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Synthesis and Lithium Ammonia Reduction of
Homoconjugated Dienedione Systems
in Steroids

presented by

Hans R. Taneja

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of the requirements for

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William H. Reusch

Major professor

Date September 2, 1977

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SYNTHESIS AND LITHIUM-AMMONIA REDUCTION OF HOMOCONJUGATED DIENEDIONE SYSTEMS IN STEROIDS

by

Hans R. Taneja

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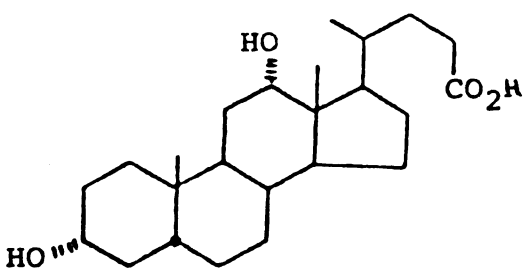
ABSTRACT

SYNTHESIS AND LITHIUM-AMMONIA REDUCTION OF
HOMOCONJUGATED DIENEDIONE SYSTEMS
IN STEROIDS

By

Hans R. Taneja

The synthesis of dienedione 2, which is a bis-vinylog of cyclohexan-1,3-dione, was achieved by two slightly different methods starting from 7-deoxycholic acid 1.



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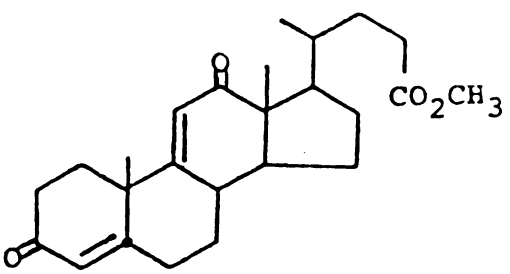
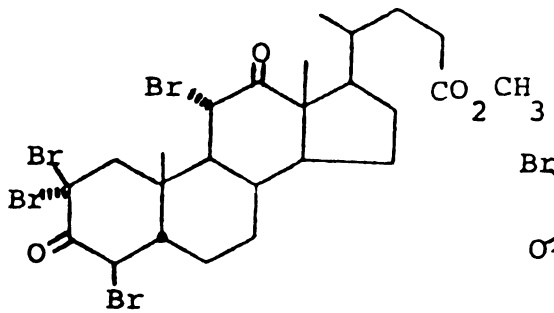


2

Attempts to oxidize the two hydroxy groups in 1 followed by α-bromination at the 4- and 11-positions simultaneously resulted in the formation of tetrabromide 3 which on dehydrobromination gave 2-bromo trienedione 4.



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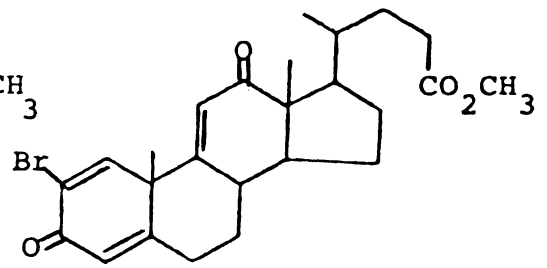
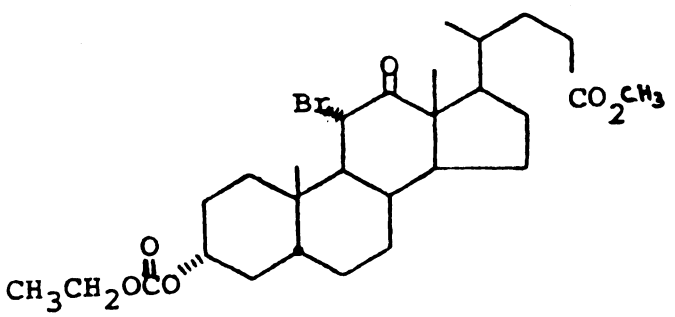


4

A stepwise introduction of 9,11- and 4,5-double bonds was a logical alternative. Selective protection of the 3-hydroxy function as a carbonate ester was followed by oxidation of the 12-hydroxy group and bromination of the α-methylene group at C-11. Dehydrobromination of the resulting bromoketone 5 gave enone 6.



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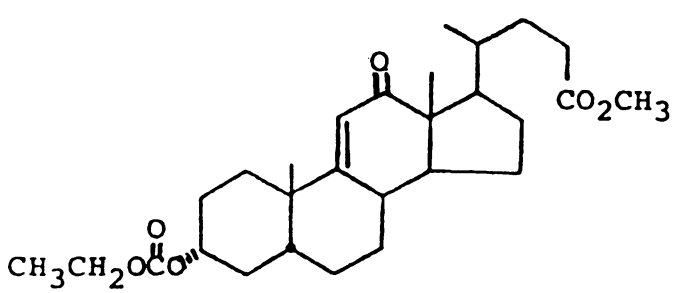
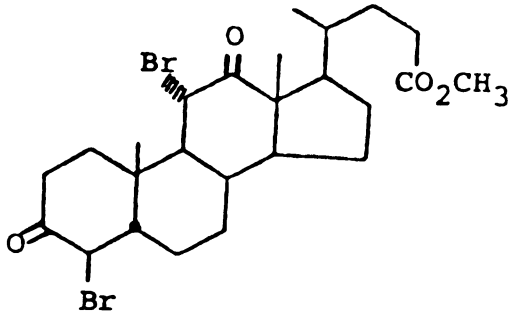


6

Hydrolysis of the 3-carbonate functions in 5 and 6 followed by oxidation and α-bromination with N-bromoaceta acetamide in aqueous acid gave bromo steroids 7 and 8 respectively.



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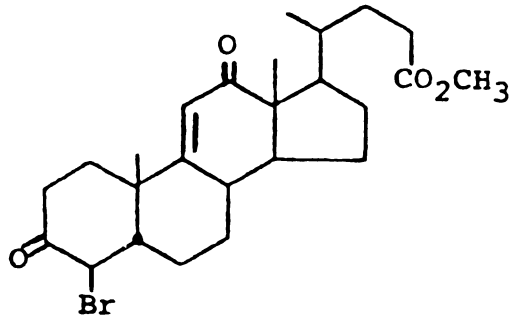

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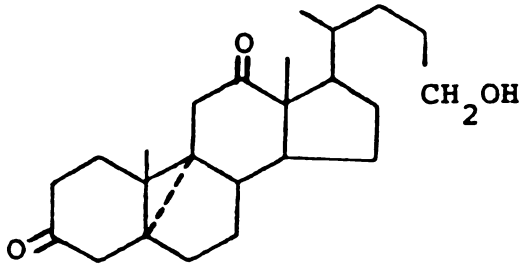
Dehydrobromination of 7 or 8 yielded dienedione 2 in moderate yields. Lithium and ammonia reduction of 2 produced the expected cyclopropane 9.



9

DEDICATION

This dissertation is dedicated to the following:

Madhu, my wife, whose love and encouragement has made these years good and worthwhile;

My parents, brothers and sisters whose love, understanding and moral support over the years have made this opportunity possible.

ACKNOWLEDGEMENT

The author is deeply greateful to Professor William H. Reusch for his guidance, for his vigorous intellectual example and his willingness to listen and to make suggestions during this endeavor.

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

Finally, the author would like to thank the National Institute of Health and Michigan State University for finnancial support.

The chemist who can extract from
his Heart's element compassion,
respect, longing, patience, regret,
surprise and forgiveness and com-
pound them into one, can create
that atom which is called Love.

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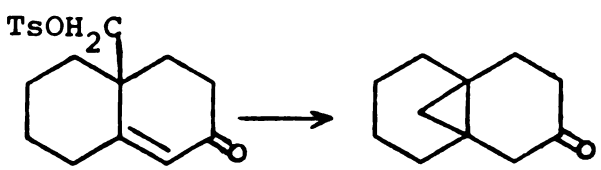
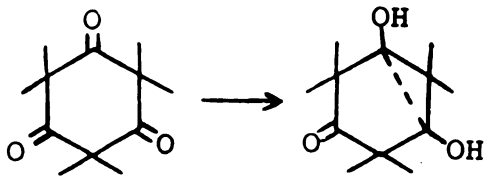
INTRODUCTION

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



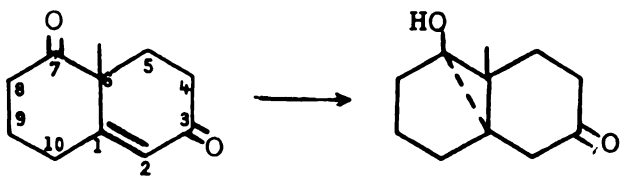
1 2

In fact, even relatively reactive compounds such as cyclopropanols[3] have been prepared by this kind of transformation. It was recognized that cyclopropane ring formation during dissolving metal reductions of bi- and polyfunctional compounds is probably a general phenomena. This concept has been applied to the synthesis of vic.- cyclopropanediols.[4] 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.



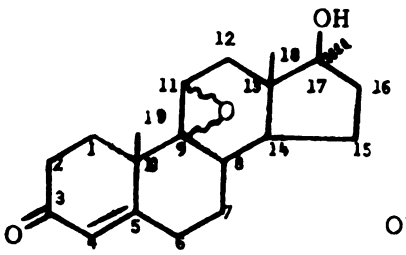
3 4

A logical extension of this work would be to apply this concept to vinylogs of 1,3-diketones. To this end, Wieland-Miescher ketone 5 was subjected to reduction with lithium in liquid ammonia and gave the cyclopropanol 6.[5]



5 6

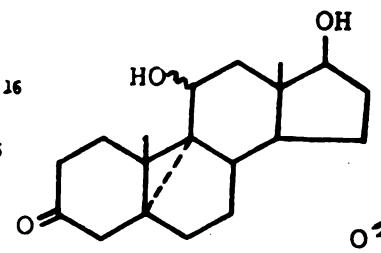
Eight alkyl-substituted derivatives of Wieland-Miescher ketone 5 were prepared and subjected to lithium and ammonia reduction with similar results.[6] Other tri-functional compounds examined were the steroids 9,11α- and β-oxido methyl testosterones 7a and 7b, which upon lithium in ammonia reduction did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



7

a = α

b = β



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a = α

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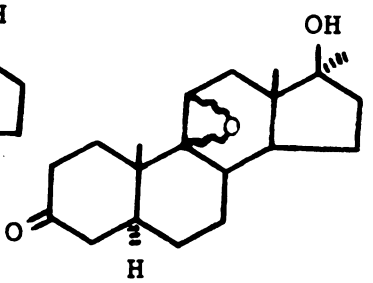
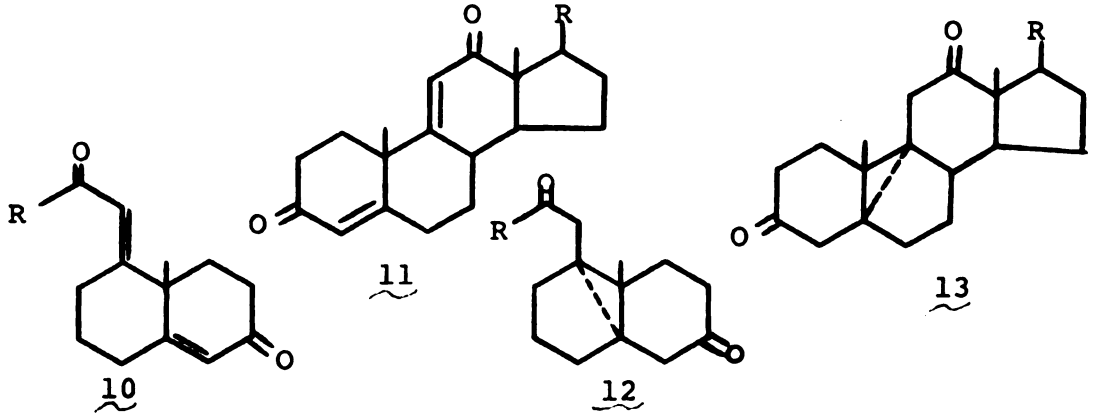


9

a = α

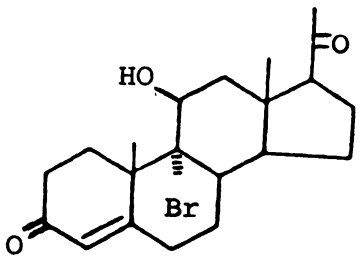
b = β

A further extension of this work would be to apply this concept to bis-vinylogs of 1,3-diketones, such as the Wieland-Miescher ketone derivative 10 or the steroid 11. On lithium and ammonia reduction these compounds would be expected to give the cyclopropanes 12 and 13 respectively.



All attempts to introduce an unsaturated carbonyl function at C-7 in Wieland-Miescher ketone met with no success,[8] probably due to the steric hinderance offered by the C-6 angular methyl group. A major part of this thesis is, therefore, devoted to work leading to the synthesis of steroid 11, since no steroid having the functionality shown in formula 11 has been reported in the literature.

The 5,9-cyclosteroid 15, representative of the cycloreduction product expected from 11, has been isolated by D.H.R. Barton et al.[9] during the chromous acetate reduction of 9α-bromo,11β-hydroxy-progesterone 14.



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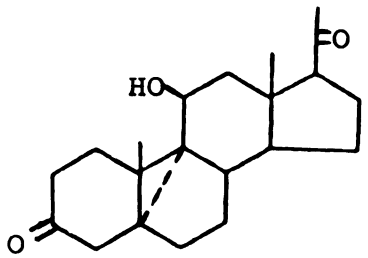


15

The synthesis of conjugated enone systems in steroids is usually accomplished by one of two fundamentally different strategies:

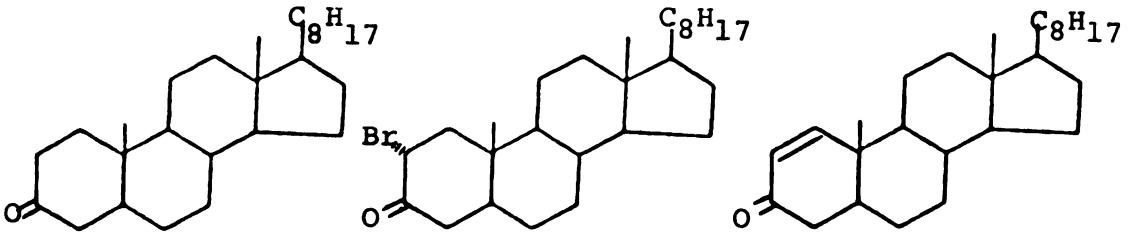
1) A double bond is introduced adjacent to an existing carbonyl function.
2) An existing double bond is oxidized at an allylic site.

Some of the methods available for introducing double bonds adjacent to carbonyl functions are:

a) α - halogenation followed by dehydrohalogenation
b) α - selenation followed by oxidative elimination of selenium-oxy acids.
c) Dehydrogenation with selenium dioxide.
d) Quinone dehydrogenation with DDQ or chloranil.

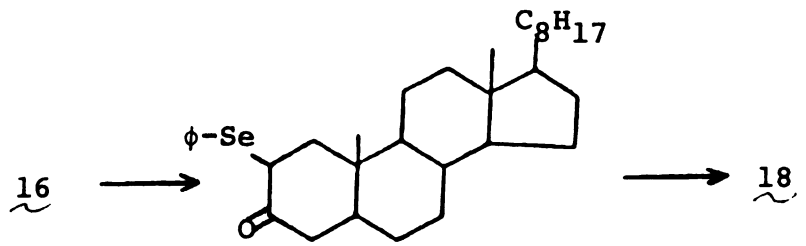
The α - bromination of cholestan-3-one 16 was first described

by Butenandt (1935),[10] and later shown by Corey[11] to give the 2α-bromocholestan-3-one 17. This bromoketone, on dehydromination with pyridine, gave Δ^1-cholestan-3-one 18.



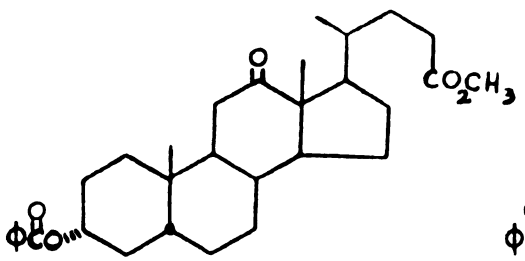
16 17 18

Recently, Sharpless[12] reported the synthesis of Δ^1-cholestan-3-one 18 by α-selenation of cholestan-3-one 16 with Phenyl Selenium Chloride to give 2α-phenylseleno compound 19, followed by oxidative elimination to 18 with an alkaline solution of hydrogen peroxide.



19

Kendall and his co-workers[13] introduced a 9,11-double bond in the 12-ketocholic acid derivative 20 by treatment with selenium dioxide to give the $\Delta^{9,11}$,12-keto steroid 21.



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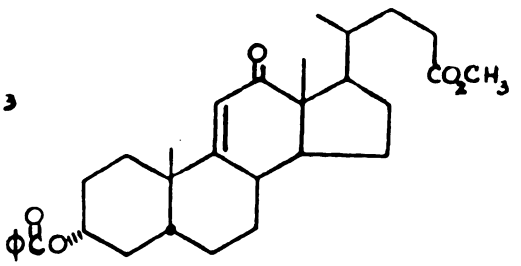
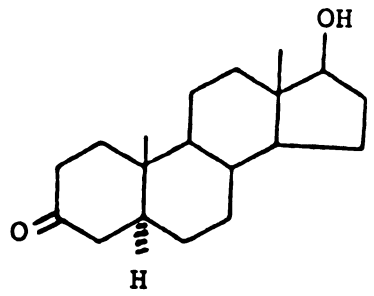


21

The alternative synthesis of 17β-hydroxy androst-1-en-3-one 23 by DDQ dehydrogenation of 17β-hydroxy androstan-3-one 22, was reported by Ringold and Turner.[14]



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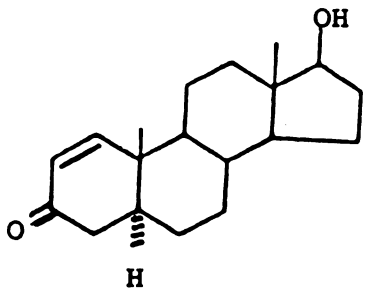


23

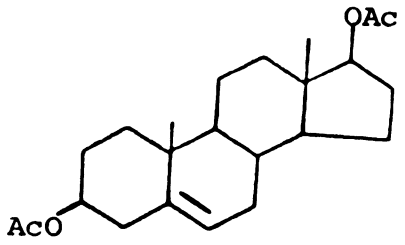
The allylic oxidation of unsaturated steroids has been accomplished in several different ways, including:

a) Allylic oxidation with t-butyl chromate, chromium trioxide or sodium dichromate.

b) Allylic dibromination with N-bromosuccinimide followed by base hydrolysis.

Heusler and Wettstein[15] have used t-butyl chromate for

allylic oxidation of 3β, 17β-diacetoxy androst-5-ene 24, the 7-oxo derivative 25 being the major product.



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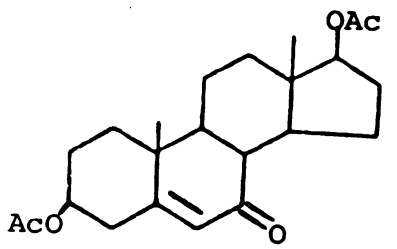
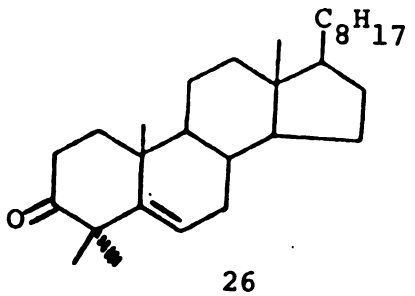


25

Dauben et al.[16] report that the chromium trioxide-pyridine complex accomplishes this same allylic oxidation, but in better yield. In a similar approach, Jones et al.[17] used sodium dichromate to effect allylic oxidation of 4,4-dimethyl cholest-5-ene-3-one 26 to the corresponding 7-keto steroid 27.



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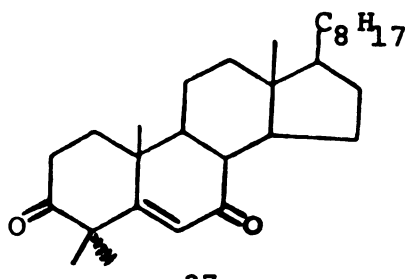

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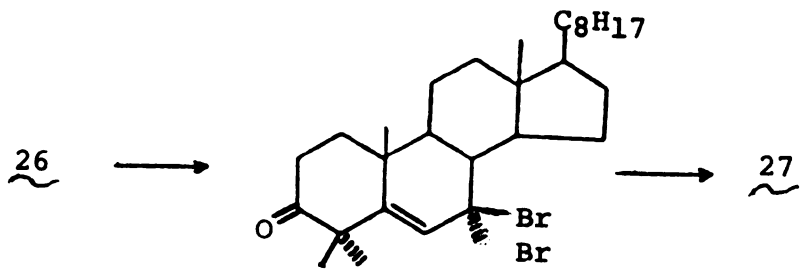
Allylic dibromination of 26 by irradiation in the presence of N-bromosuccinimide gave the 7,7-dibromo compound 28, which was converted to enone 27 by treatment with aqueous sodium carbonate.[18]



26 → 27

28

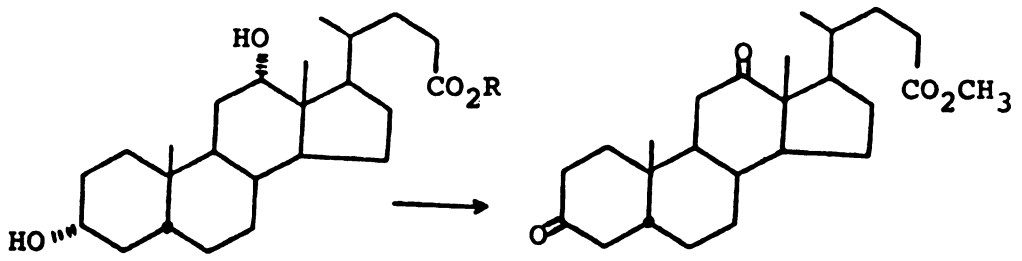
A similar procedure in which allylic dibromination and hydrolysis occur in the same step was reported by Thomson et al.[19]

Of course, other reaction sequences may be used to prepare enones, but many of these have not been widely used with steroids. The author intends to explore some of them in this thesis.

RESULTS AND DISCUSSION

Deoxycholic acid is an inexpensive and promising starting material for the synthesis of dienedione 11. Esterification of deoxycholic acid 29 followed by Jones oxidation[20] provided the required 3- and 12-carbonyl functions (Equation 1). The synthesis of 11 thus becomes a matter of inserting double bonds at the 4,5- and 9,11-positions.

(1)



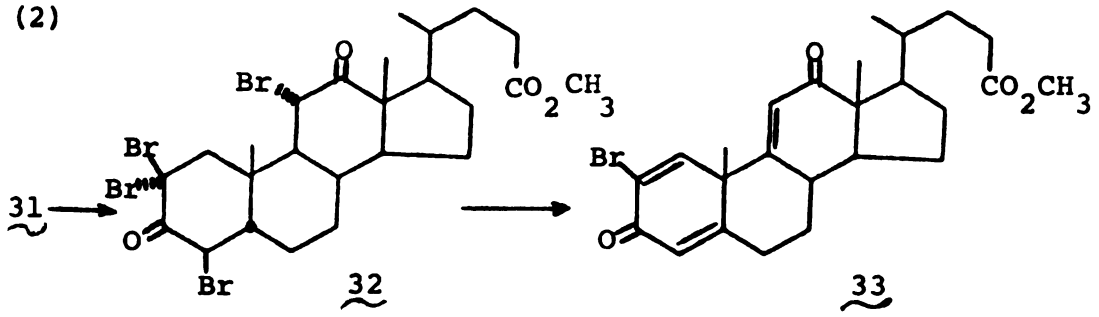
29 R = H
30 R = CH_3

31

One simple method that might be used to introduce the required double bonds would involve simultaneous α-bromination of the two carbonyl functions, followed by dehydrobromination. A major problem with this approach was lack of control over bromination at different α-sites. Thus, the 3,12-diketosteroid 31 upon bromination in the presence of boron trifluoride etherate[21] gave a bromo derivative which

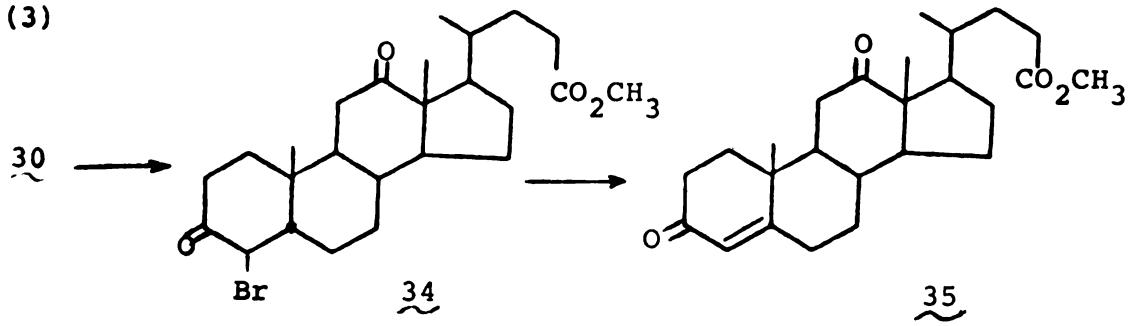
was tentatively regarded as methyl-2,2,4,11-tetrabromo-3,12-diketo cholanate 32. Field desorption mass spectroscopy of 32 did not give a parent ion; however, dehydrobromination with lithium carbonate and dimethylformamide[22] gave a tris-dehydrobrominated product, which was established by proton magnetic resonance (Pmr) and mass spectra to be methyl-2-bromo-3,12-diketo-$\Delta^{1,4,9(11)}$ cholatrienate 33 (Equation 2).

(2)



Another procedure, capable of giving oxidation and α-bromination in the same step involved treatment of methyl deoxycholate 30 with hydrobromic acid and an excess of N-bromoacetamide[23]. The product obtained in this case was identified as methyl 4β-bromo-3,12-diketo cholanate 34, which on treatment with lithium carbonate and dimethyl-formamide[22] gave methyl 3,12-diketo-Δ^4-cholenate 35 (Equation 3)

(3)



A second approach involving bis α-selenation of the two carbonyl functions in 31 with phenyl selenium halides[12], as a prelude to oxidative elimination, proceeded in very poor yield. Over 90% of the starting material 31 was recovered unchanged from the reaction mixture.

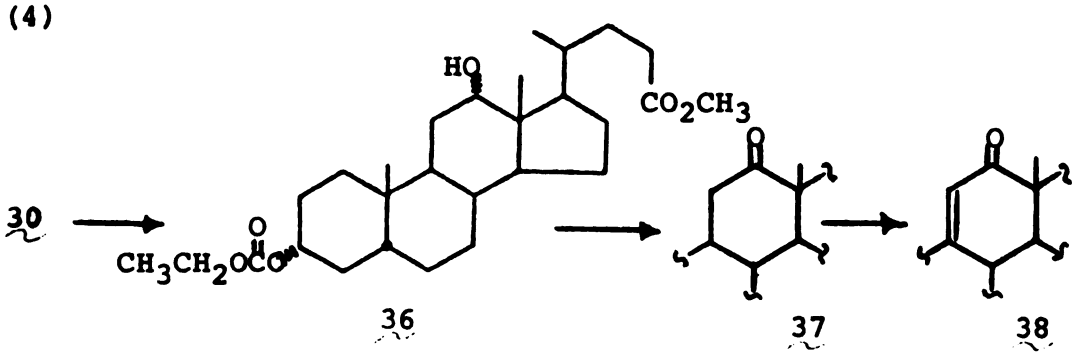
Finally, dehydrogenation of the diketone 31 with selenium dioxide or DDQ introduced double bonds in rings A and B only, and not at all in ring C[24]. The crude product mixture did not show a signal near δ5.6 in proton magnetic resonance (Pmr) spectra, a feature which is characteristic of ring C enone systems. Indeed, Nozoe and co-workers[24] have reported that there is no introduction of 9,11-double bond in diketone 31 under similar conditions.

Since the simultaneous introduction of both double bonds was not effective, a logical alternative was to study the stepwise introduction of double bonds at the 9,11- and 4,5-positions.

One of the two approaches employed here was first to selectively protect the 3-hydroxy group of methyl

deoxycholate 30 as the carbonate ester by treatment with ethyl choloroformate in pyridine[25]. Oxidation of the free 12-hydroxy group with Jones reagent[20], followed by introduction of the 9,11-double bond by treatment with selenium dioxide[26] gave enone 38 (Equation 4).

(4)

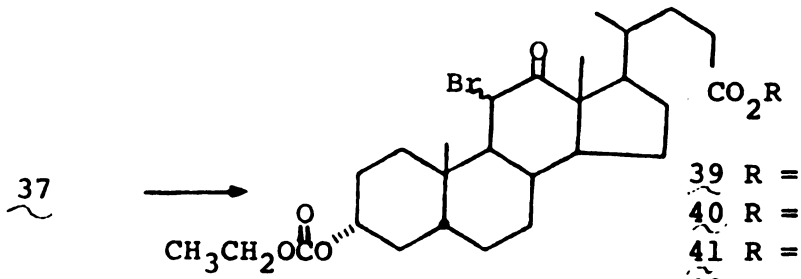


However compound 38 obtained in this way was contaminated with the saturated keto steroid 37, and this mixture could not be separated by fractional crystallization from ten different solvents and solvent mixtures. Furthermore, preparative thin layer chromatography, column chromatography (silica gel and alumina) and high pressure liquid chromatography (silica gel and C-18 reverse phase columns) failed to resolve the mixture, as indicated by Pmr, infra-red and mass spectroscopy. Efforts to separate this sharp melting mixture (mp 163-4°) of saturated and α,β-unsaturated keto steroids in subsequent steps of the synthesis also met with no success. Seebeck and Reichstein[27] have reported that 3α-hydroxy, 12-keto-$\Delta^{9(11)}$-cholenic acid does not depress

the melting point of 3α-hydroxy,12-keto-cholanic acid and that the melting point of a mixture of the methyl esters of these two acids is not depressed below that of the lower melting component. Likewise, E. C. Kendall and co-workers[26] were unable to separate a mixture of 3α-hydroxy,12-keto-cholanic acid and 3α-hydroxy,12-keto,$\Delta^{9(11)}$-cholenic acid by crystallization. A similar lack of mixture melting point depression was noted in the case of methyl 3α-ethoxycarbonyloxy,12-keto cholonate (mp 158-9°) and methyl 3α-ethoxycarbonyloxy,12-keto,$\Delta^{9(11)}$-cholenate (mp 167-8°), made in another reaction sequence discussed later.

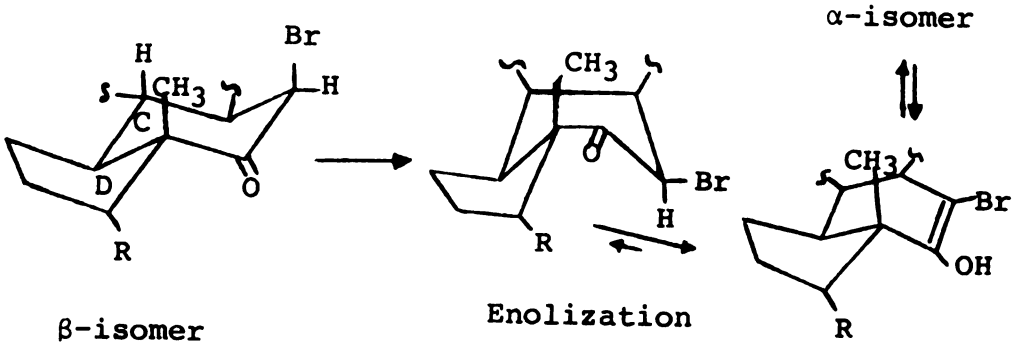
A second approach involving the α-bromination of 12-keto steroid 37 followed by dehydrobromination gave excellent results. Bromination in the presence of boron trifluoride etherate[21] in glacial acetic acid solution produced 3-ethoxycarbonyloxy,11-bromo,12-keto cholanic acid in nearly quantitative yield (Equation 5). The product was, however, found to be an epimeric mixture of 11α-bromo, 12-keto steroid 39 (95%) and 11β-bromo,12-keto steroid 40 (5%). The corresponding methyl esters 41 and 42 were separated easily by fractional crystallization, with melting points of 97-8° and 172-3° and optical rotations of 46.6° and 36.3° (C = .85, CH_2Cl_2) respectively. Mass spectra of 41 and 42 did not show parent ions (P), the fragment ion (P-Br) being the highest mass fragment in the spectrum.

(5)



Infrared spectroscopy played a key role in establishing the configurations of the two epimeric 11-bromo,12-keto steroids; the carbonyl stretching frequencies being 1735 cm^{-1} and 1710 cm^{-1} respectively. Jones and co-workers[28] have reported that an α-halogen atom having an axial orientation to the carbonyl group causes only a slight displacement in the location of the carbonyl stretching frequency, but an equitorially oriented bromine atom shifts the carbonyl stretching frequency to a higher value by about 20 cm^{-1}. This clearly indicated that the lower melting isomer ($\bar{\nu}_{max}$ 1735 cm^{-1}) had configuration 41 and the higher melting isomer ($\bar{\nu}_{max}$ 1710 cm^{-1}) configuration 42. The 11β-bromo,12-keto steroid 42 underwent a facile epimerization to 11α-bromo,12-keto steroid 41 in the presence of hydrobromic acid[21]. This isomerization probably proceeds by an enolization of the bromoketone in which the stereoelectronic effects favoring axial hydrogen loss is accommodated by bending of ring C. Thus an apparently equatorial hydrogen atom becomes pseudo-axial in the flexible or boat configuration of ring C (Scheme I).

Scheme I



Debromination of the 11α-bromo,12-keto steroid 41 or its β-isomer 42, by refluxing with zinc dust and glacial acetic acid[29] yielded the 12-ketosteroid 37 in each case, confirming that 41 and 42 are epimeric 11-bromo,12-keto steroids.

An attempt to eliminate hydrogen bromide from 11α-bromo, 12-keto steroid 41 by refluxing with methanolic potassium hydroxide gave an unidentified acidic substance that was clearly not the desired enone 38. The product, however, showed a parent ion at m/e 406 in its mass spectrum, and on treatment with diazomethane gave a substance with a parent ion at m/e 420, indicating the presence of only one carboxyl group. These facts suggest that in addition to the hydrolysis of the 3-carbonate ester and 24-methyl ester groups, an S_N2 substitution of the 11-bromo group by hydroxide ion might have taken place, giving 11-hydroxy,12-keto deoxycholic acid (m.w. 406). However, the hydrolysis

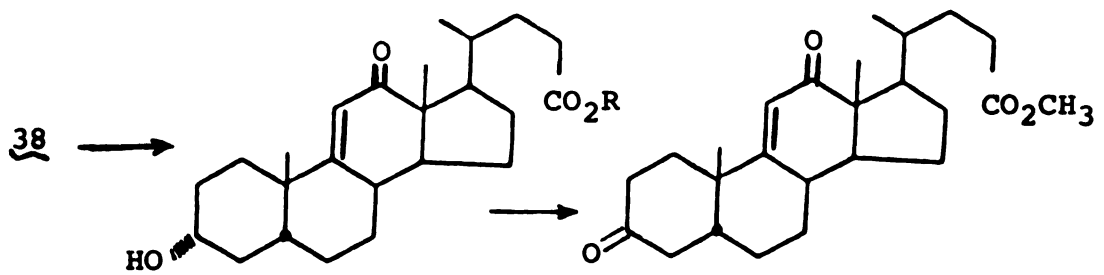
of 11α-bromo,12-keto steroid 41 with methanolic potassium hydroxide at room temperature gave 3α-hydroxy,11α-bromo, 12-keto deoxycholic acid.

Reaction of 11α-bromo,12-keto steroid 41 with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and dimethylsulfoxide (DMSO)[30] at room temperature was monitored by thin layer chromatography. In two weeks, only partial conversion to enone 38 had occurred, but in six weeks, conversion was complete. Fortunately, a more effective dehydrobromination procedure was found. Thus treatment of 11α-bromo,12-keto steroid 41 with a refluxing solution of lithium carbonate in dimethylformamide[22] gave enone 38 in almost quantitative yield in 5.5 hours. A two step conversion of saturated ketone 37 to enone 38 by bromination with boron trifluoride etherate and dehydrobromination with dimethylformamide and lithium carbonate was thereby achieved in very high yield (>95%).

As expected, enone 38 gave 12-keto,$\Delta^{9(11)}$-deoxycholenic acid 43 on hydrolysis with methanolic potassium hydroxide. The Pmr spectra of 43 showed a two proton signal at δ6.5. Since the signal disappeared on treatment with D_2O, it is probably the result of a fast exchange between the 3-hydroxy and the 24-carboxyl protons. Addition of freshly prepared diazomethane to a suspension of carboxylic acid 43 in ether gave the corresponding ester 44, which was oxidized to

methyl 3,12-diketo,$\Delta^{9(11)}$-deoxycholenate 45 with Jones reagent[20] (Equation 6).

(6)



43 R = H
44 R = CH_3

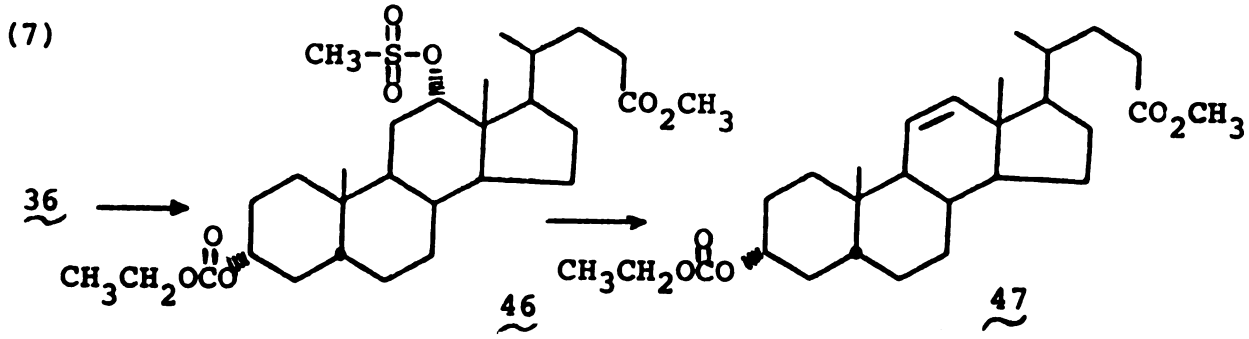
45

Although the bromination-dehydrobromination sequence from 37 is undoubtedly the best route to the $\Delta^{9(11)}$-ene-12-one functionality, another approach that was studied at the same time merits discussion because of its unusual chemistry. This procedure was based on a brief report in the patent literature[31] that aquous hypobromous acid converted 11-dehydroprogesterone to its $\Delta^{9(11)}$-ene-12-ol derivative. Such an enol could, of course, be oxidized to $\Delta^{9(11)}$-ene-12-one steroid by any of several oxidizing agents. Since hypobromous acid normally adds to carbon-carbon double bonds to give bromohydrins, and since in the case of Δ^{11}-steroids the major bromohydrin is presumed to have the 11β-hydroxy-12α-bromo configuration (structure 49), the report raised several

questions that this study has tried to answer.

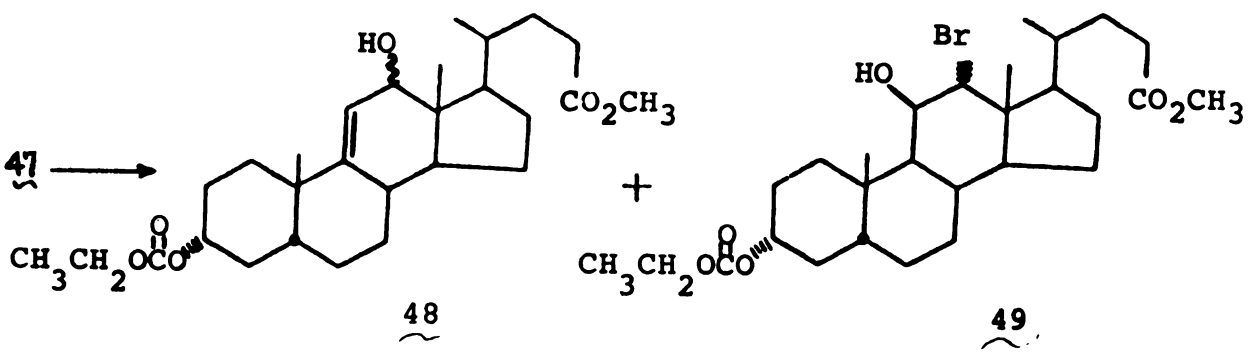
Initial efforts to prepare the Δ^{11}-steroid 47 by phosphorous oxychloride dehydration[32] of alcohol 36 proceeded in poor yield (<50%). Consequently, a stepwise reaction sequence that involved formation of a methanesulfonate 46 from alcohol 36, followed by thermolytic elimination of methanesulfonic acid[33] was developed, and gave excellent yields (>90% for two steps) of the desired alkene 47 (Equation 7).

(7)



Addition of aquous hypobromous acid to 47 gave the reported enol 48 (45%) along with bromohydrin 49 (39%), the mixture being easily separable by thin layer chromatography (Equation 8).

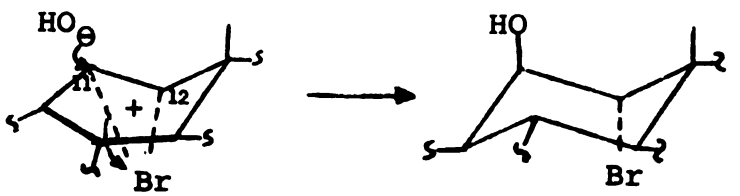
(8)



Since enol 48 was converted to enone 38 upon Jones oxidation, the structure of this product is unquestioned. It remained to be determined whether the assignment of configuration 49 to the bromohydrin product is correct, and whether this product is an intermediate in the formation of enol 48. Early studies of hypobromous acid addition to Δ^{11}-steroids by Reichstein and co-workers[34] concluded that 11-hydroxy, 12-bromo steroids were the major products, but noted that 12-hydroxy,9,11-dibromo compounds were by products. The stereochemistry of the bromohydrin was incorrectly assigned by Reichstein and was later corrected by Fieser[35] in his monograph "Steroids". Configuration 49 would in fact be predicted by application of the Fürst-Plattner rule[36] to the addition of hypobromous acid to 47. According to this rule,

addition reactions to double bonds which proceed through three-membered cyclic intermediates preferentially give trans-diaxial products[37]. Formation of a bromonium ion intermediate from 47 would undoubtedly occur at the less hindered α-face of the double bond. This bromonium ion (Scheme II) would then suffer diaxial ring opening only if a nucleophile such as water (or hydroxide) attacked C-11 from the β-side. The result of this reaction would be bromohydrin 49.

Scheme II

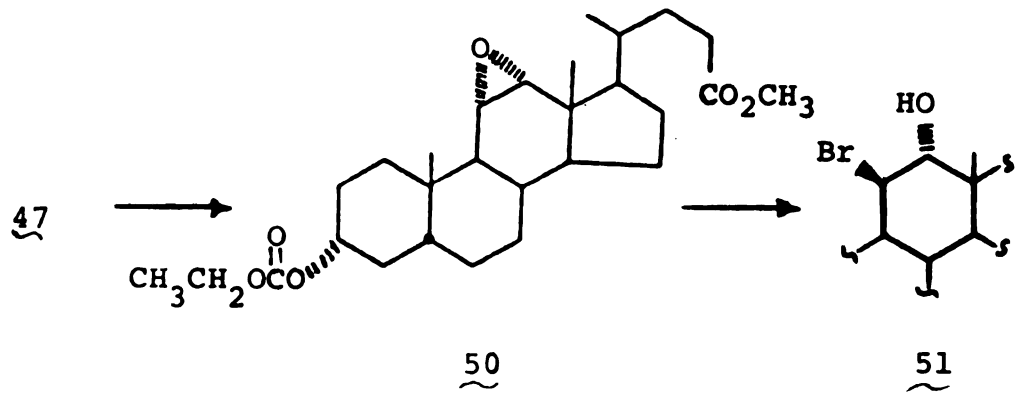


49

It is interesting to note that the anti-coplanar transition states that lead to trans-diaxial products are preferred even though severe steric hinderance may be present (as in this case). The Pmr spectrum of bromohydrin 49 agrees with the predicted structure.

It is informative to compare bromohydrin 49 with the isomer 51 obtained from epoxide 50 by addition of hydrobromic acid[29]. Epoxide 50 is prepared from alkene 47 by reaction with a peracid[38] (Equation 9).

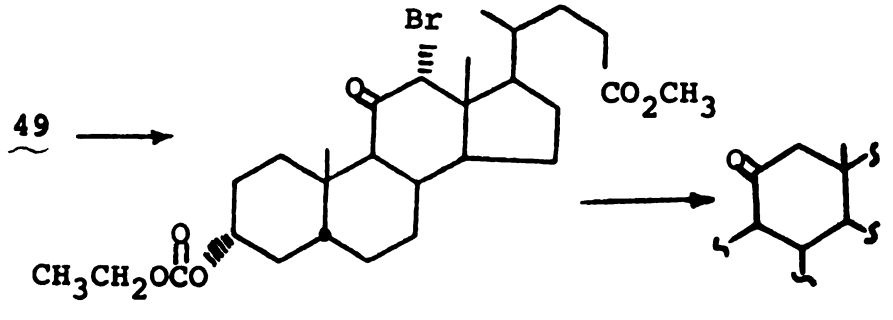
(9)



50 51

Bromohydrin 51 was clearly different from bromohydrin 49 as indicated by thin layer chromatography and Pmr spectra. Bromohydrin 51 on oxidation with chromium trioxide in glacial acetic acid[29] gave the 11β-bromo,12-keto steroid 42, which on debromination with zinc dust and glacial acetic acid[29] gave 12-keto steroid 37. Oxidation of bromohydrin 49 under similar conditions gave the 12-bromo,11-keto steroid 52, which on debromination gave 11-keto steroid 53 (Equation 10), as reported by Archer et al.[39]

(10)

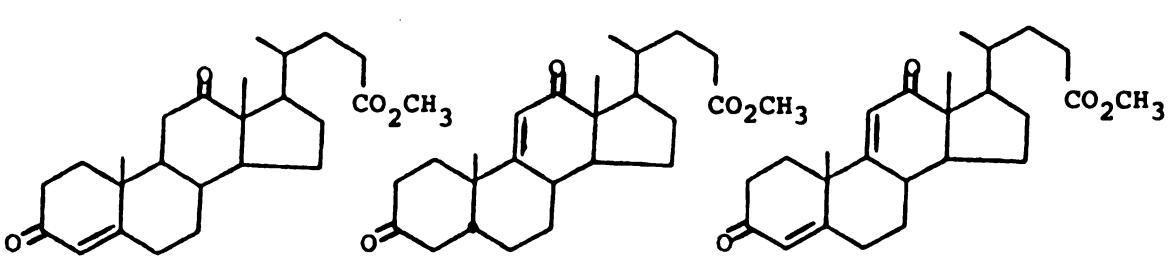


52 53

Bromohydrin 49 remained unchanged on treatment with aqueous hypobromous acid or aqueous bicarbonate.[40] Surprisingly, it did not form an epoxide even on heating with sodium hydroxide solution. All these observations indicated that enol 48 and bromohydrin 49 were being formed by two different reaction paths from the alkene 47.

Once it was recognized that enol 48 was a major product from the reaction of 47 with hypobromous acid, it was possible to modify the reaction conditions so as to give enone 38 directly. Treatment of the alkene 47 with aqueous perchloric acid and N-bromoacetamide in dark[40] gave a mixture of the enone 38 and bromohydrin 49. The enone 38 was fractionally crystallized from acetone in moderate yield (40%).

Having independently synthesized the two enedione systems 35 and 45, the next step was to put the procedures together to get the dienedione 55. This proved to be

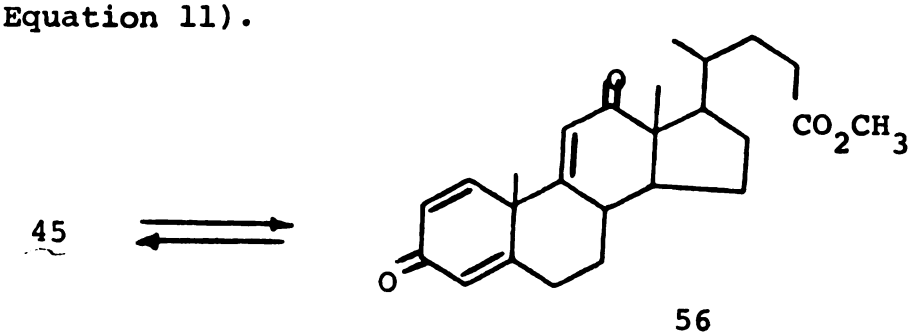


35 45 55

unexpectedly difficult. Efforts to brominate the 11- and 4-positions in 35 and 45 respectively met with no success[40]. Reactions of 35 and 45 with pyrolidone-2 hydrotribromide (PHT)[41] proceeded very poorly and also 35 and 45 remained largely unchanged on refluxing with ethyl acetate and cupric bromide[42]. Reaction of 45 with phenyl selenium halides followed by oxidative elimination[12] proceeded very poorly and most of the starting material (79%) was recovered unchanged from the reaction mixture.

Treatment of the enedione 45 with selenium dioxide in t-amyl alcohol[43] gave methyl 3,12-diketo,$\Delta^{1,4,9(11)}$-cholatrinate 56. Surprisingly, 56 was resistant to reduction by Wilkinson's catalyst (tris triphenyl chlororhodium) and hydrogen in contrast to the facile and selective reduction of the Δ^1-double bond reported for cholesta-1,4-diene-3-one[44] under similar conditions. Even more unexpected was the finding that a 1:1 mixture of tristriphenyl chlororhodium and cyclooctene rhodium complex catalyzed the reduction of both Δ^1 and Δ^4-double bonds[45], reforming enedione 45. These reactions were repeated several times with identical results (Equation 11).

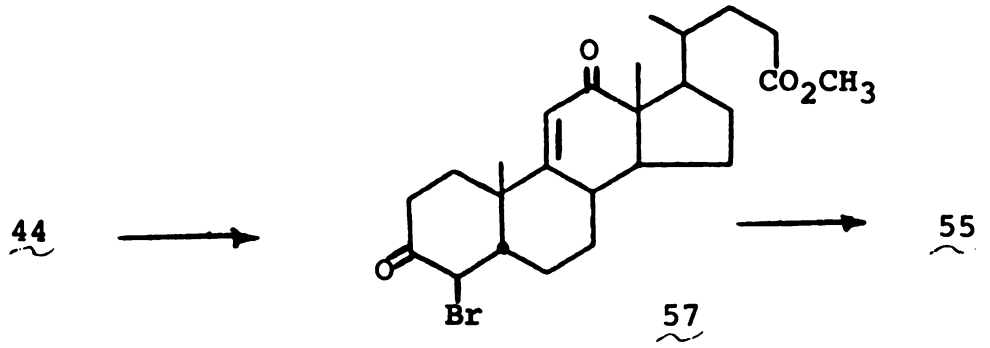
(11)



56

Efforts to simultaneously oxidize and α-brominate methyl 3α-hydroxy,12-keto,$\Delta^{9(11)}$-cholenate 44 by treatment with hydrobromic acid and an excess of N-bromoacetamide[23] produced a mixture of two compounds. One of them was established to be the expected product 57. And the other product, whose structure was not established, appeared to have added a mole of hypobromous acid across the 9,11-double bond of 44 in addition to oxidation and bromination in ring A. This was indicated by Pmr, infra red and mass spectra of the compound. However, addition of exactly two equivalents of N-bromoacetamide and hydrobromic acid to 44 gave only 57, which on dehydrobromination with a refluxing solution of lithium carbonate in anhydrous dimethylformamide[22] gave dienedione 55 (Equation 12).

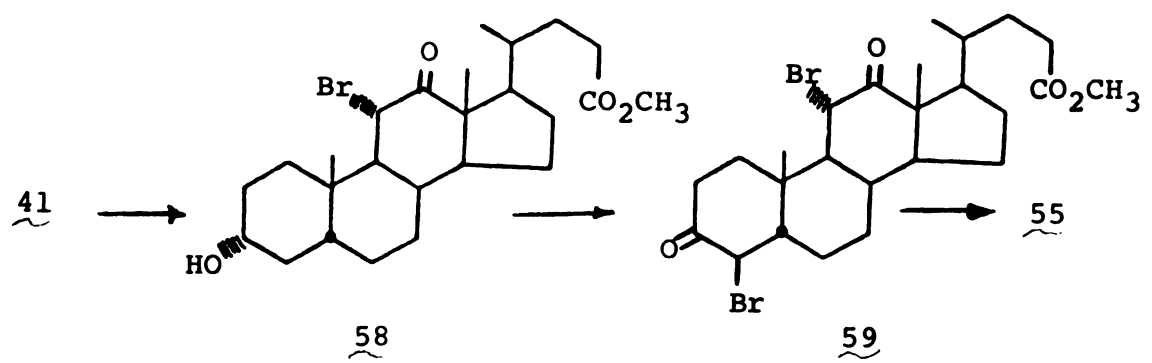
(12)



Another approach involved oxidation and α-bromination of methyl 3α-hydroxy, 11α-bromo,12-keto cholanate 58, which was obtained by hydrolysis of methyl 3α-ethoxycarbonyloxy, 11α-bromo,12-keto cholanate 41 with a 2.5% methanolic potassium hydroxide solution followed by esterification with

diazomethane. Steroid 58 on treatment with two equivalents of N-bromoacetamide and hydrobromic acid gave dibromide 59, which on bis dehydrobromination with lithium carbonate and dimethylformamide[22] gave dienedione 55 (Equation 13).

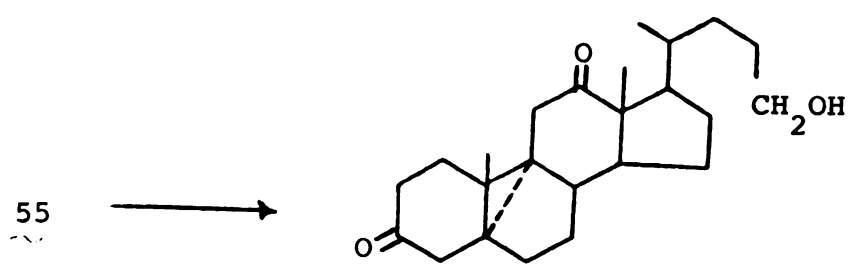
(13)



Synthesis of methyl 3,12-diketo,$\Delta^{4,9(11)}$-choladienate 55 by two different approaches had achieved the first goal of this research. The next step would be to subject $\Delta^{4,9(11)}$-dien-3,12-dione 55 to lithium and ammonia reduction and see if the two ring A and ring C enone systems behave independently or 55 behaves as a bis-vinylog of cyclohexane-1,3-dione.

Lithium and ammonia reduction of diendione 55 gave a product that could not be purified by either crystallization or chromatography (silica gel or alumina). Further work needs to be done for characterization of the product. However, the initial examination of the spectral data on the

crude product indicated that 55 behaved as a bis-vinylog of cyclohexan-1,3-dione. In addition, the C_{24}-ester seemed to have been reduced to the corresponding alcohol. The product was tentatively assigned the structure 60.



60

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 and lithium and ammonia reduction. Organic extracts were generally dried over anhydrous magnesium sulfate, before being concentrated, unless otherwise specified. The progress of most reactions was followed by thin layer chromatography (Tlc) using 30% sulfuric acid as spray reagent and subsequent heating or ultraviolet (UV) light.

Preparative Tlc was carried out on a 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 either a Hoover-Thomas apparatus (capillary tube) or 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 ($CDCl_3$) or carbon tetrachloride (CCl_4) solutions with a

Varian T-60 or Bruker Spectrospin (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 or LKB 9000 mass spectrometers. Optical rotations were measured with a Perkin-Elmer 141 Polarimeter using methylene chloride solutions with concentrations of 8-10 mg/ml.

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

General procedure for oxidation with Jone's reagent

To a solution of the compound in acetone kept in a water bath at 30-35°, a solution of 8 N chromium trioxide-sulfuric acid (8 N Cro_3-H_2SO_4), made by dissolving 26.72 g Cro_3 in 23 ml concentrated H_2SO_4 and diluting to 100 ml with distilled water, was added dropwise until yellow color persisted. Excess of Jone's reagent was destroyed by dropwise addition of methanol. After concentrating the green solution in vacuo, water was added and the precipitated product filtered and air dried.

General procedure for esterification with diazomethane on .001 M scale

In a 500 ml round bottom flask with side arm condenser kept in an ice bath was added N,N'-dinitroso-N,N'-dimethyl

terephthalamide (0.3 g, Dupont EXR-101), 7.5 ml of 30% sodium hydroxide solution, 2 ml of diethylene glycol monoethyl ether and 25 ml of diethyl ether. Ice bath was removed, the reaction flask was heated carefully on a steam bath and a solution of diazomethane in ether was condensed over a solution or slurry of the carboxylic acid using water condenser. The reaction mixture was stirred in a hood for 1-4 hour period and then the ether removed. Excess of diazomethane precursor was destroyed by dropwise addition of acetic acid.

General procedure for bromination of keto steroids using BF_3 catalyst

To a solution of the keto steroid in glacial acetic acid under Argon, bromine was added dropwise followed by addition of boron trifluoride etherate. The reaction mixture was stirred at room temperature for five days, diluted with water and sufficient sodium bisulfite was added to destroy excess bromine. The precipitated product was filtered, washed with water and air dried.

General procedure for oxidation and α-bromination of hydroxy steroids

The starting material was dissolved in t-butyl alcohol by heating on a steam bath. To this solution at room temperature, were added 2-3 ml of water, 48% hydrobromic acid and N-bromoacetamide. After stirring at room

temperature for 43 hr, a 5% sodium sulfite solution was added to the reaction mixture to destroy excess NBA and extracted with ether. The ether extract was washed sequentially with water, sodium hydrogen carbonate solution and brine, and then dried. Removal of the solvents gave the crude product.

General procedure for dehydrobromination of α-bromo ketones with lithium carbonate and dimethylformamide

The α-bromo keto steroid was added to a suspension of lithium carbonate in dimethylformamide under Argon. The reaction mixture was heated in an oil bath at 160-70° for 5.5 hr using an air condenser. The suspension was cooled, diluted with ether and lithium carbonate was neutralized by dropwise addition of 6 N hydrochloric acid. Water was added and the two layers separated. The ether layer was successively washed with water, sodium hydrogen carbonate solution and brine, and then dried. Removal of ether gave the crude product.

Preparation of Methyl 3,12-diketocholanate 31

A solution of 10 g (.0254 M) of deoxycholic acid 29 in 100 ml of methanol containing 1 ml of 37% hydrocholric acid was refluxed for 45 min. and then condensed in vacuo to a small volume. The residue was dissolved in ether and the ether solution was washed sequentially with water, saturated

sodium carbonate solution, water, brine and dried over anhydrous sodium sulfate. After removal of the solvents, 10.29 g (99%) of methyl deoxycholate 30 obtained was pure enough for further reactions.

A solution of 30 (10.29 g) in 200 ml of acetone was oxidized to methyl 3,12-diketocholanate 31 using Jone's reagent (6.4 ml of 8N Cro_3-H_2SO_4). Recrystallization of the product from ethyl acetate yielded 9.53 g (93%) of pure 31 as prisms, mp 132-3° (lit. 129-30°), $[\alpha]_D^{25°}$ + 90.9° (lit. + 90.4° ± 4°).

Preparation of Methyl 2-bromo-3,12-diketo-$\Delta^{1,4,9(11)}$-cholatrienate 33

A solution of 31 (2.01 g, .005 M) in glacial acetic acid (50 ml) under Argon was brominated by the usual procedure using 1.06 ml (.02M) of bromine and boron trifluoride etherate (5 drops). The crude product upon esterification with diazomethane by the usual procedure followed by recrystallization from methanol gave pure methyl 2,2,4,11-tetrabromo-3,12-diketo cholanate 32, mp 112-3°, $[\alpha]_D^{25}$+ 4.6°; ir ($CDCl_3$) 1730, 1700 cm^{-1}; Pmr ($CDCl_3$) δ 1.07 (S,3 H), 1.47 (S, 3H), 3.6 (S, 3H), 4.97 (d, J = 10 Hz, 1H), 5.11 (d, J = 12 Hz, 1 H); ms, m/e 558.06970 (M^+, calc. for $C_{25}H_{32}O_4Br_2^{81}$, corresponding to P-2HBr) and 557.06647 (M^+, calc. for $C_{25}H_{33}O_4Br^{79}Br^{81}$, corresponding to P-Br-HBr).

The tetrabromo steroid 32 (1.44 g, .002 M) was tris-dehydrobrominated with lithium carbonate (2.0 g) and dimethylformamide (20 ml) by the usual procedure to give 0.75 g (95%) of the crude product as a light yellow oil. An analytical sample of methyl 2-bromo-3,12-diketo-$\Delta^{1,4,9(11)}$ cholatrienate 33 was obtained as rhombic crystals by crystallization from acetone, mp 168-9° $[\alpha]_D^{25}$+ 2.1°; ir ($CDCl_3$) 1735, 1685, 1665, 1605, 1600 cm^{-1}; Pmr ($CDCl_3$) δ1.0 (S, 3H), 1.57 (S, 3H), 3.6 (S, 3H), 5.73 (d, J = 2Hz, 1 H), 6.13 (S, 1H), 7.47 (S, 1H); ms (70 eV) m/e (rel. intensity) 476 (8), 474 (8), 396(17), 241(100), 240(90).

Anal. Calcd. for $C_{25}H_{31}O_4Br$:C, 63.16; H, 6.57;
Found :C, 63.07; H, 6.70.

Oxidation and α-bromination of Methyl deoxycholate 30

Treatment of one gram (.00246 M) of methyl deoxycholate 30 with 50 ml of t-butyl alcohol, 3.6 ml of water, 0.6 ml (.00492 M) of 48% hydrobromic acid and 2.04 g (.0148 M) of N-bromoacetamide by the usual procedure for oxidation and α-bromination of hydroxy steroids gave a light yellow solid which on recrystallization from acetone yielded 0.948 g (80%) of methyl 4-bromo-3,12-diketocholanate 34 as colorless needles, mp 121-3°; $[\alpha]_D^{25°}$+ 107.6°; ir ($CDCl_3$) 1735, 1710 cm^{-1}; Pmr ($CDCl_3$) δ0.95 (S, 3H), 1.47 (S, 3H), 3.5 (S, 3H),

5.0 (d, J = 12 Hz, 1H); ms (70 eV) m/e (rel. intensity) 482 (49), 480 (49), 401 (100).

Preparation of Methyl 3,12-diketo-Δ^4-cholenate 35

0.481 g (.001 M) of methyl 4-bromo-3,12-diketo cholanate 34 was dehydrobrominated using 0.7 g of lithium carbonate and 10 ml of dimethylformamide by the usual procedure afforded 0.395 g (99%) of crude 35, mp 118-20°. Recrystallization from acetone gave pure 35 as prisms, mp 145-6°; $[\alpha]_D^{25}$ + 116.7°; ir (CCl_4) 1735, 1710, 1675, 1615 cm^{-1}; Pmr (CCl_4) δ0.93 (S, 3H), 1.15 (S, 3H), 3.4 (S, 3H), 5.42 (s, 1H); ms (70 eV) m/e (rel. intensity) 400 (100), 285 (20), 245 (86).

Preparation of Methyl 3α-ethoxycarbonyloxy, 12-ketocholanate 37

To a solution of methyl deoxycholate 30 (4.06 g, .01 M) in dioxane (20 ml) and pyridine (3.2 ml) cooled in an ice-water bath, ethylcholoroformate (4.0 ml) was added dropwise. The ice water bath was removed and the reaction mixture stirred at room temperature for 30 min. 50 ml of water containing 2.0 ml of 37% hydrochloric acid was added and the reaction mixture was heated on a steam bath for 30 min. 250 ml of ether was added after cooling the reaction mixture and

washed sequentially with water, sodium hydrogen carbonate solution and brine, and then dried. Removal of the solvents afforded the crude product which was recrystallized from methanol to give 4.0 g (83%) of methyl 3α-ethoxycarbonyloxy deoxycholate 36, mp 142-3° (lit. 142-3°); $[\alpha]_D$ + 56° (lit. + 54° ± 2°).

The diester 36 (2.39 g, .005 M) in 70 ml of acetone was oxidized to 12-keto steroid 37 with Jones reagent by the usual procedure. Recrystallization from ethyl acetate gave 2.26 g (91%) of pure 37, mp 159-60° (lit. 157-9°), $[\alpha]_D^{25}$ + 90.6° (lit. + 91° ± 1°).

Preparation of Methyl 3α-ethoxycarbonyloxy-12-keto-$\Delta^{9(11)}$-cholenate 38

2.38 g. (.005M) of 12-keto steroid 37 was dissolved in 100 ml of a 4:1 mixture of chlorobenzene and acetic acid. 0.666 g (.006M) of selenium dioxide and a drop of hydrochloric acid were added and the reaction mixture was refluxed for 72 hr. After cooling, the reaction mixture was filtered through a short pad of Celite. The filtrate was concentrated to a small volume in vacuo, diluted with ether (250 ml) and washed successively with water, sodium hydrogen carbonate solution and brine and then dried. Removal of the solvents yielded 2.0 g (84%) of crude product. Recrystallization from acetone gave a sharp melting (163-4°) mixture of 37

(20%) and 38 (80%) as indicated by ir, Pmr and mass spectral analysis. Identical results were obtained by recrystallization from methanol, ethanol, ethyl acetate and various mixture of solvents with ether, benzene and hexanes. Chromatography on alumina or silica gel columns did not improve the percentage of 38 in the mixture. However, 99.9% pure 38 (mp 167-8°) was obtained by three different methods as discussed later.

Bromination of Methyl 3α-ethoxycarbonyloxy, 12-keto cholanate 37

A solution of 37 (4.74 g, .01 M) in glacial acetic acid (50 ml) under Argon was brominated by the usual procedure using 0.8 ml (.015 M) of bromine and five drops of boron trifluoride etherate. 5.45 g (99%) of the crude product was obtained upon addition of sodium sulfite and water. A 1.20 g portion of the crude product was chromatographed on silica gel, elution with chloroform gave 0.886 g (73.8%) methyl 3α-ethoxycarbonyloxy, 11-bromo,12-keto cholanate (A) and 0.291 g (24.2%) 3α-ethoxycarbonyloxy,11-bromo,12-keto cholanic acid (B). Treatment of B with dizaomethane in ether by the usual procedure gave A. Recrystallization of combined A from methanol gave methyl 3α-ethoxycarbonyloxy,11α-bromo,12-keto cholanate 41 (1.0 g, 90%), mp 97-8°; $[\alpha]_D^{24°}$ + 46.6°; ir (CCl_4) 1730 cm^{-1}; Pmr (CCl_4)

δ1.0 (S, 3H), 1.17 (S, 3H), 3.55 (S, 3H), 4.0 (q, J = 7 Hz, 2H), 4.27-4.62 (m, 1H), 4.81 (d, J = 10 Hz, 1H); ms (70 eV) m/e (rel. intensity) 525 (1), 523 (1), 475 (65), 474 (19), 385 (35).

Anal. Calcd. for $C_{28}H_{43}BrO_6$:C, 60.54; H, 7.80;
Found :C, 60.46; H, 7.80.

The mother liquor from A upon recrystallization from methanol gave methyl 3α-ethoxycarbonyloxy,11β-bromo,12-keto cholanate 42 (0.059 g, 5%), mp 172-3°; $[\alpha]_D^{24°}$ + 36.3°; ir (CCl_4) 1730, 1700 cm^{-1}; Pmr (CCl_4) δ1.25 (S, 3H), 1.22 (S, 3H), 3.57 (S, 3H), 4.03 (q, J = 7 Hz, 2H), 4.17-4.27 (m, 1H), 4.27-4.70 (m, 1H); ms (70 eV) m/e (rel. intensity) 525 (<1) 523 (<1), 475 (33), 474 (24), 385 (27), 384 (23).

Epimerization of 11β-bromo ketone 42 to 11α-bromo ketone 41

A mixture of 50 mg of 11β-bromo ketone 42 and a 10% hydrobromic acid solution in acetic acid (10 ml) was stirred at room temperature under Argon for two days. The reaction mixture was diluted with 100 ml of water and extracted with chloroform. Removal of the solvents and recrystallization of the residue from methanol afforded a crystalline product identical in all respects with 11α-bromo ketone 41.

Zinc and Acetic Acid Debromination of 11α-bromo ketone 41

A solution of 50 mg of 41 in 2 ml of glacial acetic acid was refluxed with 50 mg of zinc dust under Argon for one hour. After filtration the solution was diluted with 100 ml of ether and washed successively with water, sodium carbonate solution and brine, and then dried. Removal of the solvent and recrystallization of the residue from ethyl acetate gave 38 mg (88%) of crystalline product identical in all respects with 37.

Zinc and Acetic Acid Debromination of 11β-bromo ketone 42

Treatment of 30 mg of 42 in 2 ml of glacial acetic acid with 30 mg of zinc dust under similar conditions as for 41 gave 20 mg (87%) of product, after recrystallization from ethyl acetate, that was also identical in all respects with 37.

Dehydrobromination of 11α-bromo ketone 41

A. With DBU and DMSO

To a solution of 11α-bromo ketone 41 (0.555 g, .001 M) in dry DMSO (10 ml), 0.25 g (.002 M) of DBU was added and the reaction mixture stirred under Argon at room temperature.

In six weeks, all the starting material had disappeared as indicated by thin layer chromatography on a small scale ether extract of reaction mixture. 200 ml of water was added to the reaction mixture and extracted with three 100 ml portions of methylene chloride. The combined extracts were washed sequentially with five 200 ml portions of water and once with brine, and then dried. Removal of methylene chloride gave enone 38 (0.45 g, 95%) which was recrystallized from acetone, mp 167-8°.

B. With Lithium Carbonate and Dimethylformamide

11β-bromo ketone 41 (0.555 g, .001 M) was dehydrobrominated by the usual procedure using 0.833 g of lithium carbonate and 10 ml of dimethylformamide to give 0.47 g (99%) of enone 38. Recrystallization from acetone gave pure 38, mp 167-8° (lit. 158-60°), $[\alpha]_D^{25}$+ 109° (lit. 92 ± 2°); ir (KBr) 1735, 1675, 1605 cm^{-1}; Pmr ($CDCl_3$) δ0.88 (S, 3H), 1.17 (S, 3H), 3.6 (S, 3H), 4.09(q, J = 7 Hz, 2H), 4.3-4.8 (m, 1H), 5.6 (d, J = 2 Hz, 1H); ms (70 eV) m/e (rel. intensity) 474 (92), 385 (38), 384 (100), 229 (97).

Anal. calcd. for $C_{28}H_{42}O_6$:C, 70.86; H, 8.92;
Found :C, 70.91; H, 8.89.

Preparation of Methyl 3,12-diketo-$\Delta^{9(11)}$-cholenate 45

A 2.37 g (.005 M) solution of enone 38 in 40 ml of methanol containing 20 ml of 10% potassium hydroxide was refluxed for 90 min. under Argon. Methanol was removed in vacuo, the residue dissolved in water and acidified with 6N hydrochloric acid. The precipitated product was filtered, washed with water and air dried to give 3α-hydroxy,12-keto, $\Delta^{9(11)}$-cholenic acid 43 (1.89 g, 98%) which was recrystallized from methanol, mp. 177-8°; $[\alpha]_D$ + 87°; ir ($CDCl_3$) 3575, 3490, 1700, 1670, 1600 cm^{-1}; Pmr (CCl_4) δ0.9 (S, 3H), 1.0 (d, J = 4 Hz, 3H), 1.17 (S, 3H), 3.3-3.9 (m, 1H), 5.65 (d, J = 2Hz, 1H), 5.97 (bs, 24).

A suspension of 1.89 g (.0049 M) of 43 in 100 ml of ether was esterified with diazomethane by the usual procedure to give 1.94 g (99%) of the methyl ester 44. A solution of this methyl ester in 50 ml of acetone was oxidized with Jones reagent by the usual procedure to give 1.90 g (98%) of the crude product, which was recrystallized from ethyl acetate to give enedione 45, mp 131-2°; $[\alpha]_D^{25}$ + 69.3° (lit. 71.6 ± 2°); ir (KBr) 1730, 1710, 1680, 1605 cm^{-1}; Pmr (CCl_4) δ0.9 (S, 3H), 1.25 (S, 3H), 3.53 (S, 3H), 5.63 (d, J = 2Hz, 1H) ms (70 eV) m/e (rel. intensity) 400 (22), 369 (5), 245 (31), 121 (100).

Preparation of Methyl 3 -ethoxycarbonyloxy, Δ^{11}-cholenate 47

A. Dehydration of 36

A 4.78 g (.01 M) solution of 36 in 50 ml of pyridine and phosphorous oxychloride (23 g, .15 M) was stirred under nitrogen at 50° for 24 hr. After cooling, the reaction mixture was diluted with ice water and extracted with three 100 ml portions of ether. The combined ether extracts were washed sequentially with water, 1N hydrochloric acid and brine, and then dried. Removal of ether gave an oil that crystallized out from dioxane to yield 47 (2.3 g, 50%), mp 135-6°.

B. Via Mesylate 46

Methanesulfonyl chloride (1.6 g, .014 M) was added dropwise to an ice cooled solution of 36 (4.78 g, .01 M) in 50 ml of dry pyridine. The reaction mixture was stirred under Argon at room temperature for 24 hr, poured into ice cooled brine (100 ml) and extracted with three 100 ml portions of ether. The combined ether extracts were washed sequentially with water, 1N hydrochloric acid and brine, and then dried. Removal of ether gave mesylate 46 (5.50 g, 99%), mp 154° (d); $[\alpha]_D$ + 69.2°, ir (CCl_4) 1735 cm^{-1}; Pmr (CCl_4) δ0.75 (S, 3H), 0.91 (S, 3H), 2.97 (S, 3H), 3.53 (S, 3H), 4.03 (q, J = 7 Hz, 2H), 4.2-4.66 (m, 1H), 4.93 (bs, 1H);

ms (70 eV) m/e (rel. intensity) 460 (<1), 371 (67), 370 (96), 256 (49), 255 (100).

Anal. Calcd. for $C_{29}H_{48}O_8S$:C, 62.56; H, 8.69;
Found :C, 62.47; H, 8.70.

A mixture of 50 ml of hexamethylphosphoric triamide (distilled over CaH_2), 4 g (.04 M) of potassium acetate and 5.0 g (.009 M) of mesylate 46 was stirred under N_2 at 100° for two days. After cooling, the reaction mixture was poured into 500 ml of ice water. The precipitated product was filtered, washed with water and air dried. Recrystallization from dioxane afforded 47 (3.93 g, 95%), mp 135-6°; $[\alpha]_D$ + 39.5°; ir (KBr) 1735, 1615 cm^{-1}, Pmr (CCl_4) δ0.7 (S, 3H), 0.87 (S, 3H), 3.53 (S, 3H), 4.0 (q. J = 7 Hz, 2H); 4.27-4.63 (m, 1H), 5.25 (d, J = 10 Hz, 1H), 5.97 (dd, J = 10 Hz, 3 Hz, 1H); ms (70 eV) m/e (rel. intensity) 460 (<1), 370 (100), 255 (85).

Anal. Calcd. for $C_{28}H_{44}O_5$:C, 73.01; H, 9.63;
Found :C, 73.06, H, 9.67.

Addition of Hypobromous Acid to Alkene 47

To a mixture of alkene 47 (0.46 g, .001 M) and N-bromoacetamide (0.276 g, .002 M) in 50 ml of dioxane under Argon, 27.5 ml of 0.16N perchloric acid was added dropwise. After stirring for 20 min. at room temperature, excess N-bromoacetamide was destroyed by adding a 10% sodium sulfite

solution and the reaction mixture extracted with chloroform. The chloroform extract was washed sequentially with water, sodium hydrogen carbonate solution and brine, and then dried. Removal of solvents gave 0.56 g of an oil. Thin layer chromatography indicated it to be a mixture of two different compounds. Addition of ether to the oil gave 100 mg of a white solid which was recrystallized from methanol to give bromohydrin 49, mp 179-80°; $[\alpha]_D$ + 51°; ir (KBr) 3400, 1735 cm^{-1}; Pmr (CCl_4) δ1.18 (S, 3H), 1.22 (S, 3H), 3.57 (S, 3H), 4.06 (q, J = 7 Hz, 2H), 4.3-4.63 (m, 1H), 4.7 (d.d, J = 2 Hz and 3 Hz, 1H), 4.97 (d, J = 2 Hz, 1H); ms (70 eV) m/e (rel. intensity) 541 (2.5), 539 (2.5), 458 (31), 270 (56), 369 (100).

In another experiment, 100 mg of the crude product was separated by preparative thin layer chromatography on a 2 mm silica gel plate to give 39 mg of bromohydrin 49 and 45 mg of enol 48, mp 145° (d); ir (CCl_4) 3460, 1735, 1600 cm^{-1}; Pmr (CCl_4) δ0.83 (S, 3H), 1.17 (S, 3H), 3.53 (S, 3H), 4.06 (q, J = 7 Hz, 2H), 4.23-4.80 (m, 2H), 5.57 (d, J = 2 Hz, 1H); ms (70 eV) m/e (rel. intensity) 476 (16), 386 (60), 231 (100).

Enol 48 on oxidation with Jones reagent by the usual procedure gave enone 45.

Preparation of 11α,12α-epoxide 50

To a solution of alkene 47 (0.46 g, .001M) in 20 ml of chloroform, 0.25 g (.0011 M) of 75% m-chloroperbenzoic acid was added and the reaction mixture stirred under N_2 at room temperature for 4 hr. After diluting with 200 ml of chloroform, the reaction mixture was washed successively with water, sodium carbonate solution and brine, and then dried. Recrystallization from methanol gave 11 ,12 -epoxide 50 (0.45 g, 95%), mp 147.5-8°; $[\alpha]_D^{25}$+ 34°; ir (CCl_4) 1735, 1260 cm^{-1}; Pmr (CCl_4) δ0.67 (S, 3H), 0.9 (S, 3H), 2.67 (d, J = 4 Hz, 1H), 2.86 (d, J = 4 Hz, 1H), 3.5 (S, 3H), 4.0 (q, J = 7 Hz, 2H), 4.2-4.7 (m, 1H); ms (70 eV) m/e (rel. intensity) 476 (6), 386 (45), 271 (49), 253 (100).

Anal. Calcd. for $C_{28}H_{44}O_6$:C, 70.56; H, 9.30;
Found :C, 70.53; H, 9.39.

Preparation of Bromohydrin 51

To a solution of epoxide 50 (0.238 g, .0005 M) in 20 ml of acetone, 1 ml of 48% hydrobromic acid was added dropwise. After stirring under nitrogen for 2 hr. at room temperature, acetone was removed under vacuo, the residue diluted with water and extracted with ether. The ether extract was washed successively with water, sodium hydrogen carbonate solution and brine, and then dried. An excess

diazomethane in ether was added and the solvent removed after stirring for 1 hr. at room temperature to give bromohydrin 51 (0.25 g, 90%) as an oil. A 139 mg portion of the crude product was separated on a silica gel column by high pressure liquid chromatography (25% ethyl acetate in hexane elutant) to give 111 mg (80%) of bromohydrin 51 as an oil which could not be crystallized, ir (CCl_4) 3600, 3480, 1735 cm^{-1}; Pmr (CCl_4) δ1.0 (S, 3H), 1.17 (S, 3H), 2.57-3.07 (m, 1H), 3.52 (s, 3H), 4.0 (q, J = 7 Hz, 2H), 4.2-4.7 (m, 3H), ms (70 eV) m/e (rel. intensity) 509 (<1), 507 (<1), 459 (61) 458 (30), 370 (64), 369 (100), 253 (96).

However, bromohydrin 51 on oxidation with chromium trioxide and glacial acetic acid gave 11β-bromo,12-ketone 42.

Oxidation and Debromination of Bromohydrin 49

To a solution of 50 mg of bromohydrin 49 in 5 ml of glacial acetic acid, 1.0 ml of 0.56 N chromium troxide in acetic acid was added. The reaction mixture was stirred overnight at room temperature and then excess chromium trioxide destroyed by addition of methanol. Water was added to the reaction mixture and extracted with two 100 ml portions of ether. The combined ether extracts were washed successively with water, sodium carbonate solution and brine, and then dried. Removal of the solvents and recrystallization

of the residue from methanol gave 38 mg of 12-bromo,11-ketone 52, mp 168-9°; ir (CCl_4) 1735 cm^{-1}; Pmr (CCl_4) δ1.23 (S, 3H), 1.33 (S, 3H), 3.55 (S, 3H), 4.0 (q, J = 7 Hz, 2H), 4.2-4.7 (m, 2H).

Treatment of 52 with zinc and acetic acid gave 11-keto steroid 53, which was recrystallized from acetone, mp 145-6° (lit.[39] 146-147.5°).

Preparation of Methyl 3,12-diketo, $\Delta^{1,4,9(11)}$-cholatrienate 56

A 0.4 g (.001 M) solution of enedione 45 in 100 ml of t-amyl alcohol was refluxed with 0.22 g of selenium dioxide under nitrogen. After 4.5 hr, more selenium dioxide (0.2 g) was added and the solution was refluxed for a further 18 hr. The volume of the solution was then reduced to 10 ml under vacuo, the residue dissolved in chloroform and washed successively with water, sodium carbonate solution and brine, and then dried. Removal of the solvents and chromatography of the crude product on alumina (chloroform elutant) afforded 0.22 g (55%) of trienedione 56, which was recrystallized from methanol, mp 132-4°; $[\alpha]_D^{25}$+ 88.5°; ir (CCl_4) 1735, 1685, 1670, 1640, 1600 cm^{-1}; Pmr (CCl_4) δ0.93 (S, 3H), 1.25 (S, 3H), 3.52 (S, 3H), 5.57 (S, 1H), 5.90 (S, 1H), 6.07 (d.d, J = 10 Hz and 2Hz, 1H), 7.0 (d, J = 10 Hz, 1H); ms (70 eV) m/e (rel intensity) 396 (95), 365 (24), 242 (84), 241 (100).

Anal. Calcd. for $C_{25}H_{32}O_4$:C, 75.73; H, 8.13,
Found :C, 75.63; H, 8.21.

Homogeneous Catalytic Reduction of 56

A 50 ml pear shaped flask containing 5 ml of dry benzene was cooled to 0°, evacuated and filled with hydrogen. 10 mg of Tris triphenylphosphine chlororhodium (Wilkinson's catalyst) was added and the process of freezing, evacuating and refilling with hydrogen repeated three times. A 50 mg solution of 56 in 5 ml of dry benzene, after freezing, evacuating and refilling with hydrogen, was added to the above solution. The reaction mixture was stirred at room temperature for 4 hr under hydrogen at atmospheric pressure. Filtration through a short path alumina column followed by elution with chloroform gave 45 mg of unreacted 56.

In another experiment under similar conditions, reduction of 45 mg of 56 with Wilkinson's catalyst (10 mg), cyclooctene rhodium chloride complex (10 mg) and hydrogen gave a product which after recrystallization from acetone was found to be identical in all respects to 45.

Preparation of Methyl 3,12-diketo-$\Delta^{4,9(11)}$-choladienate 55

A. Oxidation and α-bromination of 44 and dehydrobromination of 57

0.2 g (.0005 M) of 44 was oxidized and brominated in ring A with 0.138 g (.001 M) of N-bromoacetamide and 0.1 ml of 48% hydrobromic acid (.0006 M) by the usual procedure to give 0.28 g of crude 57 as an oil, ir ($CDCl_3$) 1735, 1675, 1600 cm^{-1}; Pmr ($CDCl_3$) δ0.9 (S, 3H), 1.3 (S, 3H), 3.55 (S, 3H), 4.23 (d, J = 12 Hz, 1H), 5.68 (d, J = 2 Hz, 1H).

Without further purification, 0.28 g of 57 was dehydrobrominated with 0.42 g of lithium carbonate and 10 ml of dimethylformamide by the usual procedure yielding 0.18 g of the crude product. Preparative thin layer chromatography on a 2 mm silica gel plate (2% methanol in chloroform elutant) gave 0.10 g (51%) of methyl 3,12-diketo-$\Delta^{4,9(11)}$-choladienate 55, which was recrystallized from acetone, mp 116-8°; $[\alpha]_D^{25}$+ 105.7; ir (CCl_4) 1735, 1675, 1620, 1600 cm^{-1}; Pmr ($CDCl_3$, 180 M Hz) δ1.44 (S, 3H), 1.53 (S, 3H), 3.58 (S, 3H), 5.65 (d, J = 2 Hz, 1H), 5.68 (d, J = 2 Hz, 1H); ms (70 eV) m/e (rel. intensity) 398 (56), 243 (100), 241 (48).

Anal. Calcd. for $C_{25}H_{34}O_4$:C, 75.39; H, 8.60;
Found :C, 75.11; H, 8.54.

B. Oxidation and α-bromination of 58 and bis dehydrobromination of 59

A mixture of 11α-bromo ketone 41 (0.555 g, .001 M) and 50 ml of 2.5% methanolic potassium hydroxide solution was stirred overnight under Argon at room temperature. Methanol was removed under vacuo, the residue dissolved in water and neutralized with 6N hydrochloric acid. The precipitated product was filtered, washed with water, air dried and treated with an excess of diazomethane in ether. Removal of ether followed by oxidation and α-bromination in ring A with N-bromoacetamide (0.276 g, .002 M) and 0.2 ml of 48% hydrobromic acid (.0012 M) by the usual procedure gave 0.54 g (83%) of the crude product. Recrystallization from carbon tetrachloride gave dibromide 59, mp 79-80°; $[\alpha]_D^{25}$+ 34.9°; ir ($CDCl_3$) 1730 cm^{-1}; Pmr ($CDCl_3$) δ1.07 (S, 3H), 1.32 (S, 3H), 3.6 (S, 3H), 4.57-5.13 (m, 2H).

0.18 g (.00033 M) of dibromide 59 was bis dehydrobrominated with 0.5 g of lithium carbonate and 10 ml of dimethylformamide by the usual procedure to give 96 mg of crude product. Preparative thin layer chromatography on a 2 mm silica gel plate (2% methanol in chloroform elutant) gave 80 mg (60%) of product which was identical in all respects to 55.

Lithium and Ammonia Reduction of $\Delta^{4,9(11)}$-diene-3,12-dione 55

In a 100 ml three neck round bottom flask, flame dried under nitrogen, 50 ml of ammonia was condensed over a small lump of sodium. The ammonia was then distilled through Tygon tubing into another 100 ml three neck round bottom flask under nitrogen, fitted with a dry ice condenser and a mechanical stirrer, and cooled by a dry ice-isopropanol bath. 0.07 g of lithium (.01 M) was added to the reaction flask and upon completion of condensation of ammonia, dienedione 55 (0.1 g, .00025 M) dissolved in 10 ml of dry THF was added dropwise over a one hr period. The blue color of the reaction was discharged by dropwise addition of ethylene dibromide, following which 1 g of finely ground ammonium carbonate was added in one portion. The dry ice-isopropanol bath and dry ice condenser were removed and ammonia was evaporated into the hood under a stream of nitrogen. The residue was taken up in 100 ml of water and extracted with three 100 ml portions of ether. The combined ether extracts were washed sequentially with water and brine, and then dried. Removal of the solvents gave 85 mg of crude product which could not be recrystallized. The product did not separate very well on silica gel or alumina Tlc slides in various different solvents, so no attempts were made to purify it by column chromatography. The crude product was

tentatively assigned structure 60 on the strength of ir (CCl_4) 3600, 3375, 1705 cm^{-1}, Pmr (CCl_4) δ2.9-3.15 (m, 1H, D_2O exchangeable), 3.15-3.9 (m, 2H) and mass spectra (70 eV) m/e (rel. intensity) 372 (40), 207 (38), 149 (77).

REFERENCES

REFERENCES

1. a) M. Smith in "Reduction", R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968.
   b) G. Stork and S. D. Darling, J. Amer. Chem. Soc., 86, 1761 (1964).

2. G. Stork, P. Rosen, N. Goldman, R. Coombs and J. Tsuji, ibid., 87, 275 (1965).

3. P. S. Venkataramani and W. Reusch, Tet. Lett., 5283 (1968).

4. William Reusch and D. B. Pridday, J. Amer. Chem. Soc., 91, 3677 (1969).

5. P. S. Venkataramani, J. E. Karoglan and W. Reusch, J. Amer. Chem. Soc., 93, 269 (1971).

6. W. Reusch et al., J. Amer. Chem. Soc., 99, 1953 (1977).

7. D. B. Priddy, unpublished results from this lab.

8. a) J. Martin, Ph.D. dissertation, M.S.U.
   b) H. R. Taneja, Unpublished results.

9. DHR Barton et al., J. Amer. Chem. Soc., 88, 3016 (1966).

10. A. Butenandt et al., Chem. Ber., 68, 2091 (1935).

11. E. J. Corey, J. Amer. Chem. Soc., 75, 4832 (1953).

12. K. B. Sharpless, J. Amer. Chem. Soc., 95, 6137 (1973).

13. E. C. Kendall et al., J. Biol. Chem., 173, 271 (1948).

14. H. J. Ringold and A. Turner, Chem. & Ind., 211 (1962).

15. Von K. Heusler and A. Wettstein, Helv. Chim. Acta, 35, 284 (1952).

16. W. G. Dauben et al., J. Org. Chem., 39, 3587 (1969).

17. W. R. Jones et al., J. Chem. Soc. (c), 1444 (1966).

18. W. N. Speckamp et al., J.C.S. Chem. Comm., 350 (1972).

19. B. W. Finucane and J. B. Thomson, J.C.S. Chem. Comm., 1220 (1969).

20. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946).

21. Yehuda Yanuka and Gideon Halperin, J. Org. Chem., 38, 2587 (1973).

22. M. P. Hartshorn and E. R. H. Jones, J. Chem. Soc., 1312, (1962).

23. A. R. Hanze, G. S. Fonken, A. V. McIntosh, Jr., A. M. Searcy and R. H. Levin, J. Am. Chem. Soc., 76, 3179 (1954).

24. Kyosuke Tsuda, Shigeo Nozoe and Kazuhiko Ohata, Chem. Pharm. Bull., 11, 1265 (1963).

25. Louis F. Fieser and Srinivasa Rajagopalan, J. Am. Chem. Soc., 72, 5530 (1950).

26. B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, J. Biol. Chem., 173, 271 (1948).

27. E. Seebeck and T. Reichstein, Helv. Chim. Acta, 26, 536 (1943).

28. R. Norman Jones, D. A. Ramsay, F. Herling and Konrad Dobriner, J. Am. Chem. Soc., 74, 2828 (1952).

29. T. F. Gallagher and William P. Long, J. Biol. Chem., 162, 495 (1946).

30. T. R. Kowar and E. LeGoff, J. Org. Chem., 41, 3760 (1976) cf. H. Oediger and F. Möller, Angew. Chem. I.E., 6, 76 (1967).

31. Josef Fried and Josef E. Herz, Chem. Abs., 52, 5491 (1958); U.S. 2,814,629, Nov. 26, 1957.

32. Daniel Levy and Robert Stevenson, J. Org. Chem., 33, 2804 (1968).

33. C. H. Chen, Synthesis, 125 (1976).

34. H. Reich and T. Reichstein, Helv. Chim. Acta, 26, 562 (1943).

35. L. F. Fieser and M. Fieser, "Steroids", Reinhold Pub. Co., New York, N. Y., 1959, pages 634-9.

36. A. Fürst and P. A. Plattner, Abstr. Papers 12th Int. Congress Pure and Appl. Chem., New York, 1951, p. 409.

37. G. H. Alt and D. H. R. Barton, J. Chem. Soc., 4284 (1954).

38. J. Fried, J. W. Brown and M. Applebaum, Tet. Lett., 849 (1965).

39. S. Archer, T. R. Lewis, C. M. Martini and Mary Jackman, J. Am. Chem. Soc., 76, 4915 (1954).

40. Hans R. Taneja, Unpublished results from this lab.

41. D. V. C. Awang and S. Wolfe, Canad. J. Chem., 47, 706 (1969).

42. P. B. Sollman and R. M. Dodson, J. Org. Chem., 26, 4180 (1961).

43. M. M. Coombs and H. R. Roderick, J. Chem. Soc. (c), 1819 (1967).

44. Carl Djerassi and J. Gutzwiller, J. Am. Chem. Soc., 88, 4537 (1966).

45. Hans R. Taneja and Ed Sweet, Unpublished results from Chemistry Department Michigan State University.

APPENDIX

SPECTRA

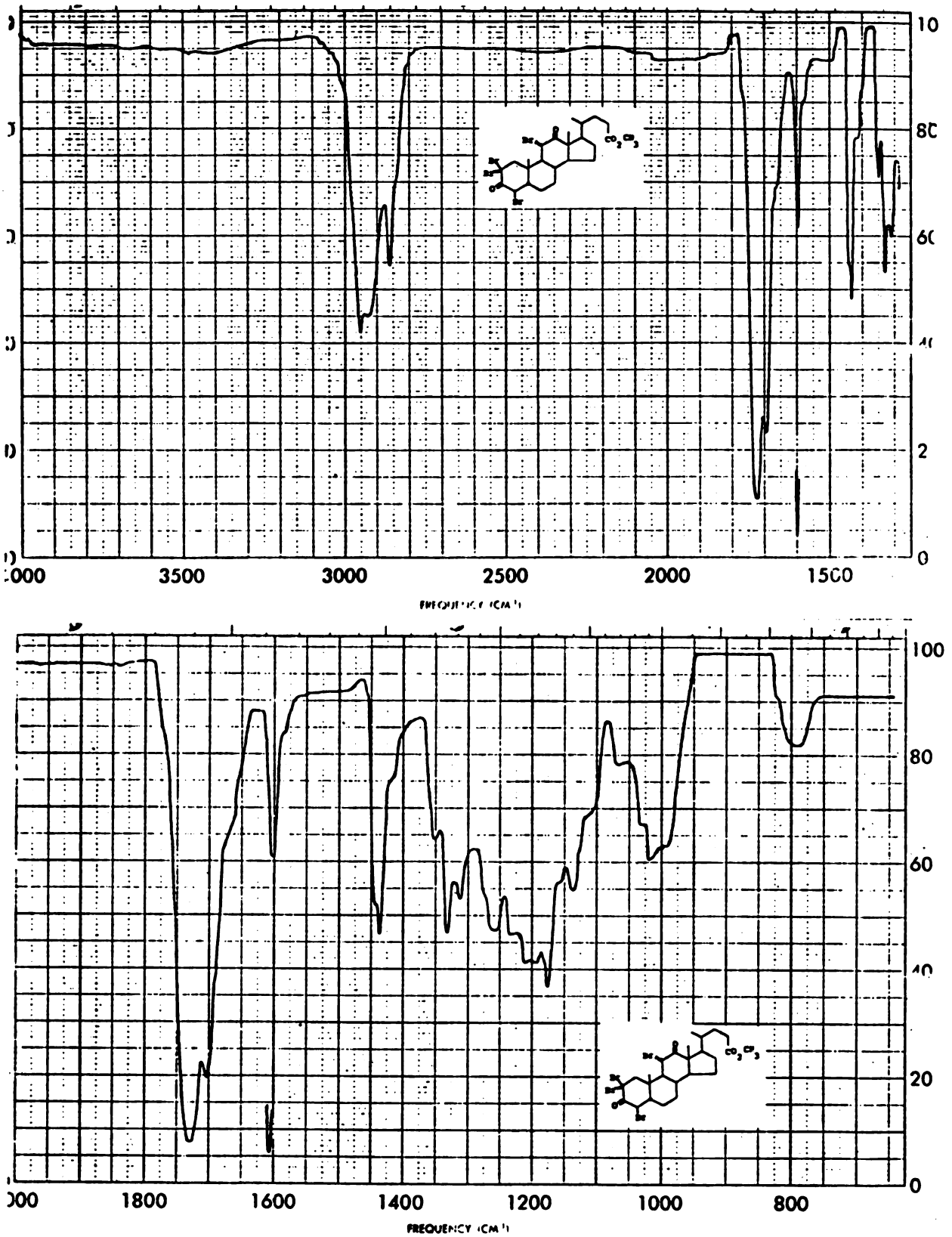


Figure 1. Infrared Spectrum of 32

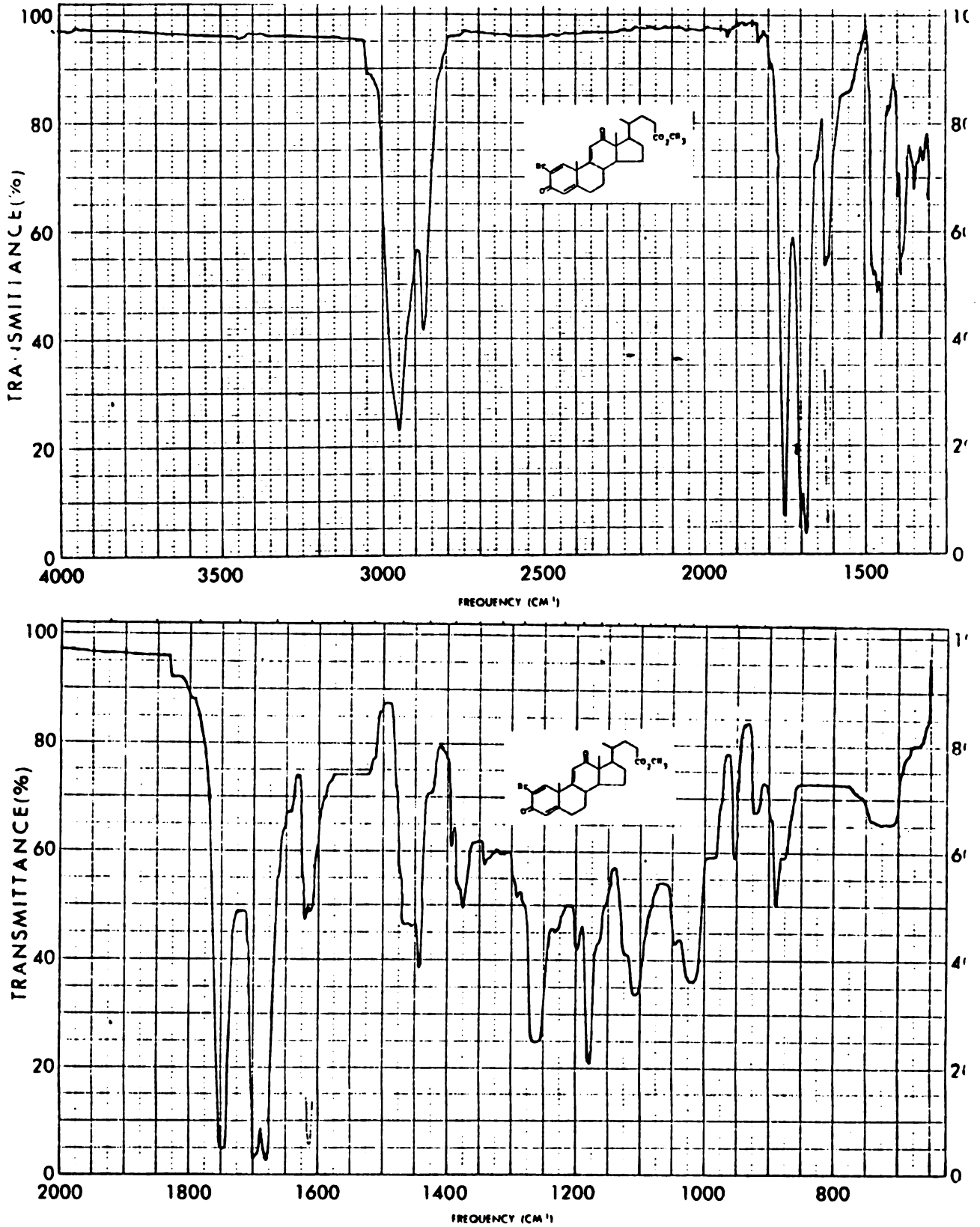


Figure 2. Infrared Spectrum of 33

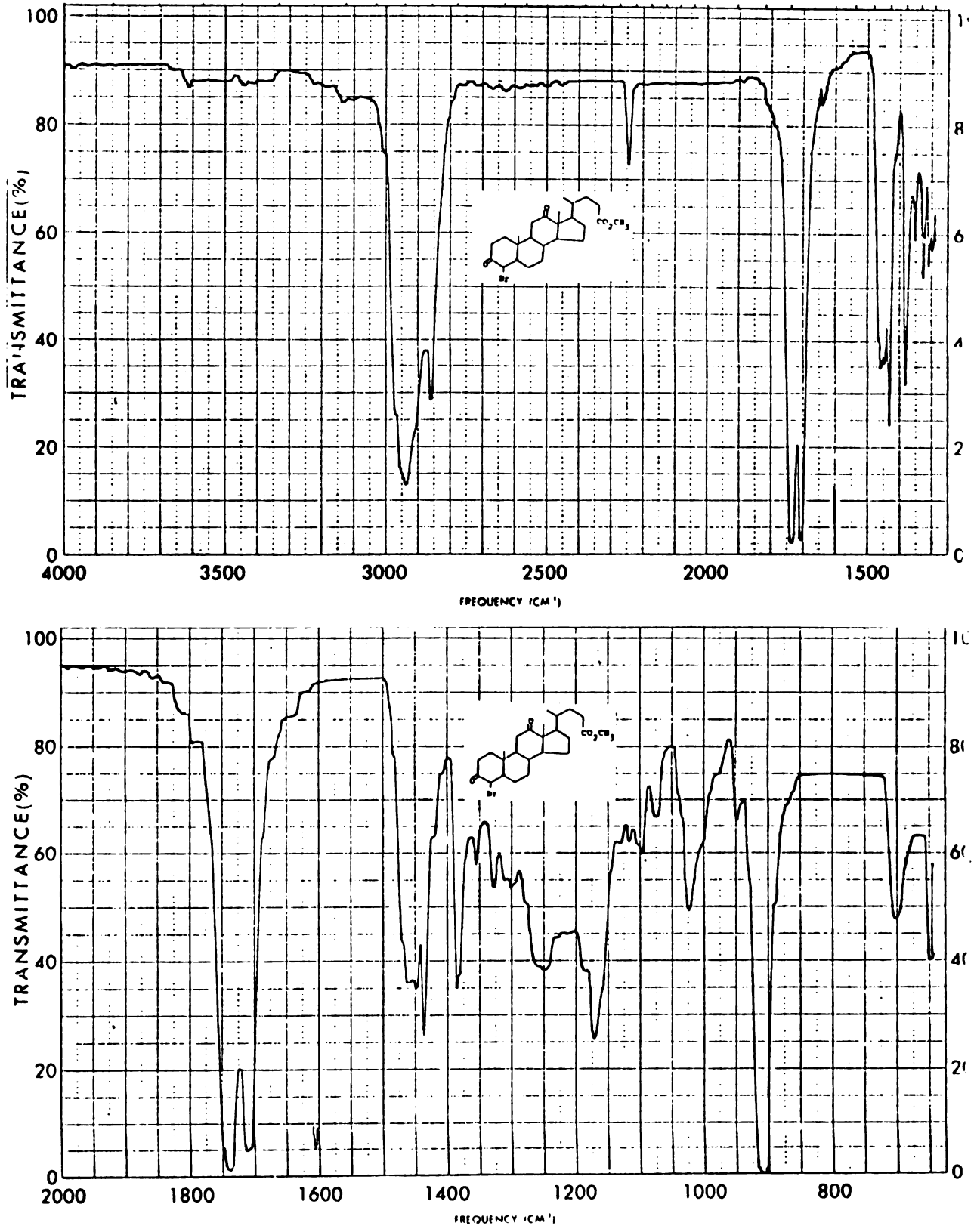


Figure 3. Infrared spectrum of 34

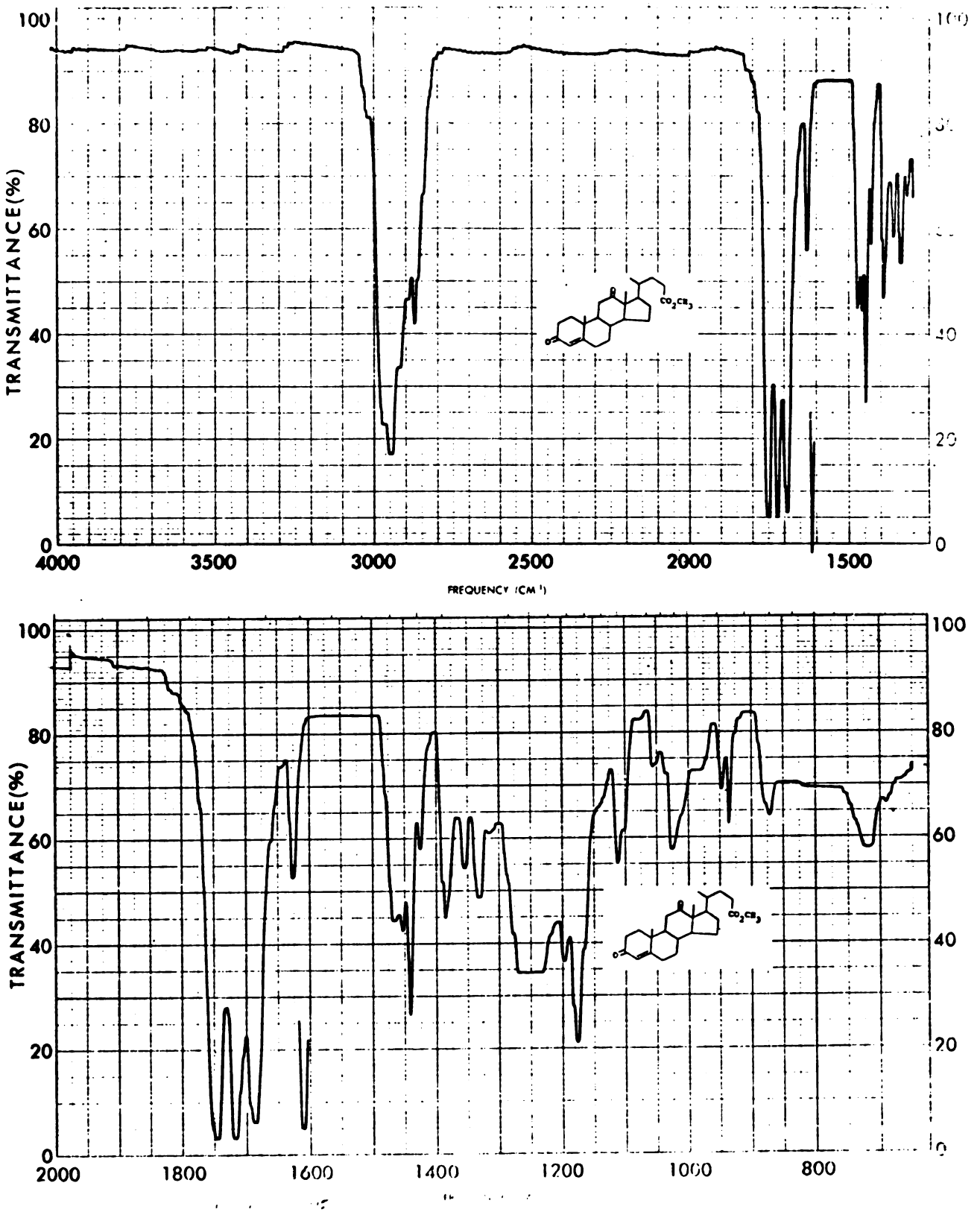


Figure 4. Infrared spectrum of 35

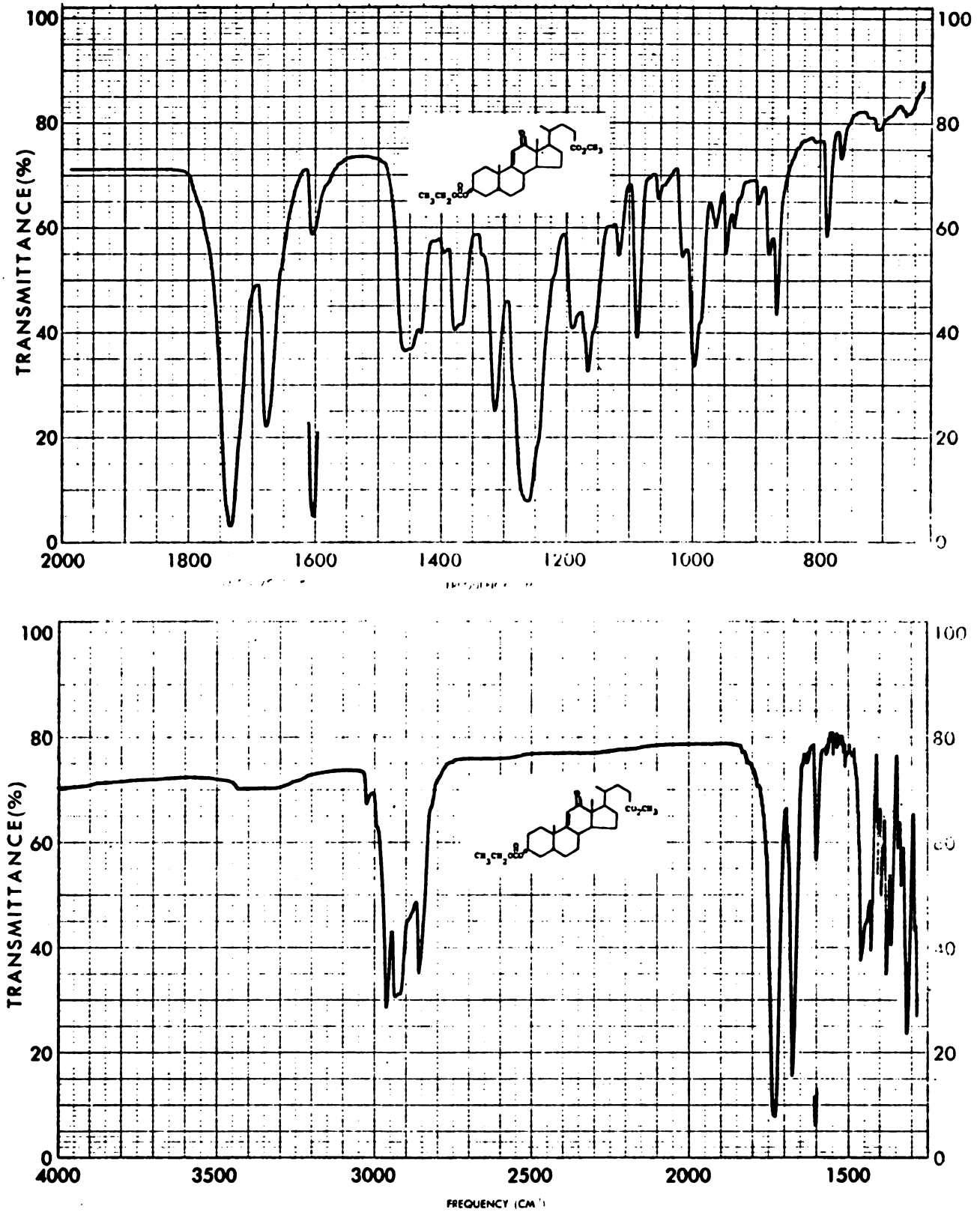


Figure 5. Infrared spectrum of 38

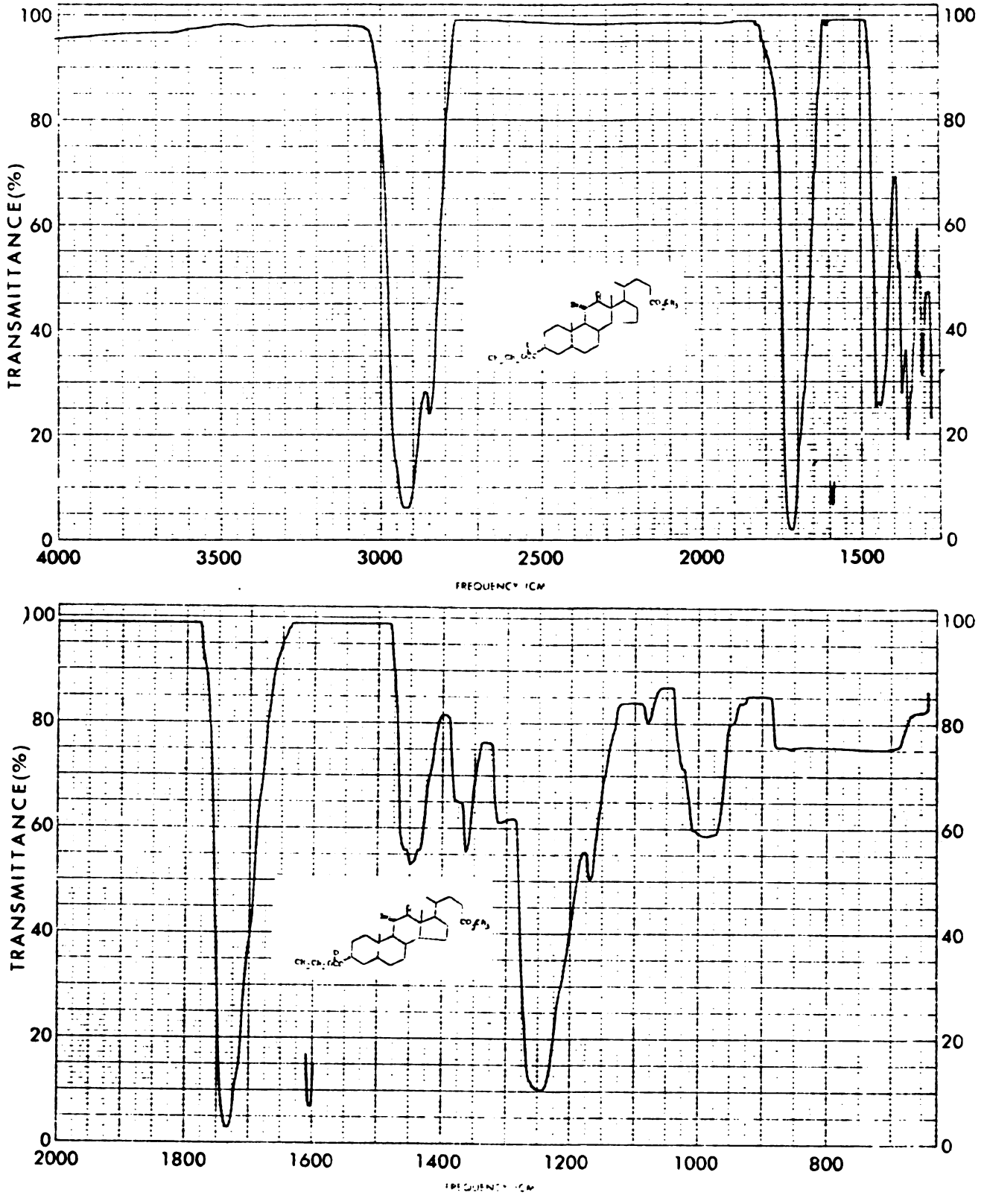


Figure 6. Infrared spectrum of 41

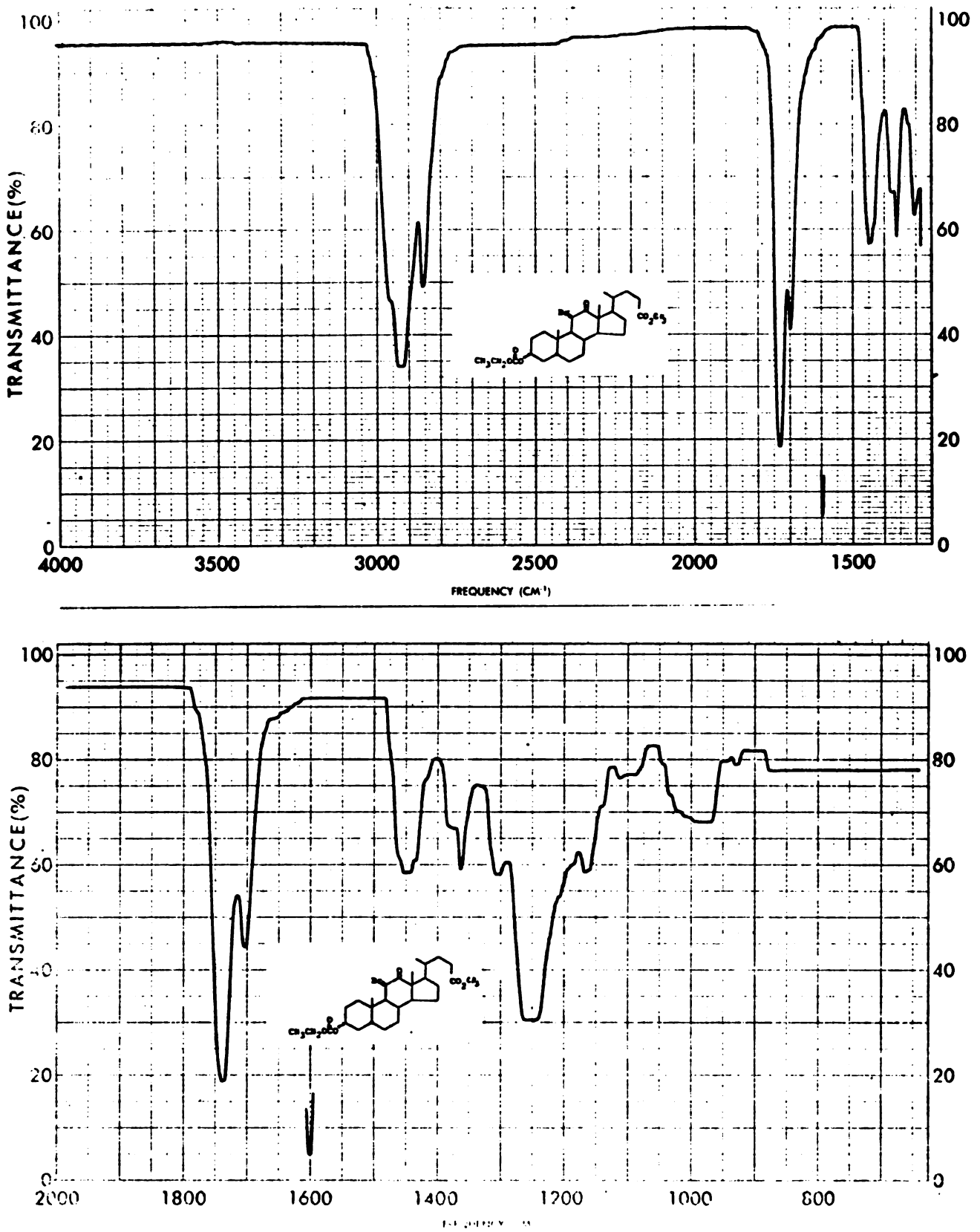


Figure 7. Infrared spectrum of 42

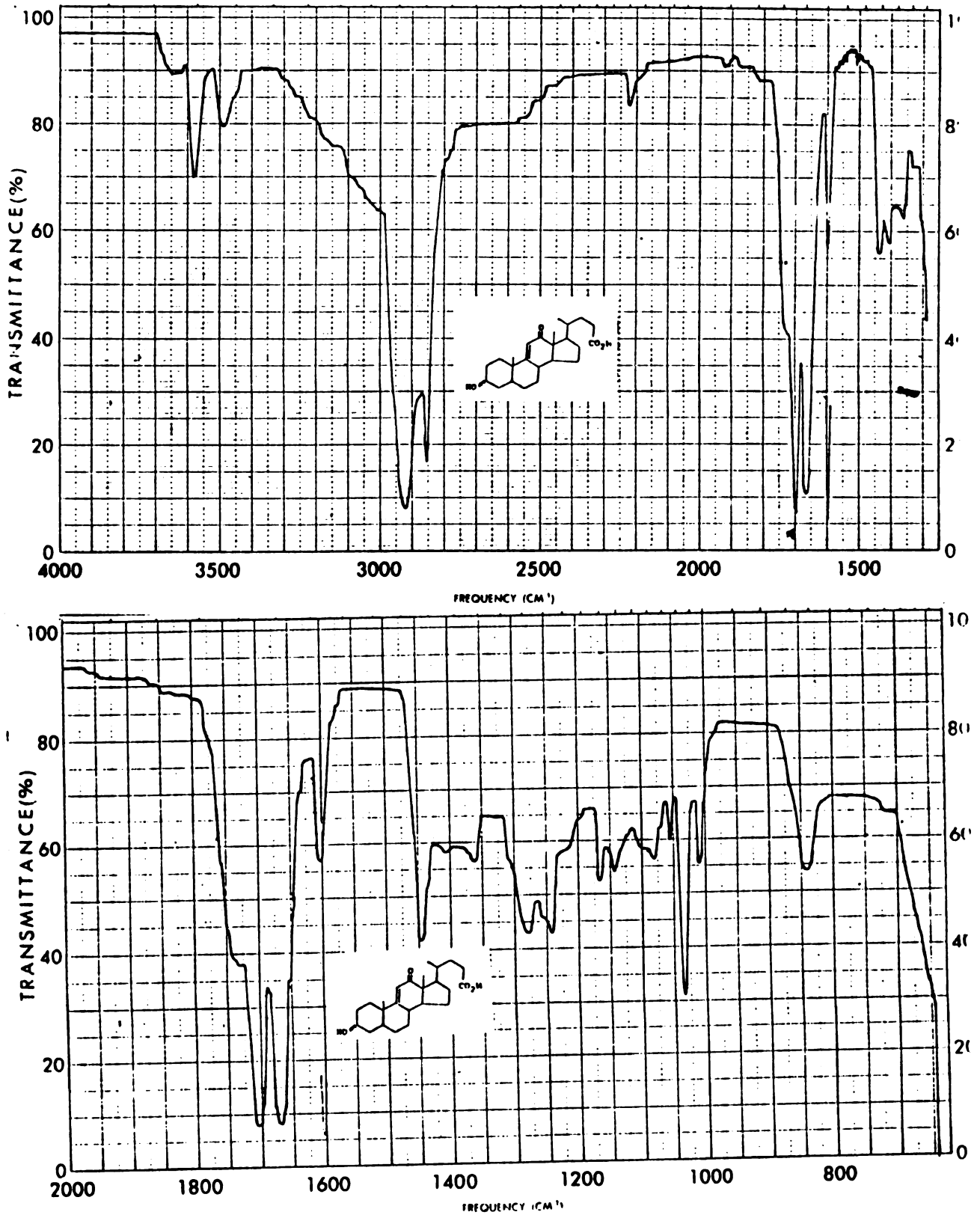


Figure 8. Infrared spectrum of 43

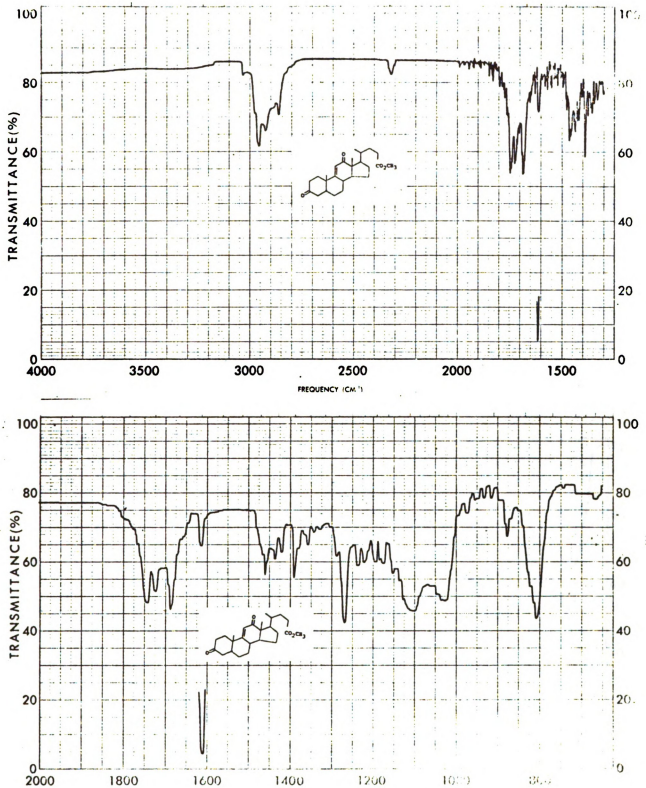
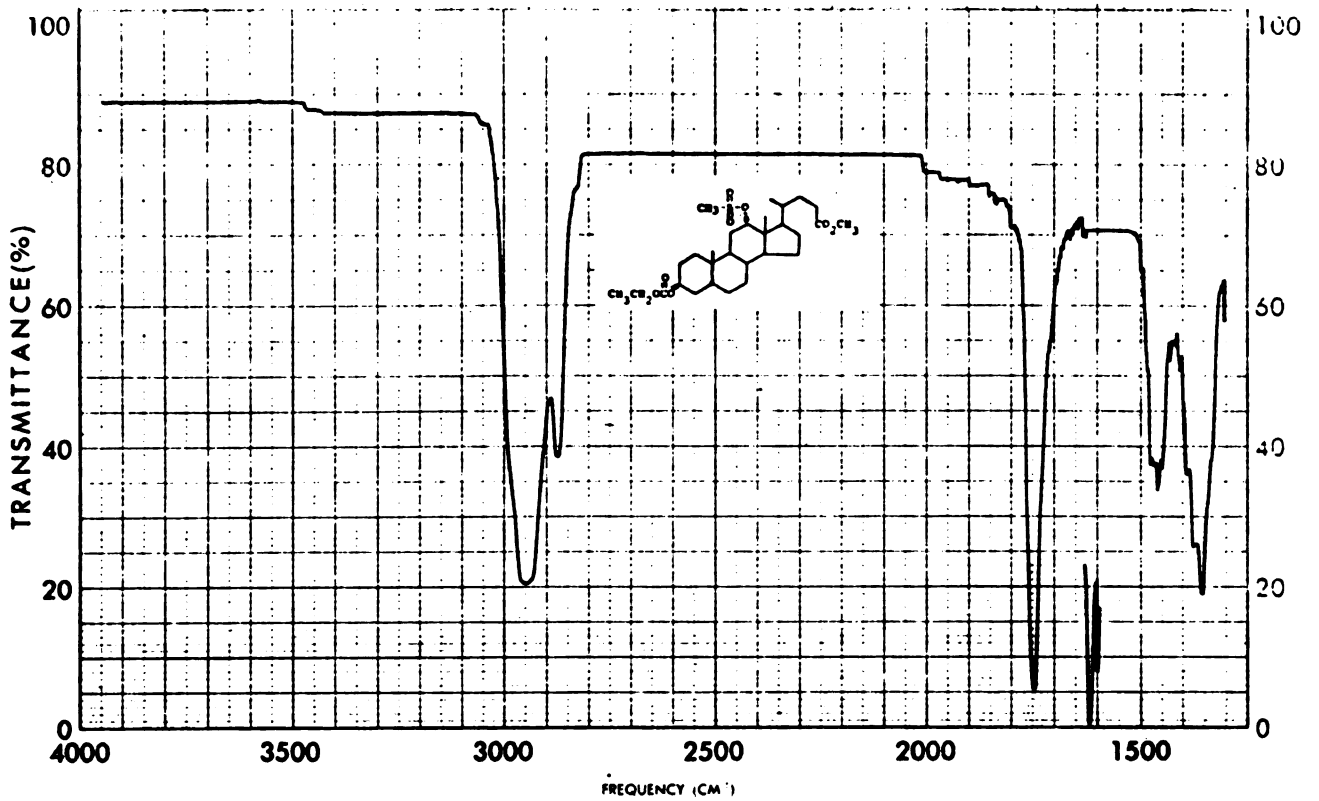


Figure 9. Infrared spectrum of 45



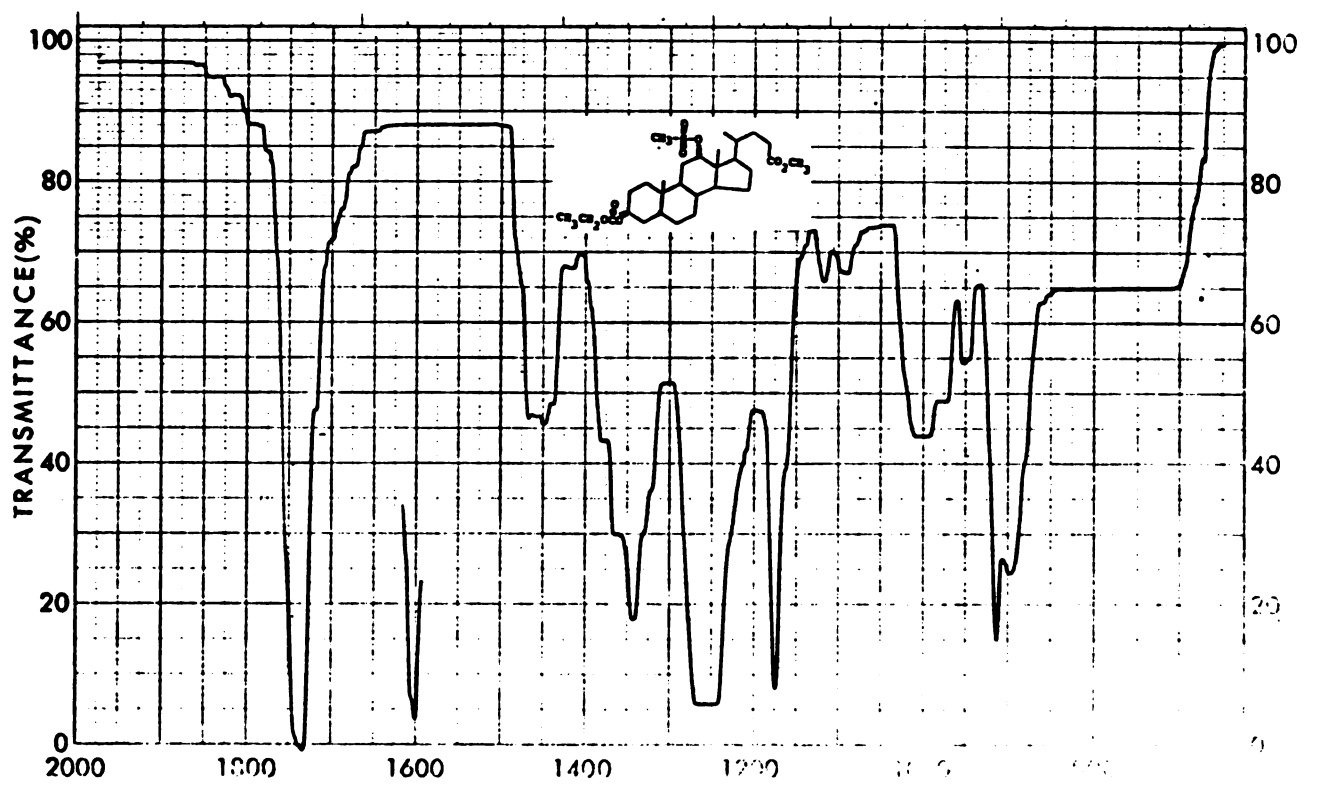
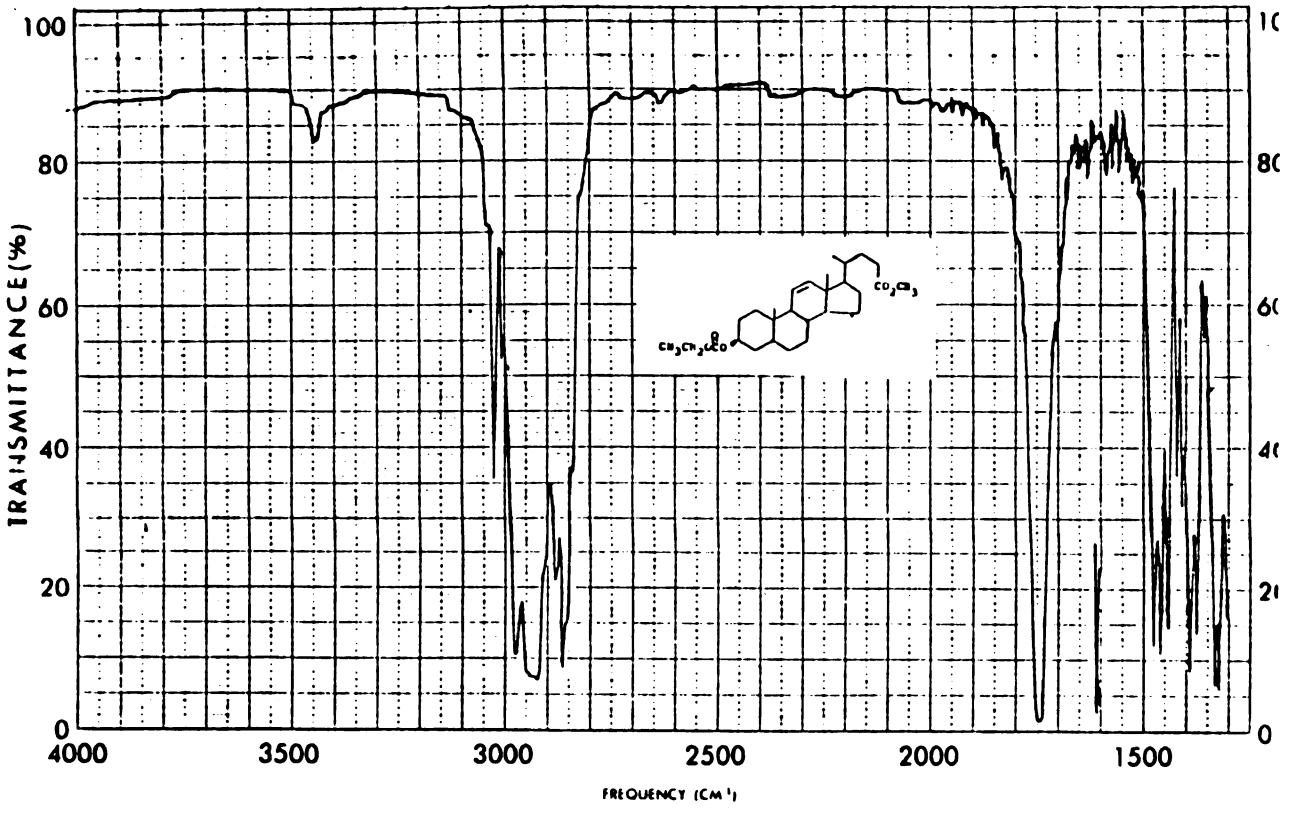


Figure 10. Infrared spectrum of 46



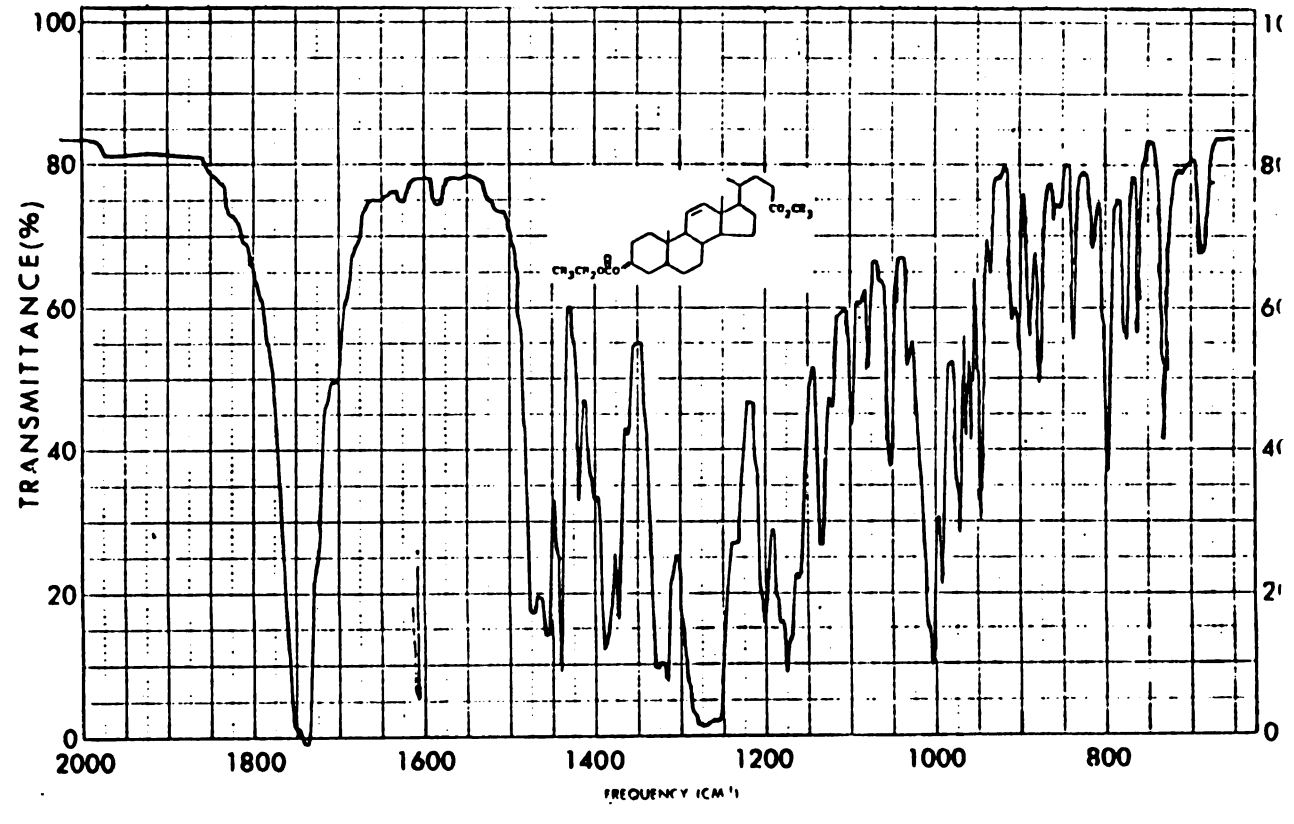


Figure 11. Infrared spectrum of 47

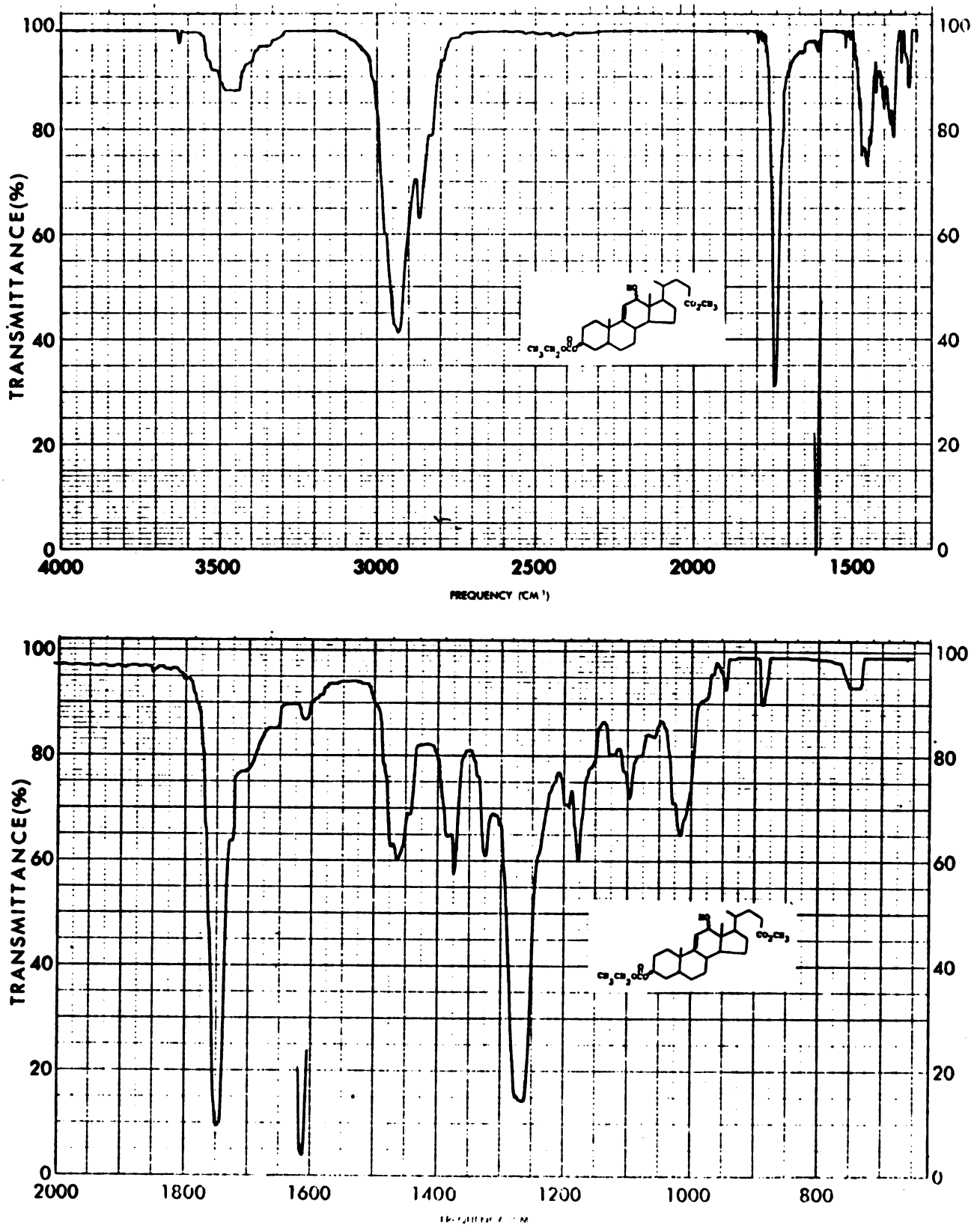


Figure 12. Infrared spectrum of 48

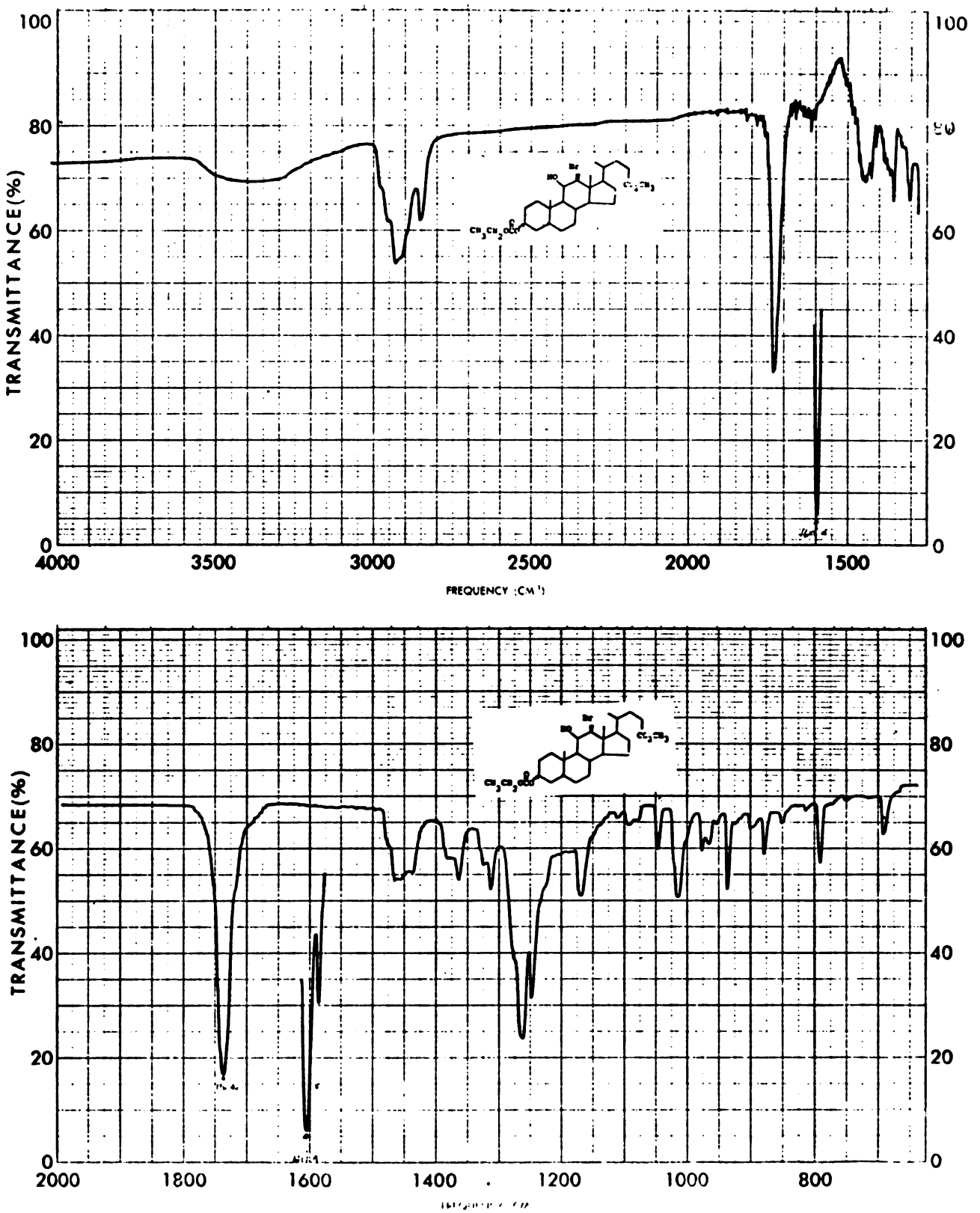


Figure 13. Infrared spectrum of 49

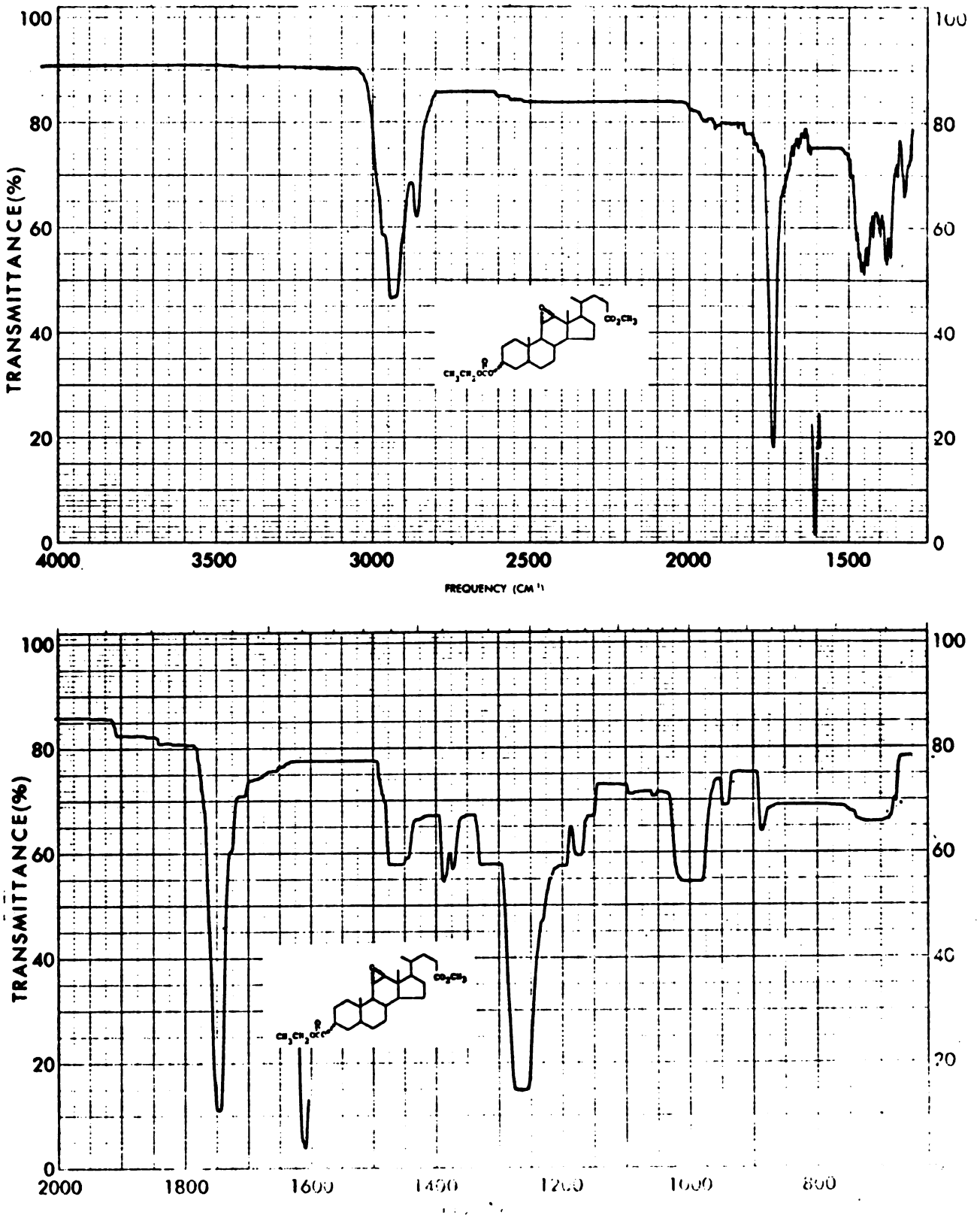


Figure 14. Infrared spectrum of 50

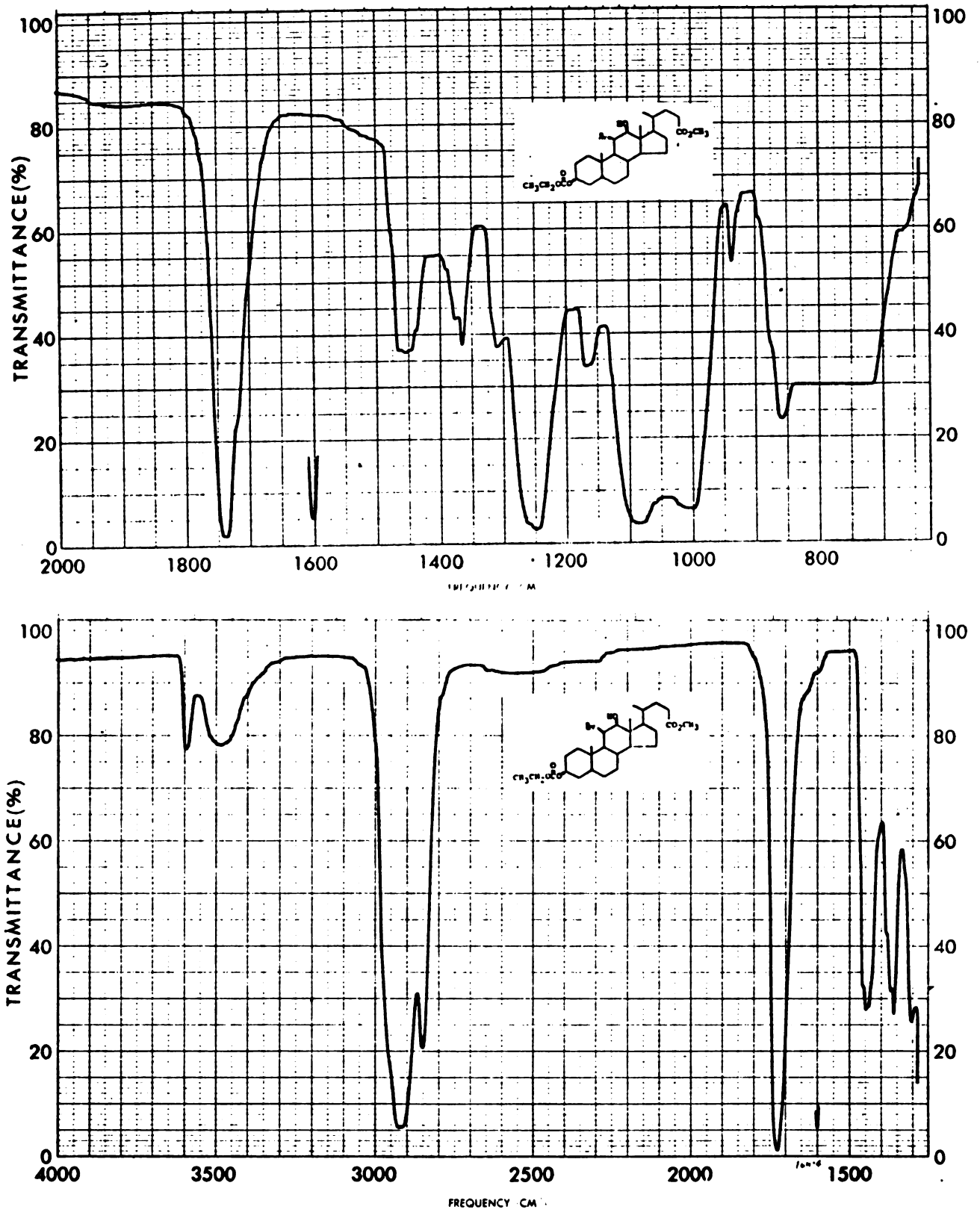
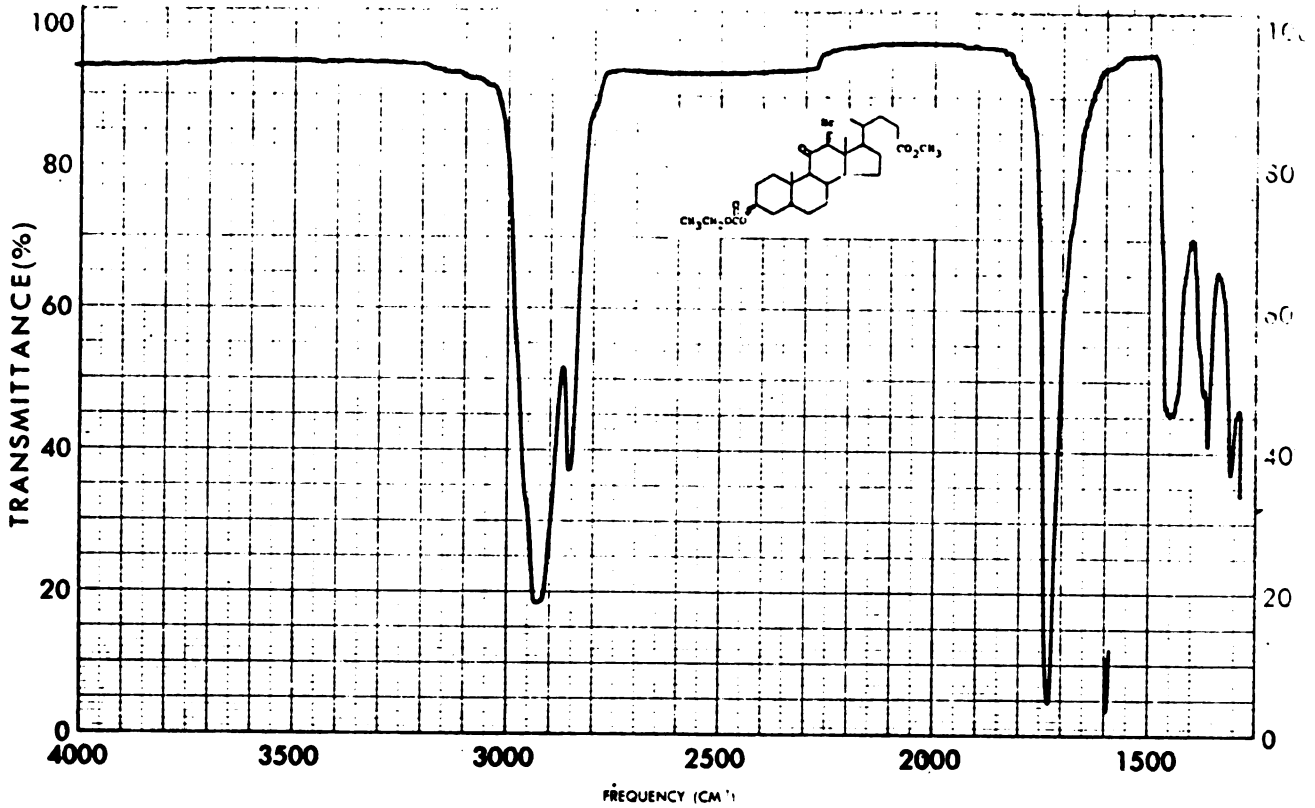


Figure 15. Infrared spectrum of 51



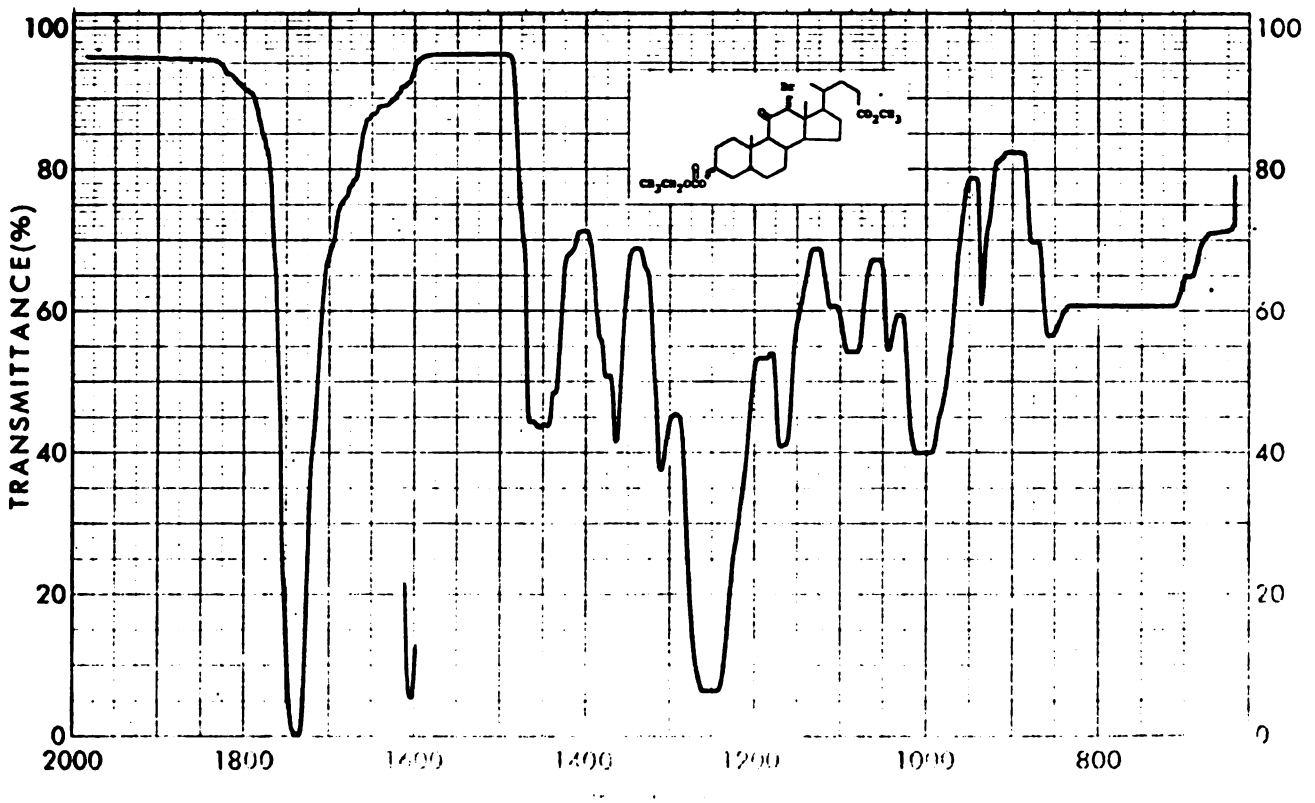


Figure 16. Infrared spectrum of 52

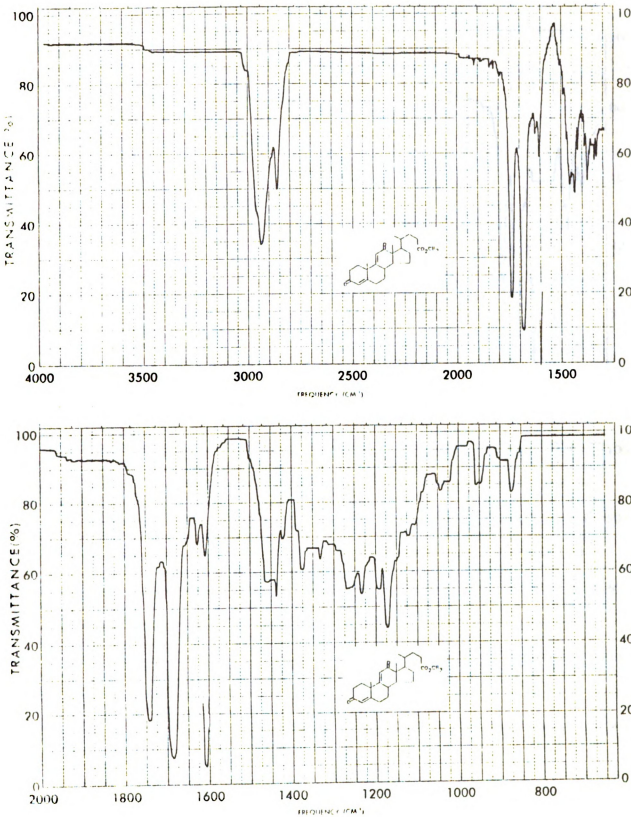


Figure 17. Infrared spectrum of 55

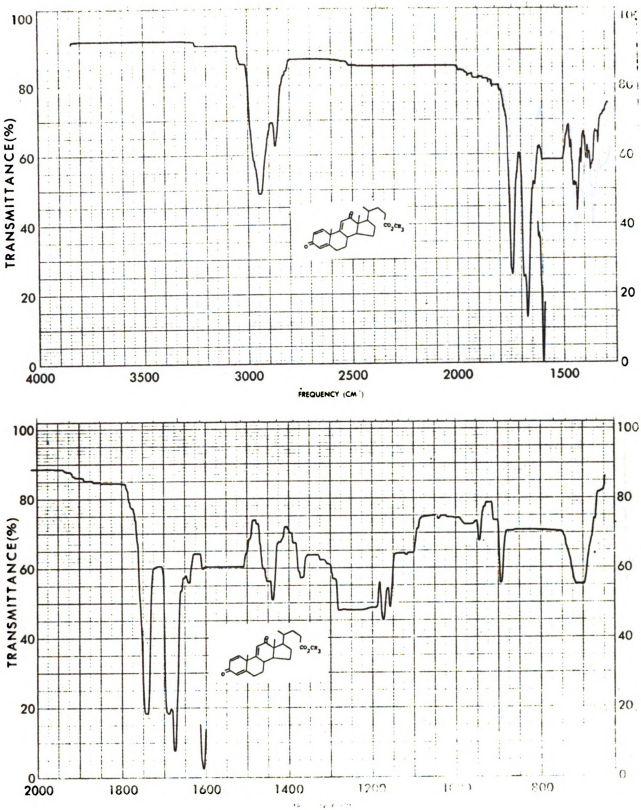


Figure 18. Infrared spectrum of 56

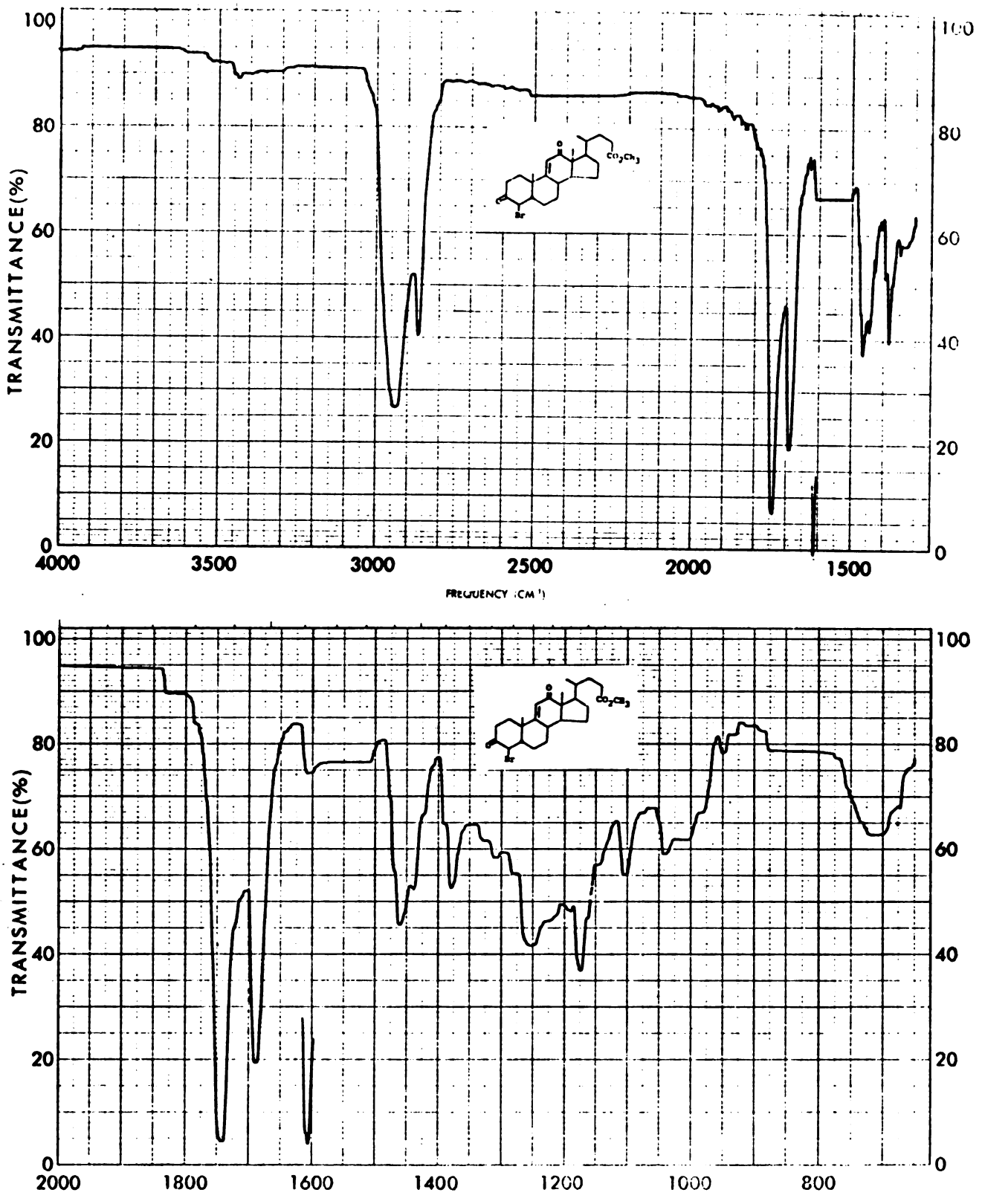


Figure 19. Infrared spectrum of 57

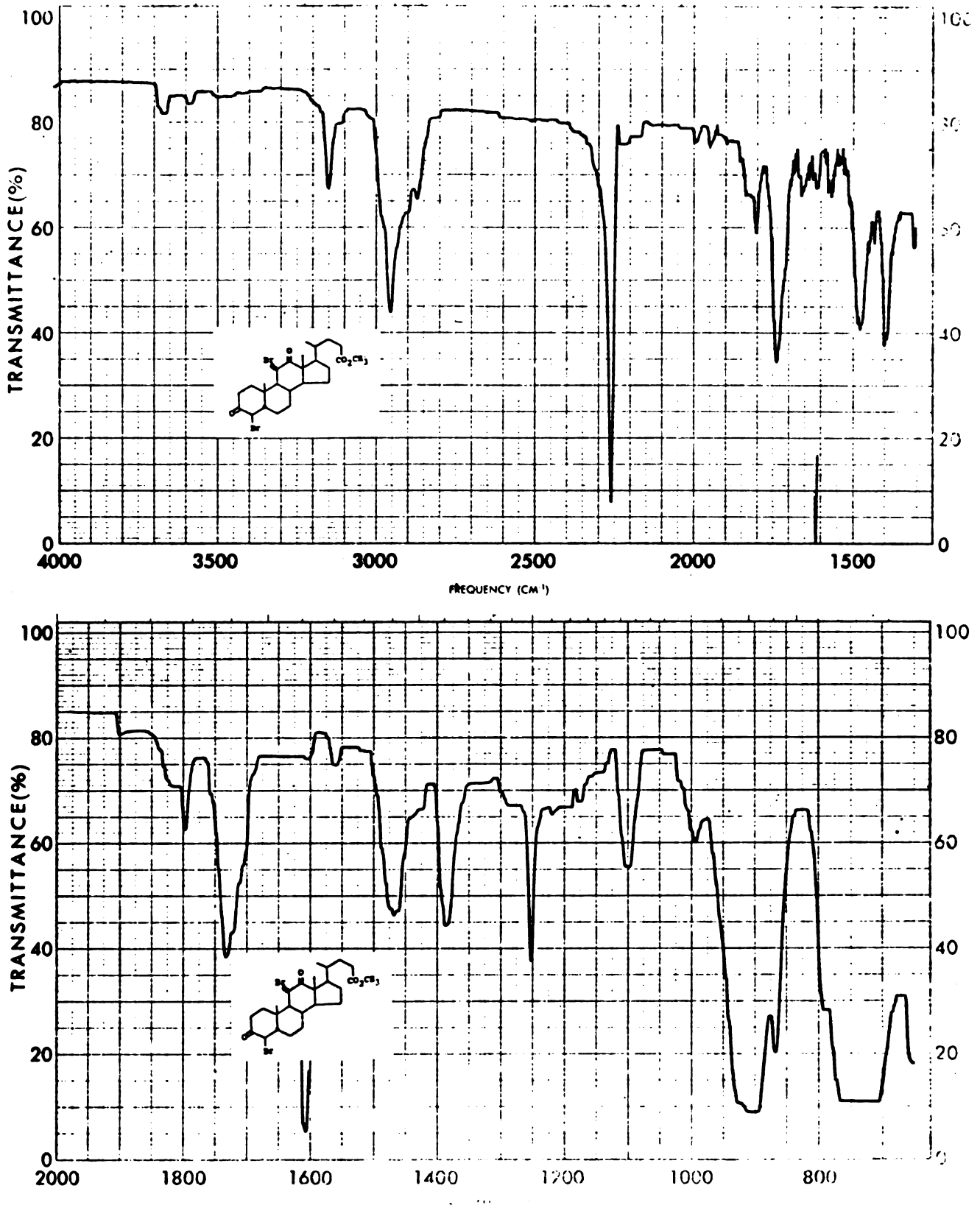


Figure 20. Infrared spectrum of 59

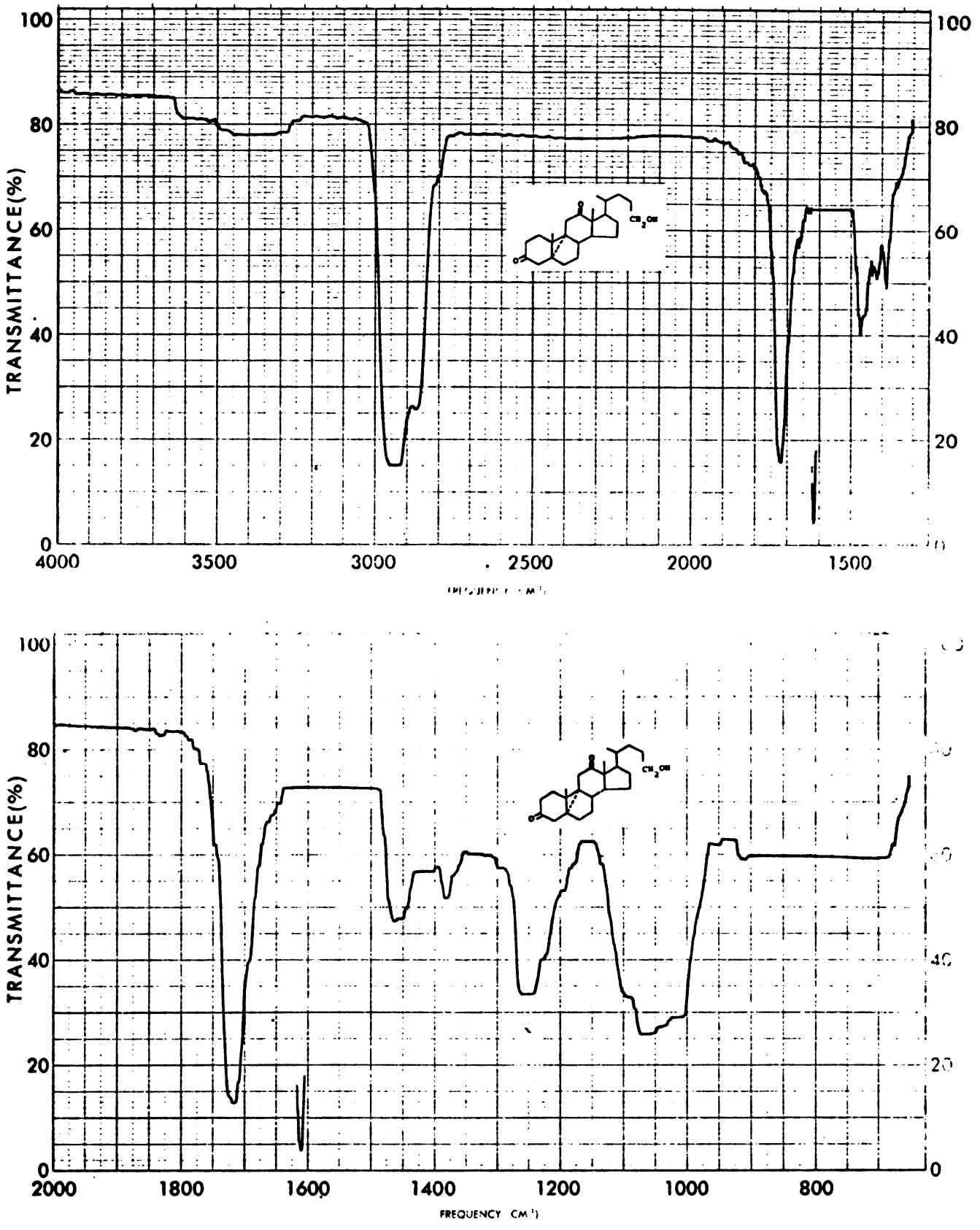


Figure 21. Infrared spectrum of 60

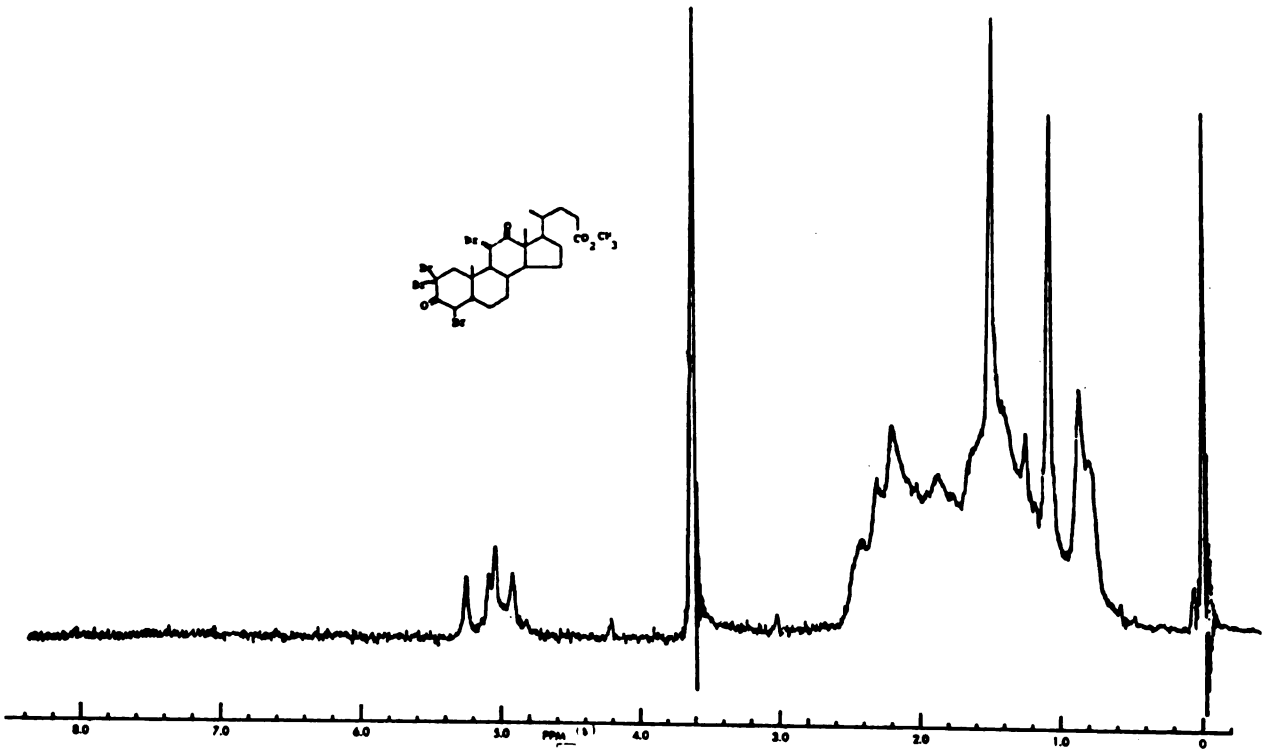


Figure 22. Pmr spectrum of 32

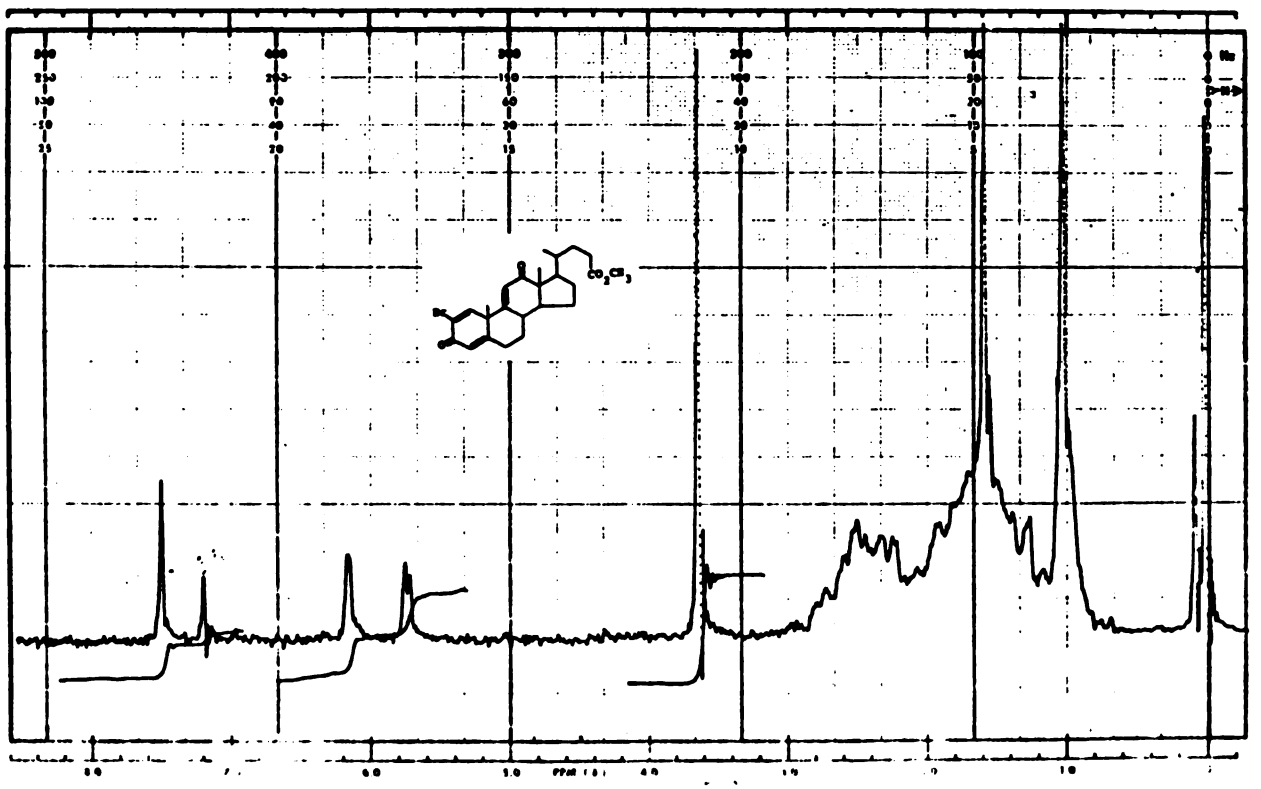


Figure 23. Pmr spectrum of 33

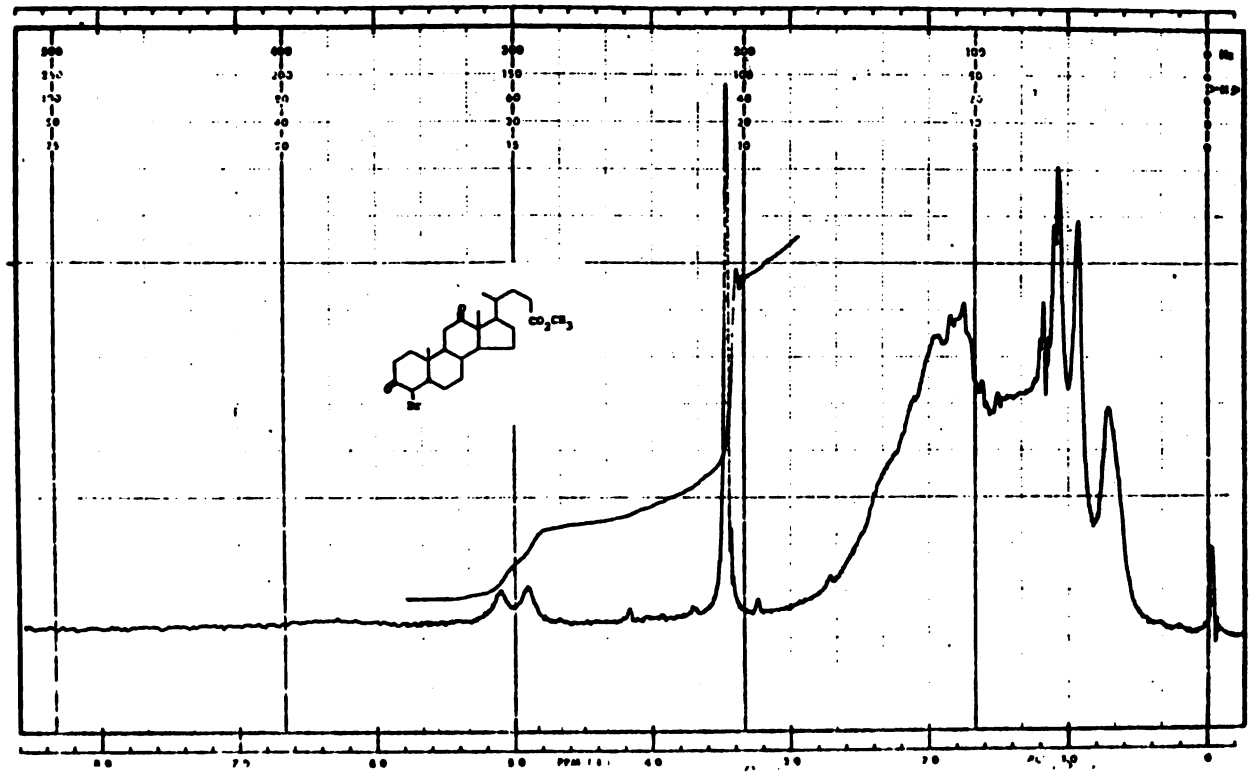


Figure 24. Pmr spectrum of 34

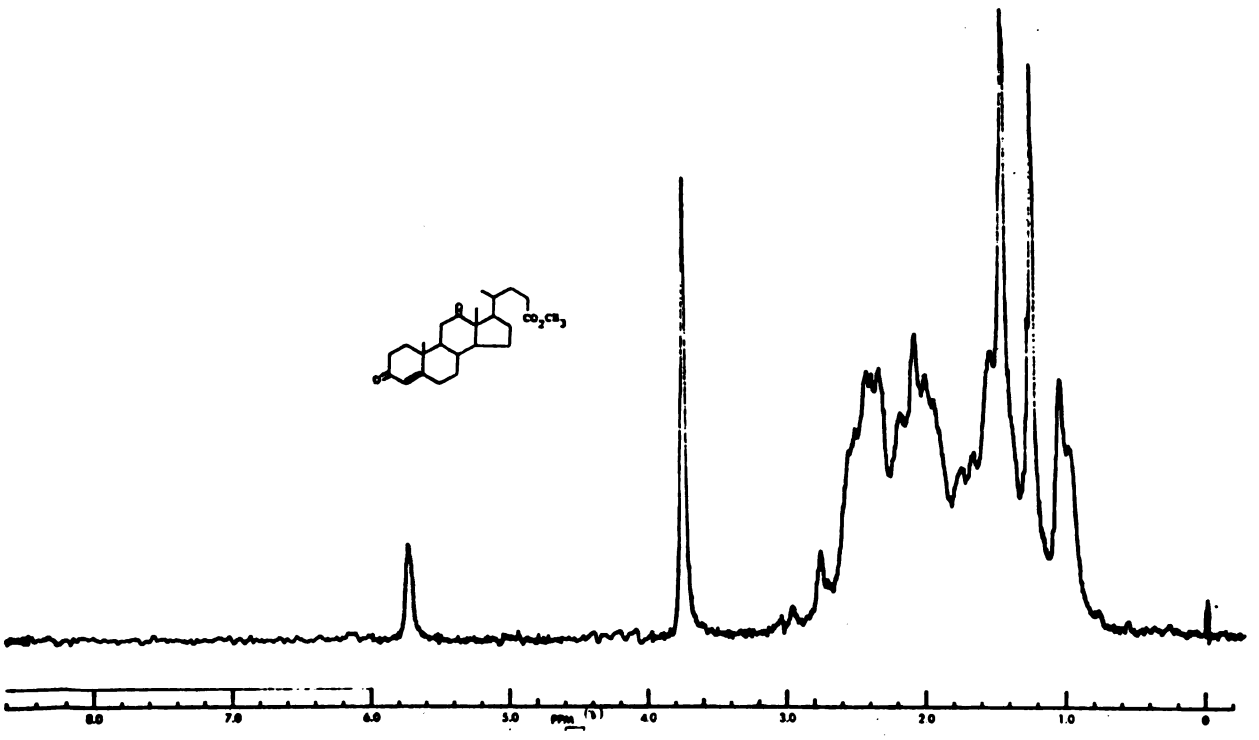


Figure 25. Pmr spectrum of 35

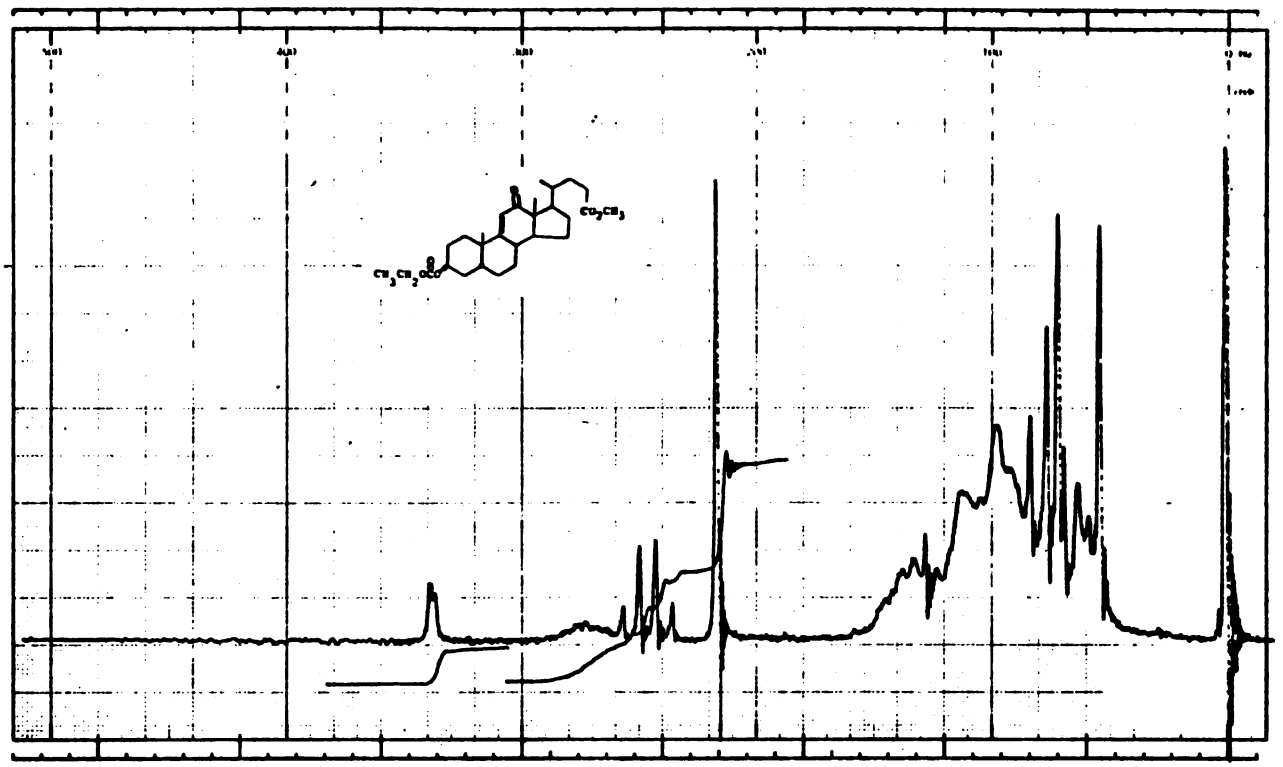


Figure 26. Pmr spectrum of 38

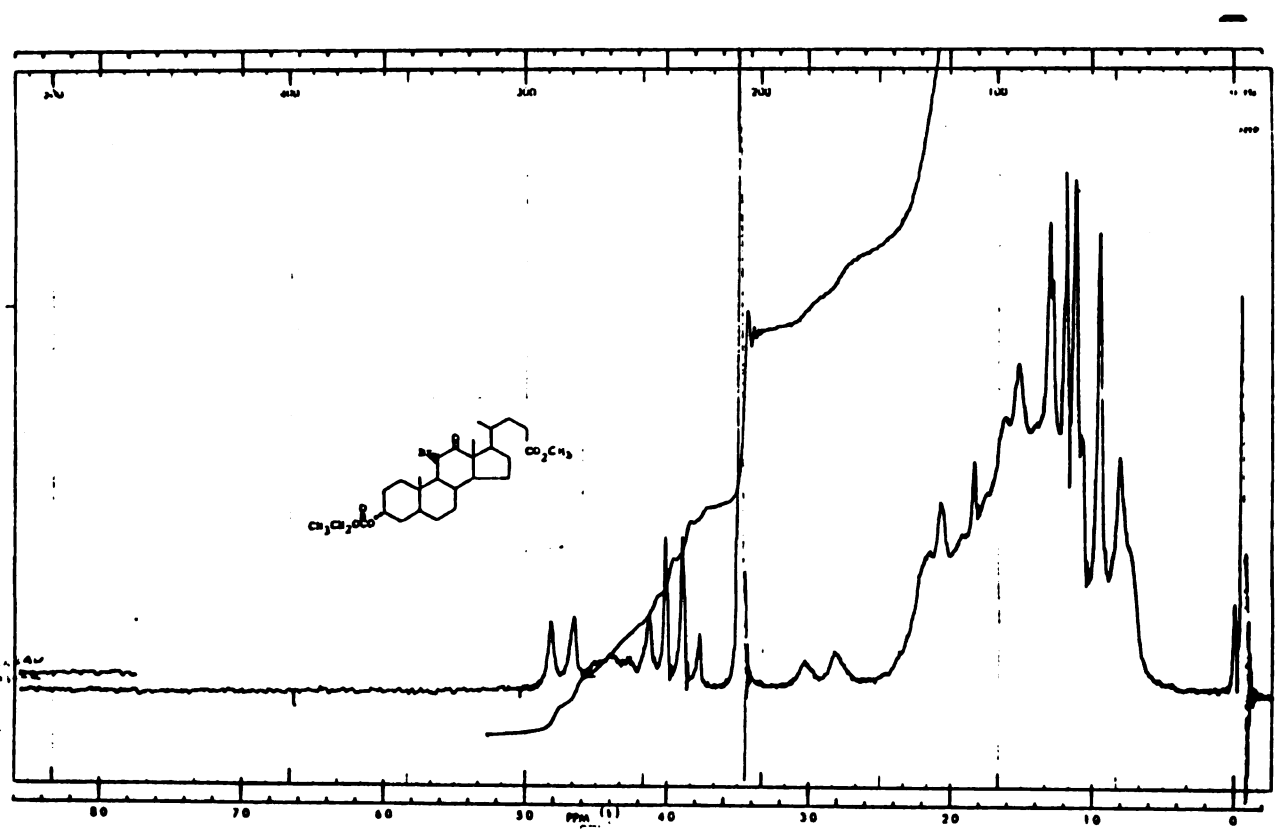


Figure 27. Pmr spectrum of 41

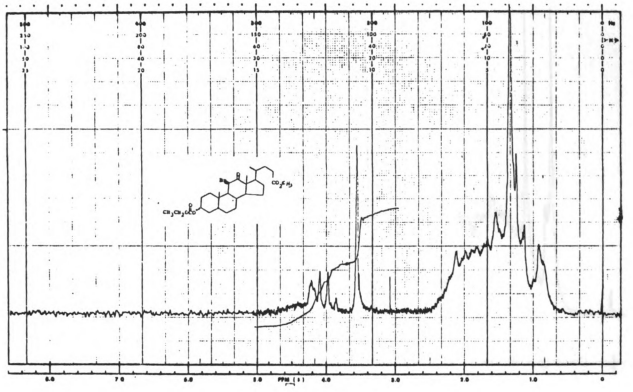


Figure 28. Pmr spectrum of 42

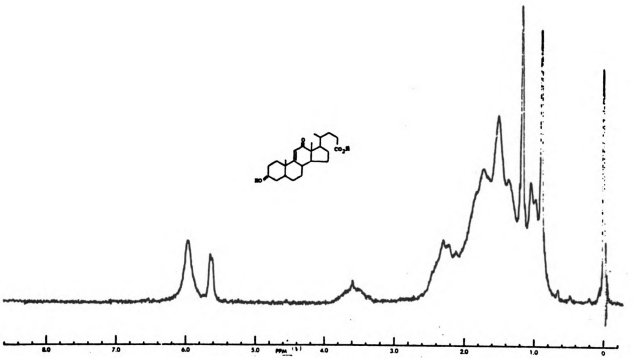


Figure 29. Pmr spectrum of 43

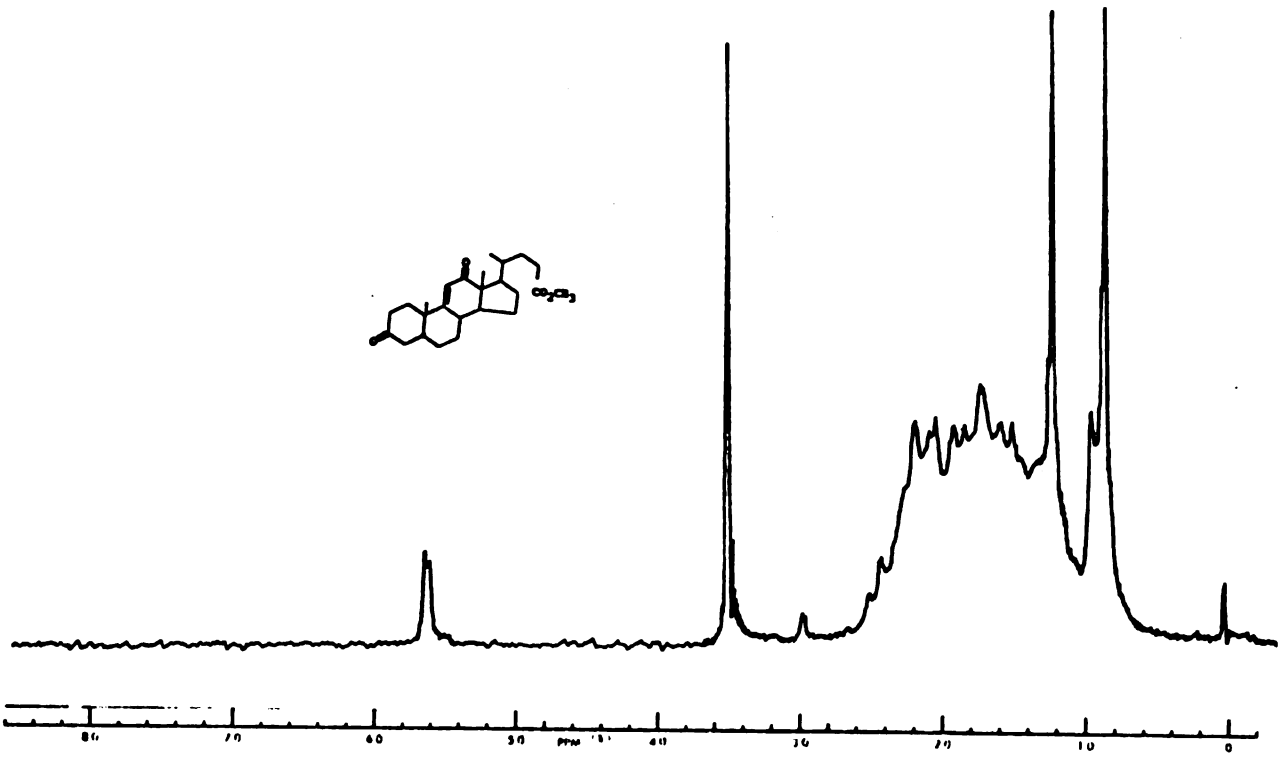


Figure 30. Pmr spectrum of 45

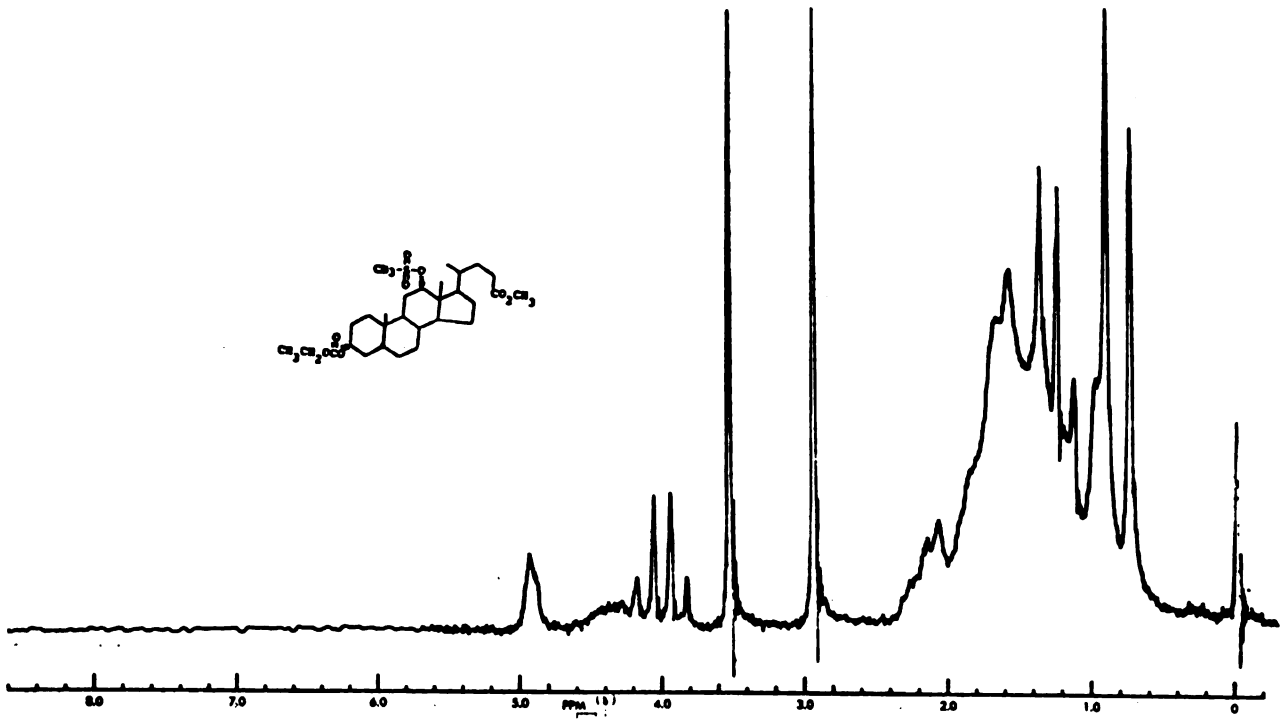


Figure 31. Pmr spectrum of 46

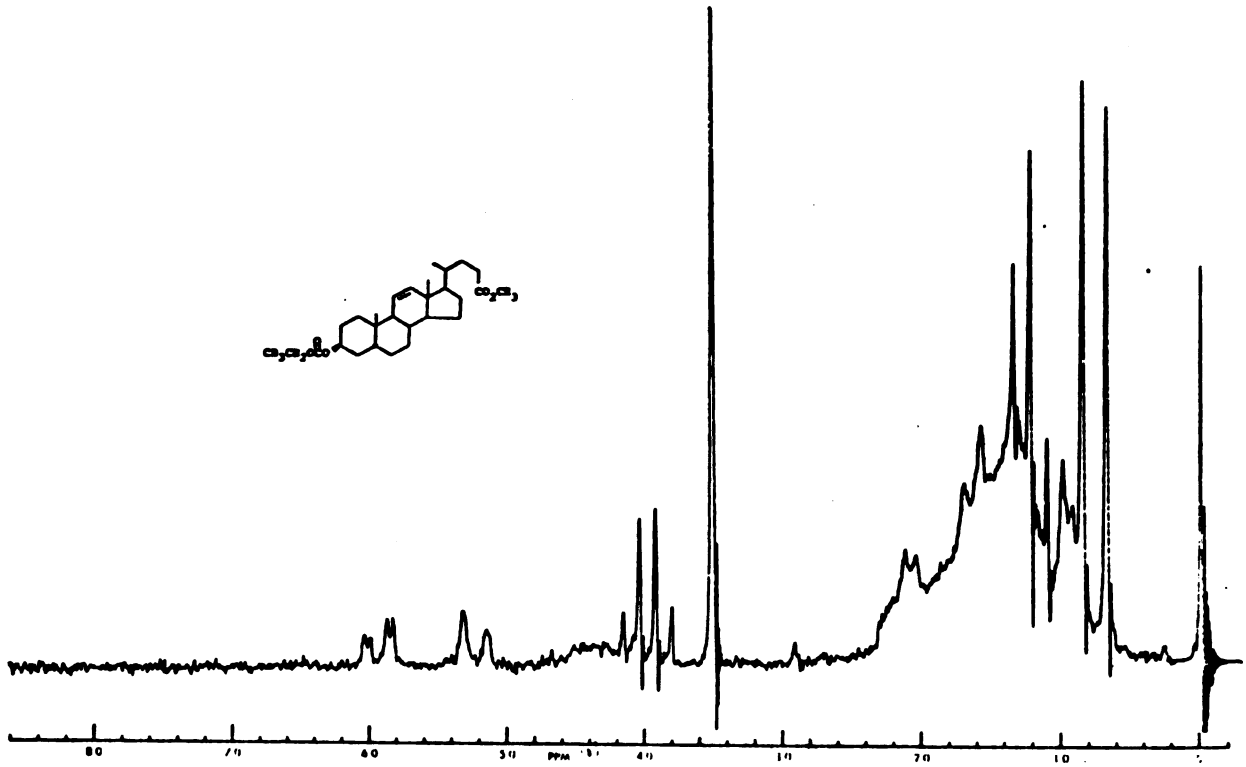


Figure 32. Pmr spectrum of 47

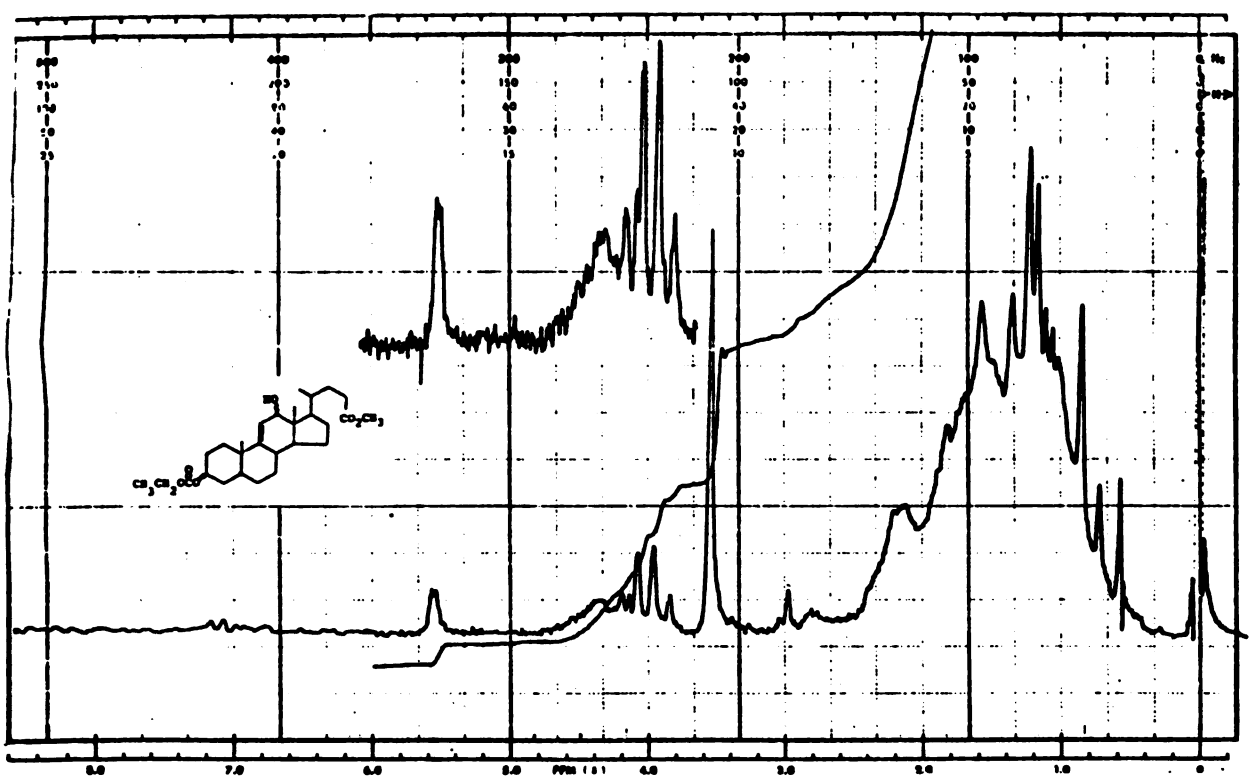


Figure 33. Pmr spectrum of 48

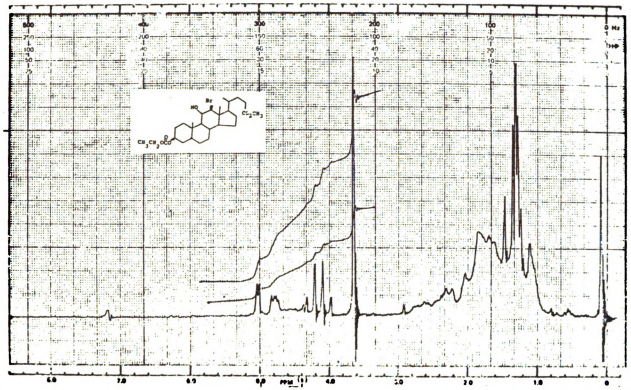


Figure 34. Pmr spectrum of 49

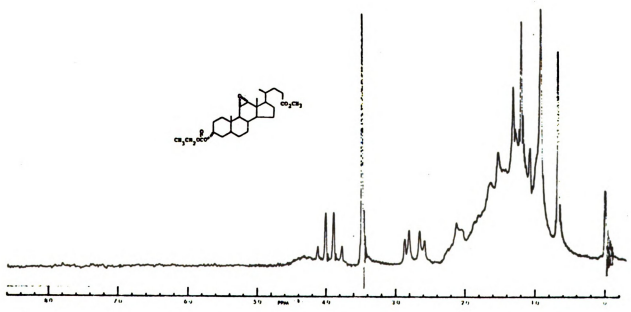


Figure 35. Pmr spectrum of 50

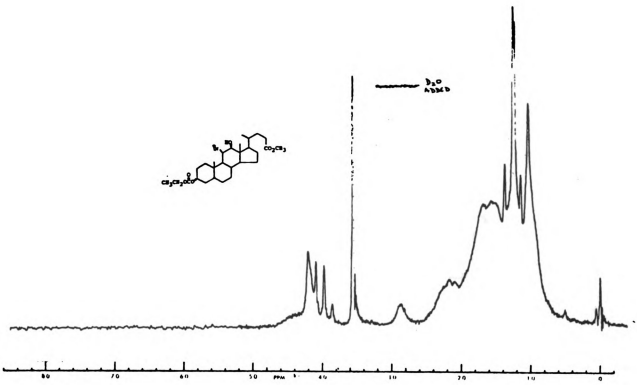


Figure 36. Pmr spectrum of 51

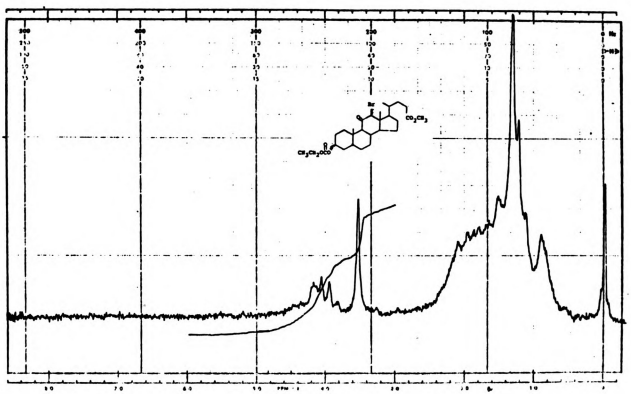


Figure 37. Pmr spectrum of 52

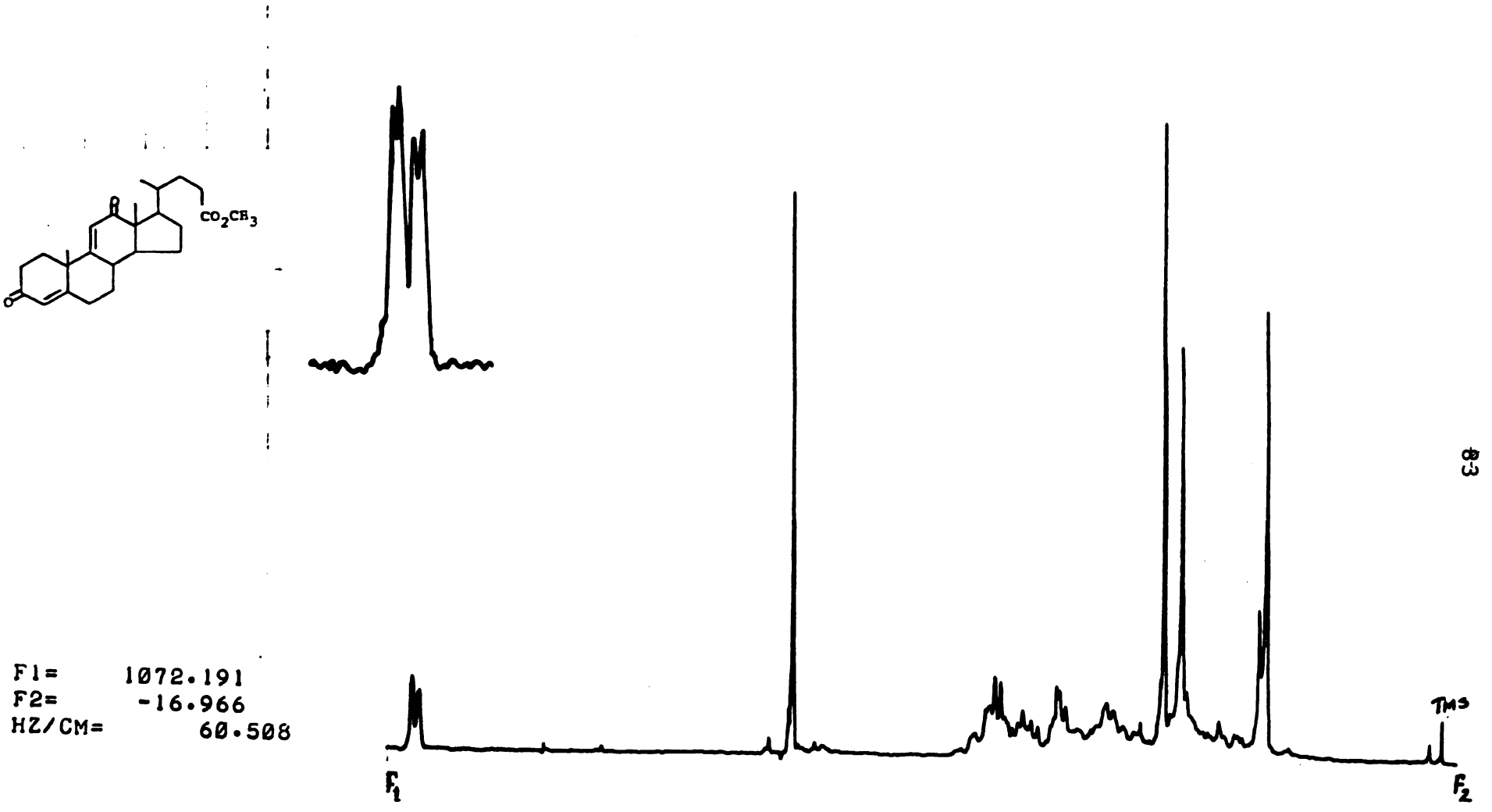


Figure 38. Pmr spectrum of 55

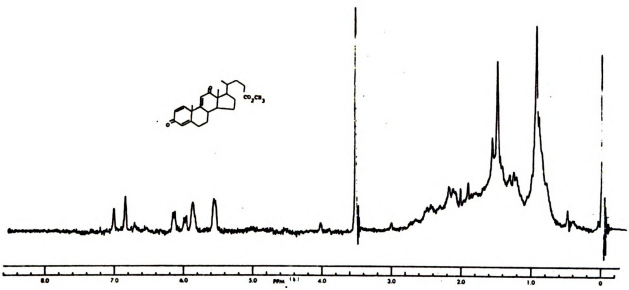


Figure 39. Pmr spectrum of 56

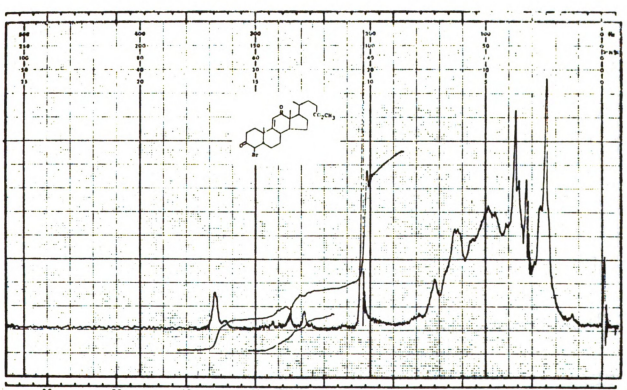


Figure 40. Pmr spectrum of 57

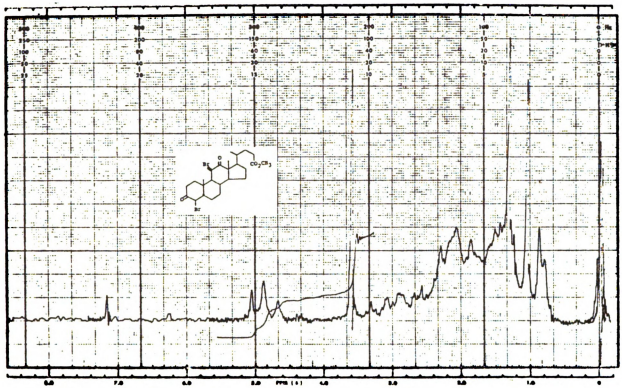


Figure 41. Pmr spectrum of 59

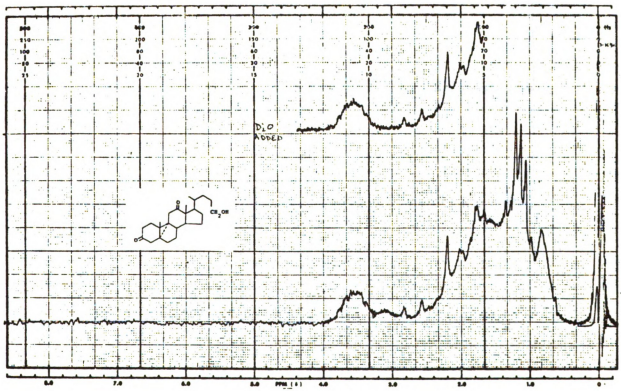


Figure 42. Pmr spectrum of 60

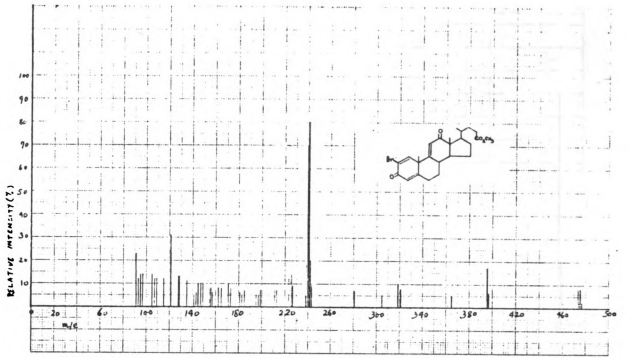


Figure 43. Mass spectrum of 33

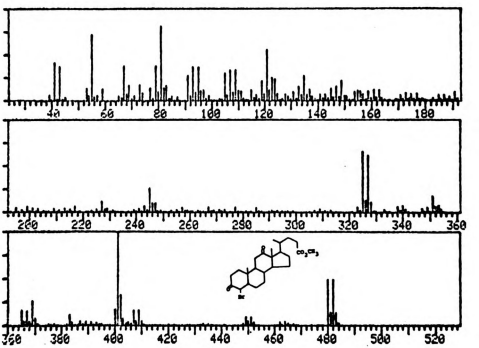


Figure 44. Mass spectrum of 34

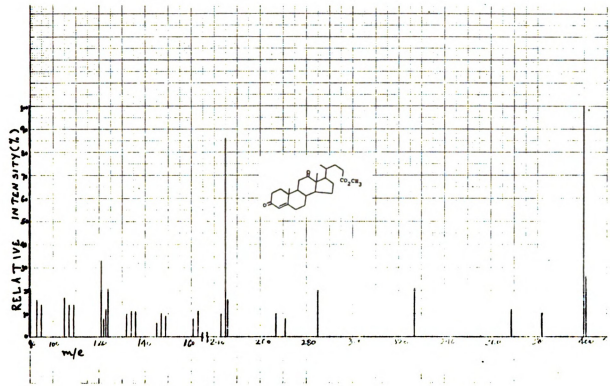


Figure 46. Mass spectrum of 35

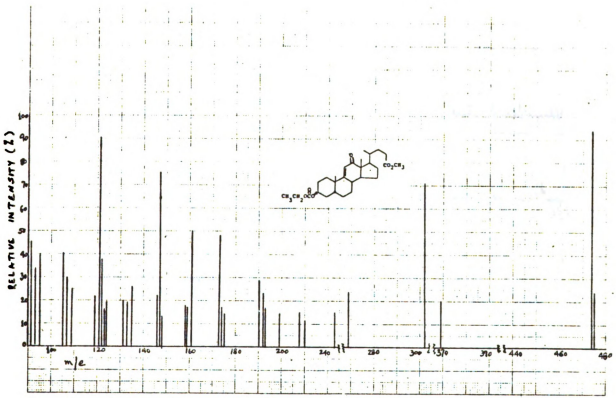


Figure 47. Mass spectrum of 38

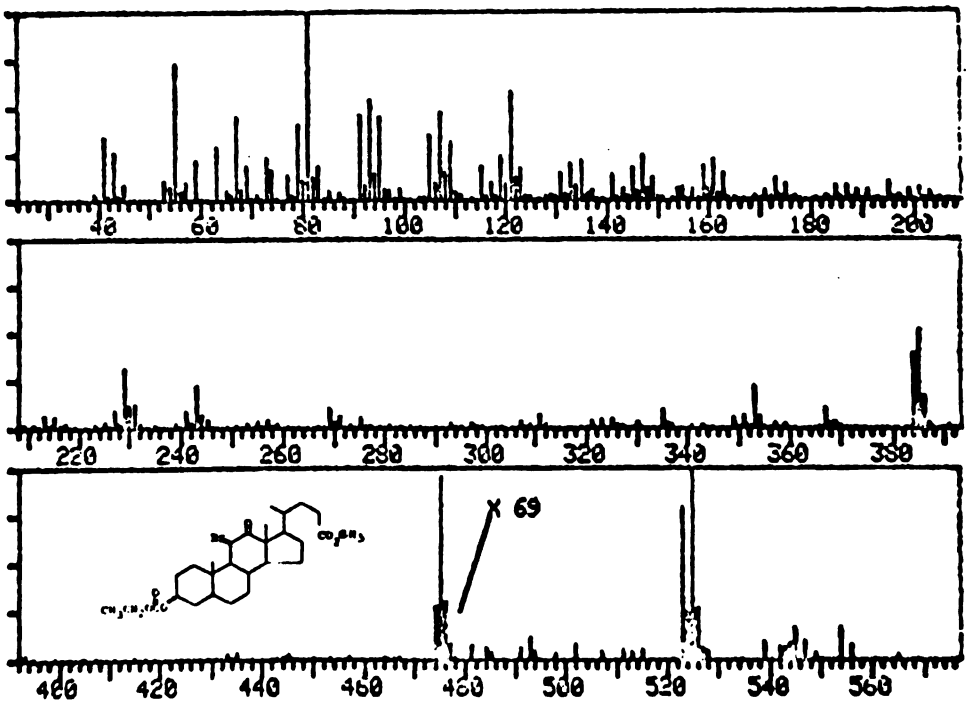


Figure 47. Mass spectrum of 41

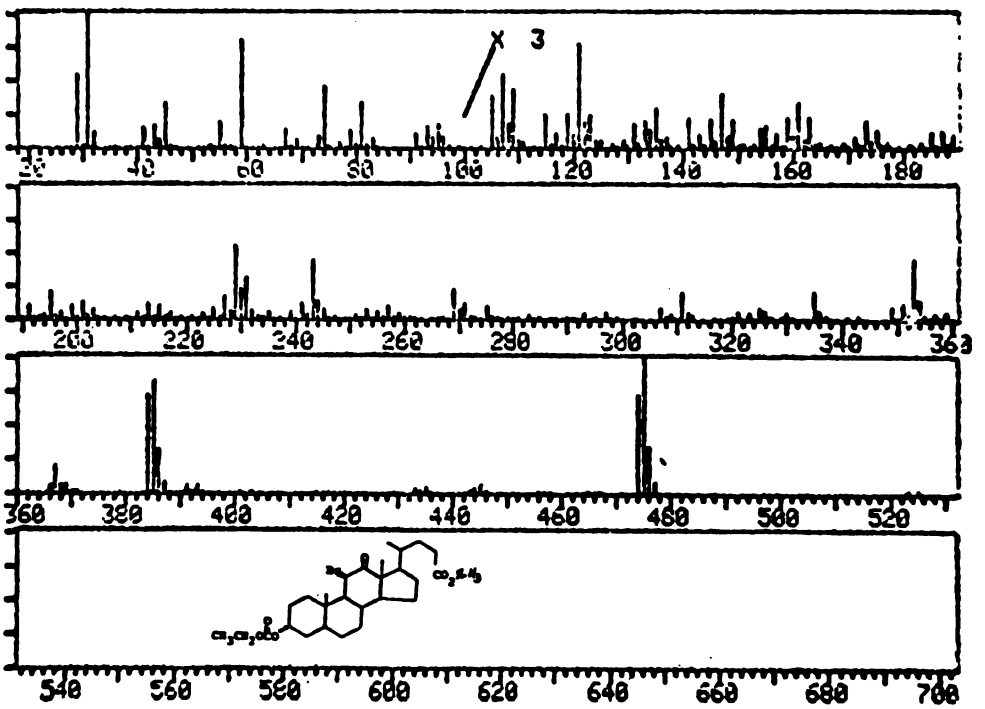


Figure 48. Mass spectrum of 42

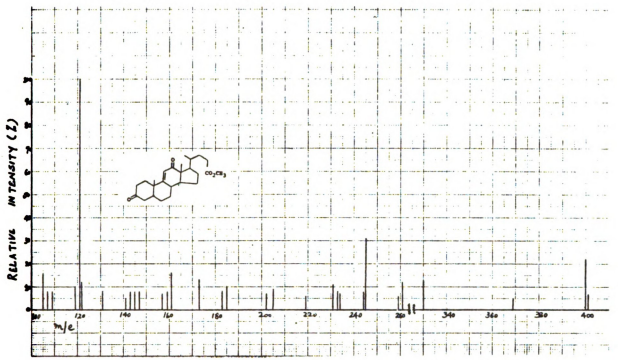


Figure 49. Mass spectrum of 45

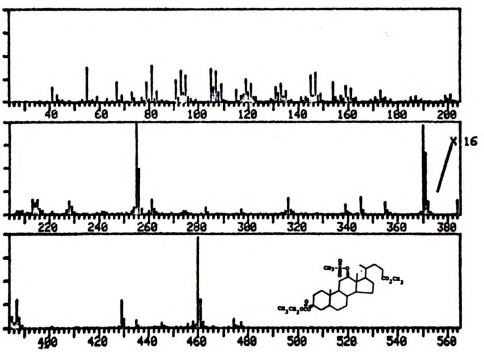


Figure 50. Mass spectrum of 46

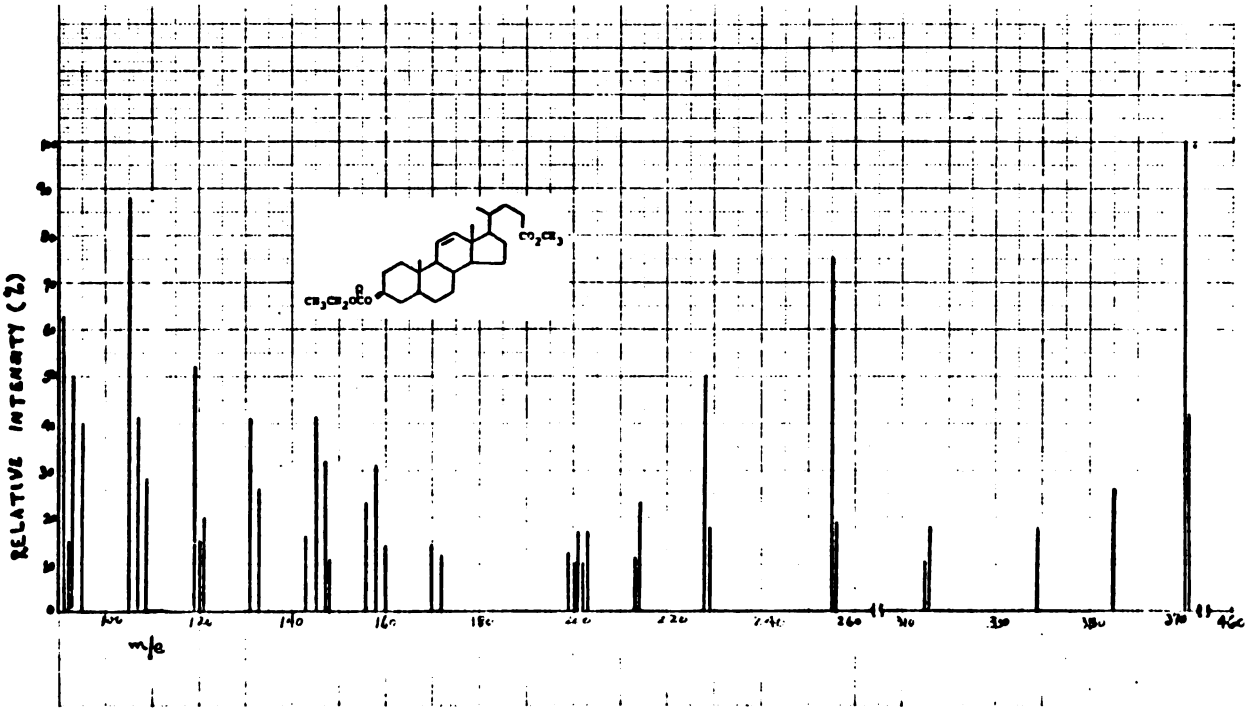


Figure 51. Mass spectrum of 47

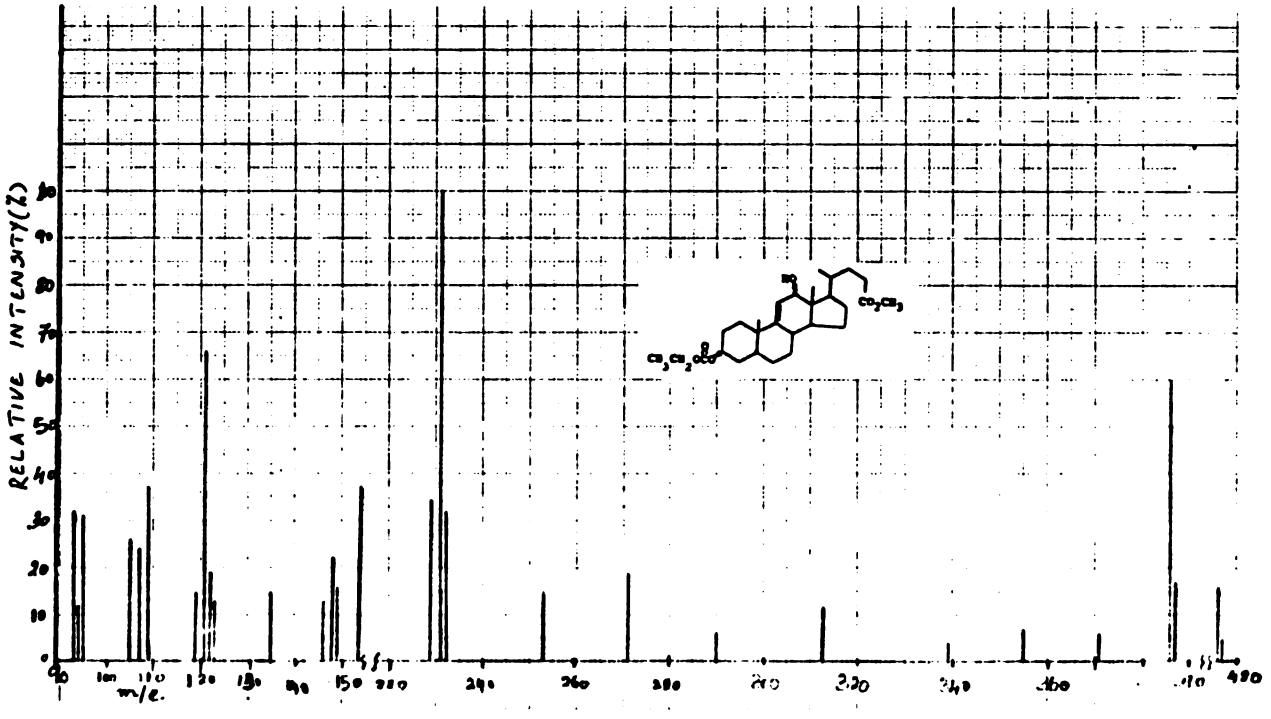


Figure 52. Mass spectrum of 48

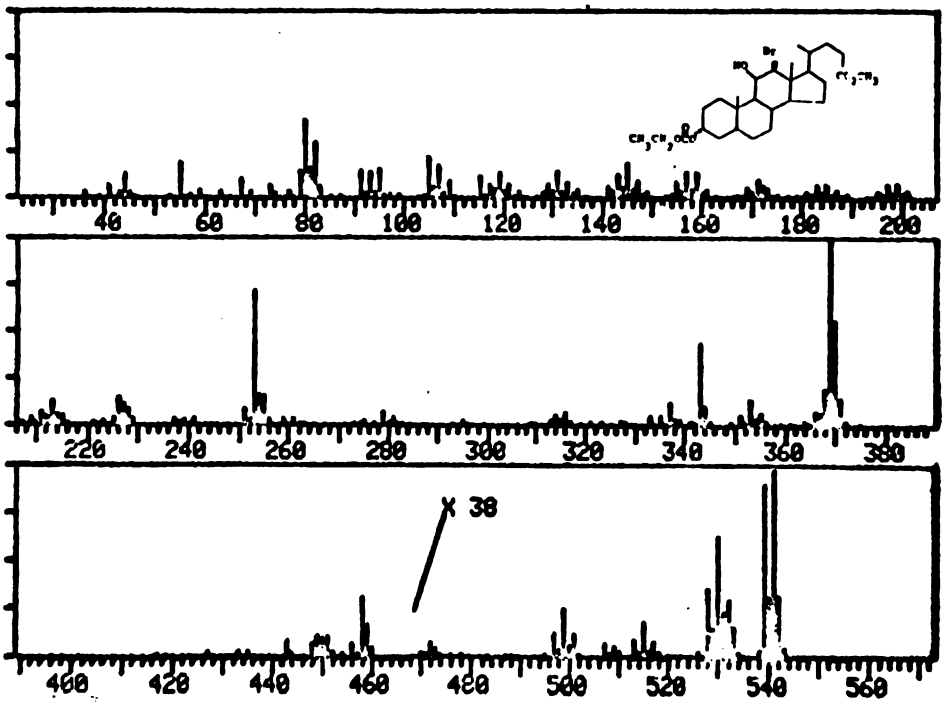


Figure 53. Mass spectrum of 49

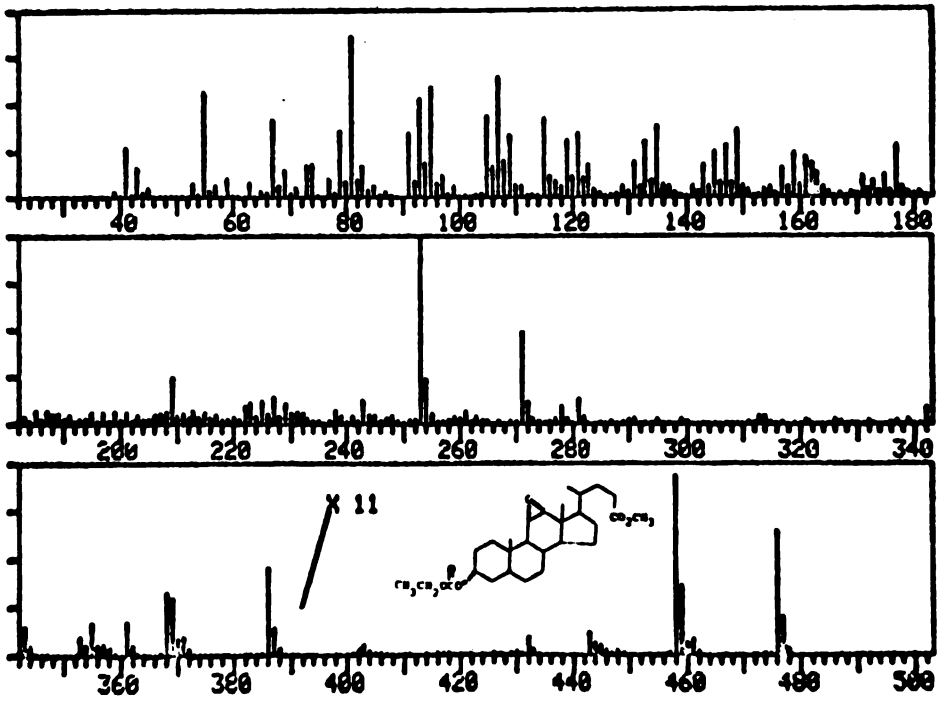


Figure 54. Mass spectrum of 50

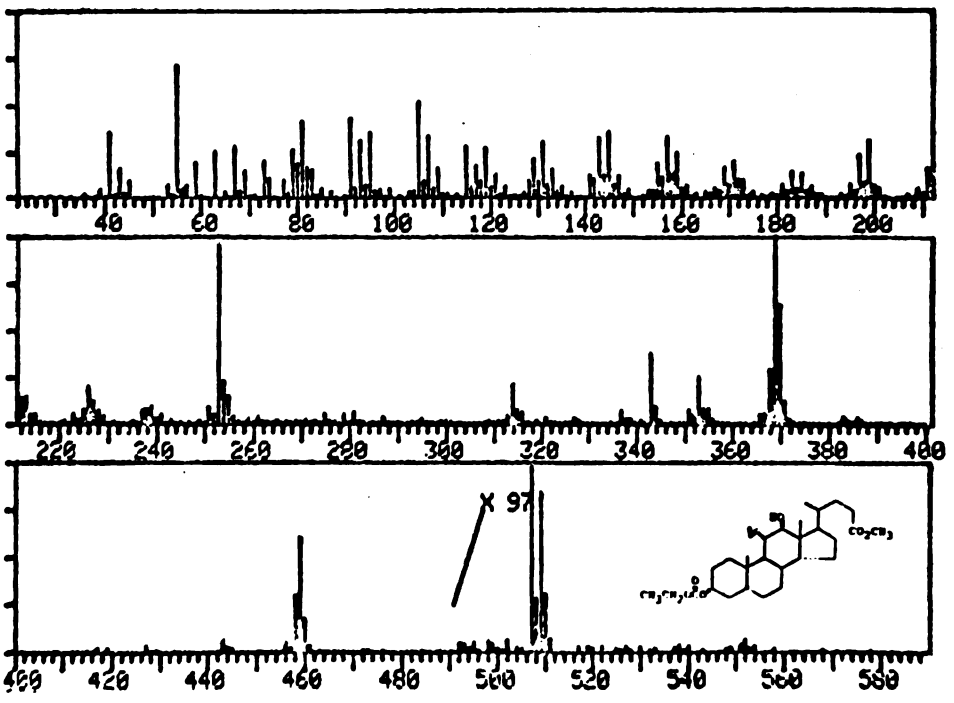


Figure 55. Mass spectrum of 51

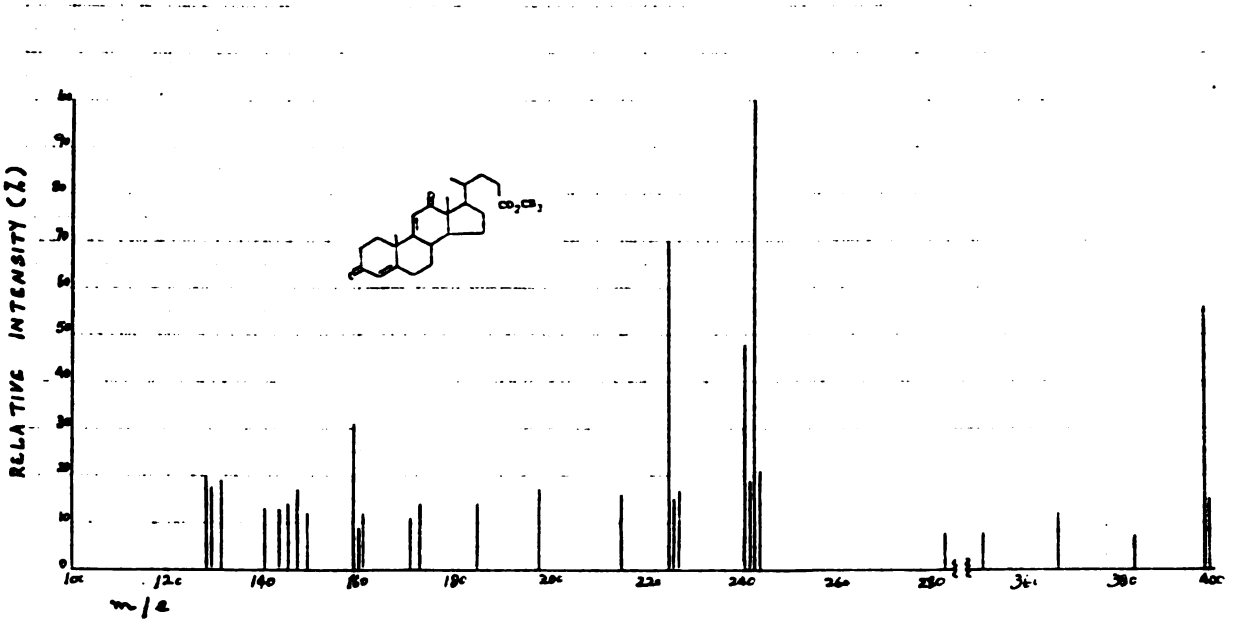


Figure 56. Mass spectrum of 55

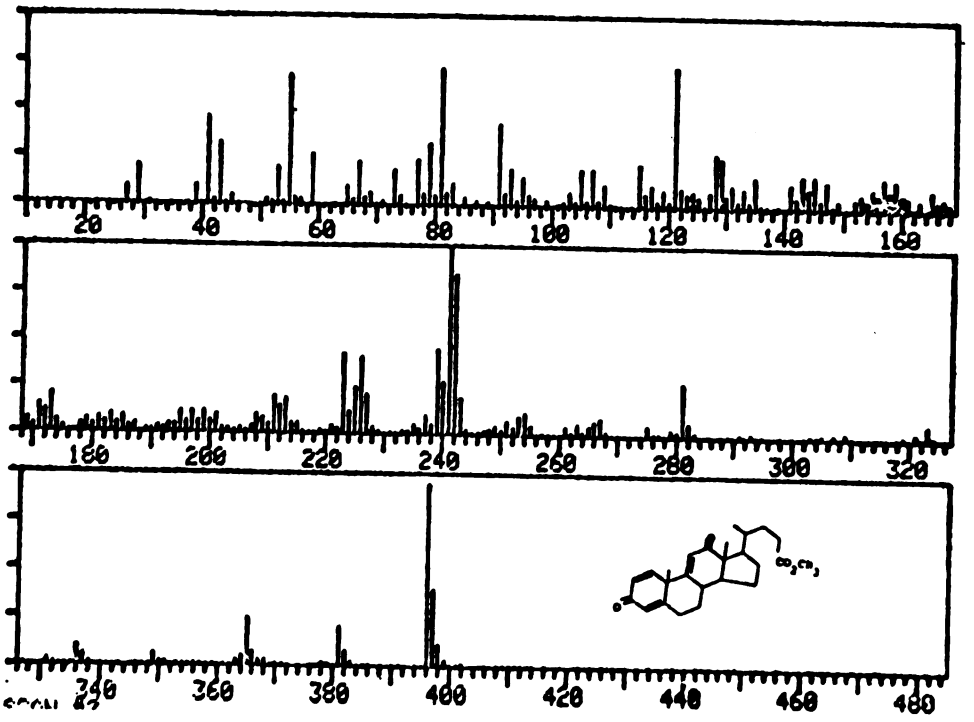


Figure 57. Mass spectrum of 56

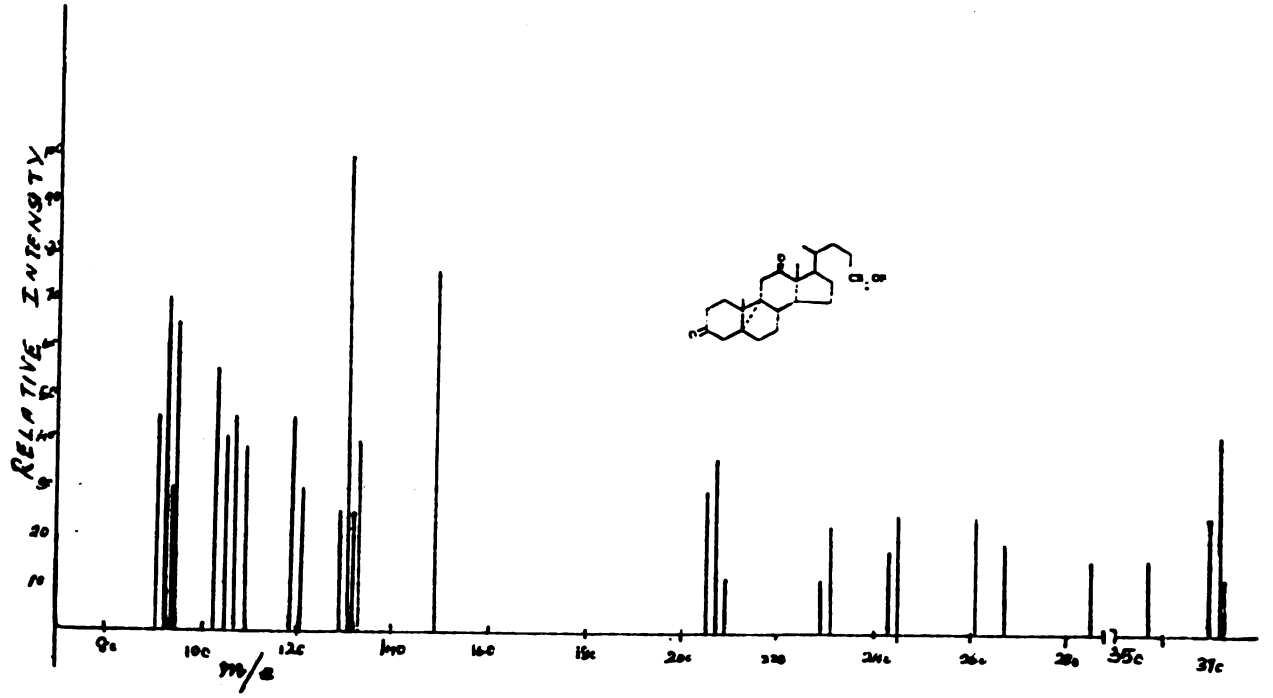


Figure 58. Mass spectrum of 60