl_3$) identical with nmr spectrum of 62 except for the absence of the δ 4.25 (CH-OH) signal [Figure 16]; mass spectrum (70 eV, direct probe, ion source 230°) m/e (rel intensity) 398 (4), 388 (22), 387 (72), 372 (42), 369 (100), 354 (23), [Figure 24].

B) 3β-Hydroxydeuteromethyl-A-norcholest-5-ene (84): mp 99° (from methanol); ir ($CHCl_3$) 2140 cm^{-1} (C-D); nmr ($CDCl_3$) two doublets at δ 3.56 and 3.62 (combined area 1 H, J = 7.2 and 7.2 cps) [Figures 17 and 20]; mass spectrum (70 eV, direct probe, ion source 230°) m/e (rel intensity) 389 (5), 388 (30), 387 (100), 373 (9), 372 (30), 355 (50), [Figure 25].

C) 4,6β-Dideuterocholest-4-ene (85): mp 99° (from acetone); ir ($CHCl_3$) 2220, 2100 cm^{-1} (C-D); nmr ($CDCl_3$) vinyl hydrogen signal present in the nmr spectrum of 57 at δ 5.25 is absent in the spectrum of 85 [Figure 18]; mass spectrum (70 eV, glc inlet, ion source 230°) m/e (rel intensity) 374 (5), 373 (31), 372 (100), 357 (31), [Figure 26].

Jones Oxidation of Cholest-5-en-4α-ol (62). Jones reagent[75] (8N, 0.85 ml) was added dropwise to a solution of 1.125 g (2.92 mM) of alcohol (62) in 100 ml of acetone at 20°. The solution was allowed to warm to room temperature and then diluted with an equal volume of water. This solution was extracted with ether and the ether extract was washed with water (2×), a saturated sodium bicarbonate solution, and with brine. Evaporation of the solvent and crystallization from acetone gave 0.9 g (81%) of pure cholest-5-en-4-one (67): mp 111-112°; uv max (EtOH) 241 mμ (ε 6,000), [lit[74] mp 111-112°, uv max (EtOH) 241 mμ (ε 7,200)]; ir ($CHCl_3$) 1675 and 1620 cm^{-1}.

Reaction of Sodium Hydride with 3β-p-Toluenesulfonoxy-cholest-5-en-4α-ol (54). To a stirred solution of 500 mg (0.9 mM) of tosylate 54 in 25 ml of tetrahydrofuran (THF) under a nitrogen atomosphere, 41.0 g (0.9 mM) of sodium hydride on mineral oil (52.8% NaH) was added in small portions. The mixture was heated at reflux for 3 hrs, cooled, and one equivalent of water was added dropwise. The resulting solution was filtered and evaporated to dryness at reduced pressure. The brown residue which resulted was dissolved in ether and the ether solution was washed with water (2×), 5% sodium bicarbonate, and brine, then dried over sodium sulfate. Evaporation of the solvent gave 0.45 g of crude product. Column chromatography on 20 g of silica gel (E. Merk), starting the elution with benzene and progressing to methylene chloride, afforded 165 mg (48%) of cholest-5-en—4-one (67): mp 111-112° (from acetone); ir ($CHCl_3$) identical with infrared spectrum of 67 obtained from Jones oxidation of cholest-5-en—4α-ol (62).

Lithium Aluminum Hydride Reduction of Cholest-5-en—4-one (67). To a slurry of 380 mg (10 mM) of lithium aluminum hydride in 5.8 ml of refluxing anhydrous ether, 200 mg (0.52 mM) of ketone 67 in 3.0 ml of dry benzene was added in three portions. The resulting slurry was heated at reflux for 24 hrs. The usual work-up gave a crude product that tlc indicated contained cholest-5-en—4α-ol (62) but no cholest-4-ene (57). Crystallization of the crude product

from hexane gave 190 mg (95%) of 62: mp 140-141°; ir ($CHCl_3$) identical with known 62.

FIGURES

Figure 1

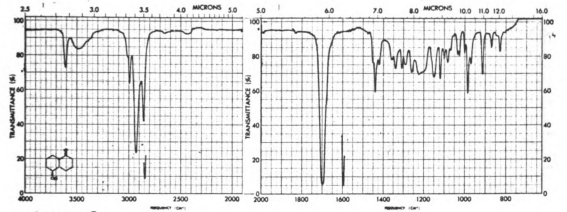
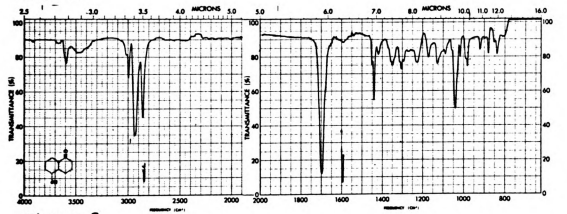


Figure 2



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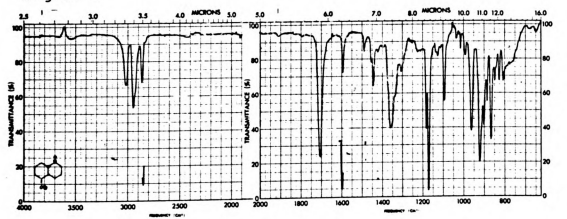

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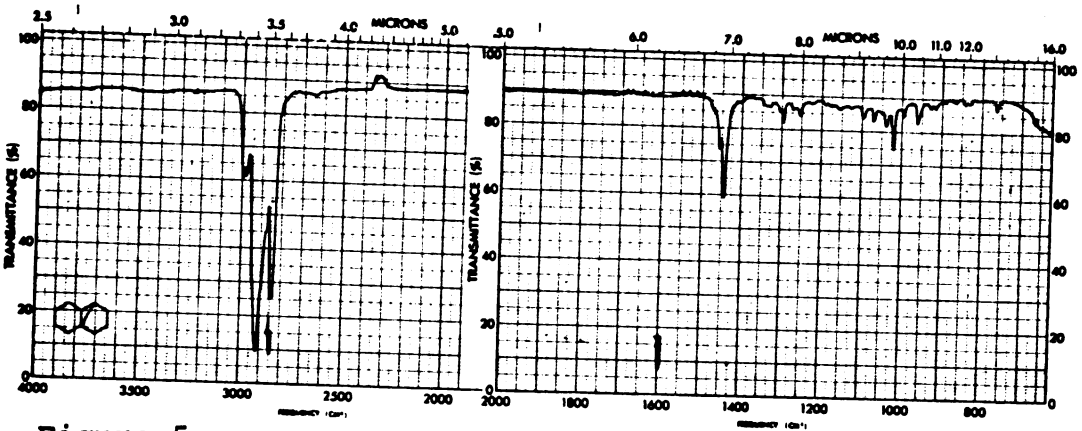

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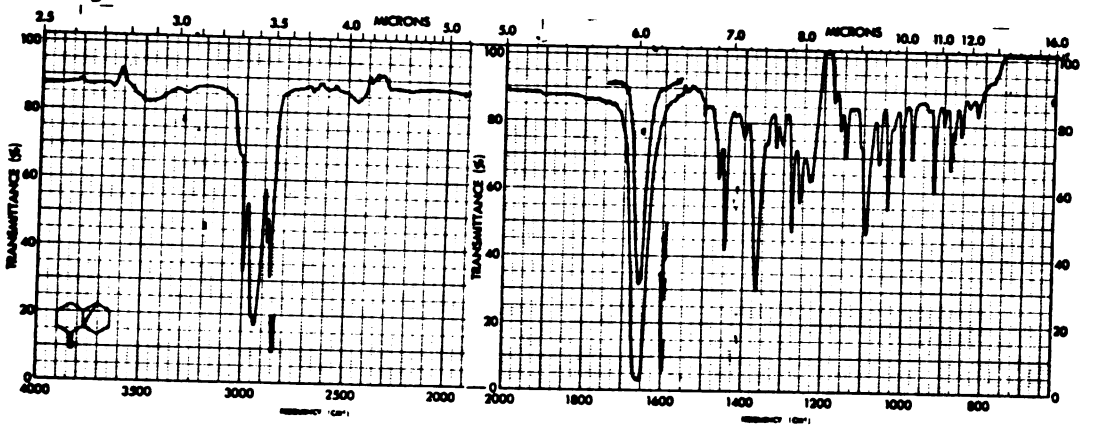

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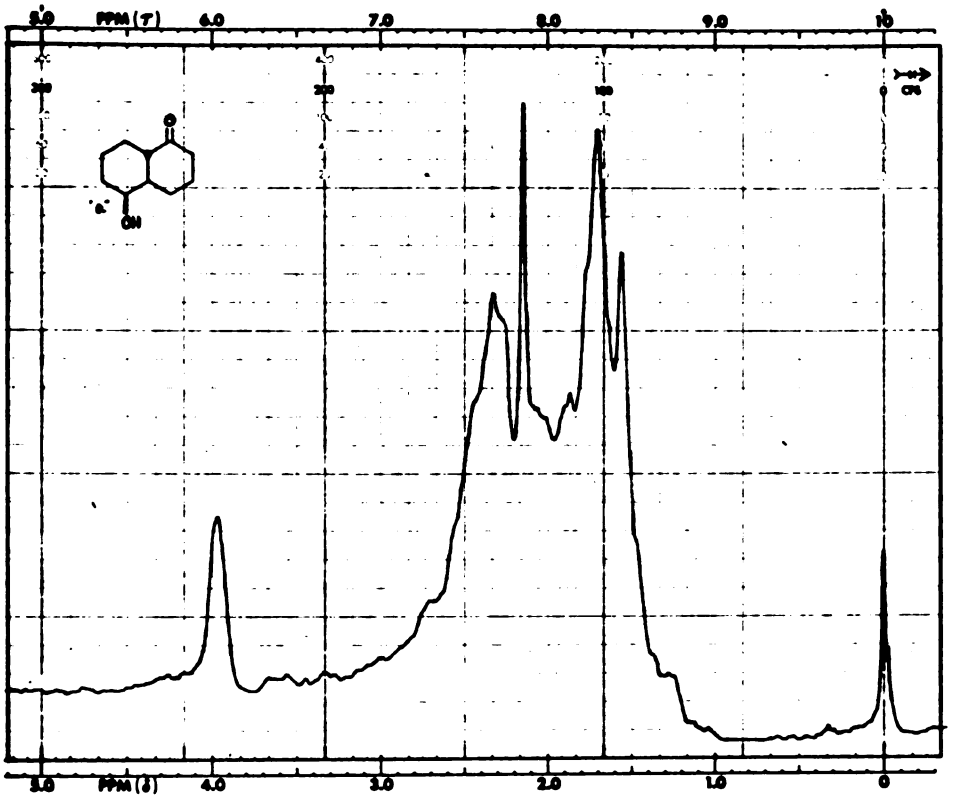

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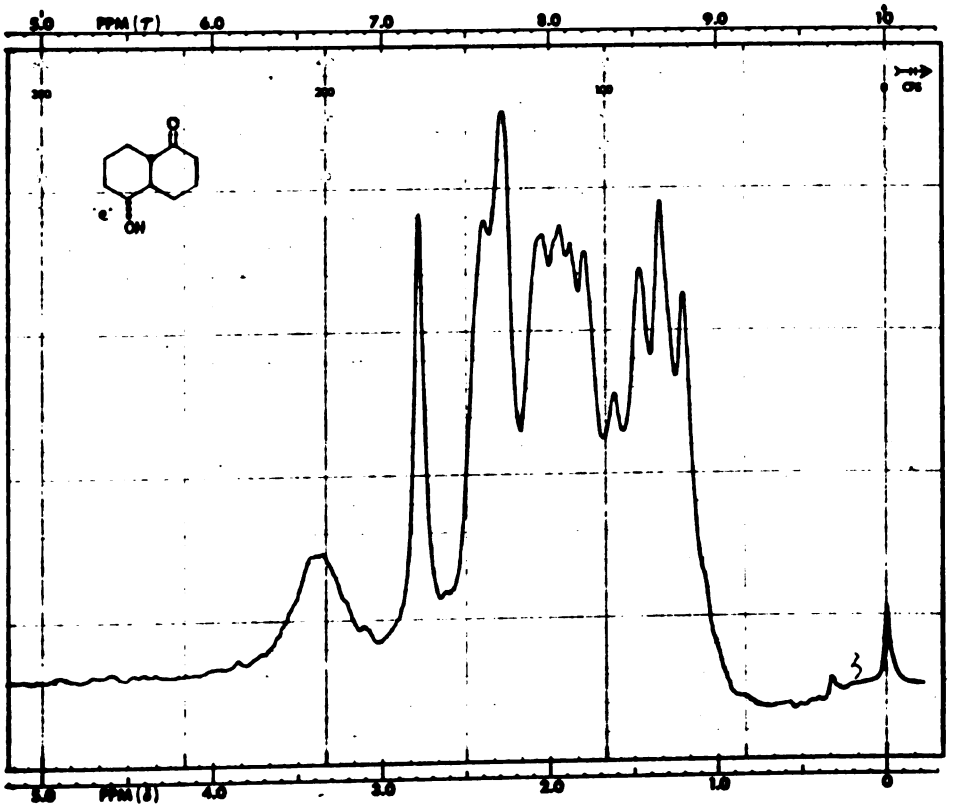

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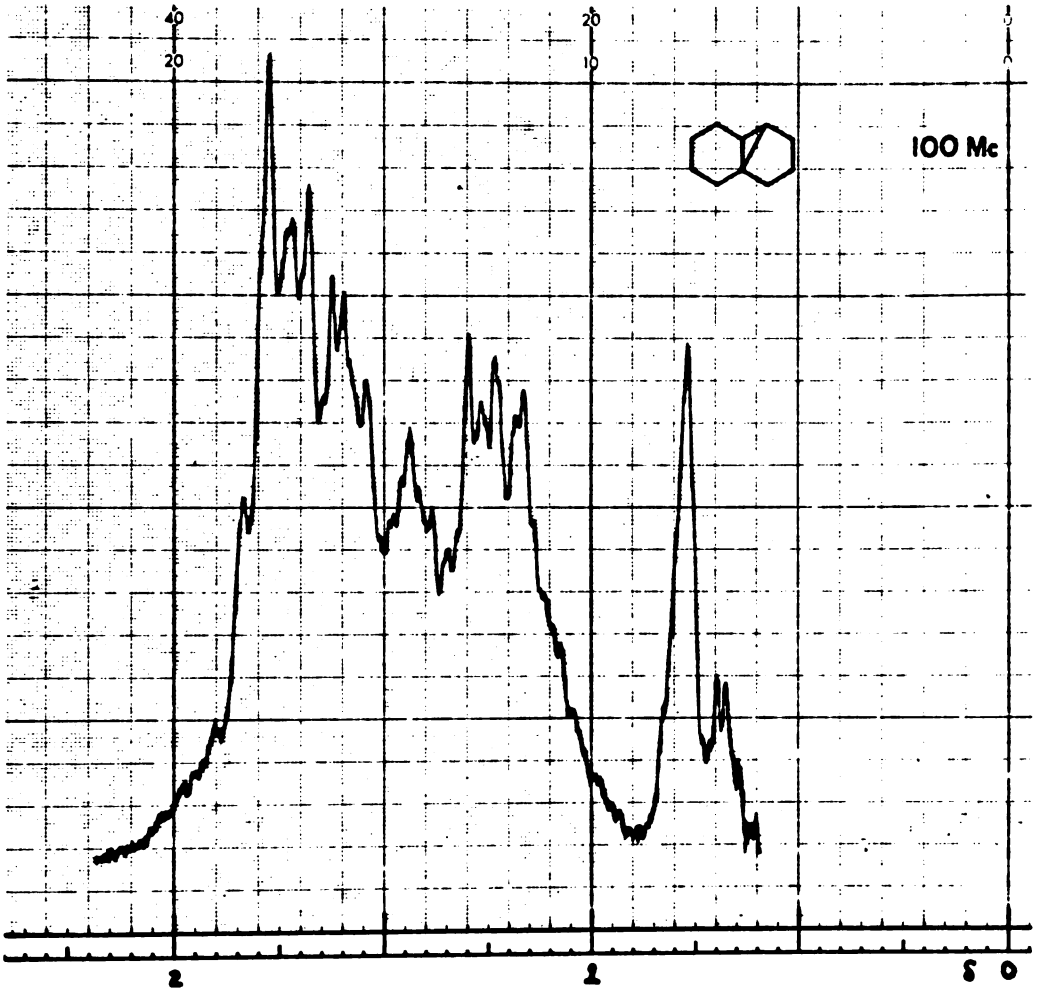

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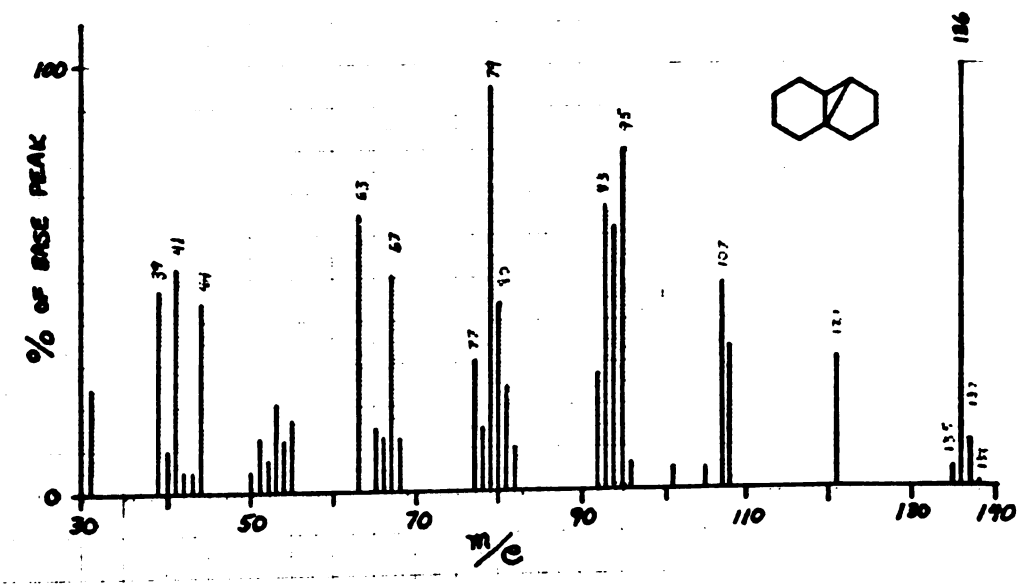
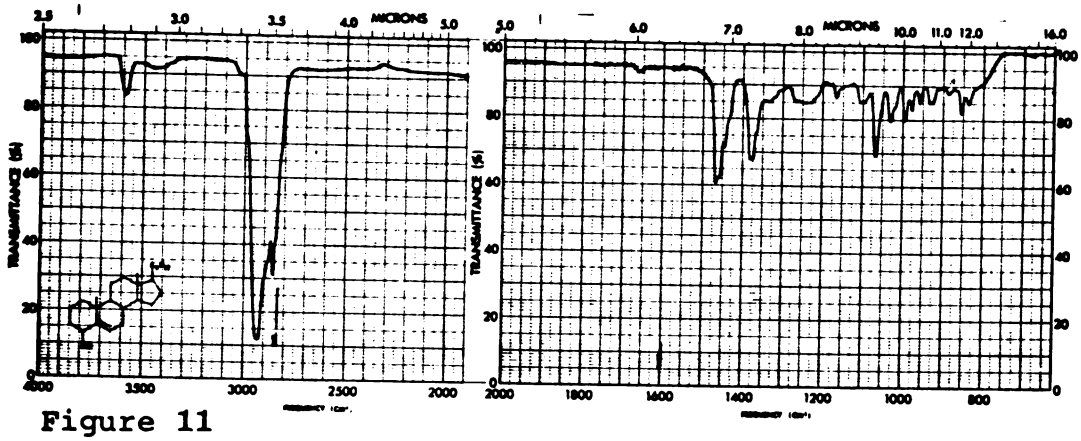


Figure 10



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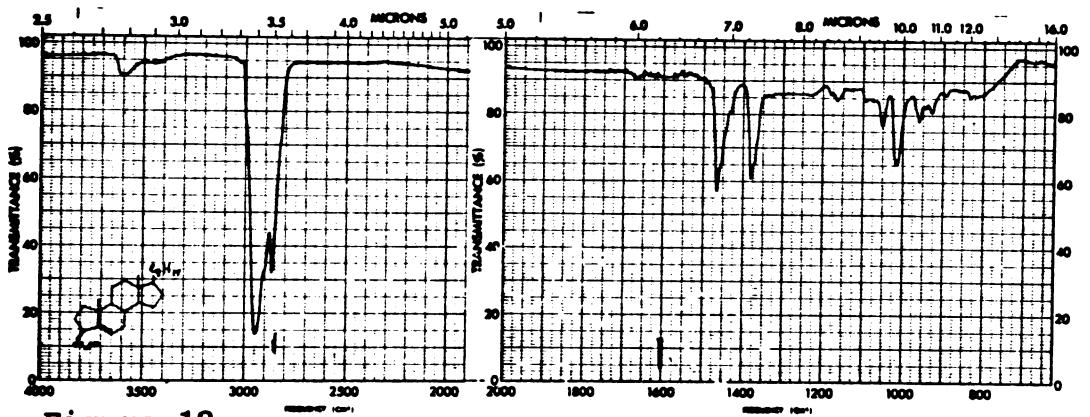

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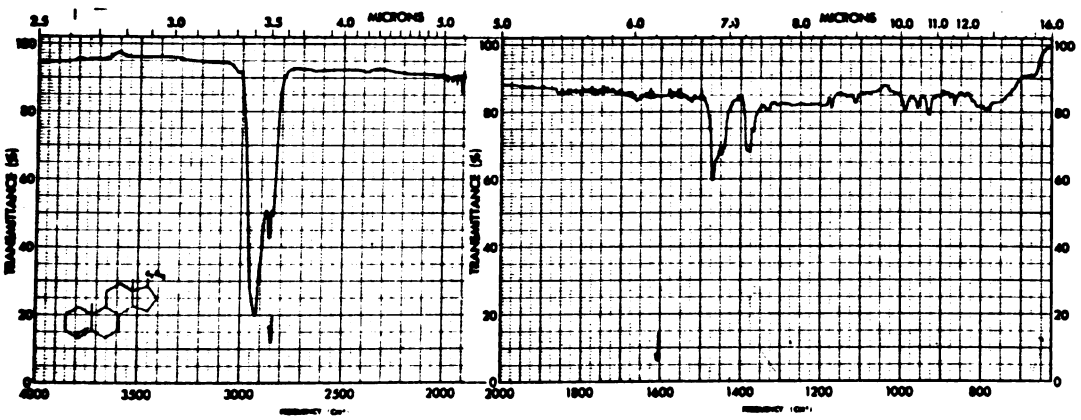
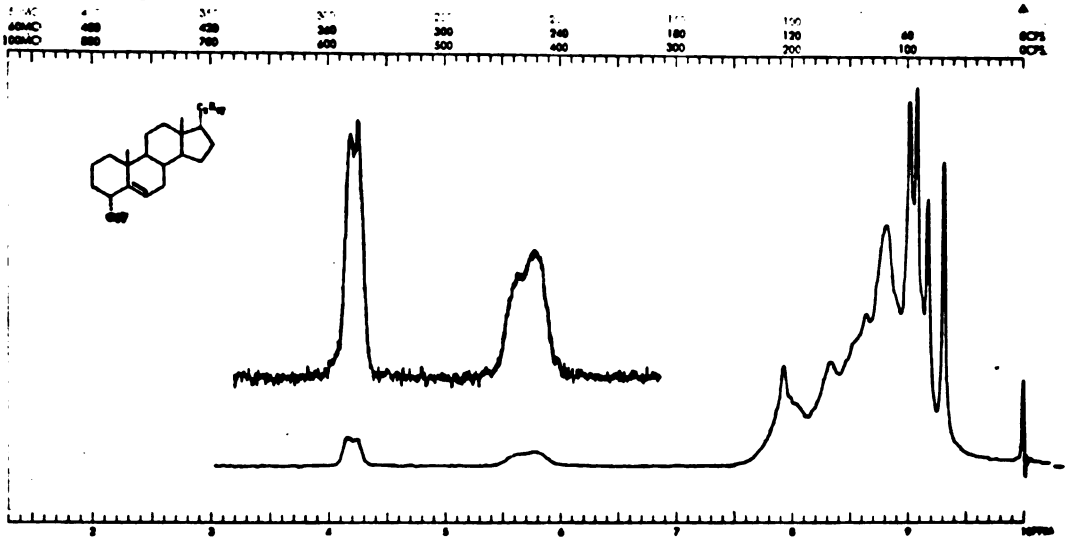


Figure 13



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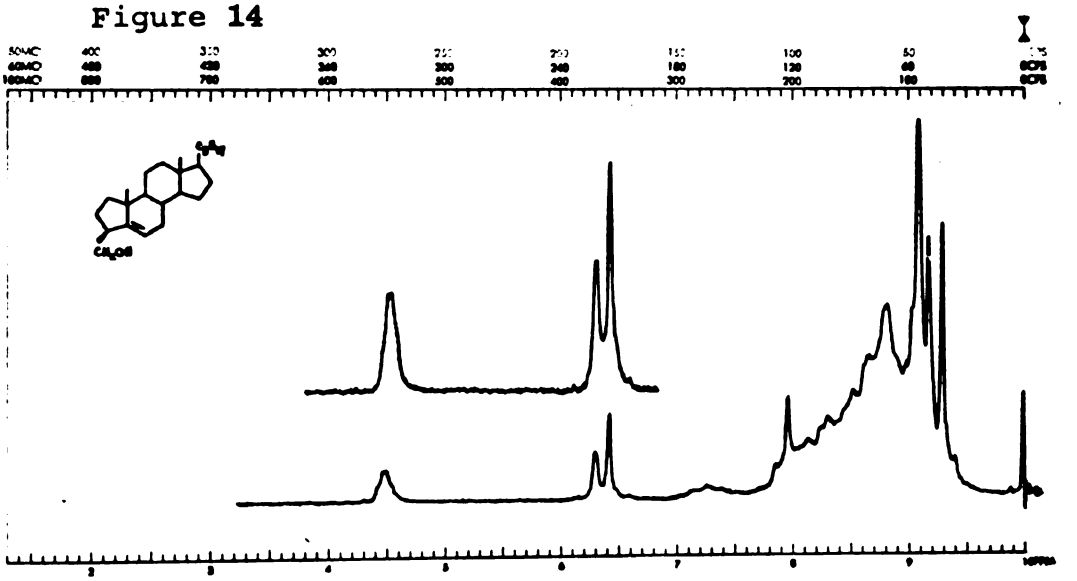

Figure 15

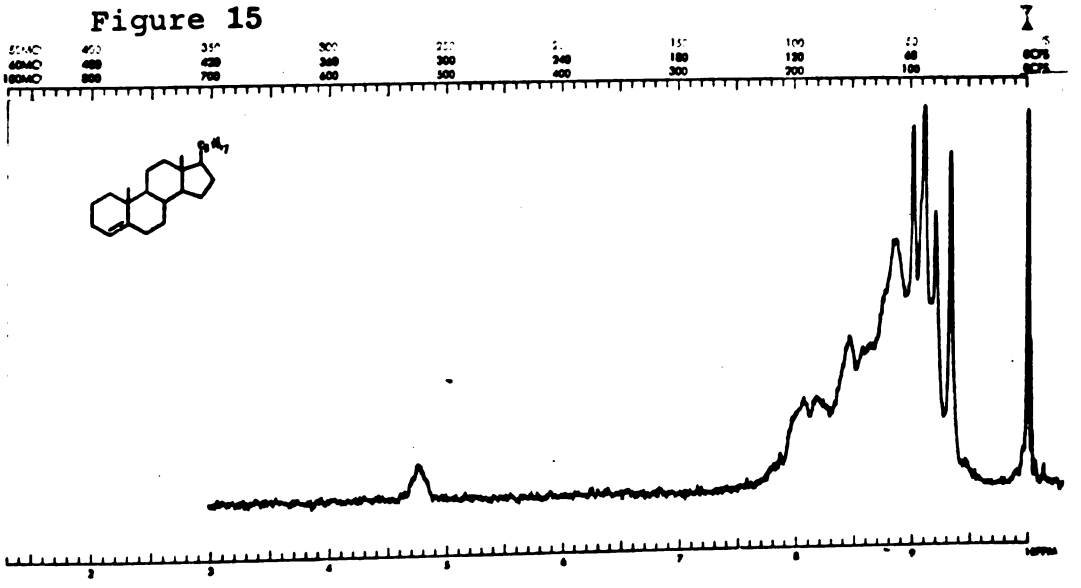

Figure 16

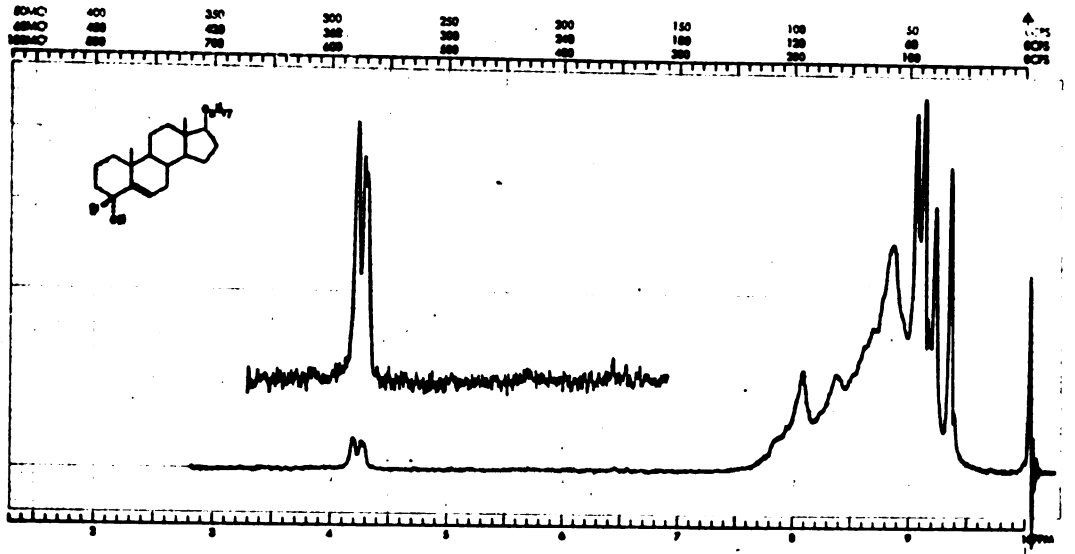

Figure 17

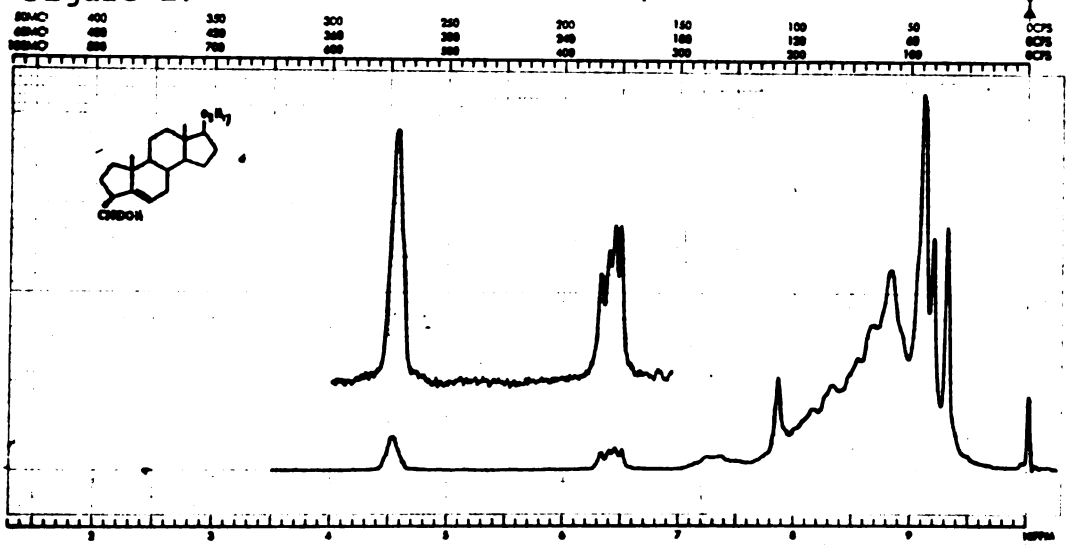

Figure 18

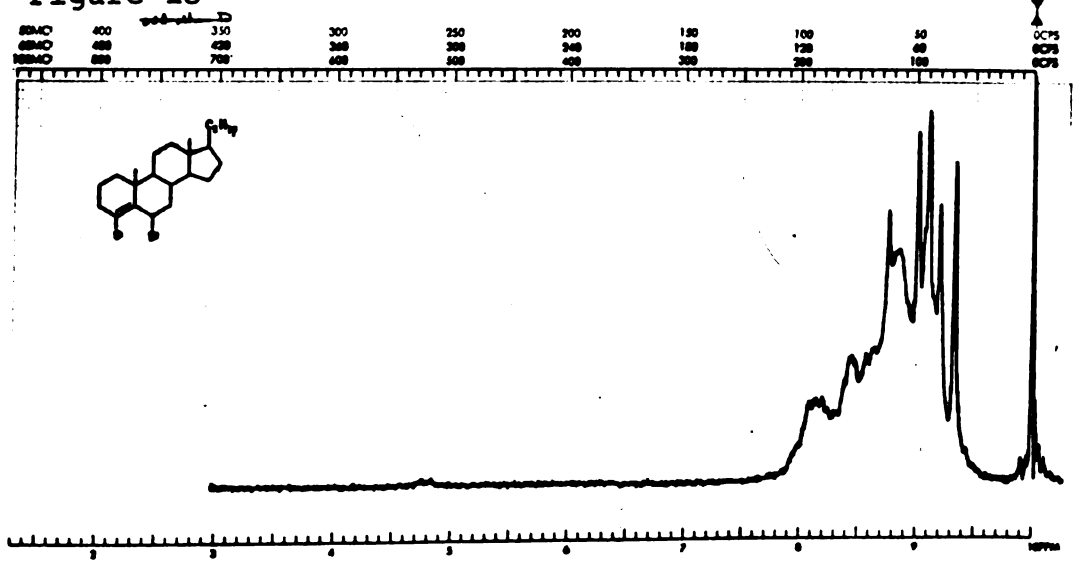

Figure 19

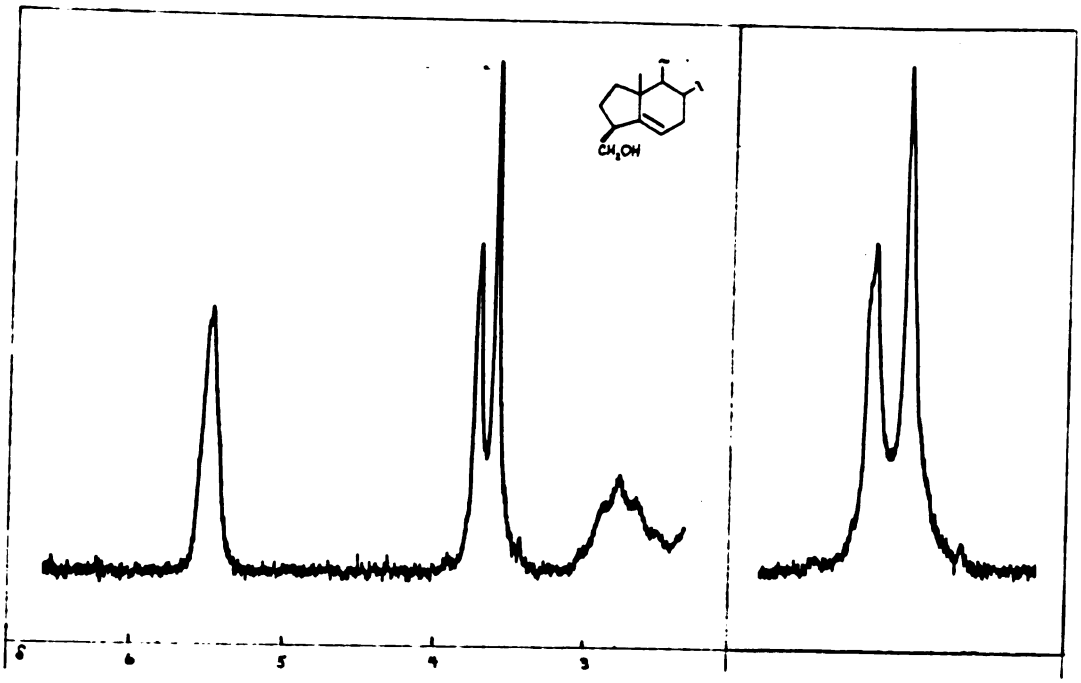

Figure 20

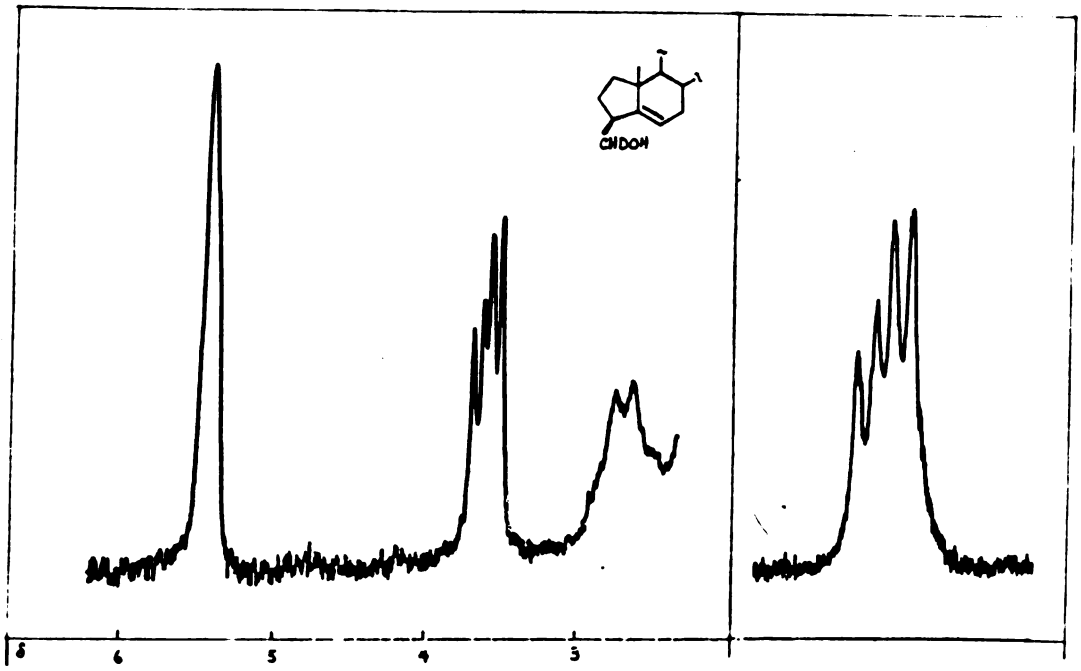

FIGURE 21

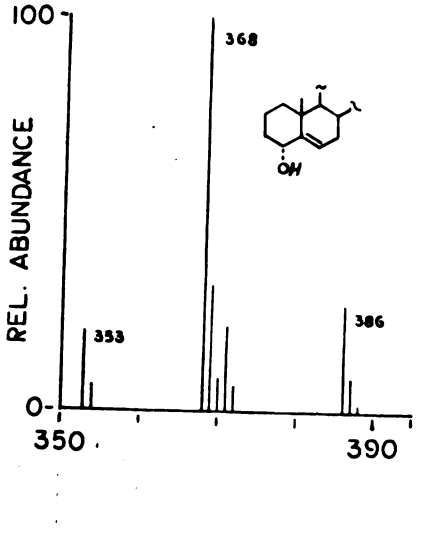

FIGURE 22

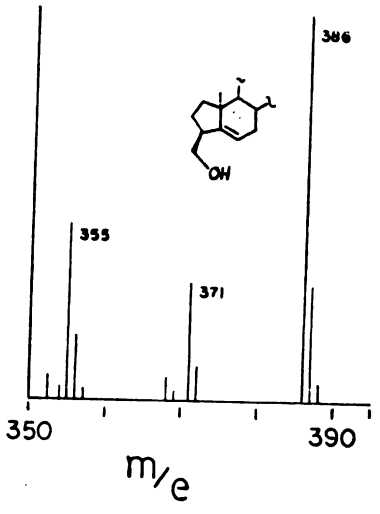

FIGURE 23

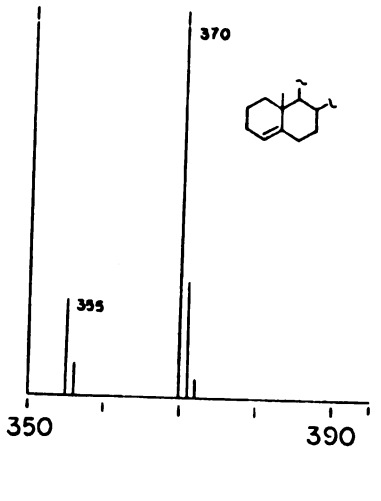

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FIGURE 24

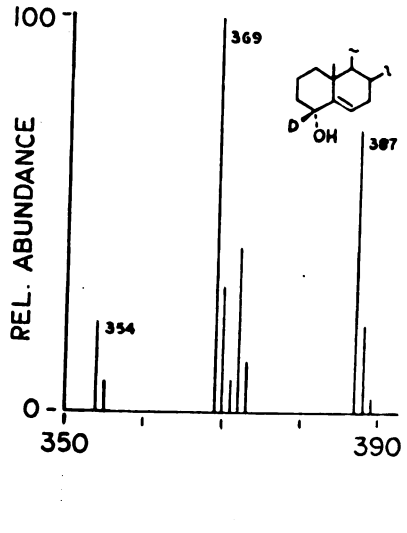


FIGURE 25

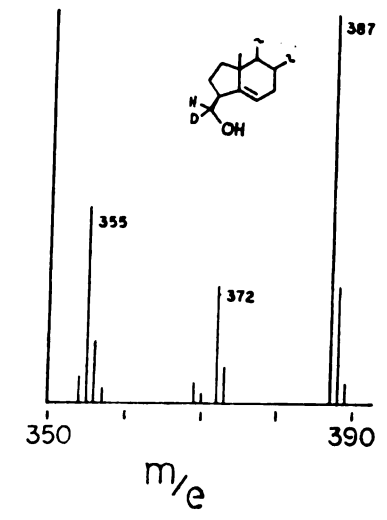
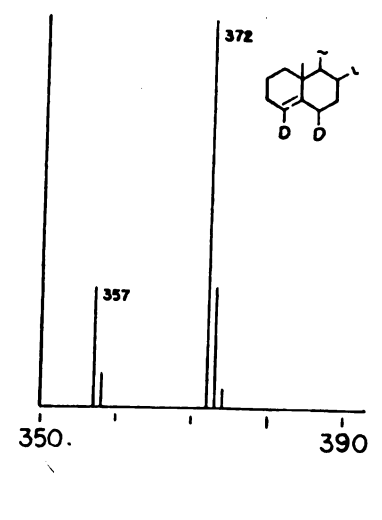


FIGURE 26



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