THE SYNTHESIS OF 1α,3α,7α-CHOLESTA-4-ENE-TRIOL

By

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ABSTRACT

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An approach to the synthesis of cholesta-5-ene-1,7-dione (1) has been devised and successfully implemented to the key intermediate 1α,3α,7α-cholesta-4-ene-triol (2). Thus reduction of either 1α,2α,6α,7α-diepoxy-cholesta-4-ene-3-one (3) or 3α-acetoxy-1α,2α,6α,7α-diepoxy-cholesta-4-ene (4) with lithium aluminum hydride gave 2.

Compound 3 was prepared from cholesterol in threee steps either by peracid epoxidation or autoxidation of 1α,2α-epoxy-cholesta-4,6-diene-3-one. Although the desired functionality and stereochemistry was achieved, the yields were low. To get around this difficulty, the deactivating carbonyl group was removed by reduction with sodium borohydride, and the resulting hydroxyl function protected by acetylation.

Through this modification, compound 4 was readily propared in good yield by epoxidation with m-chloroperbenzoic acid. The stereochemical assignments made here were confirmed by high resolution pmr spectrometry.

DEDICATION

To My Parents

ACKNOWLEDGMENTS

I would like to express my sincere appreciation to my advisor, Professor William H. Reusch, for his patient guidance, assistance and encouragement throughout my research.

I would also like to thank Professors E. LeGoff, A. Timnick and M. Rogers for serving on my committee.

Appreciation is also extended to my colleagues for stimulating and informative discussions and their friendship.

I also want to express my appreciation to my sister, Yue-Mei Lin whose love and understanding over the years have made this opportunity possible.

Finally, I wish to express my deepest appreciation to my husband, Biau-Hung, for his love, inspiration and understanding.

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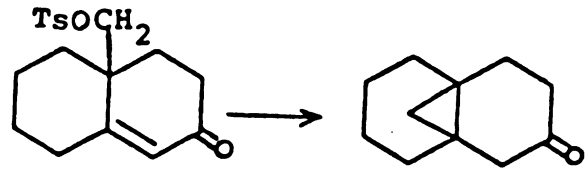
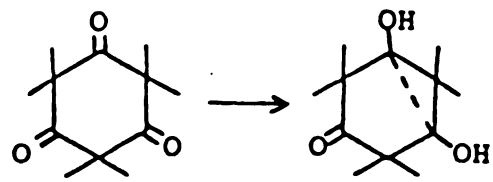
INTRODUCTION

Reductions of unsaturated carbonyl compounds by alkali metals in ammonia solutions generates reactive nucleophilic intermediates which are capable of intra- and inter-molecular attack on electrophilec functions.[1-3] This course of reaction was first observed during lithium in ammonia reduction of 10-hydroxymethyl-$\Delta^{1,9}$,2-octalone tosylate 1 by Stork and co-workers.[2]



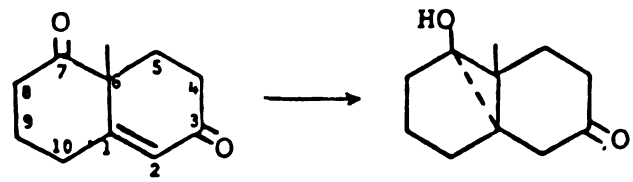
1 2

It is now recognized that cyclopropane ring formation during dissolving metal reductions of bi- and polyfunctional compounds is probably a general phenomenon. In fact, even relatively reactive compounds such as cyclopropanols[3] have been prepared by this kind of transformation. Thus reduction of 2,2,4,4,6,6-hexamethyl cyclohexane-1,3,5-trione 3 with lithium in liquid ammonia produced the corresponding cyclopropanediol 4.[4]



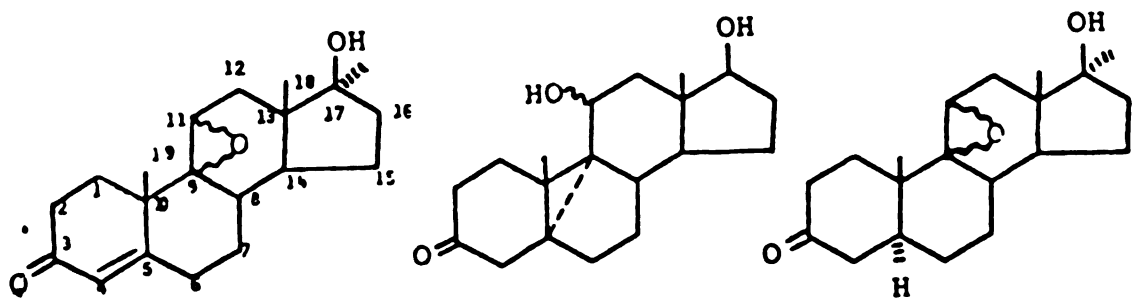
3 4

In an extension of this transformation to vinylogs of 1,3-diketones, Wieland-Miescher ketone 5 was found to give the versatile cyclopropanol 6[5] during lithium and ammonia reduction.



5 6

Eight alkyl-substituted derivatives of Wieland-Miescher ketone 5 were prepared and subjected to lithium in ammonia reduction with similar results.[6] The steroids 9,11α- and β-oxido-17-methyl testosterones 7a and 7b did not yield the expected products 8a and 8b upon lithium in ammonia reduction, but gave only the saturated compounds 9a and 9b.[7]

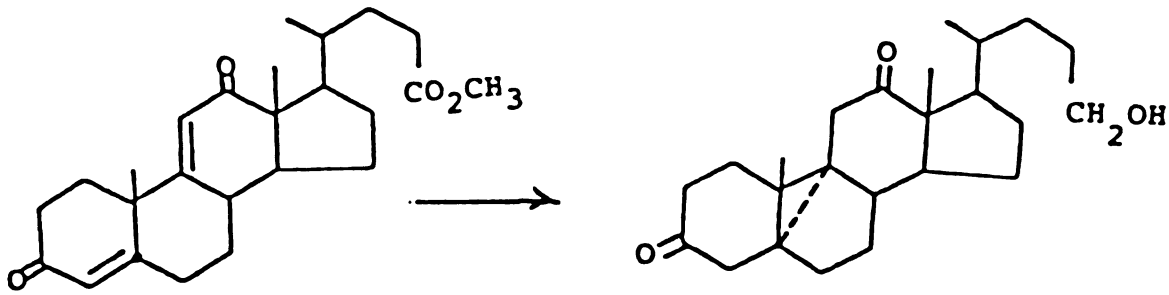


7 8 9

a = α

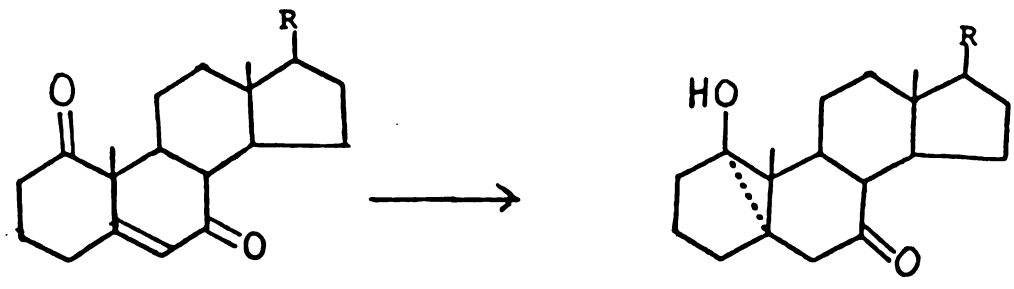
b = β

However, methyl 3,12-diketo-$\Delta^{4,9(11)}$-choladienate 10 did produce the expected cyclopropane 11.[8]



10 11

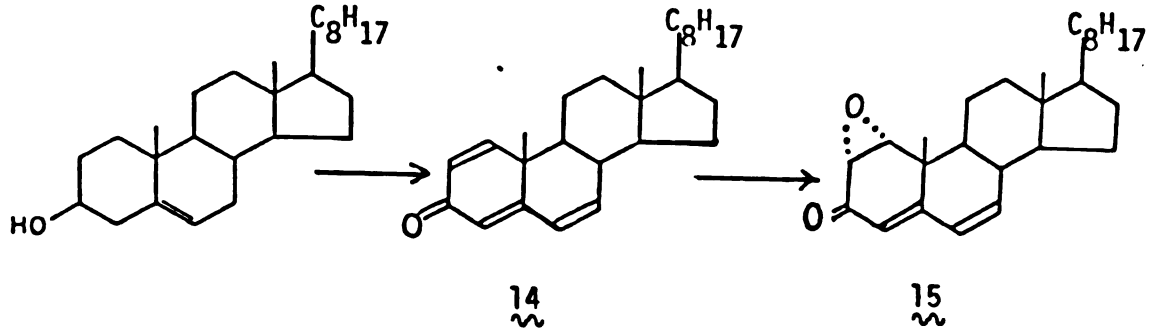
To extend the cyclopropanol findings to steroids, a preparation of steroid 12 (cholestane series) was needed. Reduction of 12 with lithium in ammonia should yield cyclopropane 13. Since no steroid having the functionality shown in formula 12 has been reported in the literature, a major part of this thesis is devoted to work leading to the synthesis of steroid 12.



12 13

Cholesterol is an enexpensive and promising starting material for the synthesis of homoconjugated enedione 12. 1α,2α-Epoxycholesta-4,6-dien-3-one 15 was synthesized by E. Glotter[9] et al by DDQ (2,3-dicyano-5,6-dichlorobenzoquinone) dehydrogenation of cholesterol, followed by alkaline epoxydation (Equation 1). To provide the required 7-carbonyl function, epoxydation at positions 6 and 7 has been examined and is described in this thesis.

(1)

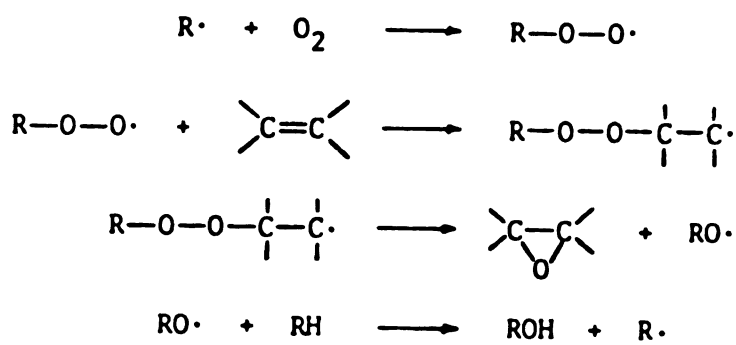


14 15

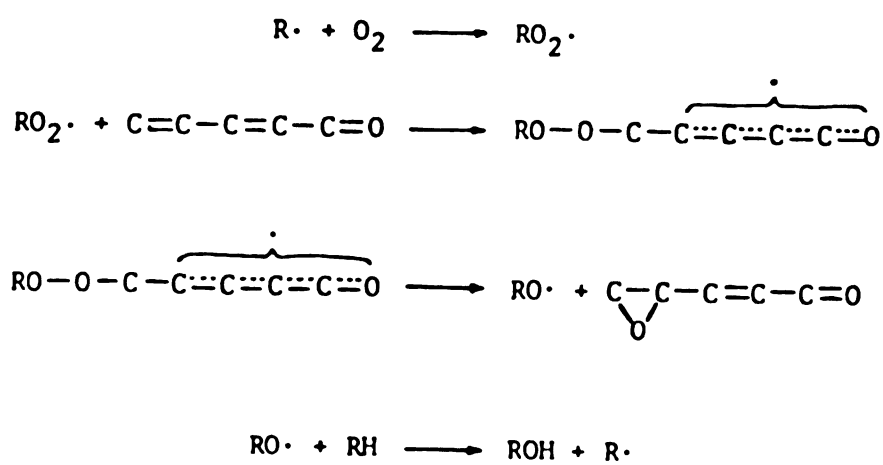
Preparation of γ,δ-epoxyenones from conjugated dienones can be carried out by a number of methods, the most frequently employed and generally applicable of which is peracid oxidation.[10] The most common peracids used to convert dienones to epoxides are perbenzoic acid,[11] monoperphthalic acid[12] and m-chloroperbenzoic acid.[13] The latter is convenient to use, since it is commercially available and reacts at a somewhat faster rate than perbenzoic acid.

Peracid epoxidation reactions proceed by an electrophilic attack upon the double bond, thus the rate of epoxidation is very sensitive to the electron density at the olefinic site.[10] The preferential epoxidation of the γ,δ-double bond over the α,β-double bond in conjugated dienones reflects this characteristic.

In addition to peracid epoxidation, other less general methods are available.[14] Among these is the autoxidation of olefins.[15] This autoxidation process is not well understood but probably involves a free radical mechanism of the following type:[16]



In 1974, H. Hart et al described a synthetically useful epoxidation with molecular oxygen.[17] Conjugated dienones and diene esters are epoxidized at the γ,δ-double bond by molecular oxygen when heated in solvents which have readily abstractable hydrogen atoms. The following mechanism was suggested:



Because of competition among other free radical processes, the yields were not high. However, the γ,δ-epoxidation of conjugated dienone by this simple approach is still of preparative value.

It is the purpose of this thesis to examine some of these epoxidation reactions of conjugated dienones and employ a number of modifications to overcome some difficulties encountered with selectivities and yields.

RESULTS AND DISCUSSION

1α,2α,6α,7α-Diepoxy-cholesta-4-ene-3-one was prepared from cholesterol by the sequence of steps outlined in Figure 1. Cholesterol was oxidized with 2,3-dicyano-5,6-dichloro-benzoquinone (DDQ) to cholesta-1,4,6-triene-3-one 14,[18,19,20] which was epoxidized by alkaline hydrogen peroxide as described by E. Glotter et al[9] to give crystalline 1α,2α-epoxy-cholesta-4,6-diene-3-one 15. Its melting point; the infrared and nuclear magnetic resonance (NMR) spectra all agreed well with the literature values. Treatment of epoxyketone 15 with excess m-chloroperbenzoic acid for twelve hours afforded 1α,2α,6α,7α-diepoxy-cholesta-4-ene-3-one 16, accompanied by more-polar by-products from which the diepoxyketone 16 was separated in 30% yield by crystallization and column chromatography.

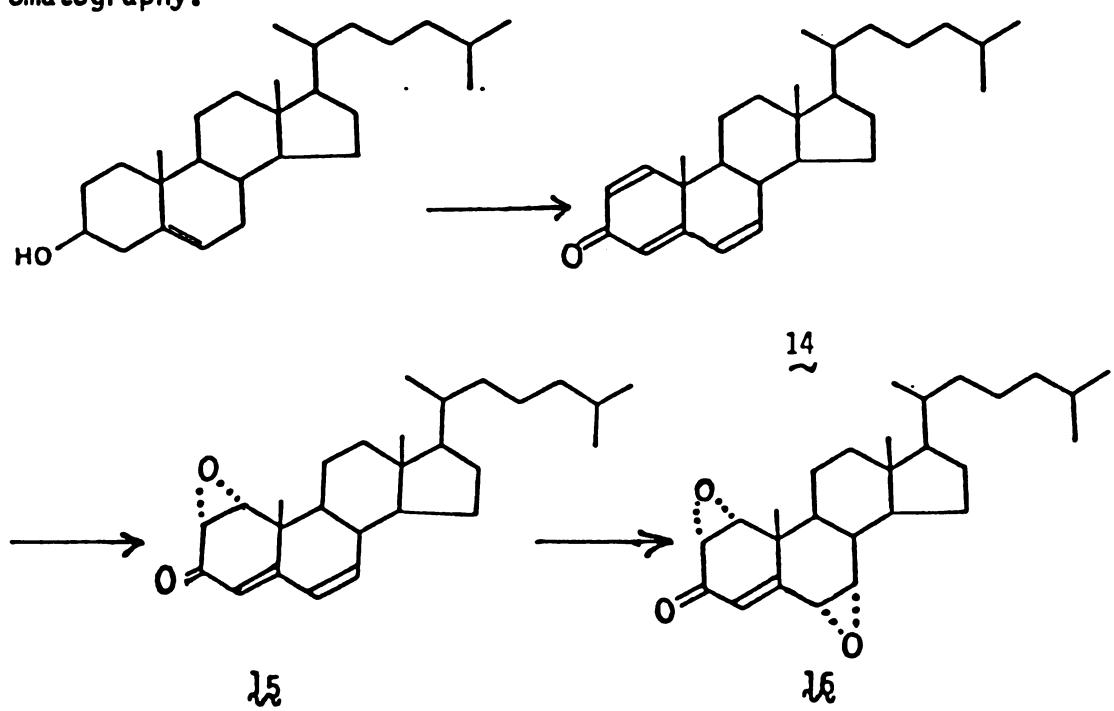


Figure 1. The Synthesis of 16

Compound 16 has not been previously described. Its structure is established by its spectral properties and chemical transformation. The molecular formula $C_{27}H_{40}O_3$ was comfirmed by the mass spectrum (parent peak m/e 412) and elemental analysis. The ir spectrum showed a strong absorption at 1675 cm^{-1} for a conjugated C=O, and the uv spectrum was also consistent with such conjugation, having a λ_{max} at 250 nm. An examination of the proton nmr spectrum of 16 shows the presence of a double bond in the α,β-position, and epoxide rings in the α',β' and γ,δ-positions. Although the T-60 spectrum does not show a clear splitting pattern for the four epoxy protons at positions 1, 2, 6 and 7 (Figure 2a), the 180 MHz nmr resolves them well (Figure 2b). Integration of this spectrum indicates the relative areas under the peaks at δ3.53, 3.47 and 3.33 to be 1:2:1, suggesting the signals of C_2-H and C_6-H have overlapped. Expansion of this region displays the splittings very well (Figure 2c). The proton at position 2 couples with C_1-H (doublet at δ3.53) to form a doublet (J=4 Hz) which is further split by a long range coupling with C_4-H (J=2 Hz) to form a doublet of doublets at δ3.45. These doublets overlaps with a doublet from C_6-H, which is coupled with C_7-H (J=4 Hz). Finally C_7-H gives a doublet at δ3.33 which is further split by a small coupling with C_8-H (J=1 Hz).

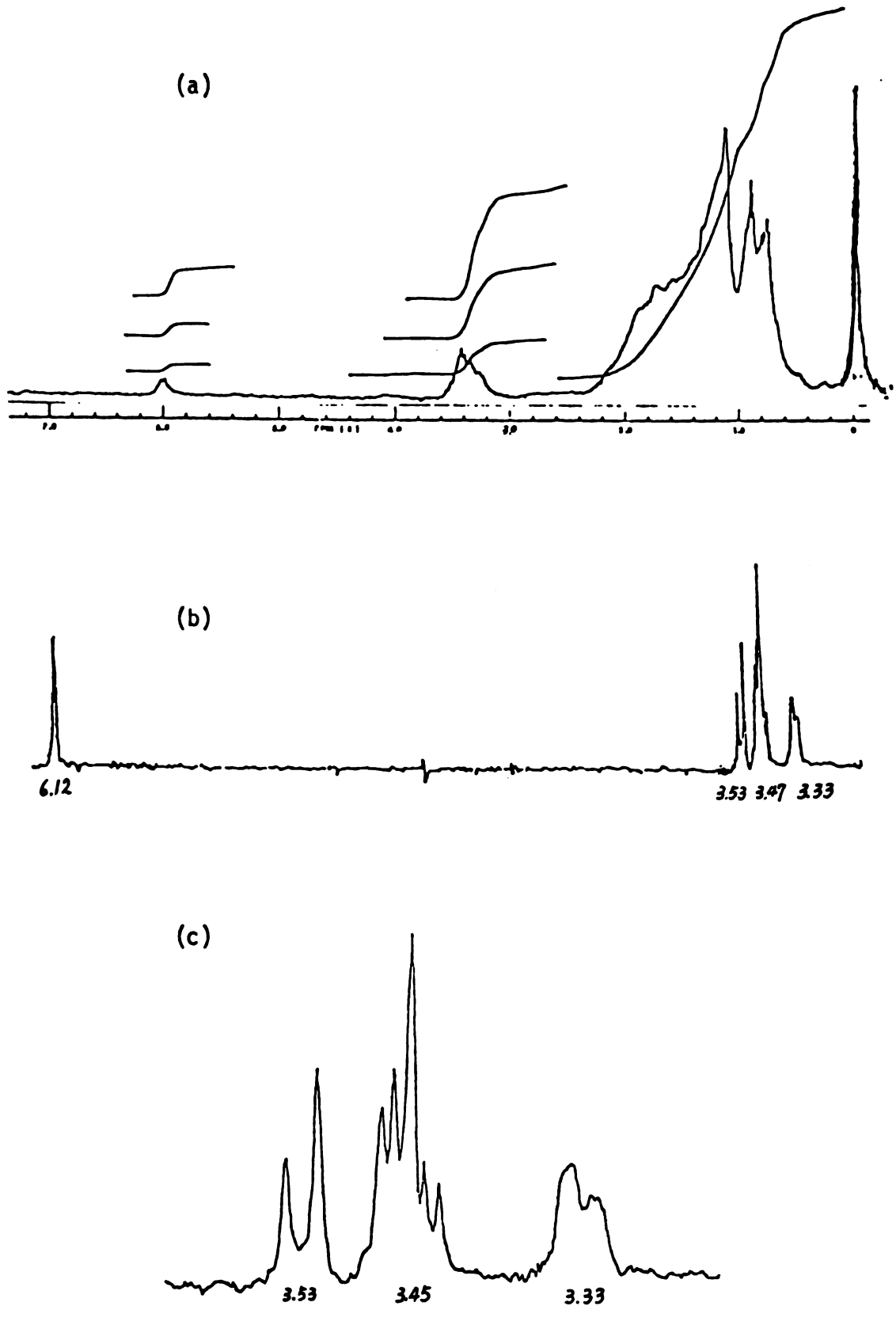
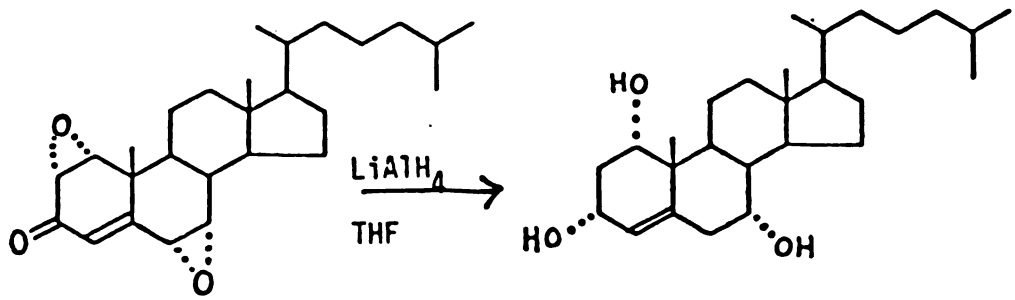


Figure 2. Pmr Spectra of 16

Assignment of stereochemistry to 16 is based on the chemical transformation of 16 into 1α,3α,7α-cholesta-4-ene-triol 17 with lithium aluminum hydride reduction (Equation 2). According to the Furst-Plattner rule[21], an oxirane ring fused to a rigid cyclohexane moiety usually undergoes ring-opening so as to form the trans-diaxial product. Consequently, ring-opening reduction of 16 with lithium aluminum hydride should selectively form the 1α and 7α hydroxyl groups. Treatment of diepoxyketone 16 with a large excess of lithium aluminum hydride in dry THF yielded 1α,3α,7α-cholesta-4-ene-triol, thus the α-configuration of the 6,7-epoxide ring of 16 was confirmed. Had the 6,7-epoxide possessed the β-configuration, its reduction with lithium aluminum hydride should have furnished, by diaxial opening, the 6β-hydroxy-isomer.

(2)



16 17

The previously unknown triol 17 was obtained as colorless crystals. Its structure was established by its mass, ir and nmr spectra and elemental analysis. The T-60 and 180 MHz spectra (Figure 3a and 3b) all showed an olefinic proton signal at δ5.65 which is apparently due to the C_4-H. Although the T-60 spectrum only showed two signals at δ3.8-4.2, the 180 MHz nmr resolved them well into three signals which are due to the protons attached to hydroxyl bearing carbon atoms (C-1, C-3 and C-7). Integration indicates the relative areas under the peaks at δ4.15, 3.89 and 3.77 is 1:1:1, as required by the assigned structure of triol 17. Because of its allylic location, the C_3-H is found downfield from the other two carbinol protons at positions 1 and 7. Since the latter have similar chemical environments, they also have similar chemical shifts. Had the triol held a 6β-hydroxyl group instead of the 7α function, the proton at C-6, which is also allylic would have been close in chemical shift to C_3-H.

Furthermore, all the carbinol protons appear to have an equatorial orientation, as indicated by the relatively narrow and poorly defined splitting displayed by each.

The two angular methyl resonance signals for C-18 and C-19 also help to establish the assigned structure of the triol.

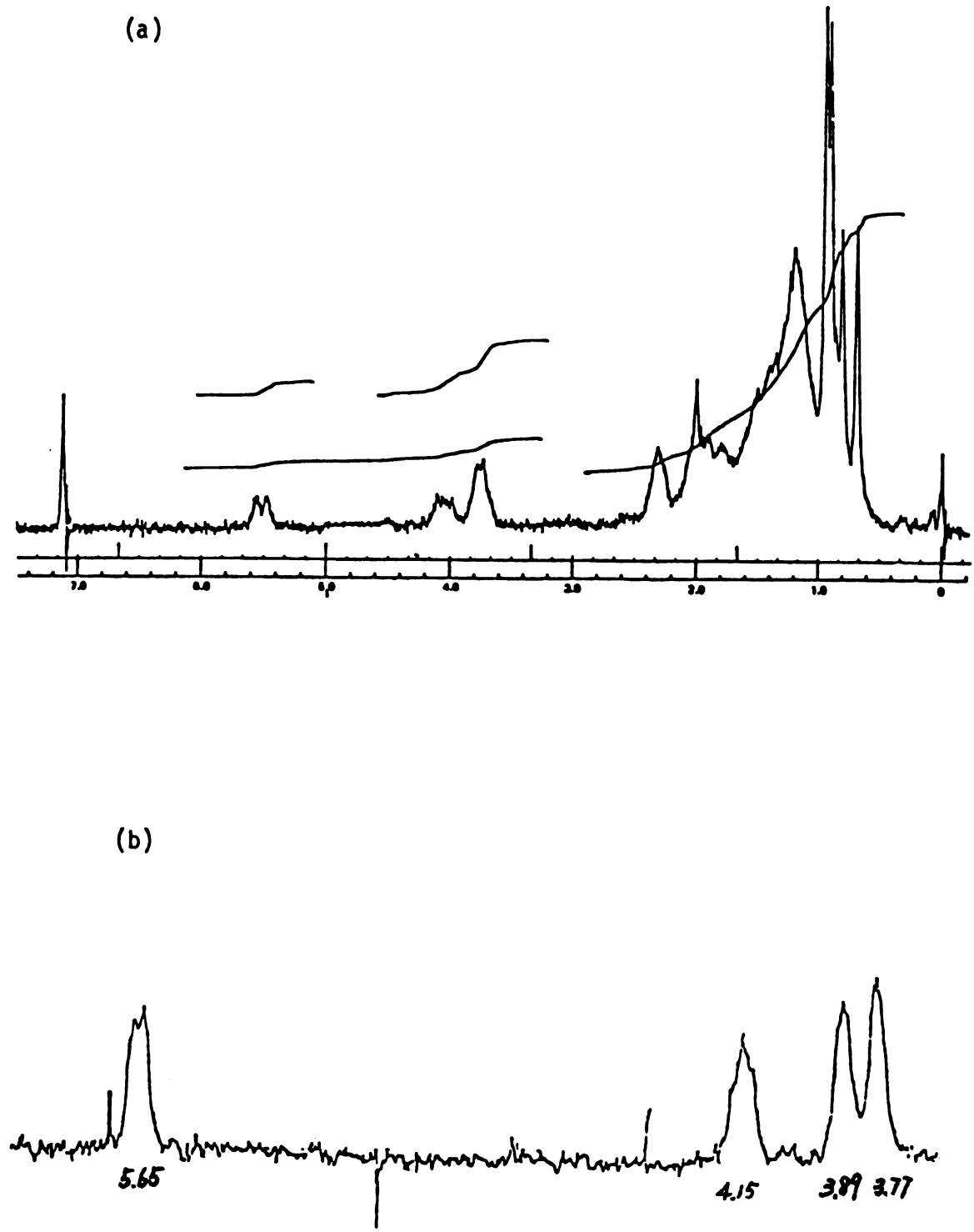


Figure 3. Pmr Spectra of 17

Bhacca and Williams[22] have tabulated the effect of functional substitution at various positions on the chemical shifts of the C-18 and C-19 protons for the 5α, 14α-androstane series. From the appropriate functional group increments, the calculated chemical shifts of the C-18 and C-19 protons in the isomeric 6β-hydroxy or 7α-hydroxy derivatives were compared with the observed values (Table 1). The good correlation of the observed and calculated chemical shift differences (Δ) for the 7α-hydroxy derivative confirmed the assigned structure of the triol. In this comparison it is assumed that a 6α,7α-epoxide will open to the 7α-hydroxy group, and a 6β,7β-epoxide will give a 6β-hydroxy group (Furst-Plattner Rule).

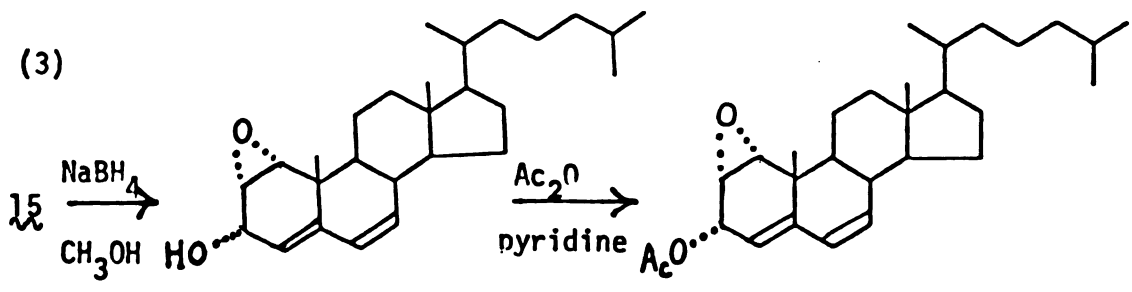
Table 1. The Observed and Calculated Chemical Shifts of C-18 and C-19 protons of 17

	δ_{C-18} methyl	δ_{C-19} methyl	$\Delta(\delta_{C-19} - \delta_{C-18})$	steroid increments used
obs	0.670	0.953	0.293	
$calcd_1$	0.717	1.034	0.317	1α-OH, 3α-OH, 7α-OH, Δ^4 and 17β-C_8H_{17}
$calcd_2$	0.751	1.234	0.483	1α-OH, 3α-OH, 6β-OH, Δ^4 and 17β-C_8H_{17}

An effort was made to prepare compound 16 by autoxidation of 15. When epoxyketone 15 was heated in xylent at 120-130° for 21 hr in the presence of air, diepoxide 16 was formed in 21% yield with many side products. The mp; nmr and ir spectra of this product were identical to the diepoxide obtained from the peracid reaction.

Although the diepoxyketone 16 could be synthesized either by peracid reaction or by autoxidation, the yields were all poor from a synthesis viewpoint. Attempts to improve the yield of diepoxide by using more peracid or a longer reaction time led to the appearance of polar by-products. The poor yield may be due to the electron-withdrawing effect of the conjugated carbonyl function in 15. To eliminate this inhibiting effect, epoxyketone 15 was reduced by sodium borohydride to give the corresponding 3α-hydroxy-derivative 18, followed by acetylation with acetic anhydride in pyridine to give 3α-acetoxy-1α,2α-epoxy-cholesta-4,6-diene 19 as colorless crystals in 90% yield (Equation 3).

(3)



18 19

Compound 19 was identified by its mass, ir and nmr spectra and elemental analysis. Although the T-60 nmr spectrum of 19 in $CDCl_3$ does not show a clear splitting pattern at δ5.5-5.9 (Figure 4a), integration of this spectrum indicates the area under this multiplet to be three protons, suggesting that the olefinic protons at positions 6 and 7 have overlapped with the C_3-H. This was confirmed by the 180 MHz nmr (Figure 4b). Expansion of this spectrum (Figure 4c) gives good resolution of these signals. It clearly indicates that the broad singlet at δ5.73 is from the proton at C-3 and the doublet at δ5.58 (J= 10 Hz) is from the proton at C-6, coupled to the C_7-H, which itself is a doublet of doublets at δ5.9 due to a small coupling with the C_8-H (J=2 Hz). The singlet at δ5.0 is assigned to the other olefinic proton at C-4. Unexpectedly, the signal at δ3.45 appears as a quintet. It is assigned to the C_2-H, which is coupled with C_1-H to form a doublet (J=4 Hz), and then further split by interactions with protons at C-3 and C-4. Since the long range coupling constant between C_2-H and C_4-H is about the same magnitude as the coupling constant between C_2-H and C_3-H, the doublet is split into a pair of overlapping triplets.

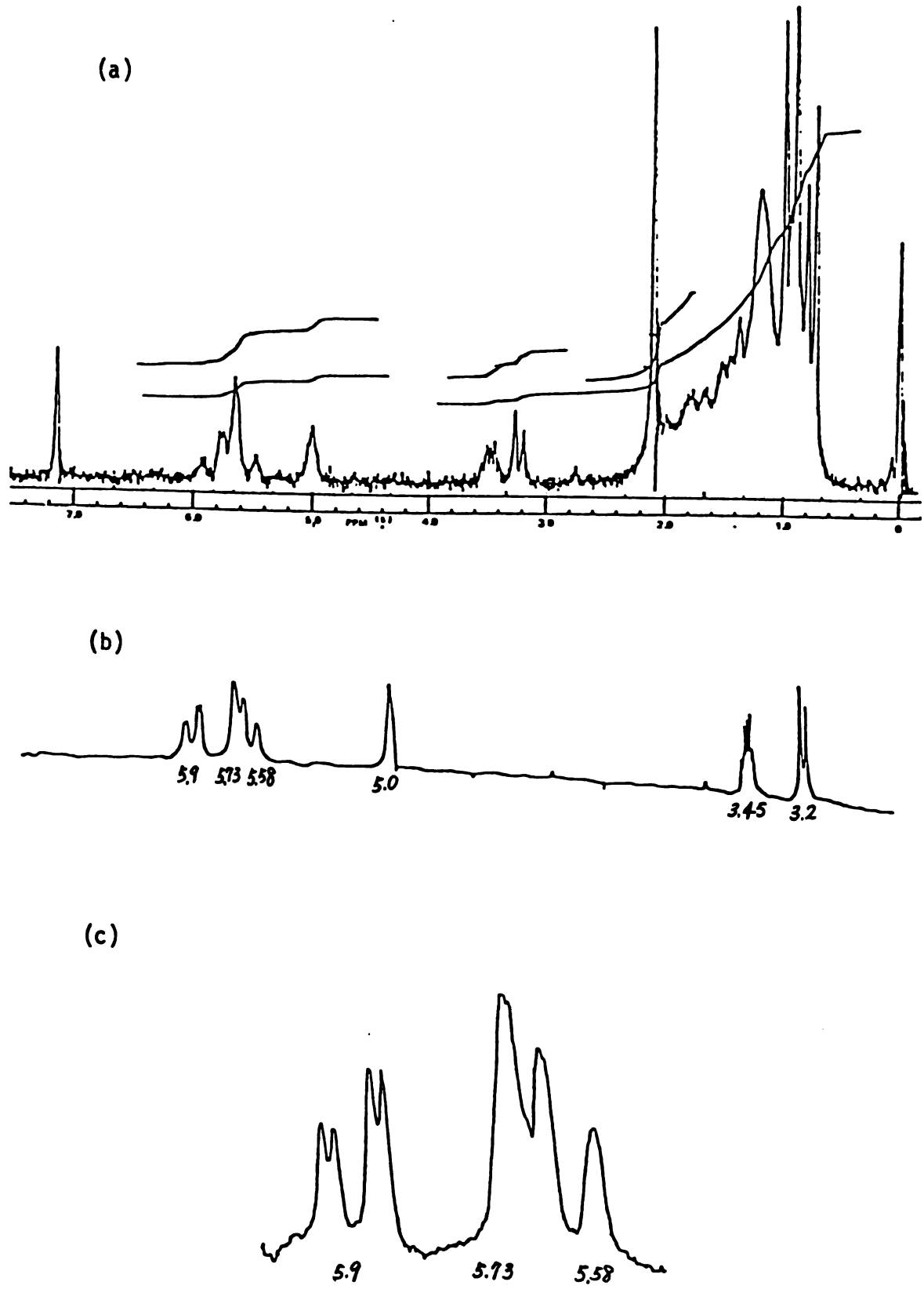
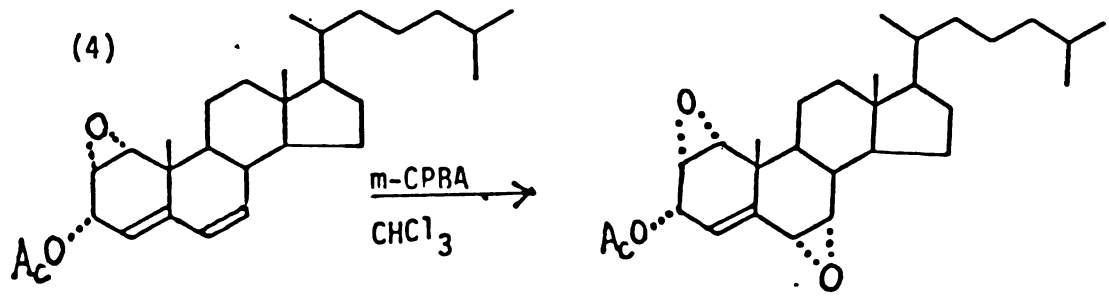


Figure 4. Pmr Spectra of 19

Peracid epoxidation of 19 was then examined. In contrast to the reaction of diepoxyketone 16, compound 19 was epoxidized quite readily by only a stoichiometric amount of m-chloroperbenzoic acid (m-CPBA) to yield 3α-acetoxy-1α,2α,6α,7α-diepoxycholesta-4-ene 20 as colorless crystals (60-65% yield), accompanied by a small amount of more-polar by-products (Equation 4).

(4)



19 20

Compound 20 has not been previously described. Its structure is established by its spectral properties and chemical transformation. The molecular formula $C_{29}H_{44}O_4$ was confirmed by the mass spectrum (parent peak m/e 456) and elemental analysis, and the ir and nmr spectra were consistent with the assigned structure. Although the signal at δ5.51 in the T-60 nmr lookd like a broad singlet (Figure 5a), integration of this spectrum indicates the relative area under this peak to be two protons, suggesting an overlap of signals from protons at position 3 and 4. These two

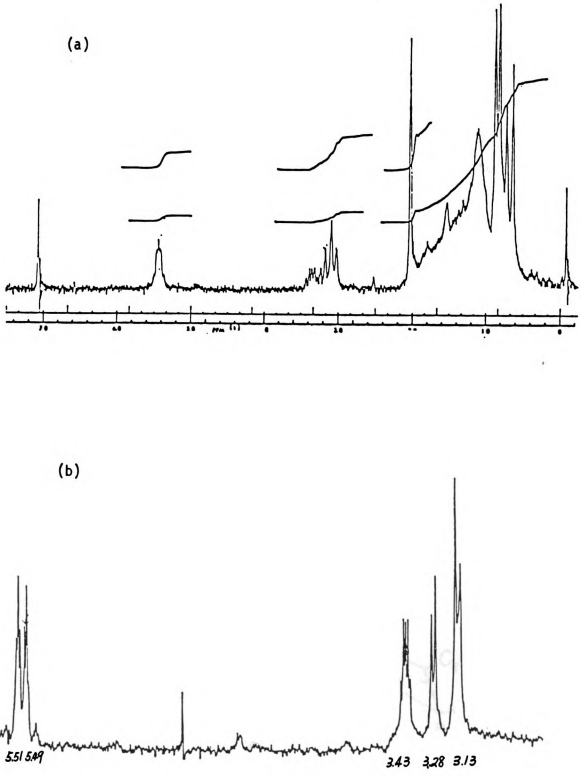
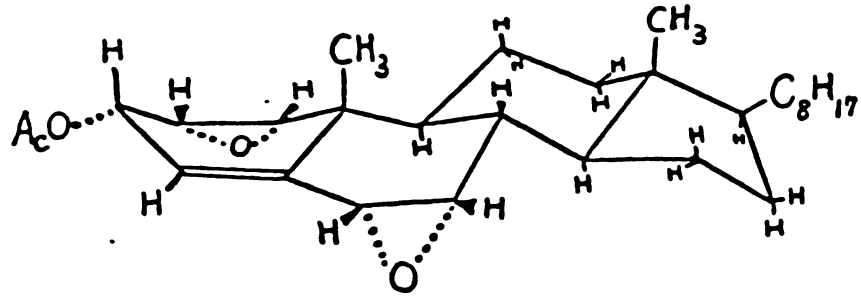


Figure 5. Pmr Spectra of 20

signals are well resolved by 180 MHz nmr into a pair of triplets at δ5.54 and 5.49 (Figure 5b). The multiplet at δ3.1-3.3 is also resolved into a quintet at δ3.43 and two doublets at δ3.28 and 3.13.

An examination of a Dreiding molecular model of 20 help to explain why the protons on C-3 and C-4 appear as similar triplets. As noted above, the long range coupling between C_2-H and C_4-H is about the same magnitude as the coupling between C_2-H and C_3-H. The formation of these two triplets indicates that the coupling constant between C_3-H and C_4-H also happen to be the same magnitude as the coupling constant between C_2-H and C_3-H. In order to have these coupling constants of the same magnitude, the orientation of the 3-OAc and the 6,7-epoxy ring must both be alpha. On this basis, the configuration of compoind 20 was established as 3α-acetoxy-1α,2α,6α,7α-diepoxy-cholesta-4-ene:

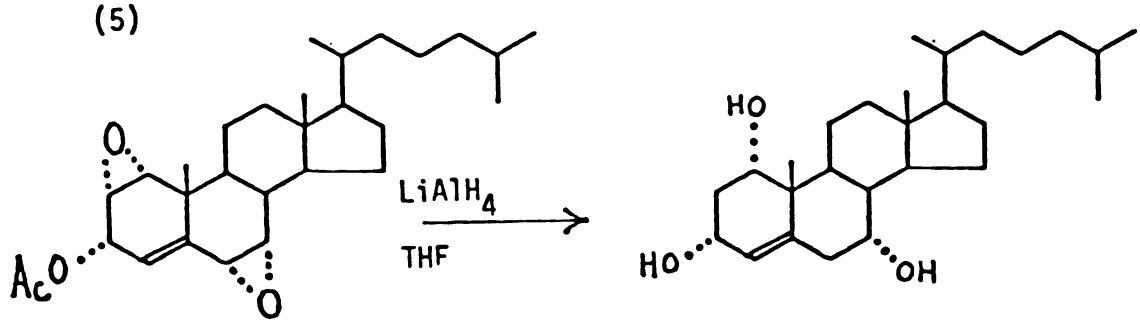


20

This rationalization was confirmed by a double-resonance experiment. Irradiation at the frequency of C_2-H induced the collapse of the C_3-H and C_4-H signals to two doublets (J=2 Hz, due to the coupling with each other), as shown in Figure 6a. Conversely, irradiation of either C_3-H or C_4-H resulted in the collapse of the C_2-H quintet to a doublet (J=4 Hz, due to the coupling with C_1-H), as shown in Figure 6b.

Treatment of 20 with a large excess of lithium aluminum hydride in dry THF yielded the same triol 17 obtained from lithium aluminum hydride reduction of 16 (Equation 5). The mass, ir and nmr spectra and mp were identical. This chemical transformation further proves, by the diaxial opening rule, the the 6,7-epoxy ring of 20 has the α-configuration; and indicates that the orientation of the 3-OH in triol 17 is also alpha.

(5)



20 17

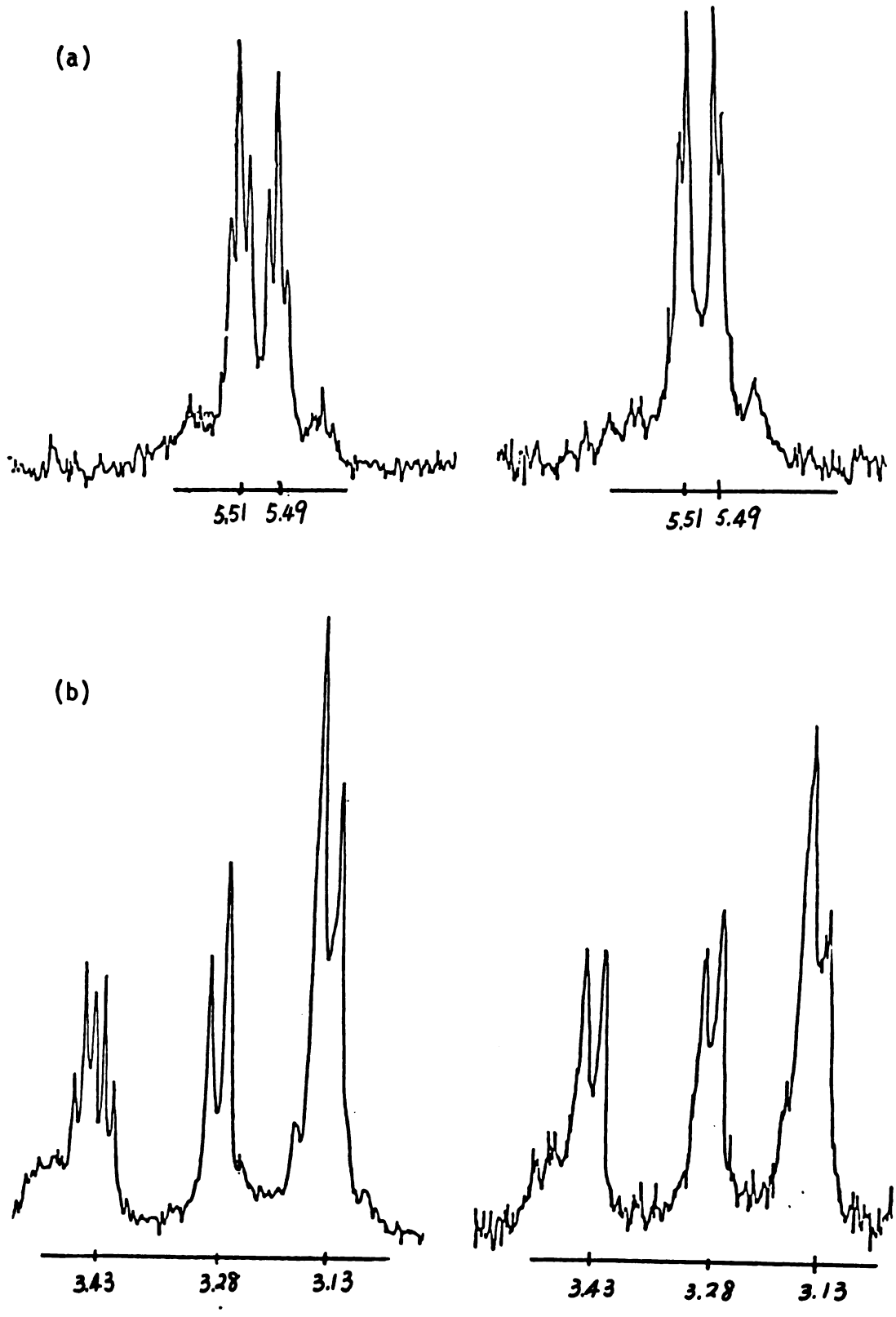


Figure 6. Double Resonance Pmr Spectra of 20

EXPERIMENTAL

General

Except as indicated, all reactions were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Magnetic stirring devices were used for most small scale reactions and mechanical stirrers for large scale reactions. Organic extracts were generally dried over anhydrous magnesium sulfate, before being concentrated. The progress of most reactions was followed by thin layer chromatography (TLC), visualized by spraying with 30% sulfuric acid followed by heating or by ultraviolet (UV) light.

Preparative TLC was carried out on 2 mm silica gel F-254 adsorbent on 20x20 cm glass plates. Visualization of preparative TLC was effected by UV light. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance (PMR) spectra were taken in deuterochloroform ($CDCl_3$) solution with a Varian T-60 or Bruker Spectrospic (180 MHz) spectrometers and are calibrated in parts per million (δ) downfield from tetramethylsilane (TMS) as an internal standard. Ultraviolet spectra were recorded on a Unicam SP-800 spectrophotometer. Mass spectra (MS) were obtained

with a Hitachi RMU 6 mass spectrometer.

Micro-analyses were performed by either Spang Microanalytical Labs. Eagle Harbor, Michigan or Galbraith Labs. Inc., Knoxville, Tennessee.

Cholesta-1,4,6-triene-3-one (14)

To a solution of 5 g (0.013 mole) of cholesterol in 100 ml anhydrous dioxane (50 mg of steroid/ml) was added 9.75 g of DDQ (0.042 mole). This mixture was refluxed for 25 hr. After filtration of precipitated hydroquinone*, the filtrate was diluted with methylene dichloride and passed through a short column of 100 g neutral alumina (20 mg of alumina/mg of steroid), eluting with 500 ml CH_2Cl_2 followed by 250 ml of 30% acetone in CH_2Cl_2. Evaporation of the combined eluant gave 2.6 g of a pale yellow oily compound. Recrystalization from methanol or petroleum ether gave 2.2 g (44% yield) colorless crystals of 14, mp 85-86^{o} (lit. 82-83^{o}).

*The recovered 2,3-dicyano-5,6-dichlorohydroquinone was oxidized by nitric acid to DDQ. A slurry of 2,3-dicyano-5,6-dichlorohydroquinone (4.6 g, 0.02 mole) in water (20 ml) and concentrated hydrochloric acid (20 ml) was treated over 15 min. with concentrated nitric acid (6.2 g, 70.9%) at a temperature of 35±3^{o}. After all the nitric acid had been added, the yellow suspension was stirred for 1/2 hr, filtered, washed with CCl_4, and dried, yielding 4 g (87%) of DDQ, mp 212-213^{o}.

1α,2α-Epoxy-cholesta-4,6-dien-3-one (15)

A solution of 14 (1.0 g, 0.0026 mole) in methanol (35 ml) was treated with 10% methanolic NaOH (0.25 ml) and 30% H_2O_2 (1.6 ml) with stirring at room temperature for 16 hr. The resulting crystalline epoxide was filtered off, washed with cold methanol and dried. Recrystallization from methanol gave 700 mg (70% yield) of 15, mp 108-110° (lit. 108-110°).

1α,2α,6α,7α-Diepoxy-cholesta-4-ene-3-one (16)

(a) With m-chloroperbenzoic acid: A solution of 15 (400 mg, 1.0 mmole) in $CHCl_3$ (10 ml) was treated with m-chloroperbenzoic acid (460 mg, 75.9% purity, 2.0 mmole), added in small portions with stirring until a clear solution was obtained. The mixture was stirred at room temperature for 12 hr. Solids were then collected on a filter and washed with a little $CHCl_3$; and the filtrate, diluted with $CHCl_3$ (50 ml), was washed with sodium bicarbonate (10%), water and brine; dried over anhydrous magnesium sulfate and taken to dryness under reduced pressure. After the addition of 5% ether solution in hexane (5 ml), crystalline 16 precipitated from the solution. Filtration gave 70 mg of 16, and the filtrate was then purified by preparative TLC with 5% ether in hexane as the eluting solvent. Another 55 mg of 16 was obtained (30% yield overall), mp 243-245°; IR ($CDCl_3$) 1680 cm^{-1}; UV maximum in methanol at 250 nm (E= 23500); PMR ($CDCl_3$) δ3.33 (C_7-H, dd, $J_{6,7}$=4 Hz,

$J_{7,8}$=1 Hz), 3.46 (C_6-H, d, $J_{6,7}$=4 Hz), 3.44 (C_2-H, dd, $J_{1,2}$=4 Hz, $J_{2,4}$=2 Hz), 3.53 (C_1-H, d, $J_{1,2}$=4 Hz), 6.12 (C_4-H, d, $J_{2,4}$=2 Hz); MS (70 eV) m/e (rel. intensity) 412 (M^+, 14), 396 (8), 95 (100).

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77

Found : C, 78.59; H, 9.79

(b) By autoxidation: A solution of 15 (190 mg, 0.48 mmole) in 2 ml of xylene was heated at 120-130° in a flask equipped with a reflux condenser for 36 hr. Air was circulated through the refluxing solution. After removal of xylene in vacuo, the residue was separated by preparative TLC, using 8% ether in hexane as the eluting solvent. The principal uv-absorbing band was collected and eluted with ethyl acetate to give 40 mg of 16 (21% yield).

1α,3α,7α-Cholesta-4-ene-triol (17)

(a) From 1α,2α,6α,7α-diepoxy-cholesta-4-ene-3-one (16): A solution of 16 (412 mg, 1.0 mmole) in freshly distilled tetrahydrofuran (20 ml) was treated with a suspension of lithium aluminum hydride (1 g, excess) in freshly distilled tetrahydrofuran (20 ml) under gentle reflux for 9 hr. After decomposition of excess reagent with ethyl acetate (20 ml) in ether (50 ml), the mixture was poured into a saturated solution of potassium sodium tartrate, and the product was extracted with chloroform. Removal of solvent

and crystallization from 15% ethyl acetate in hexane afforded 17 (255 mg, 61%) as needles, mp 178-180°; IR ($CDCl_3$) 3550-3100 cm^{-1}; PMR ($CDCl_3$) δ3.77 (C_7-H, d, $J_{7,8}$=2 Hz), 3.89 (C_1-H, s), 4.15 (C_3-H, s), 5.65 (C_4-H, d, J=5 Hz); MS (70 eV) m/e (rel. intensity) 418 (M^+, 2), 400 (100), 382 (48), 367 (16), 364 (15).

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08
Found : C, 77.16; H, 10.97

(b) From 3α-acetoxy-1α,2α,6α,7α-diepoxy-cholesta-4-ene (20): A solution of 20 (200 mg, 0.44 mmole) in freshly distilled tetrahydrofuran (10 ml) was treated with a suspension of lithium alumina hydride (0.5 g, excess) in freshly distilled tetrahydrofuran (20 ml) under gentle reflux for 9 hr. After decomposition of excess reagent with ethyl acetate (10 ml) in ether (30 ml), the mixture was poured into a saturated solution of potassium sodium tartrate, and the product was extracted with chloroform. After the removal of solvent, the crude product was chromatographed on a silica gel, elution with 30% of ethyl acetate in hexane gave 110 mg (55%) of 17, identical in all respects with the product obtained from (a).

1α,2α-Epoxy-3α-hydroxy-cholesta-4,6-diene (18)

A solution of 15 (1.5 g, 3.79 mmole) in anhydrous methanol (200 ml) was treated with sodium borohydride (0.3 g, excess). This solution was stirred for 2 hr at room temperature, then neutralized with dil. acetic acid solution. Extraction with ether gave a colorless solid (1.5 g, quantitative yield). Recrystallization from methanol afforded 18 (1.25 g, 83%) as needles, mp 98-99°; IR (CCl_4) 3500-3100 cm^{-1}; PMR ($CDCl_3$) δ3.22 (C_1-H, d, $J_{1,2}$=4 Hz), 3.47 (C_2-H, quintet), 4.2 (C_3-H, s), 5.15 (C_4-H, s), 5.55 (C_6-H, d, $J_{6,7}$=10 Hz), 5.9 (C_7-H, dd, $J_{6,7}$=10 Hz, $J_{7,8}$=2 Hz); MS (70 eV) m/e (rel. intensity) 398 (M^+, 42), 380 (56), 365 (20), 95 (100).

3α-Acetoxy-1α,2α-epoxy-cholesta-4,6-diene (19)

A solution of 18 (1.15 g, 2.88 mmole) in dry pyridine (5 ml) was treated with acetic anhydride (10 ml, excess) and stirred under nitrogen at room temperature for 12 hr. After the usual work-up and recrystallization from methanol, 19, 1.066 g (92% yield) was obtained as colorless crystals, mp 106-107°; IR($CDCl_3$) 1725 cm^{-1}; PMR ($CDCl_3$) δ2.1 (3H, s), 3.2 (C_1-H, d, $J_{1,2}$=5 Hz), 3.45 (C_2-H, quintet), 5.0 (C_4-H, s), 5.58 (C_6-H, d, $J_{6,7}$=10 Hz), 5.73 (C_3-H, s), 5.85 (C_7-H, dd, $J_{6,7}$=10 Hz, $J_{7,8}$=2 Hz); MS (70 eV) m/e (rel. intensity) 440 (M^+, 3), 398 (6), 380 (34), 365 (40), 350 (24), 141 (100).

Anal. Calcd. for $C_{29}H_{44}O_3$: C, 79.04; H, 10.07

Found : C, 79.06; H, 10.11

3α-Acetoxy-1α,2α,6α,7α-diepoxy-cholesta-4-ene (20)

A solution of 19 (1.376 g, 3.13 mmole) in $CHCl_3$ (30 ml) was treated with m-chloroperbenzoic acid (700 mg, 75.9% purity, 3.1 mmole) at 0^o and stirred in an ice-water bath for two days under argon. Solids were then collected by filtration and washed with a little $CHCl_3$. The filtrate, diluted with $CHCl_3$ (80 ml), was washed with sodium bicarbonate (10%), water and brine; dried over anhydrous magnesium sulfate and then taken to dryness under reduced pressure. Recrystallization from ethyl acetate yielded 890 mg (64% yield) of colorless crystals of 20, mp 201-203°; IR ($CDCl_3$) 1725 cm^{-1}; PMR ($CDCl_3$) δ2.1 (3H, s), 3.13 (C_1-H and C_7-H, d, J=4 Hz), 3.28 (C_6-H, d, $J_{6,7}$=4 Hz), 3.43 (C_2-H, quintet), 5.49 (C_3-H, t, $J_{2,3}=J_{3,4}$=2 Hz), 5.54 (C_4-H, t, $J_{2,4}=J_{3,4}$=2 Hz); MS (70eV) m/e (rel. intensity) 456 (M^+, 9), 414 (17), 396 (46), 380 (48), 365 (20), 350 (11), 132 (100).

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71

Found : C, 76.46; H, 9.57

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APPENDIX

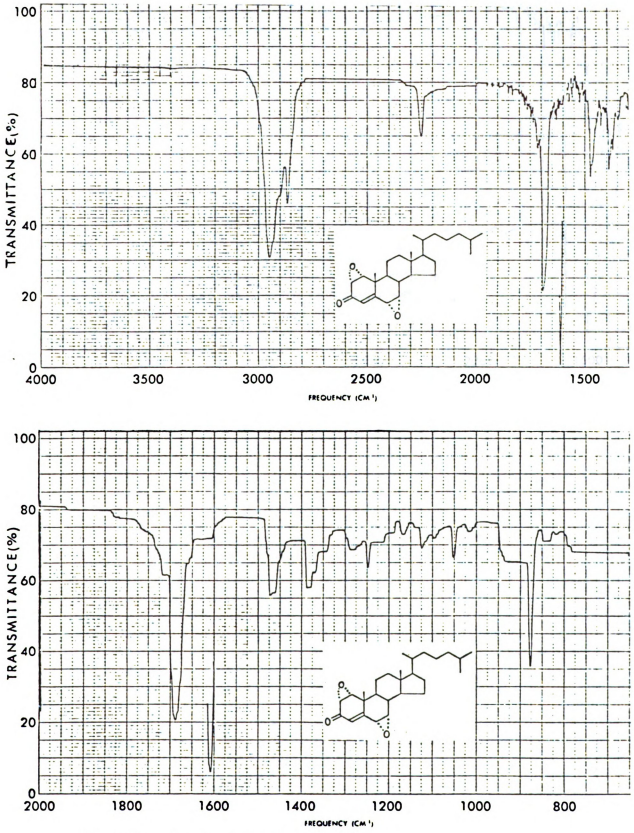


Figure 7. Infrared Spectrum of 16

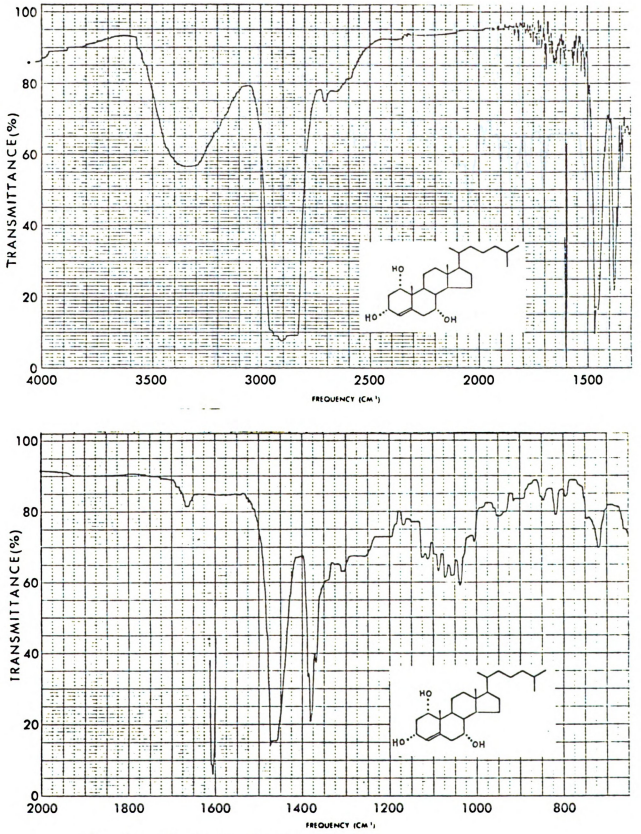


Figure 8. Infrared Spectrum of 17

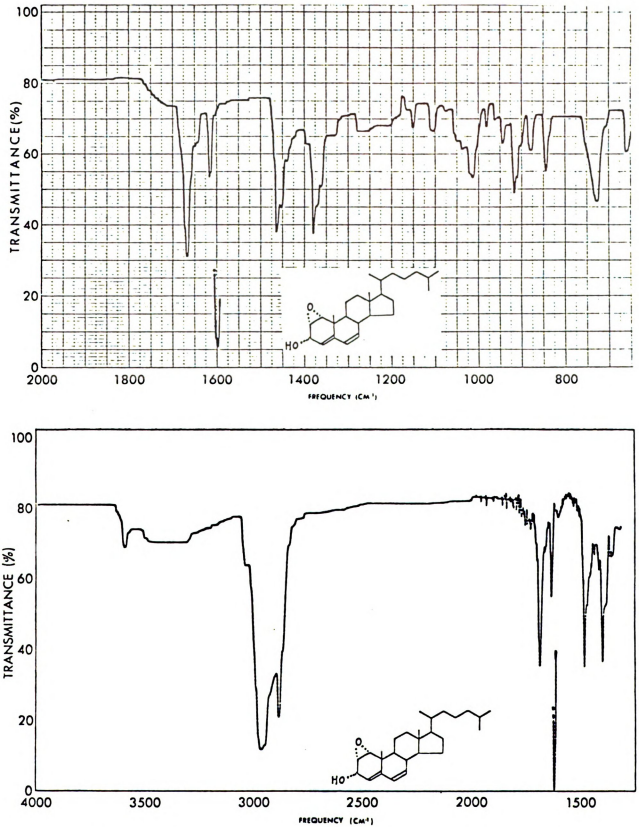
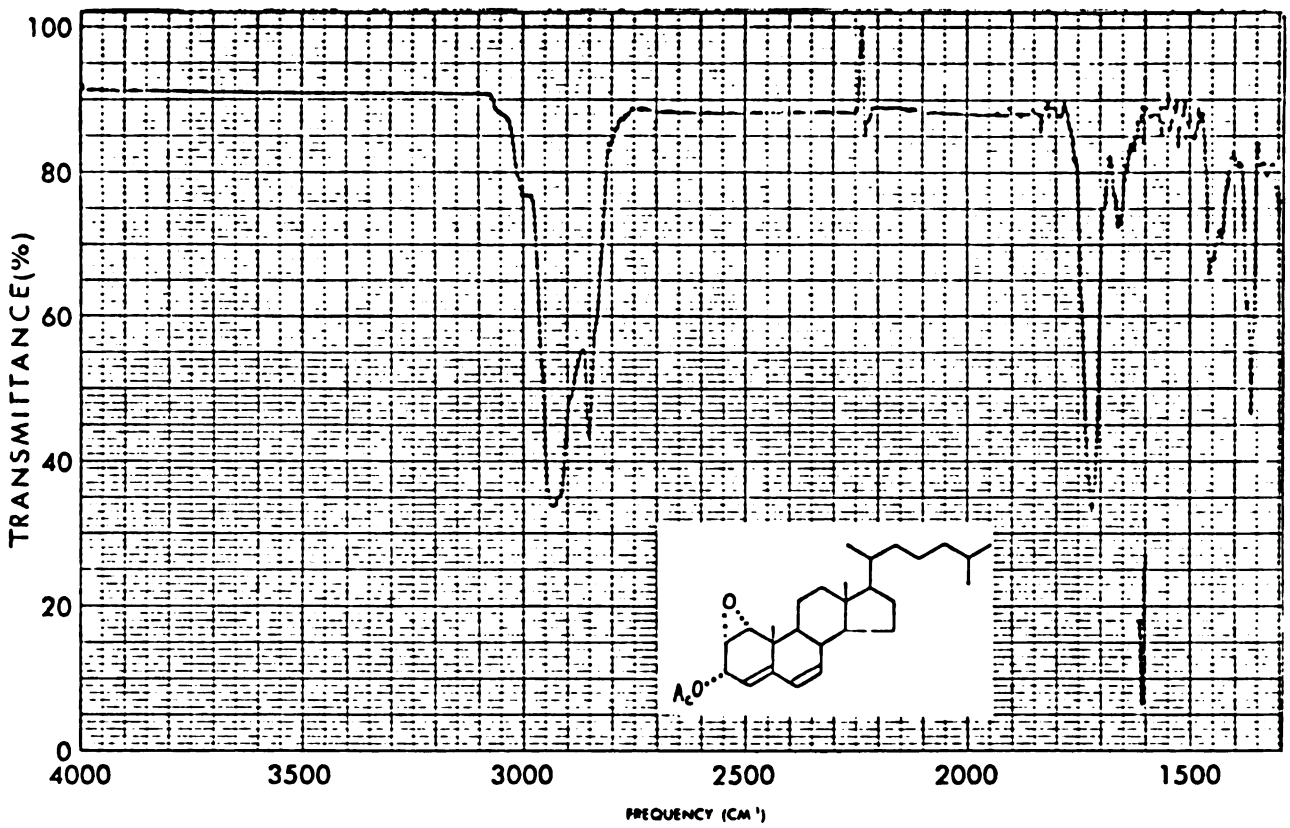


Figure 9. Infrared Spectrum of 18



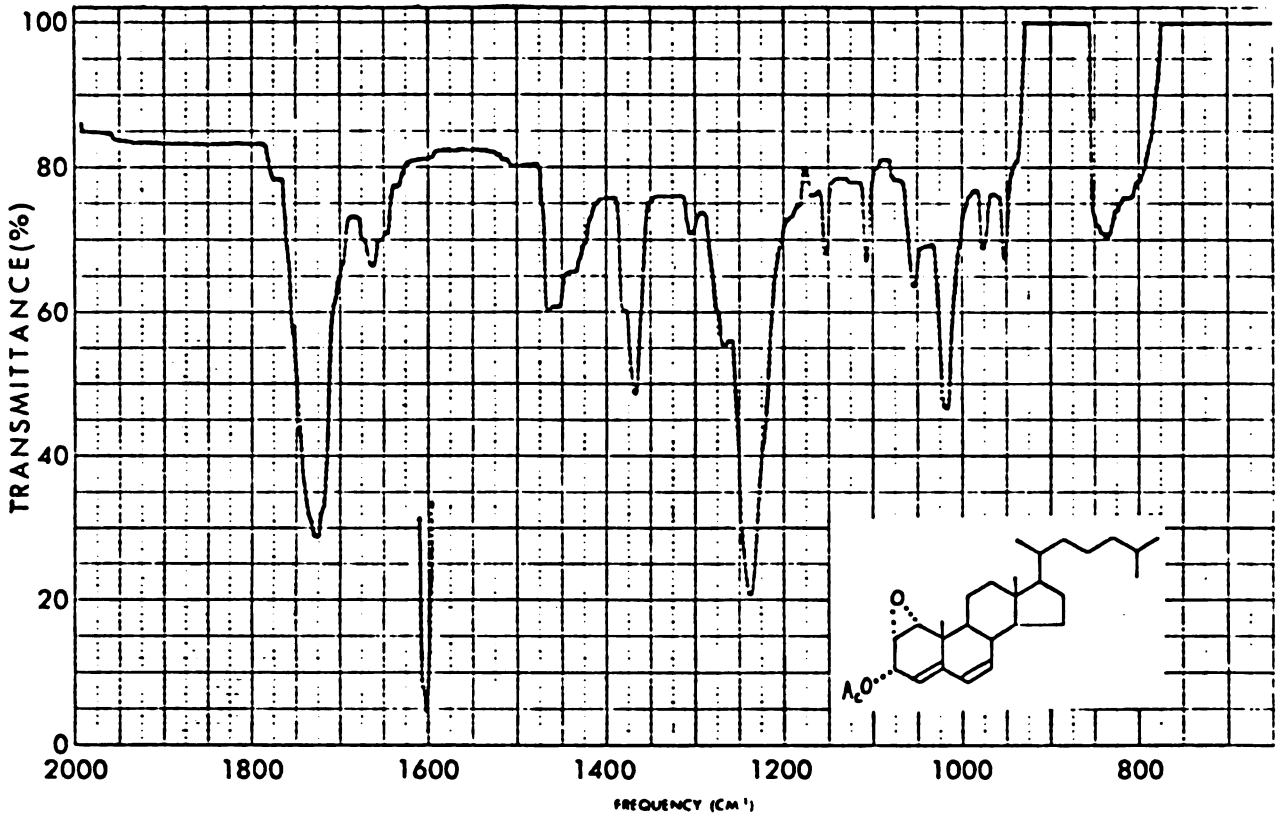
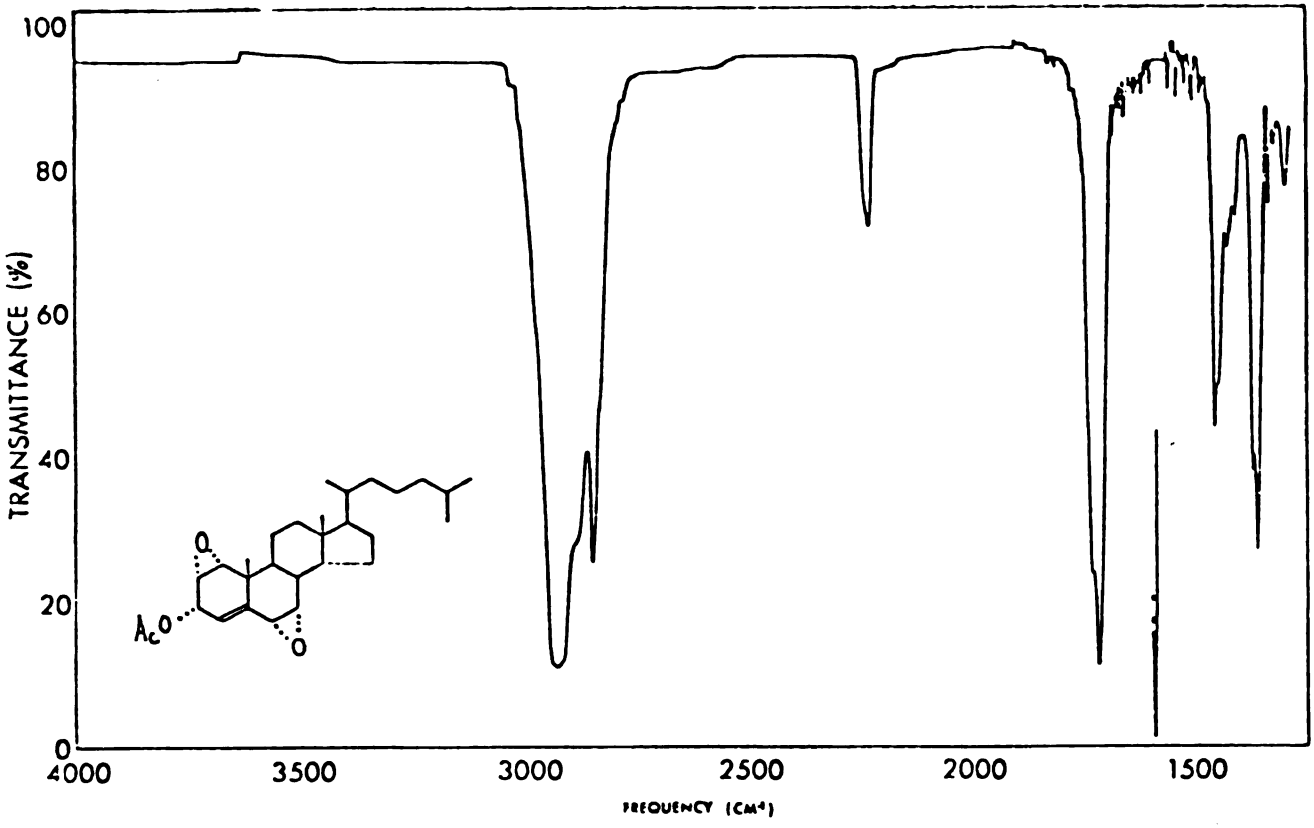


Figure 10. Infrared Spectrum of 19



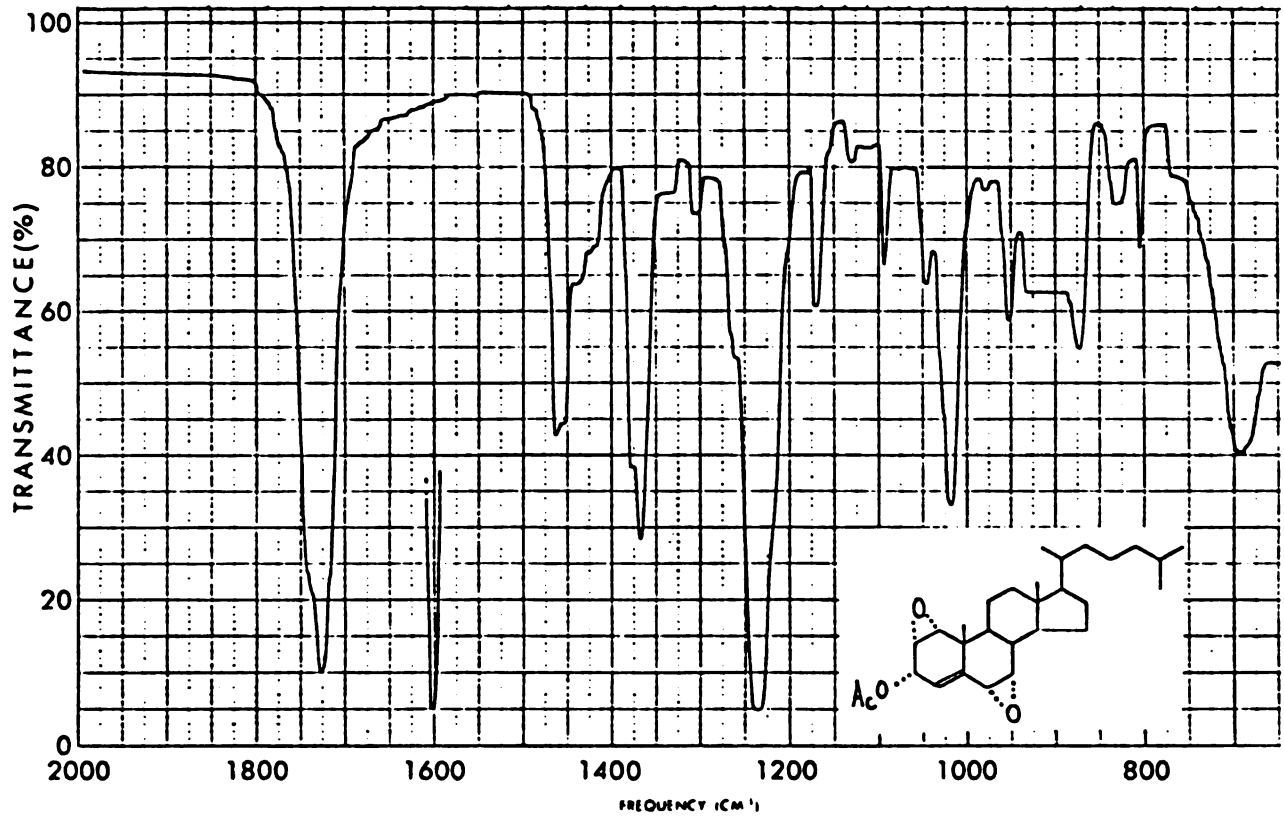


Figure 11. Infrared Spectrum of 20

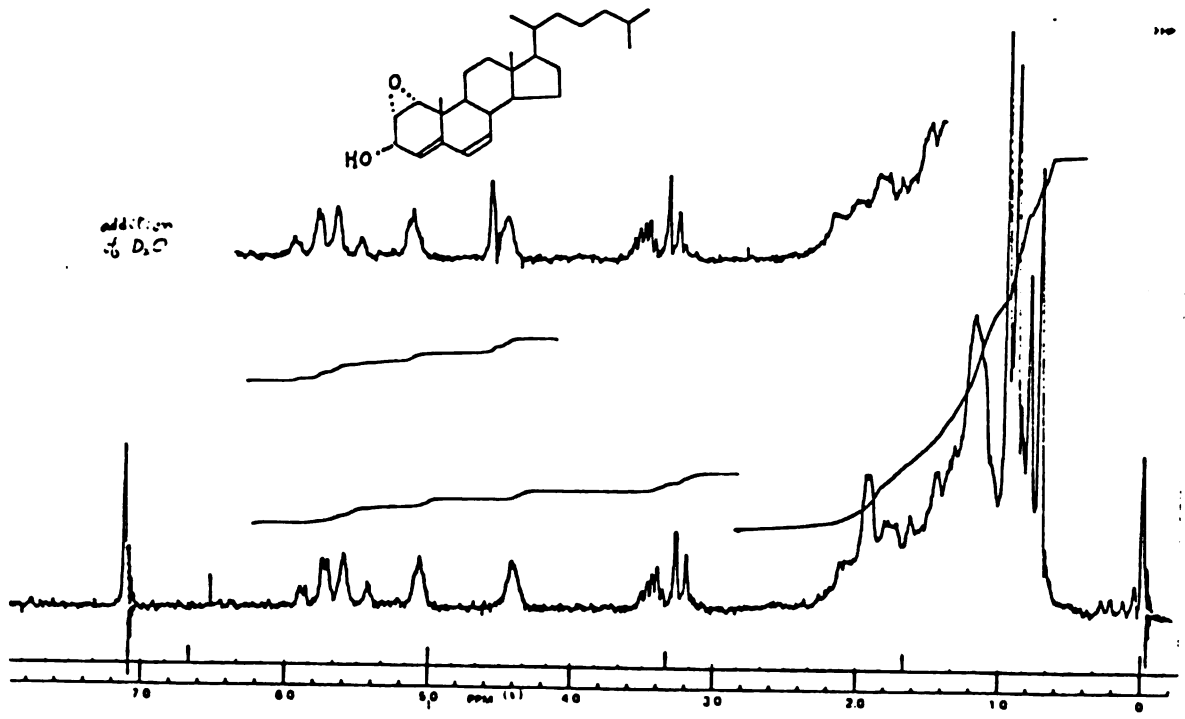


Figure 12. Pmr Spectrum of 18

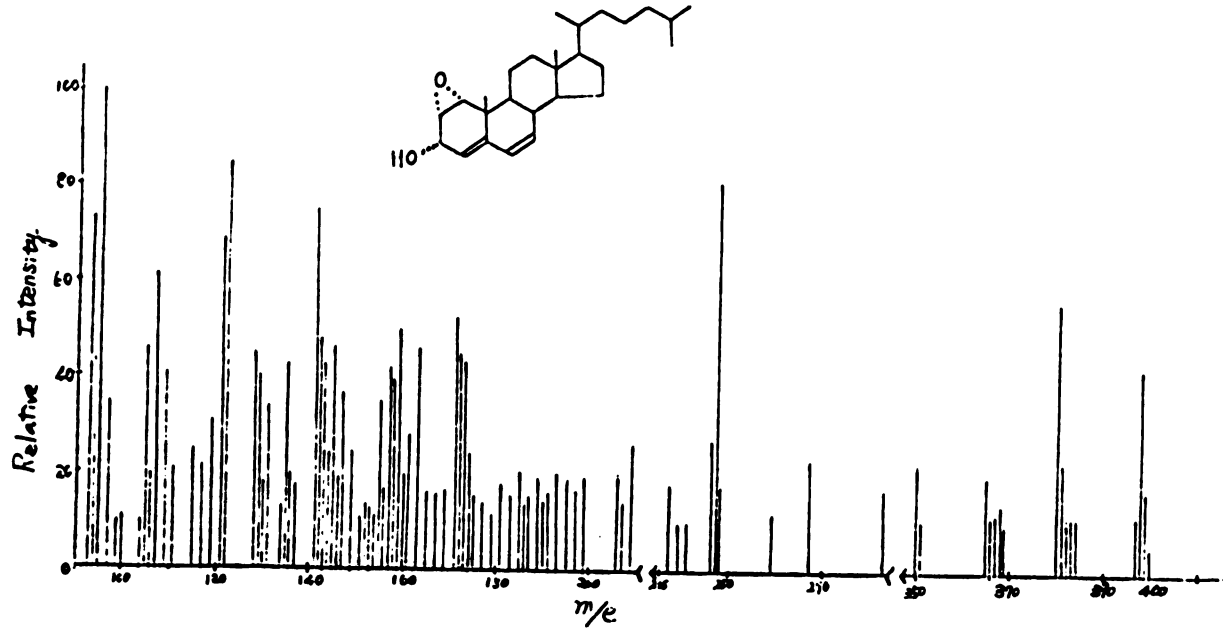


Figure 13. Mass Spectrum of 18

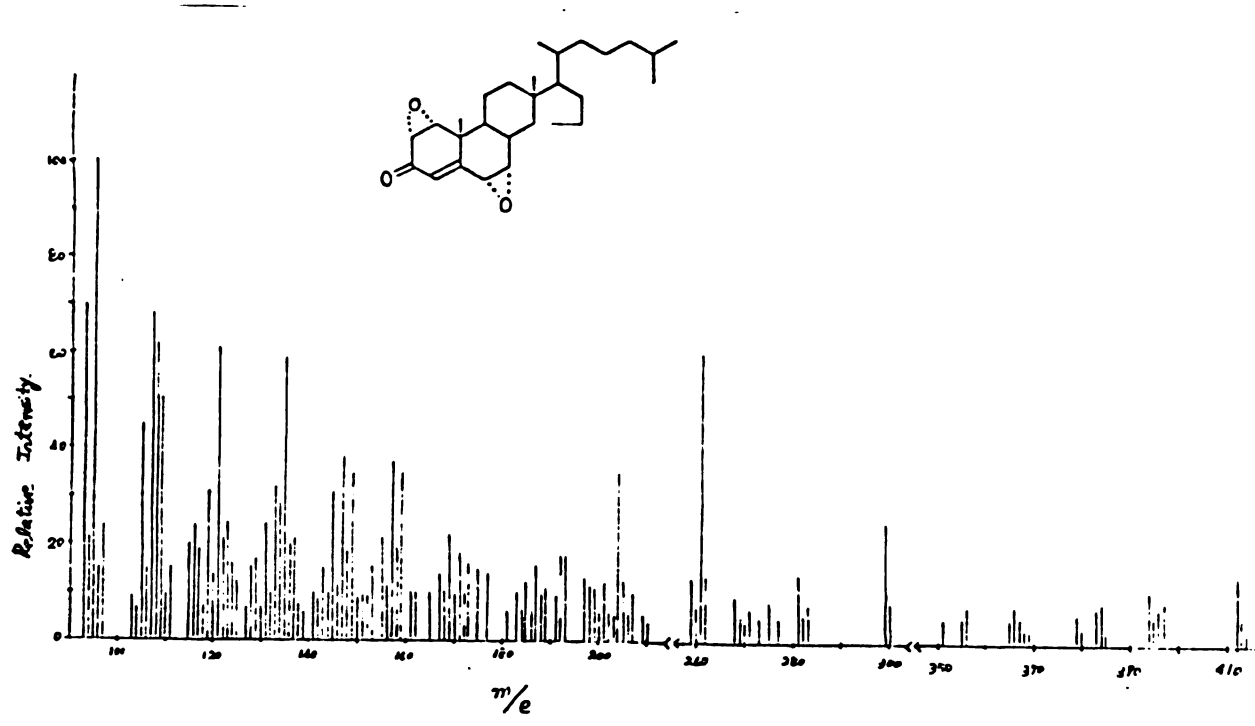


Figure 14. Mass Spectrum of 16

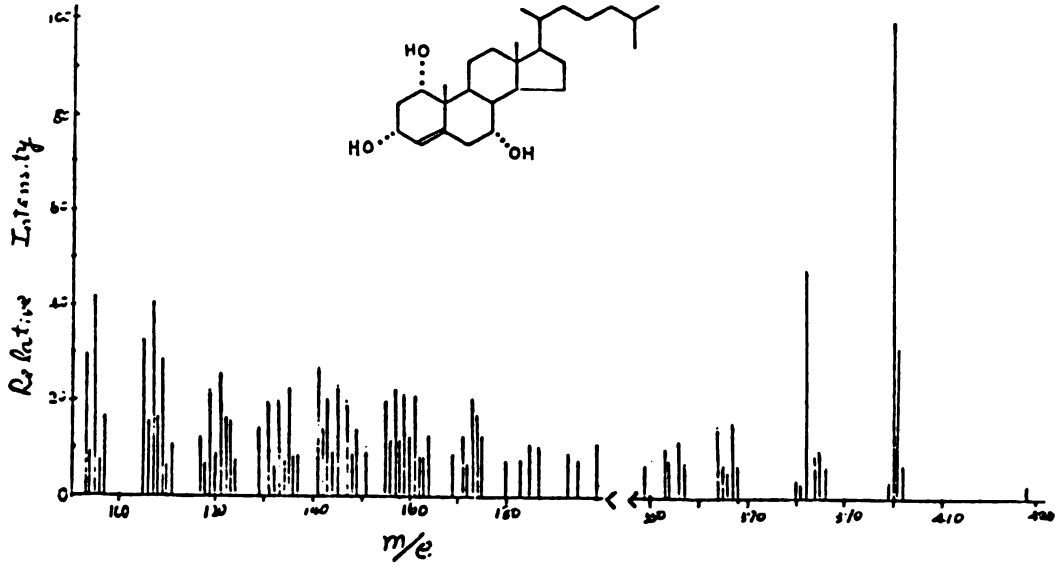


Figure 15. Mass Spectrum of 17

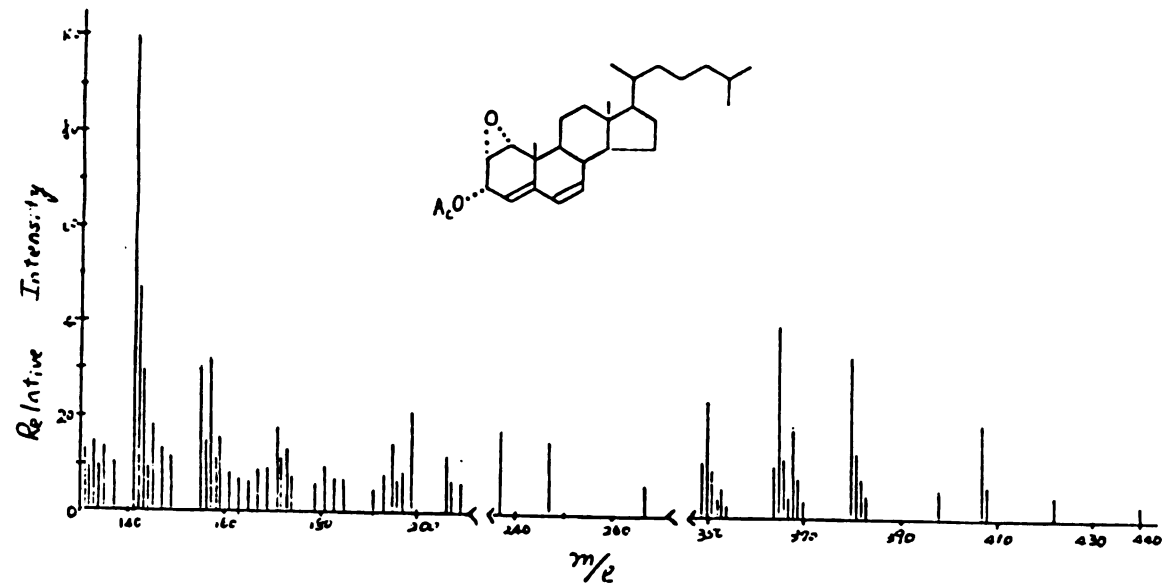


Figure 16. Mass Spectrum of 19

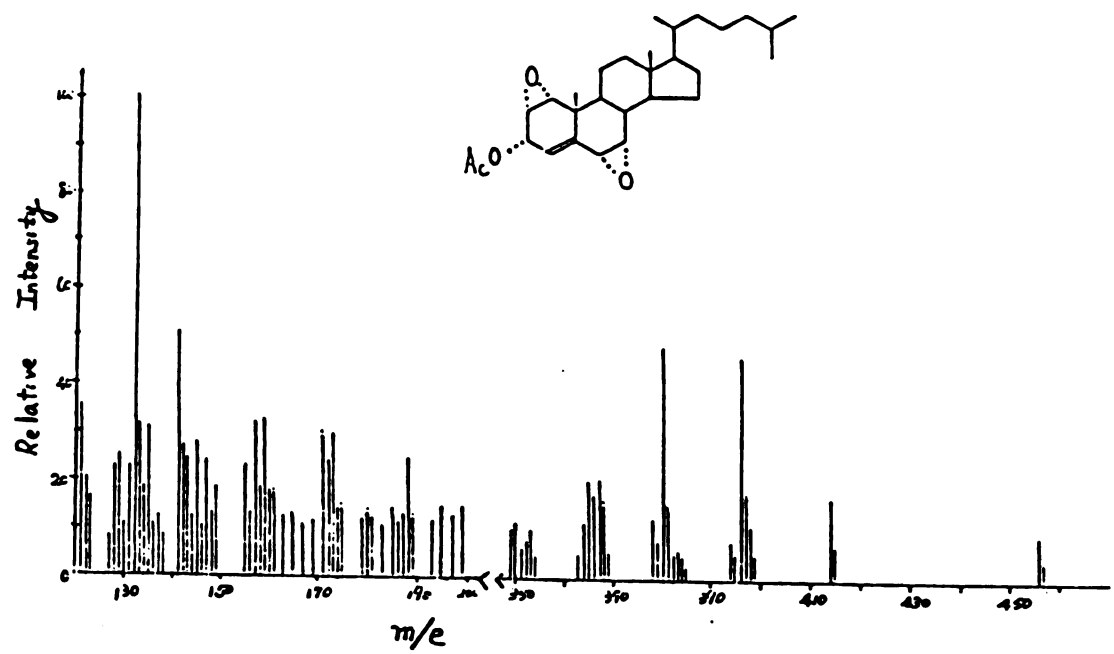


Figure 17. Mass Spectrum of 20