STUDIES ON SOME OXIDATION REACTIONS OF TRITERPENOIDS AND PHYTOCHEMICAL INVESTIGATION ON INDIAN MEDICINAL PLANTS

THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY (SCIENCE)

By
SIKHA DUTTA, M. Sc.

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1985

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I wish to express my deep gratitude to Dr. B.P. Pradhan for his help and guidance in carrying out the research.

I am thankful to Mr. Abul Hasan for valuable discussion and to members of the staff of the North Bengal University Library for assistance.

I am also indebted to Ms. Sheela Kanodia, MIT, Boston, who had kindly recorded the NMR Spectra of the compounds reported in the thesis.

Sikha Dutta

Sikha Dutta
Chemistry Department
North Bengal University

S Y N O P S I S

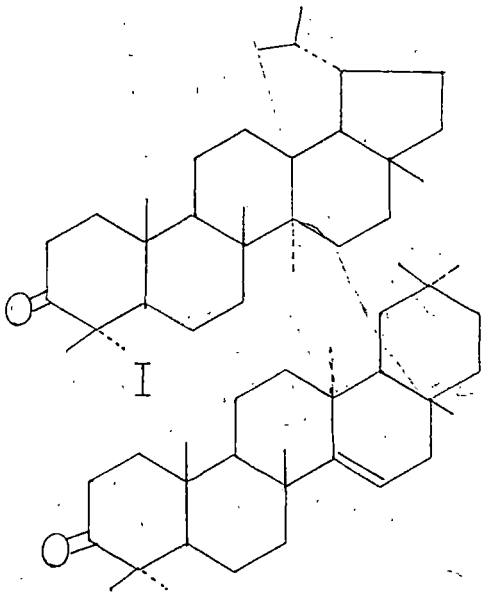
The work embodied in the present dissertation has been divided into two parts. Part I consists of oxidation of some triterpenoids, while isolation and identification of three plants of Flacourtiaceae family, namely, F. Jangomas, C. Kurzii and C. Graveolens have been incorporated in Part II. Part I has been divided into four chapters.

Chapter - I

In view of the fact that a substantial portion of Part I deals with oxidation of some triterpenoids by hydrogen peroxide in presence of selenium dioxide, it was felt pertinent to present a brief account of different oxidative transformation reactions with selenium dioxide, hydrogen peroxide and a combination of selenium dioxide and hydrogen peroxide. The review constitutes the subject matter of Chapter I of the thesis.

Chapter - II

This chapter deals with the oxidation of lupanone (I), friedelin (II) and taraxerone (III) by hydrogen peroxide in the presence of selenium dioxide.



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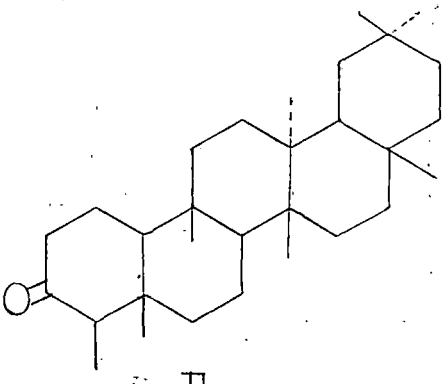
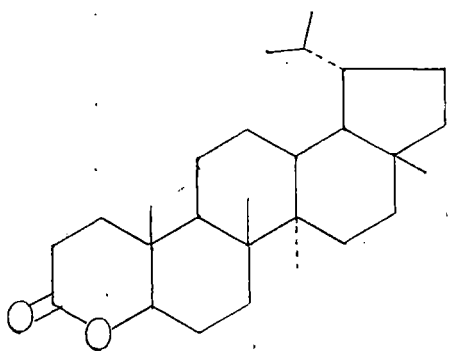


II

III

As the reaction results in bisdemethylation of ring A, some works on bisdemethylation has been reviewed in Section A.

Section B constitutes the results and discussion of the reaction of H_2O_2 with lupane in the presence of SeO_2 . It has been found that the reaction results in the conversion of ring A of the triterpenoid into δ -lactone (IV) by elimination of the gem dimethyl group. Other products formed as a result of the reaction include lup-1-ene-3-one (V), 2α-carboxy-A-nor-lupane (VI) and 2, 3-seco-lupane dicarboxylic acid (VII).



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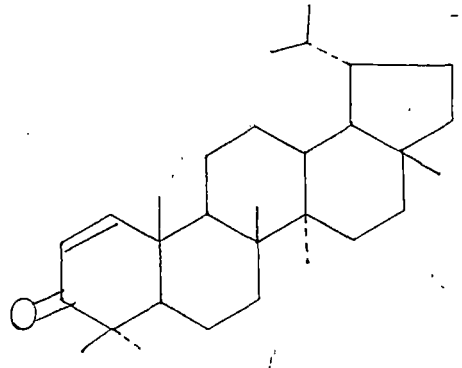

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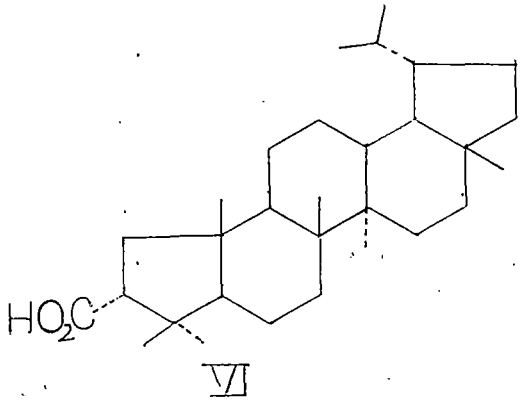

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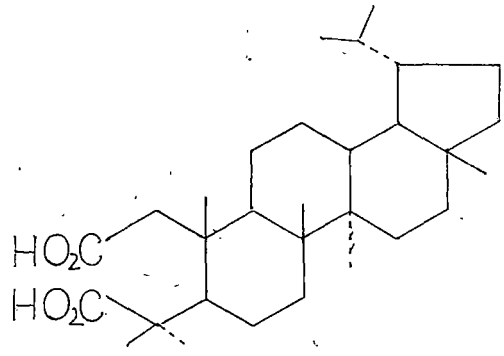
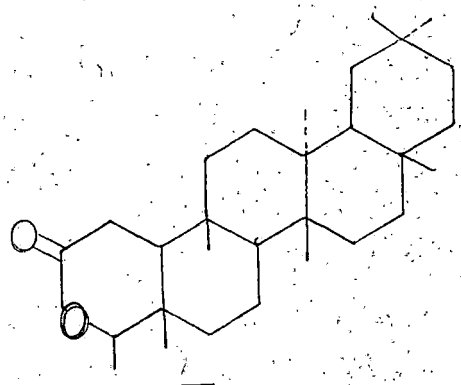
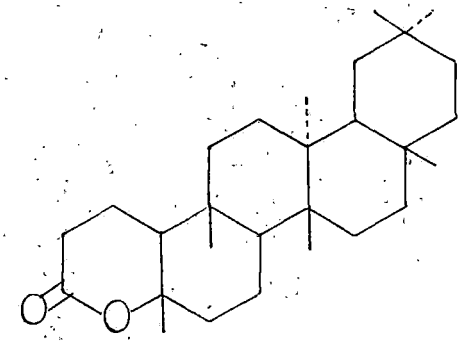


VII

The reaction of friedelin (II) with H_2O_2 in presence of SeO_2 in the same reaction medium has been reported in Section C of Chapter II. Friedelin also afforded a δ-lactone (VIII) but elimination of methyl group on C-4 position did not take place. The δ-lactone (VIII) is also different from the one (IX) reported earlier by oxidation of with per acetic acid. Other products isolated are 2,3-seco-friedelanic acid (X) and 2α-carboxy-A-nor-friedelin (XI).



VIII



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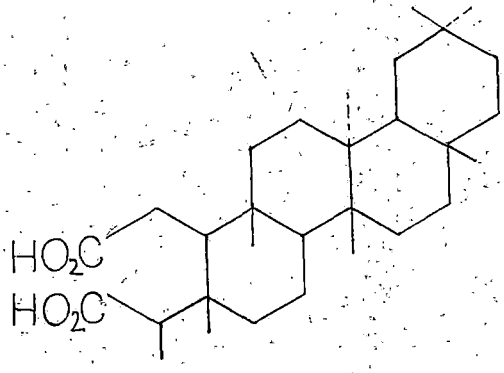
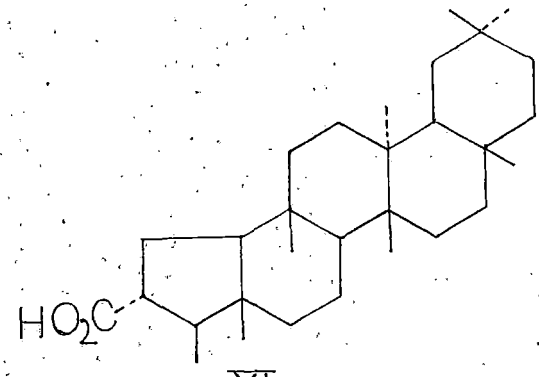
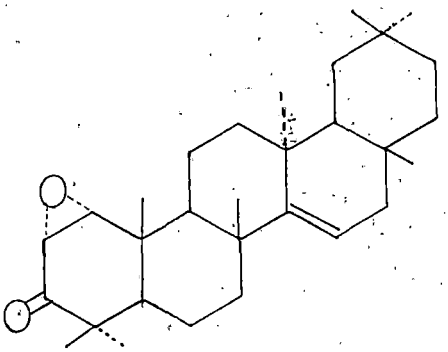


X

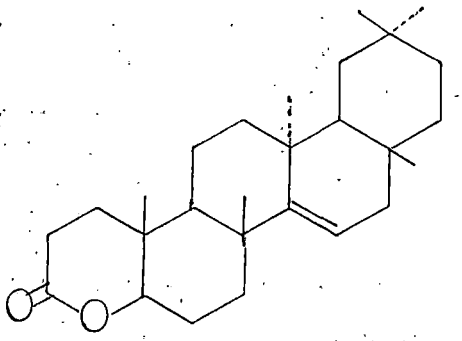


XI

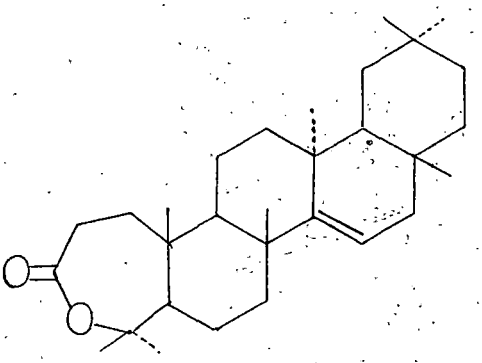
Section D contains the results of the reaction of hydrogen peroxide and selenium dioxide on Taraxerone (III). The products isolated are 1α , 2α-epoxy-3-one (XII); 4, 23, 24-tri-nor-taraxerene -3 $\longrightarrow$ 5-olide, a δ-lactone (XIII) and taraxerene - ϵ -lactone (XIV) from neutral part and 2α-carboxy-A-nor-taraxerene (XV) together with taraxerene-2, 3-seco-dicarboxylic acid (XVI) from the acid part.



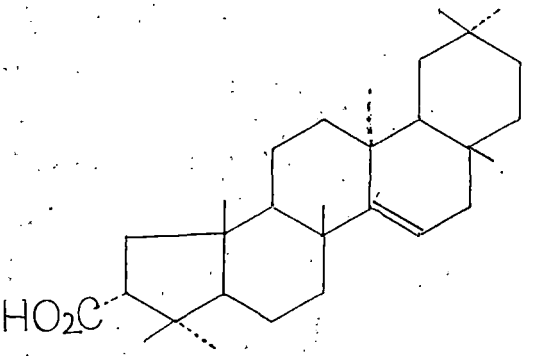
XII



XIII



XIV



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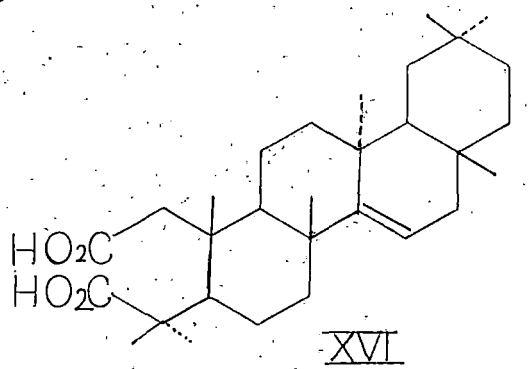


XVI

The possible mode of formation of α,β unsaturated ketone, dicarboxylic acids, A-nor-carboxylic acid and δ-lactones have been discussed in Section E.

The formation of α,β unsaturated ketone in the case of lupanone and 1α, 2α epoxide in the case of taraxerone,

though in small quantities, indicate that dehydrogenation at positions α and β to the carbonyl group takes place. In the case of friedelin, however, dehydrogenation seems not to occur. The reason has been attributed to steric factor.

The formation of seco-dicarboxylic acids has been explained on the basis of intermediate stage of 2, 3 diketones, which in turn is further oxidised by H_2O_2 to carboxylic acids. The formation of A-nor-carboxylic acid, obtained in poor yield, has been explained on the basis of oxidation of 3-ketones by selenic acid followed by oxidation with hydrogen peroxide and subsequent rearrangement.

The formation of δ -lactone in the case of lupanone and taraxerone proceeds via the formation of ϵ lactone, which undergoes hydrolysis and by Baeyer-Villiger oxidation results in the formation of δ -lactone. In the case of friedelin the reaction follows a different path. It is probable that selenium dioxide converts friedelin to 2, 3 diketone. One mole of H_2O_2 may attack the diosphenol to give the intermediate α -keto -ϵ -lactone, which then undergoes hydrolysis to furnish the α -keto acid. The acid on decarboxylation furnishes 3, 4-seco-C-3-nor-4-hydroxy friedelin-2-carboxylic acid, which undergoes lactonisation to form the δ -lactone.

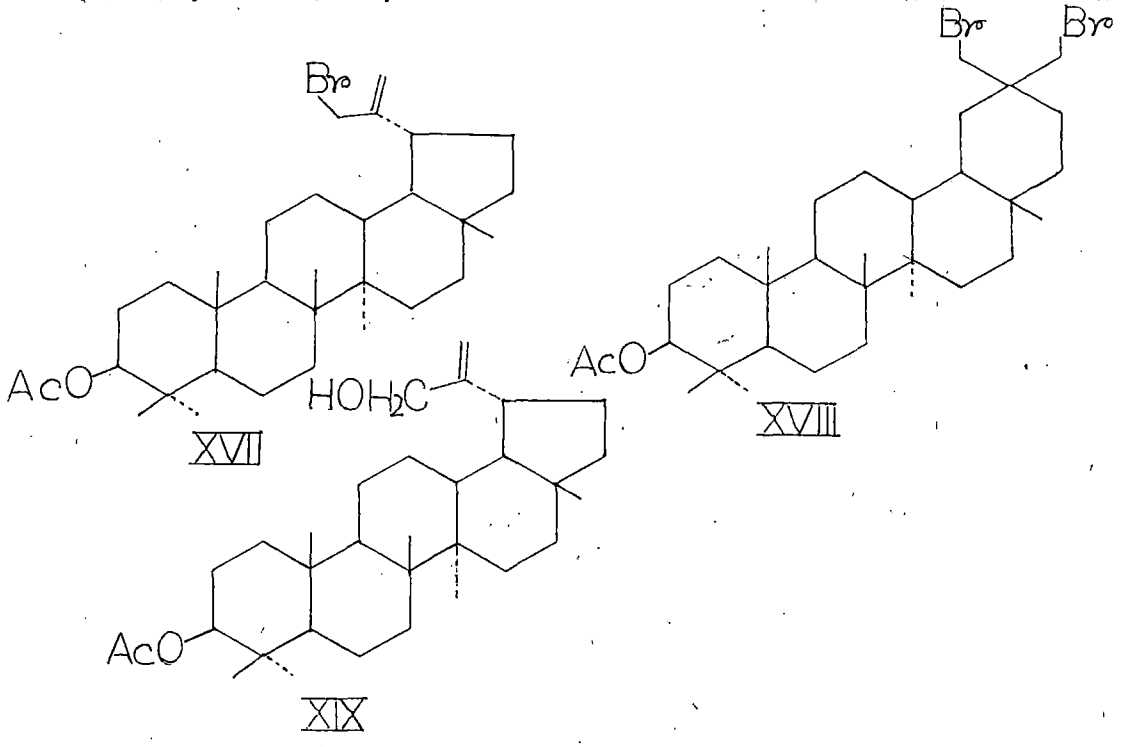
Section F describes the experimental details of the works contained in Chapter II.

Chapter-III

Chapter III contains the isolation and characterisation of the products formed as a result of reaction of N-bromosuccinimide with lupenyl acetate.

A short review of the reactions of N-bromosuccinimide with steroids and triterpenoids constitutes Section A of Chapter III. Particular emphasis has been given on bromination and dehydrobromination, oxidation of allylic methylene to carbonyl group and allylic hydroxylation.

Section B contains results and discussion of the reaction of NBS with lupenyl acetate. Compounds (XVII), (XVIII) and (XIX) have been isolated and characterised.



The formation of the dibromo compound has been proposed to take place following rearrangement of lupane system to oleanane system. It is suggested that 30-bromo-lup-20(29-en-3 -acetate has been attacked by the bromonium ion present in DMSO, the solvent that has been used in the reaction, on C 20-29 bond causing the formation of a carbonium ion, which probably compels carbon skeleton transformation from lupane to oleanane system.

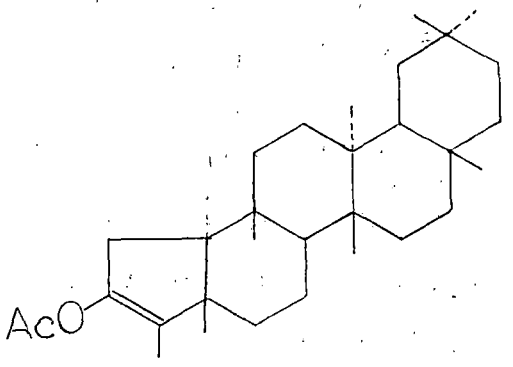
Section C contains the experimental details of Chapter III.

Chapter - IV

This chapter contains isolation and characterization of products formed following autoxidation of friedelin. A possible mode of formation has been suggested.

A short review of the works on autoxidation and isomerisation in ring A of some triterpenoids, namely, Euphol, Oleanolic acid, Lupeol, Lanostenyl acetate, -amyrone, Moretanone has been discussed in Section A.

Section B consists of results and discussion of the autoxidation of friedelin. The compounds identified are (XX), (XXI) and (XXII).



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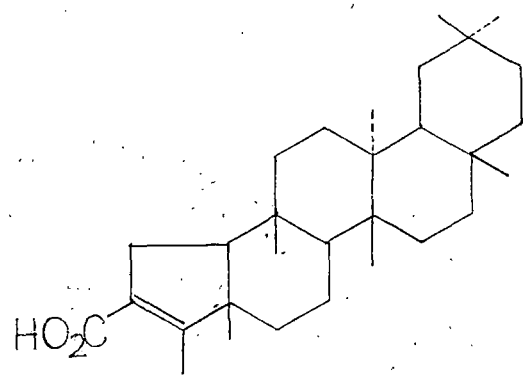
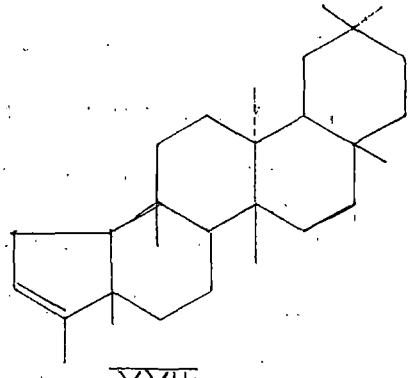


XXI



XXII

The formation of 3-nor- Δ2(4)-friedelin-2-acetate (XX) has been proposed to proceed through the formation of α-hydroperoxy ketone, which cleaved subsequently to seco-2-aldehyde-3-carboxylic acid. This undergoes further oxidation to form 2,3 seco-dicarboxylic acid, which upon cyclization forms the anhydride. The anhydride under basic medium rearranges to form β-keto acid. This undergoes decarboxylation followed by acetylation to afford compound XX.

Friedelin undergoes enolisation to give friedel-3(4)-en-3-ol, which may undergo oxygenation to form 3, 4-seco-4-keto-friedelin-3-carboxylic acid. This in turn cyclizes to give 3-nor-$\Delta^{2(4)}$-friedelin-2-carboxylic acid (XXI). This α,β unsaturated carboxylic acid undergoes easy decarboxylation in pyridine to yield the unsaturated hydrocarbon, the nor friedelin (XXII).

Section C describes the experimental details of Chapter IV.

Part II has been divided into four chapters.

Chapter - I

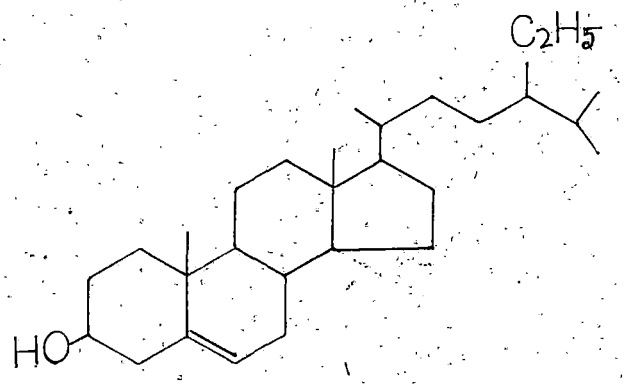
This chapter contains the morphological features of the plants of Flacourtiaceae family in Section A, while some previous works on the plants of the same family have been reported in Section B.

Chapter - II

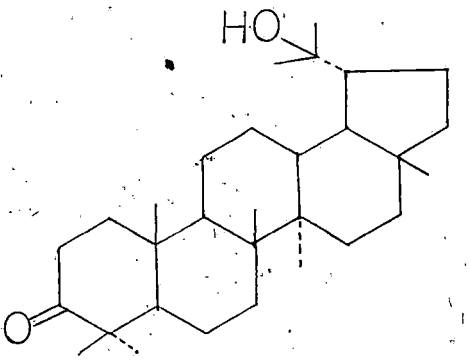
Chapter II comprises of the works done on the constituents of neutral and acid parts of benzene extract of Flacourtiaceae Jangomas.

In Section A extraction of trunk, bark and Stem of F. Jangomas by benzene as well as separation of neutral and acid parts of the extract has been described.

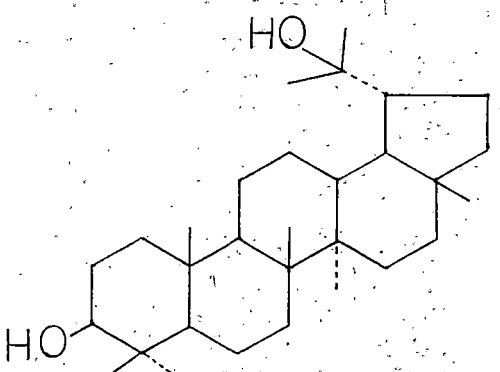
The isolation and characterization of compounds present in neutral and acid parts have been discussed in Section B. The neutral part has been found to contain 1-hexacosanol (XXIII), β-sitosterol (XXIV), 20-hydroxy lupanone (XXV) and 20-hydroxy lupanol (XXVI). The acid part containe ursolic acid (XXVII). Physical data and



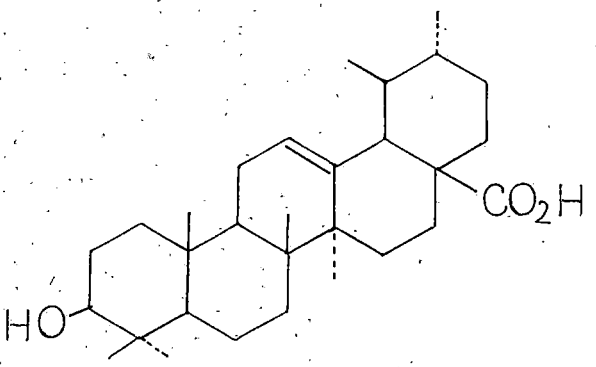
XXIV



XXV



XXVI



XXVII

chemical reactions in support of the characterization of the compounds have been reported.

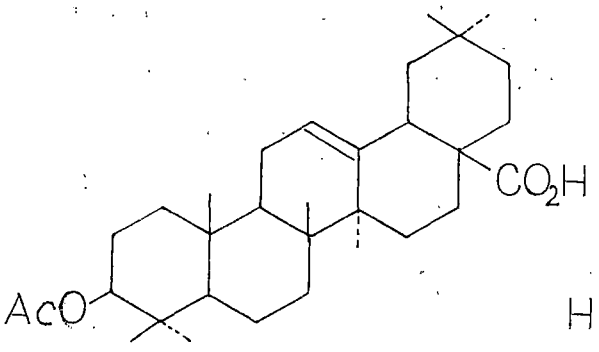
Section C describes the experimental details of the works reported in Chapter II.

Chapter - III

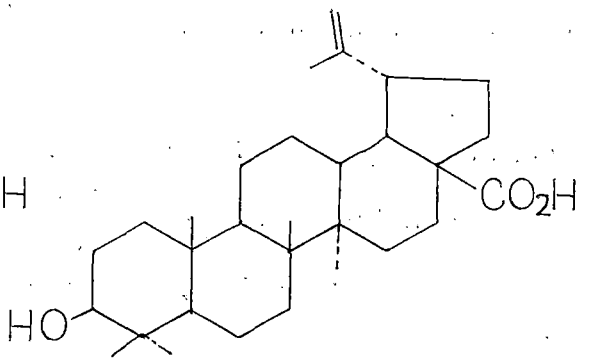
In Chapter III investigations on the neutral and acid parts of the benzene extract of bark and stem of caseria kurzii clark have been reported.

Section A describes the extraction of the plant material with benzene and separation of benzene extract into neutral and acid parts.

Section B deals with the isolation and identification of the compounds. 1-hexacosanol (XXIII) and β-sitosterol (XXIV) have been isolated from the neutral part while acetyl oleanolic acid (XXVIII) and betulinic acid (XXIX) have been found to be present in the acid part.



XXVIII



XXIX

The experimental details of the works presented in Chapter III has been described in Section C.

Chapter - IV

Chapter IV consists of investigations on the neutral and acid parts of the benzene extract of bark and stem of Caseria Graveolens Dalz.

Section A describes the extraction of the plant material with benzene and separation of benzene extract into acid and neutral parts.

Section B deals with isolation and identification of the constituents. The neutral part has been found to contain 1-hexacosanol (XXIII) and β-sitosterol (XXIV) and the acid part contains betulinic acid (XXIX).

Section C describes the experimental details of the works presented in Chapter IV.

C O N T E N T S

PART - I

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PART - II

CHAPTER - I

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P A R T - I

CHAPTER - I

The chemistry of terpenoids abounds in fascinating molecular rearrangements, which may be accomplished with relatively simple reagents. Besides demonstrating the combined role of steric and electronic factors in the study of reaction mechanism in general, the vast array of the rearrangement reaction has helped in ascertaining structures, stereochemistry and biogenetic pathway of formation of the terpenoids. The oxidative transformation, which are effected photochemically and by oxidants like mercuric acetate, lead tetra-acetate, chromic acid, N-bromosuccinimide, organic peracid, hydrogen peroxide etc. have been extensively studied[1-12]. Oxidation of triterpenoids by hydrogen peroxide with

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1. J.M.Allison, W.Lawrie, J. Mclean and G.R.Taylor, J.Chem.Soc. 3353 (1961); ibid J.Chem.Soc. 5224 (1961)
2. C.S.Chopra and (the late) D.E.White, Tetrahedron, 22, 897 (1966)
3. H.N.Khastgir and S.N.Bose, Tet.Lett. 1, 39 (1968)
4. S.N.Bose and H.N.Khastgir, J.Ind.Chem.Soc., 46, 860 (1969)
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selenium dioxide as catalyst are scanty. The reagents have, however, been used in the oxidation of acrolein[13], cyclo and bicyclo alkanones[14], and steroidal ketones[15,16]. In view of the fact that the succeeding chapter deals with oxidation of some triterpenoids by hydrogen peroxide in presence of selenium dioxide, it is pertinent to present in this chapter a brief account of different oxidative transformation reactions with selenium dioxide, hydrogen peroxide and a mixture of selenium dioxide and hydrogen peroxide.

Selective Oxidations with Selenium Dioxide

Selenium dioxide has been in use since Riley's pioneering work[17] in which he reported conversion of a monocarbonyl compound having an adjacent methylene unit to an α-dicarbonyl compound. The transformation of a ketone or an aldehyde to an α-dione, allylic oxidation and the conversion of a monoketone or a

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10. T. Mezzetti, G.Orzalesi and V.Bellavita, Plant Medica, 20(3), 244 (1971)
11. M. Fukuoka and S.Natori, Chem. Pharm. Bull., 20(5), 974(1972)
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14. L.Stall and Jucker, Helv.Chim. Acta. 36, 268 (1953)
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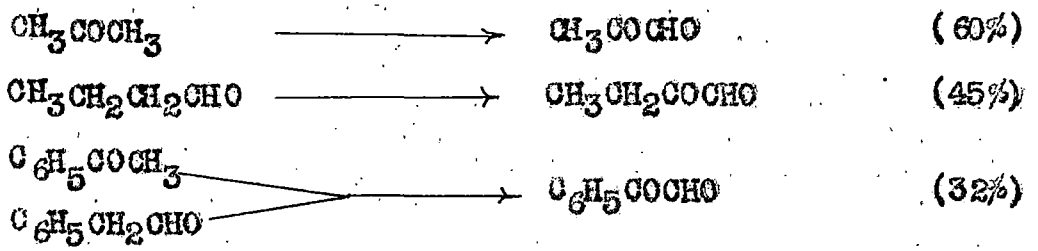
17. H.L.Riley, J.F.Morley and N.A.C. Friend, J.Chem.Soc., 1932, 1875.

1,4, diketone to an α,β -unsaturated ketone or to an ene-dione are the major areas in which the reagent has found rather wide application.

Formation of α -dione

Both ketones and aldehydes would react with selenium dioxide to give reasonable yields of products as shown below.



Excellent yields can be obtained if the ketone being oxidised contains structural features which prevent side or competing reactions from occurring. Thus, A-nor allobetulone-3 and A-nor-4, 4-dimethyl cholest-5-ene-3-one both of which have the monoketone unit, partial structure 1, are oxidised to the diketone 2 in 87% and 92% yield[18].

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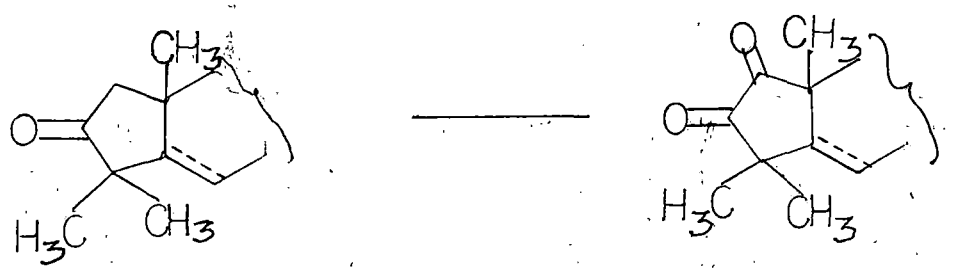
18. R. Hanna and G. Onrisson, Bull. Soc. Chim. Fr., 1945 (1961)



1 2

Mechanism:

The most critical study of the reaction was made by Corey and Schaefer[19], who studied the oxidation of desoxybenzoin in 70% acetic acid at 89.2°. They found the reaction to be second order; first order in ketone and first order in selenium (IV) reagent and to be catalyzed by added strong acid. Various p-substituted desoxybenzoins with substituents in the benzyl or benzoyl moiety were studied. Electron supplying substituents in the benzoyl increased the rate of reaction (ρ = -0.56) while the effects in benzyl group was to decrease the reaction rate (ρ = +0.25). This is what one would expect in acid catalyzed enolization process.

The reaction exhibited an isotope effect; kH/kD for dideutorio desoxybenzoin was 6.0 and for the oxalic acid catalyzed reaction it was 5.8. Fast reversible enolisation, followed by slow

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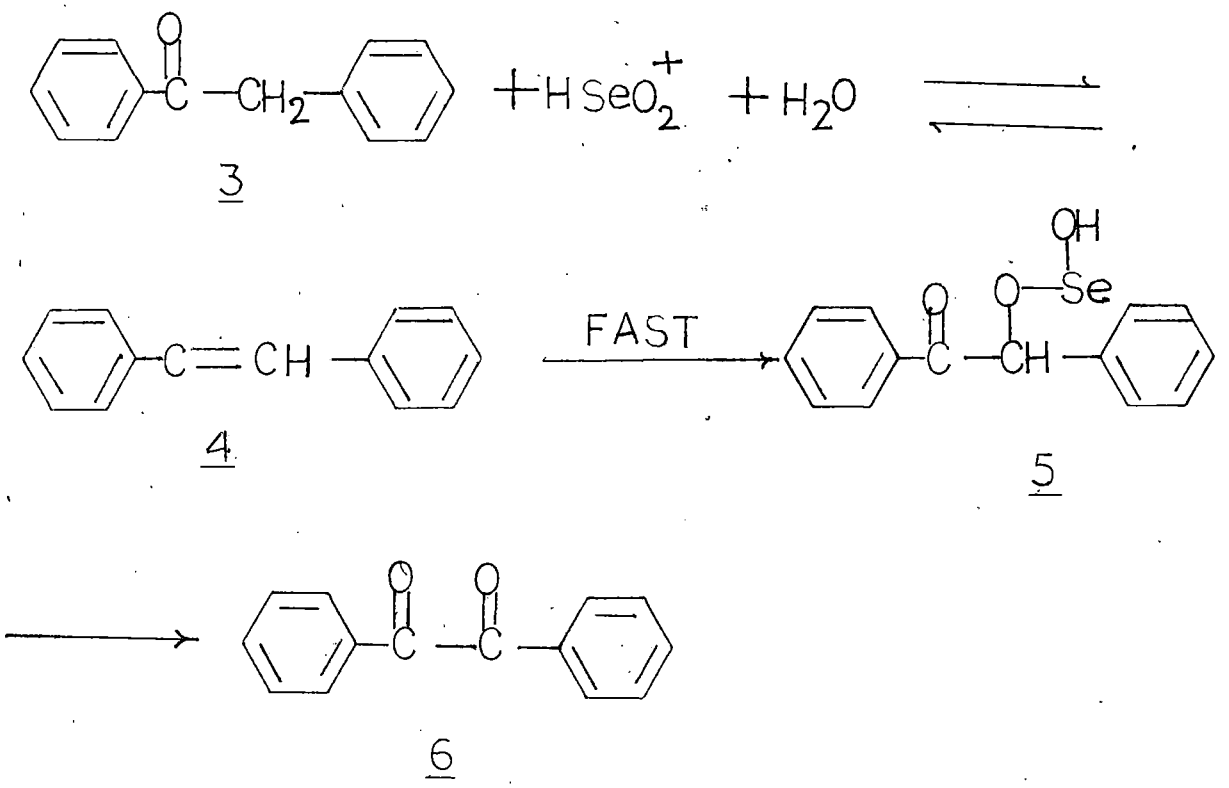
19. E.J. Corey and J.P. Schaefer, J.Am.Chem.Soc., 82, 918 (1960)

reaction of the enol with oxidant should have exchanged out the deuterium prior to reaction and kH/kD = 1.

The mechanism proposed by the authors involves attack of an electrophile, $HSeO_2^+$ or $H_3SeO_3^+$ and the nucleophile, H_2O, on desoxybenzoin, 3, in a slow step to give an end selenite ester, 4. The latter rearranges in a series of fast steps to an α - selenite (II) keto-ester 5 and finally to benzil 6 (Scheme-I).

Scheme - I



Allylic oxidation

After several publications on the oxidation of olefins[20-23], Guillemonat collected his observations in one report[24]. He found that the course of selenium dioxide oxidation of alkenes could be predicted from the following rules:

(i) The oxidations always occurred to alpha to the most substituted end of the double bond.

(ii) When the double bond was in a ring, whenever possible, oxidation occurred within the ring.

(iii) The order of preference for oxidation was $CH_2 > CH_3 > CH$.

(iv) When the double bond was terminated rather than the expected secondary alcohol or the derivative thereof, the primary alcohol was formed with the migration of the double bond.

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20. A. Guillemonat, Compt. Rend., 200, 1416 (1935)
21. A. Guillemonat, ibid 201, 904 (1935)
22. A. Guillemonat, ibid 205, 67 (1937)
23. A. Guillemonat, ibid 206, 1126 (1938)
24. A. Guillemonat, Ann. Chim. 11, 143 (1939)

Though the inadequacy of Guillemonat's proposal has been shown[25-27], the generalization is still valid with respect to site of attack in many cases.

Another early suggestion put forward by Waters without any experimental support was that the reaction involved neutral radical species[28]. Schaefer, Horvath and Klein[29] had shown that the reaction was unaffected by inhibitors and, therefore, could not be radical chain. That no free radical was generated in the system had been pointed out by Trachtenberg et al[30] as the system was incapable of initiating polymerisation of acrylonitrile under conditions of temperature and concentration, where acrylonitrile is rapidly polymerised if a source of free radical is present.

Wiberg[31] established that selenoxides, 7, rather than selenides as had earlier been proposed by Guillemonat was involved in the oxidation of cyclohexene in acetic acid - acetic anhydride

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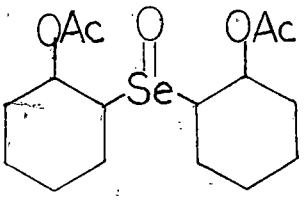
25. E.N.Trachtenberg in "Oxidation" Vol. 1 R.L.Augustine, Ed., Marcel Dekkar, New York, N.Y. 1969, pp 119-187.
26. R. Rabjon, Org. Reaction, 5, 331 (1949)
27. G.R.Watkins and G.W.Clark, Chem. Rev. 36, 235 (1945)
28. W.A.Waters, J.Chem.Soc., 1805 (1939)
29. J.P.Schaefer, B.Horvath and H.P.Klein, J. Org. Chem., 33, 2647 (1968)
30. E.T. Trachtenberg, C.H.Nelson and J.R.Carver, J.Org.Chem. 35, No. 5, 1653 (1970)
31. K.B.Wiberg and S.D.Nielsen, J.Org.Chem., 29, 3353 (1964)

reaction. Schaefer et al[29], however, showed that the analogus compound, 8, isolated from the oxidation of 1,3 diphenyl propene, 9, decomposes to 1,3 diphenyl-2-propene-1-ol acetate, 10, at too slow a rate to account for the main course of oxidation. The main pathway must involve solvolysis on an allylic selenite ester, although the structure of the latter has not been rigorously established.



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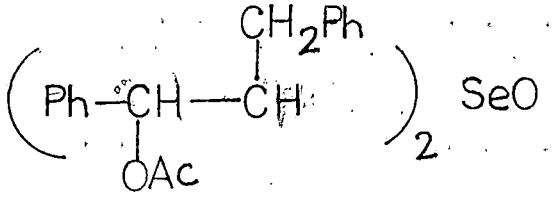

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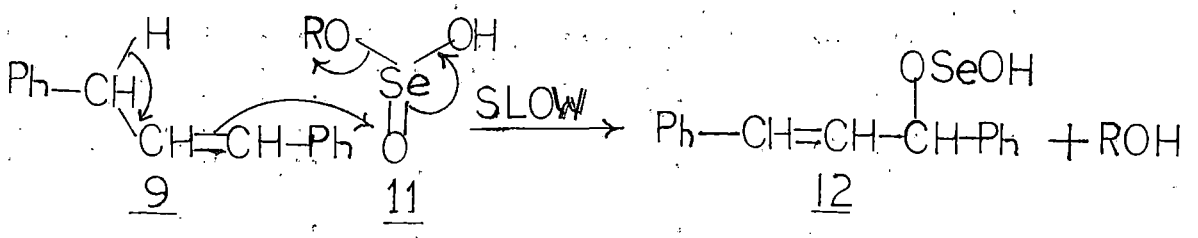
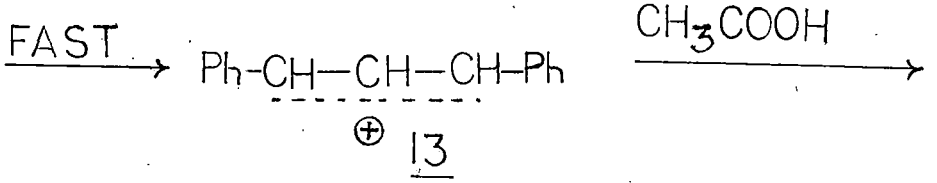
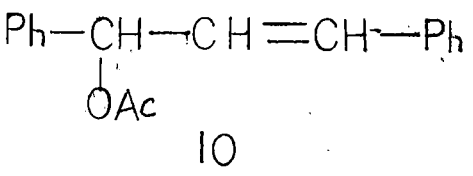
Scheme - II





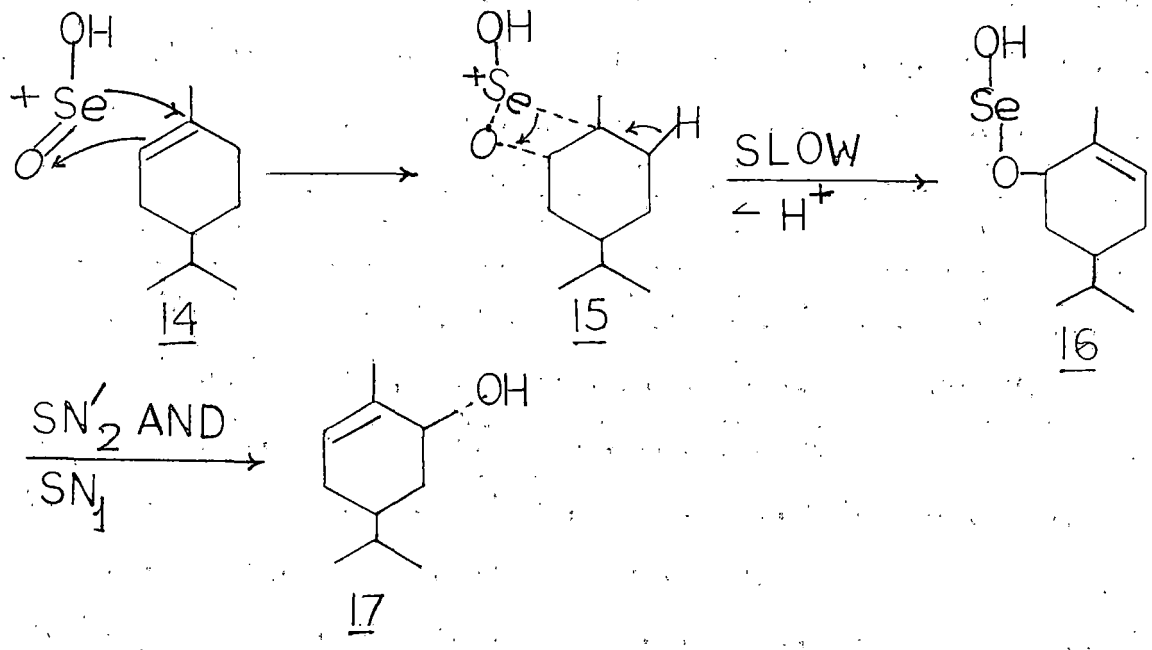


10

Since the selenium (II) ester formed, 12, was benzylic, the preference for ionisation (SN_1) rather than SN'_2 attack as found by Wiberg and Nielsen was possible[32]. Schaefer et al[33] pointed out that the intermediate which contains a C - Se bond is very likely a stable compound as are alkyl selenic acids. Thus, the intermediate as well as selenium (II) ester type intermediate, which contains on O-Se bond will not probably undergo solvolysis.

In order to explain the sterEochemical results obtained by oxidation of a number of cyclohexenyl system, Trachtenberg et al[34] proposed the following mechanism as shown in Scheme-III with D (+)-1-p-menthene as substrate.

Scheme - III



32. K.B. Wiberg and S.D. Nielsen, J. Org. Chem. 29, 3553 (1964)

33. Ref. 29 of this chapter.

34. E.N.Trachtenberg, C.H.Nelson and J.R. Carver, J. Org. Chem., 35, 1653 (1970)

The first step does not imply a concerted 2+2 cycloaddition but rather a typical Markovnikov type electrophilic addition with attack occurring through oxygen to generate positive character as the tertiary carbon, followed by cyclization. In agreement with electrophilic attack are the observations that dienes are more reactive than olefins — olefins reactivity increases with alkyl substitution and electron feeding groups slightly accelerate the rate of oxidation of 1,3 diphenyl propene[35].

Sharpless and Lauer[36] proposed different mechanism for allylic oxidation of olefins by selenium dioxide. As already discussed, Schaefer and Trachtenberg argue against involvement of allyl selenic acid, 19, because of the known inertness of benzyl selenic acid to solvolysis. However, a [2,3] sigmatropic rearrangement (path b, Scheme IV) of allyl selenic acid, 19, to a selenium (II) ester, 20, occurred to Sharpless et al as a likely alternative to the solvolysis pathway a. They suggested that the [2,3] sigmatropic shift indicated in the path b is a facile process (Scheme - IV).

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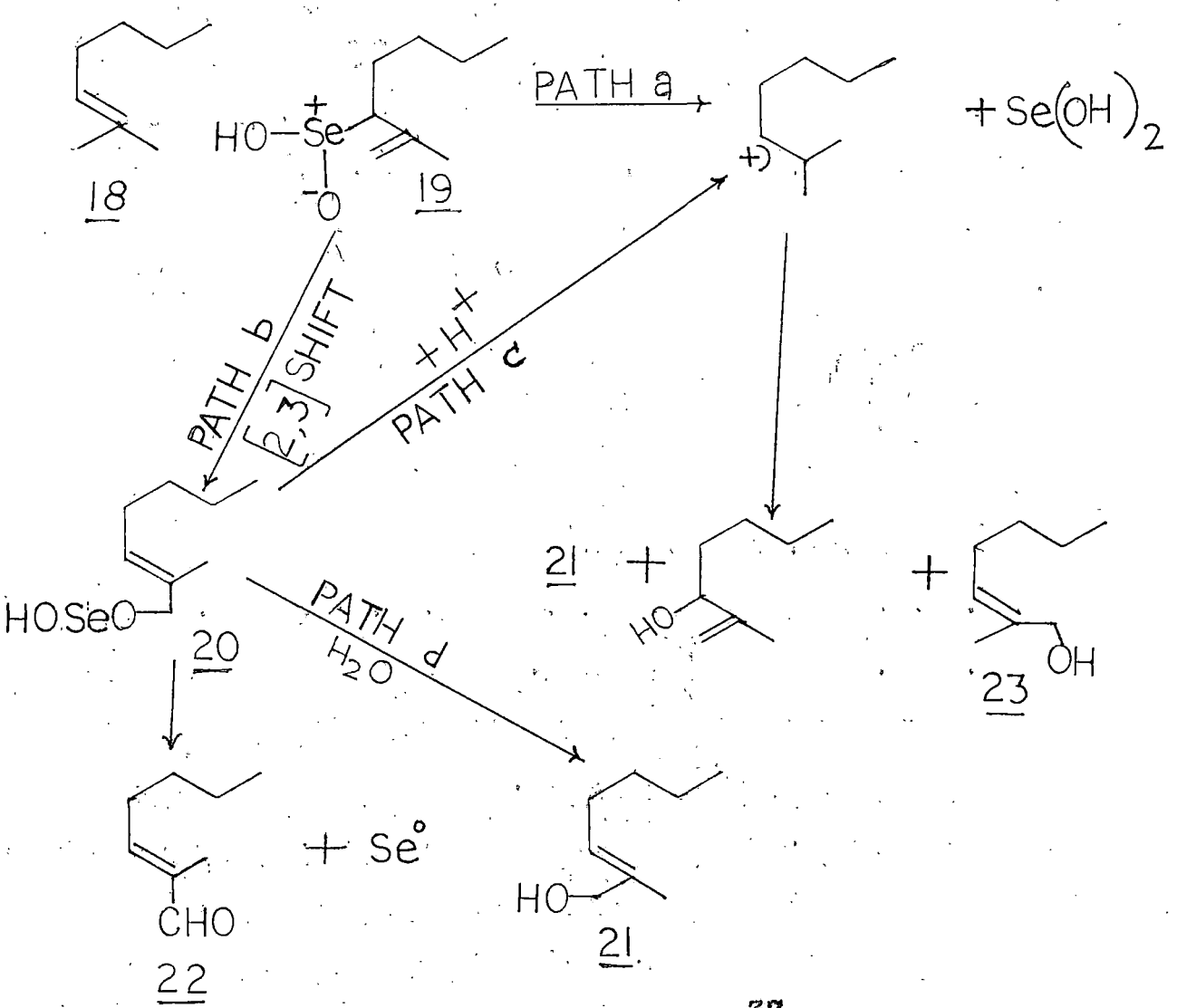
35. Ref. 29 of this chapter.

36. K.B. Sharpless and R.F. Lauer, J. Am. Chem. Soc., 94(2), 7154 (1972)

Scheme - IV



The authors had noted that Buchi and Wuest[37] had established that SeO_2 selectively attacks trisubstituted olefins such as, 18, to give only the (E) - alcohol, 21. The allyl selenic acid, 18, must

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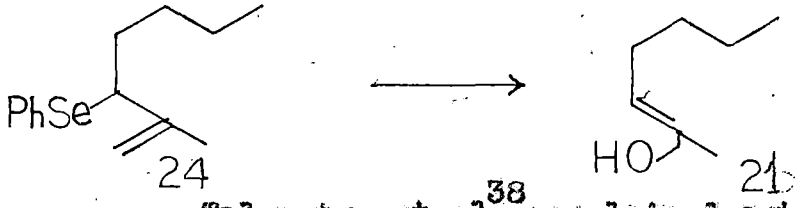
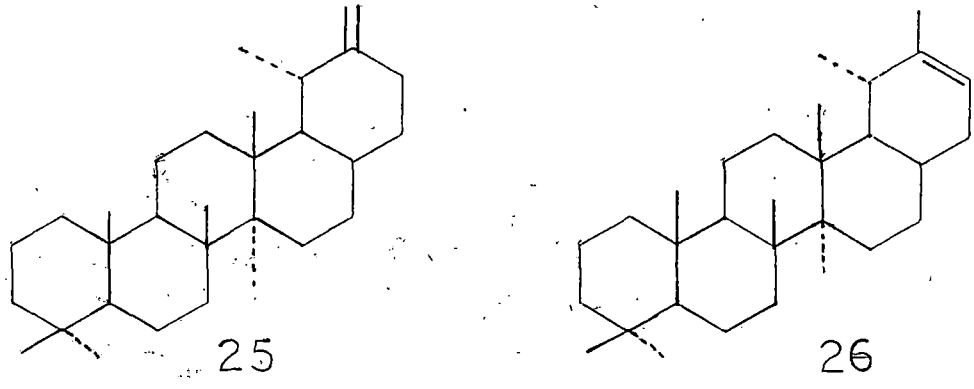
37. G. Buchi and H. Wuest, Helv. Chim. Acta., 50, 2440 (1967)

lead stereoselectively to the (E)-ester of 20 if the proposed rearrangement is correct. The mechanism was verified from the conversion of alkyl phenyl selenides 24 to 21.



24 21

Talapatra et al[38] explained oxidation of taraxastene, 25, and Ψ-taraxastene 26 to give the corresponding aldehyde[39]



25 26

on the basis of the mechanism shown in Scheme - V.

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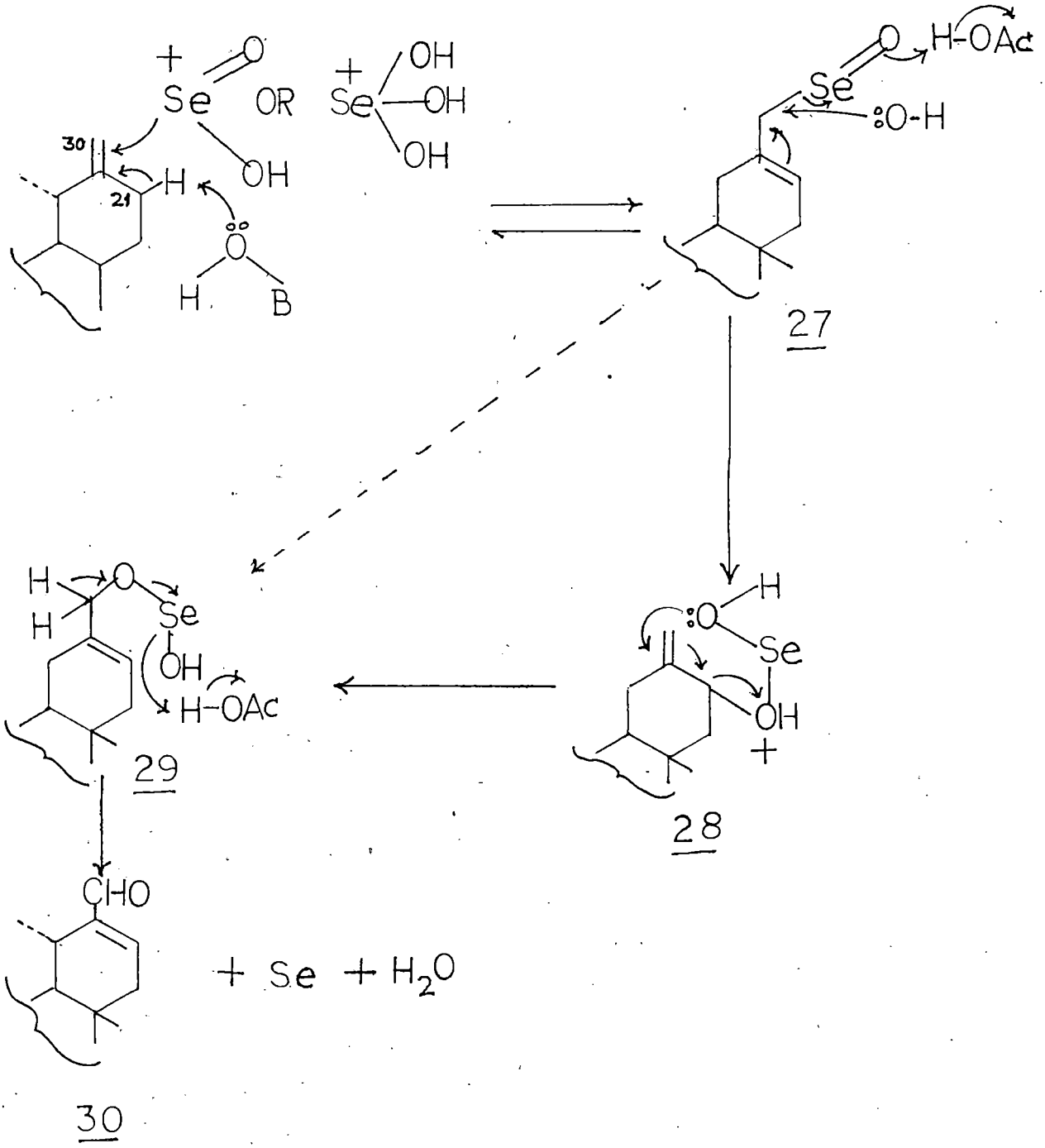
38. S.K. Talapatra, M. Bhattacharjee and B. Talapatra, Ind. J. Chem., 11, 977 (1973)

39. T.R. Ames, J.L. Beton, A.Bowers, T.G. Halsall and E.R.H. Jones, J. Chem. Soc., 1905 (1954)

Scheme - V


Se
OR
OH
30
21
H
O
H
B
OH
Se
OH
OH
O
H-OAc
Se
:O-H
27
H
H
O
Se
OH
H-OAc
29
H
:O
Se
OH
+
28
CHO
+ Se + H_2O
30

The electrophilic attack of $HSeO_2^+$ or $H_3SeO_3^+$ on the olefinic C-30 with simultaneous or subsequent nucleophilic attack on the allylic C_{21} -H leads to the formation of an unstable Se(IV) complex 27 possessing the more stable double bond parallel to the trans D/E ring juncture. The complex 27 undergoes successive rearrangements, as shown, to form the unstable Se(II) complex intermediate 28 and 29 involving 5 and 6 membered cyclic transition states respectively requiring low activation energies. The intermediate complex 29 could, alternatively, also arise directly from 27 involving a 3-membered transition state, as shown. Intermediate 29 then collapses to form the product 30 by loss of an allylic proton with concomitant deposition of selenium metal as depicted.

α,β dehydrogenation of Carbonyl Compounds

Riley reported[40] dehydrogenation of diethyl succinate to a mixture of the di and half ester of maleic acid. In 1947 Schwenk and Stahl[41] reported the discovery that selenium dioxide oxidation of a 12-keto steroid, 31, produced the $\Delta^{9,11}$-12 ketone of partial structure 32, and not the 11, 12 diketone.

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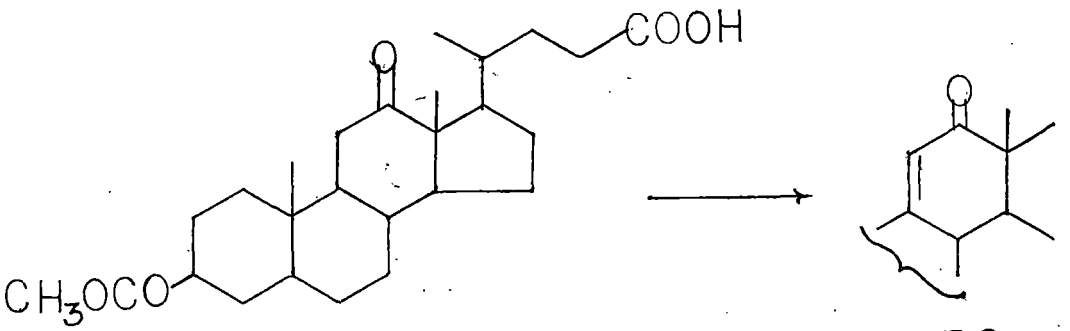
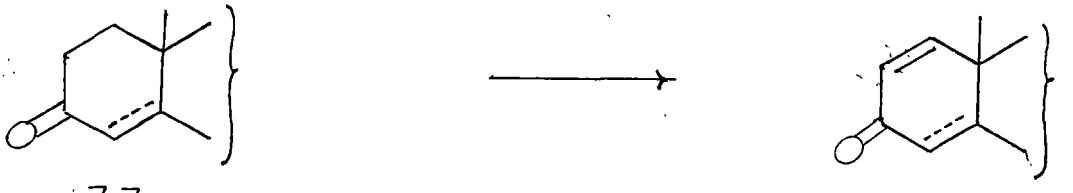
40. S. Astin, A.C.C. Newman and H.L. Riley, J. Chem. Soc. 391 (1933)

41. E. Schwenk and E. Stahl, Arch. Biochem., 14, 125 (1947)



31 32

Thus, dehydrogenation can occur without the presence of two straddling activating groups. Selenium dioxide introduces a double bond at the 1,2 position in either a 5α-3-keto steroid or Δ^4-3-keto steroid[42,43], partial structures being 33 and 34.



33 34

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42. C.Meystre, H.Frey, W.Voser and A.Wettstein, Helv.Chim.Acta. 39, 734 (1956)

43. S.A.Szpilfogel, T.A.P.Posthumus, M.S.deWinter and D.A.vanDrop, Rec.Trav.Chim., 75, 475 (1956).

Mechanism of α, β dehydrogenation:

1, 4 di-ketones:

The reaction exhibited a deuterium isotope effect of 6.5 (initial) when 1,1,2,2 tetradeuterio-1,2-dibenzoul ethane was at 90°. Schaefer[44] also showed that the biselenite ion, $HSeO_3^-$, was very likely not involved in the reaction since it did not oxidize acetone. 1,2 dibenzoyl ethylene, 38, is also oxidised but at an 1/30 th the rate of starting dione.

With these facts the following mechanism was proposed for acid catalysis: (1) production of the oxidant, $H_3SeO_3^+$, by protonation of selenious acid (Scheme VI); (2) attack of the oxidant on the substrate, 35, to give an enol selenite ester, 36, and (3) decomposition of 36 to the product via one of the two pathways. Path A involves rearrangement of 36 to the product α-selenium (II) keto ester, 37, and then to the product 38 by a 1,2 elimination. In path B 36 proceeds directly to the product 38 by 1,4 elimination. Path A is essentially the same mechanism and intermediates already proposed for α-dione formation (Scheme - I)[45].

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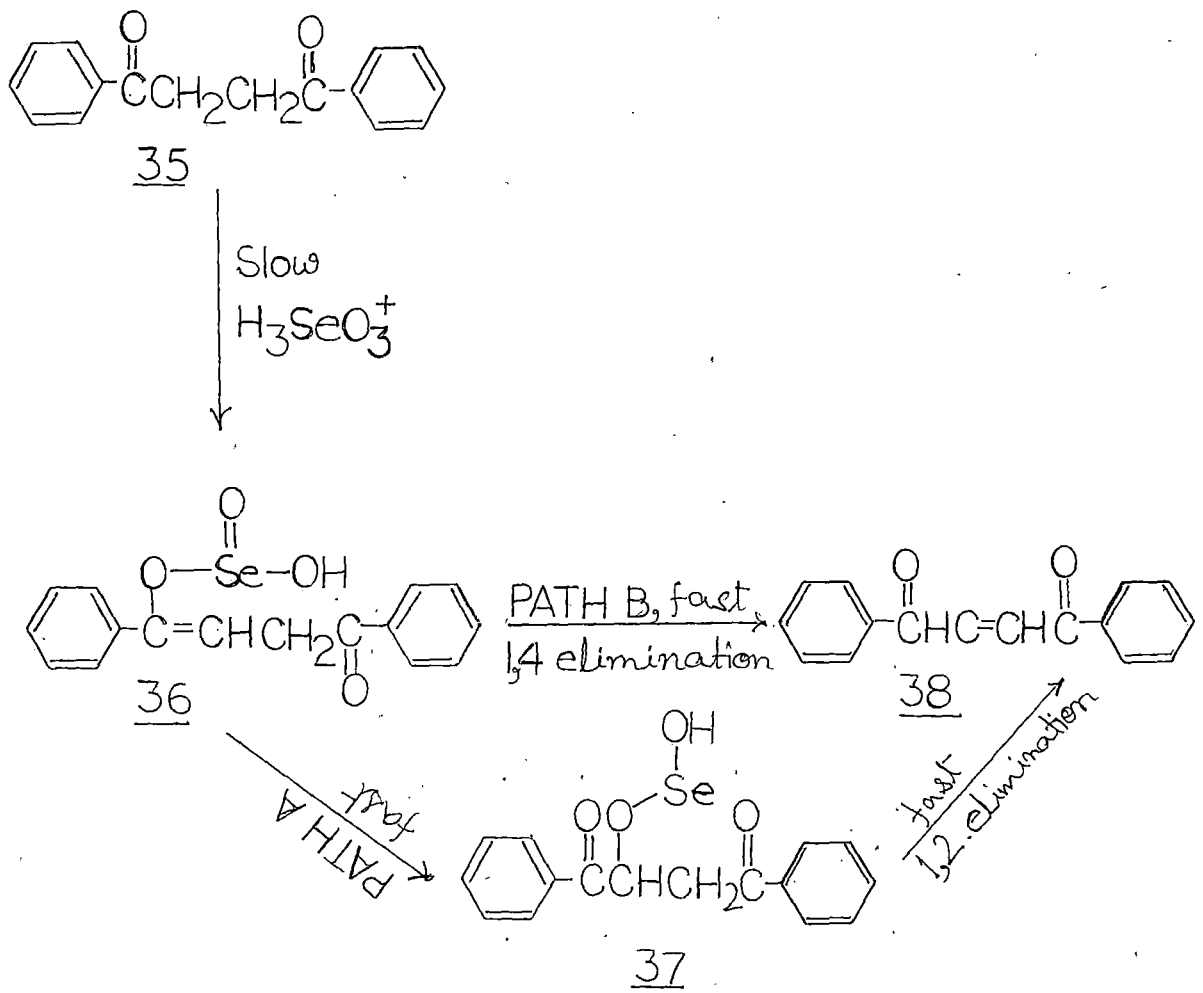
44. J.P.Schaefer, J.Am.Chem.Soc. 84, 713 (1962)

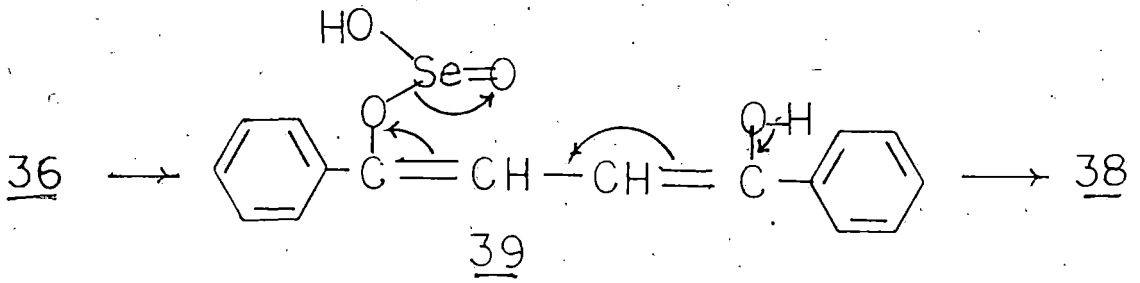
45. E.J. Corey and J.P.Schaefer, J.Am.Chem.Soc. 82, 918 (1960)

Scheme - VI



Of the two possibilities, the 1,4 elimination from the enol selenite ester, 36, is likely since this intermediate contains a doubly activated methylene unit. The latter simply requires an enolization to give the half ester of the dienol, 39, which can decompose to product 38 via bond migration, the driving force being the reduction of the selenium. The possibility of 1,2 elimination from the -selenium (II) keto ester, 37, appears

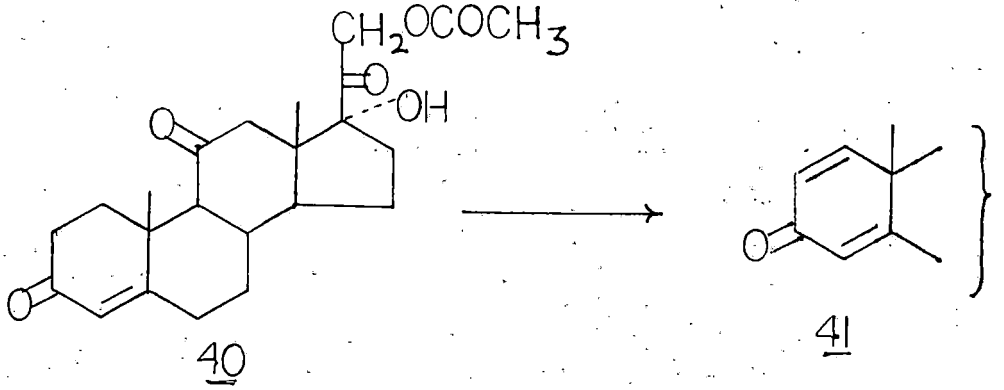
less likely in view of the fact that the alternative product of its decomposition, 1,4 diphenyl - 1,2,3 trioxobutane could not be detected[44].



36 → 39 → 38

Monoketones

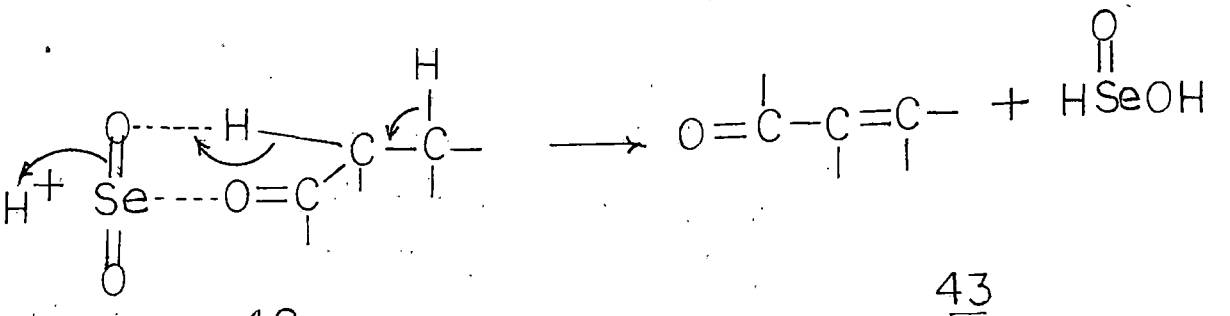
The kinetics of dehydrogenation of an α,β unsaturated ketone were studied by Langbein[46]. He obtained a second-order rate constant for the Δ^1 - dehydrogenation of cortisone acetate, 40, to 41, from a plot which contained the concentration of ketone and selenium dioxide. Langbein pictures a common intermediate, similar to 37, formed by direct attack of the oxidant



40 → 41

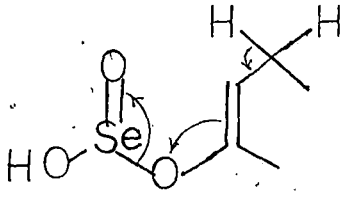
46. G. Langbein, J. Prakt. Chem. 18, 244 (1962)

on the ketone, which decomposes to form all the possible oxidation products. However, for α,β dehydrogenation, he considers the more plausible path as one that does not involve carbon-oxygen bond formation as 42.

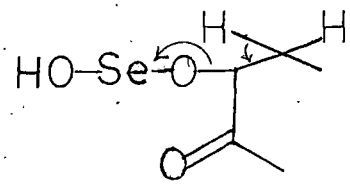


42 43

A mechanism for the dehydrogenation of a monoketone may be proposed, which involves either 1,4 elimination from 44 or 1,2 elimination from 45 . These intermediates are similar to 36 and 37, but without a second carbonyl group to activate the beta position and, therefore, should be less prone to undergo elimination. In addition, 46 is an α-keto selenium (II) ester similar to 5, which has been proposed as an intermediate in α-dione formation.



44



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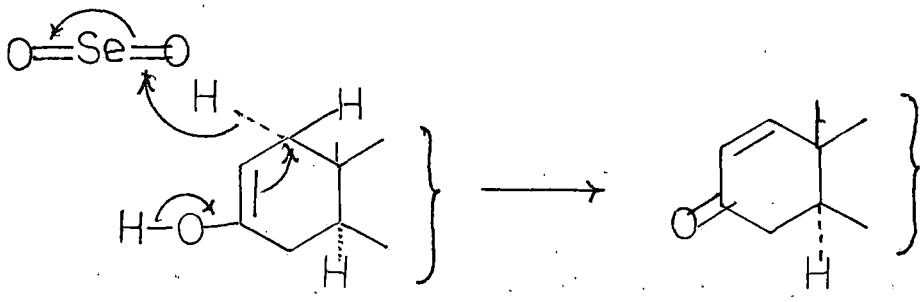

46

Another path, which circumvents the difficulty inherent in 44, would be direct attack on the allylic position in the enol, 46, by selenium dioxide to remove hydride ion. The preference is for the loss of C-1 hydrogen since C-1 hydrogen would require the oxidant to attack from the most hindered side due to the C-19 methyl group.

Why do some monoketones give α-diones and others α,β unsaturated ketones remain unanswered. This is assumed to be due partially to solvent effect. Tertiary alcohols are normally used to carry out the dehydrogenation reaction[42], but the reaction can be effected in acetic acid[47] or in aromatic solvents[48].

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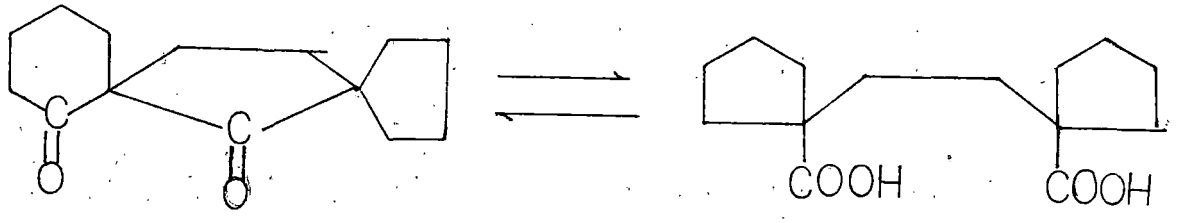
47. E.Schwenk and E.Stahd, Arch.Biochem. 14, 125 (1947)

48. H.J. Ringold, G.Rosenkranz and F.Sondheimer, J.Org.Chem., 21, 239 (1956)

α-Diones are generally produced using ethyl alcohol or dioxane[49]. The nature of the solvent effect, has, however, not been elucidated.

Selective Oxidations with Hydrogen Peroxide.

Manich[50] described the oxidation of a dispiro β-diketone, 47, with hydrogen peroxide in acetic acid solution to give α, α α′, α′, bis(tetramethylene) adipic acid, 48. It was not established whether the oxidising agent was hydrogen peroxide or peroxyacetic acid; the latter, of course, might be expected from reaction of the peroxide with acetic acid.

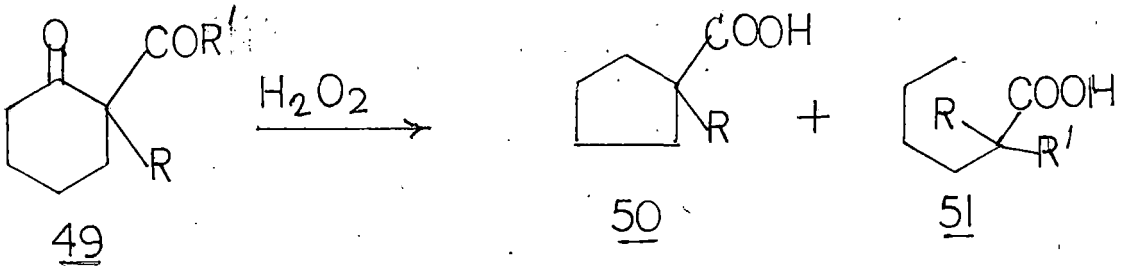


47 48

49. C.C.Hach, C.V.Banks and H.Diehl, Organic Syntheses, Coll. Volm 4, Wiley, p 229 (1963)

50. C. Mannich, Ber., 74, 1007 (1941)

Payne[51] studied oxidation of several 2-acylcyclo hexanones, 49, with hydrogen peroxide in tert-butyl alcohol solution at reflux. The reaction was found to proceed faster in presence of a trace of sulphuric acid.



49 50 51

Having achieved a rather facile oxidative ring contraction of a six membered ring to five, it was of interest to determine whether ring contraction of five membered ring to a four might be achieved. To this end, 2-acetyl cyclo pentanone 52, was oxidised in the usual way. An uncatalysed reaction was complete in sixteen hours at reflux to give α-methyl adipic acid, 53 in 93% yield. No evidence was obtained for the presence of even a trace of cyclobutane carboxylic acid.

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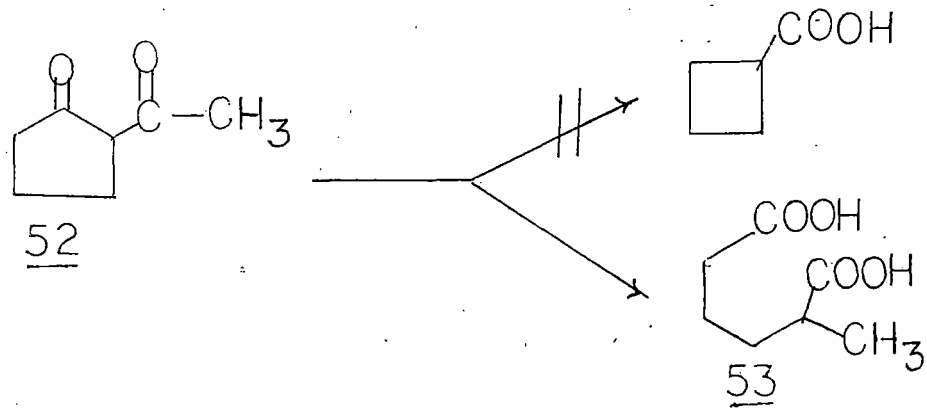
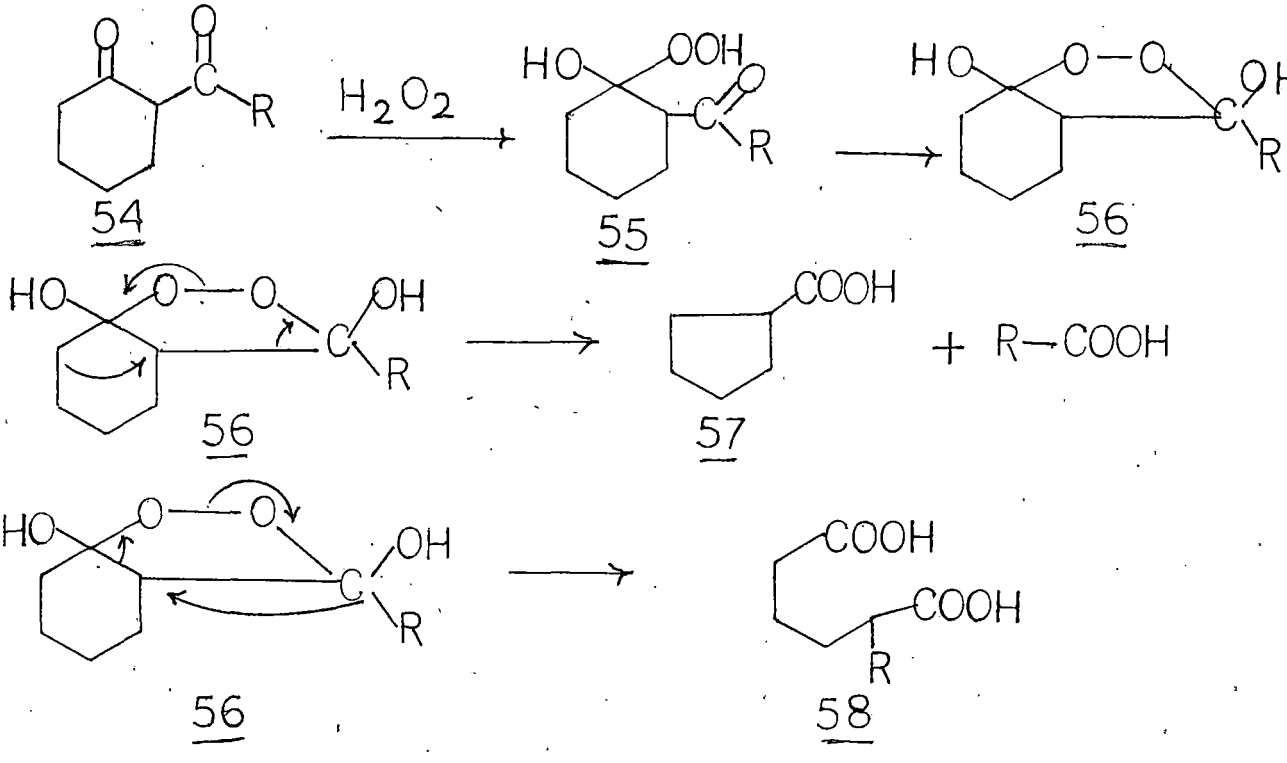
51. G.B. Payne, J. Org. Chem. 4793 (1961)



52 53

The reaction was proposed[50] to proceed by way of intermediates 55 and 56. In order to account for the two products, the breakdown of 56 was postulated by either of the following ways shown in Scheme - VII.

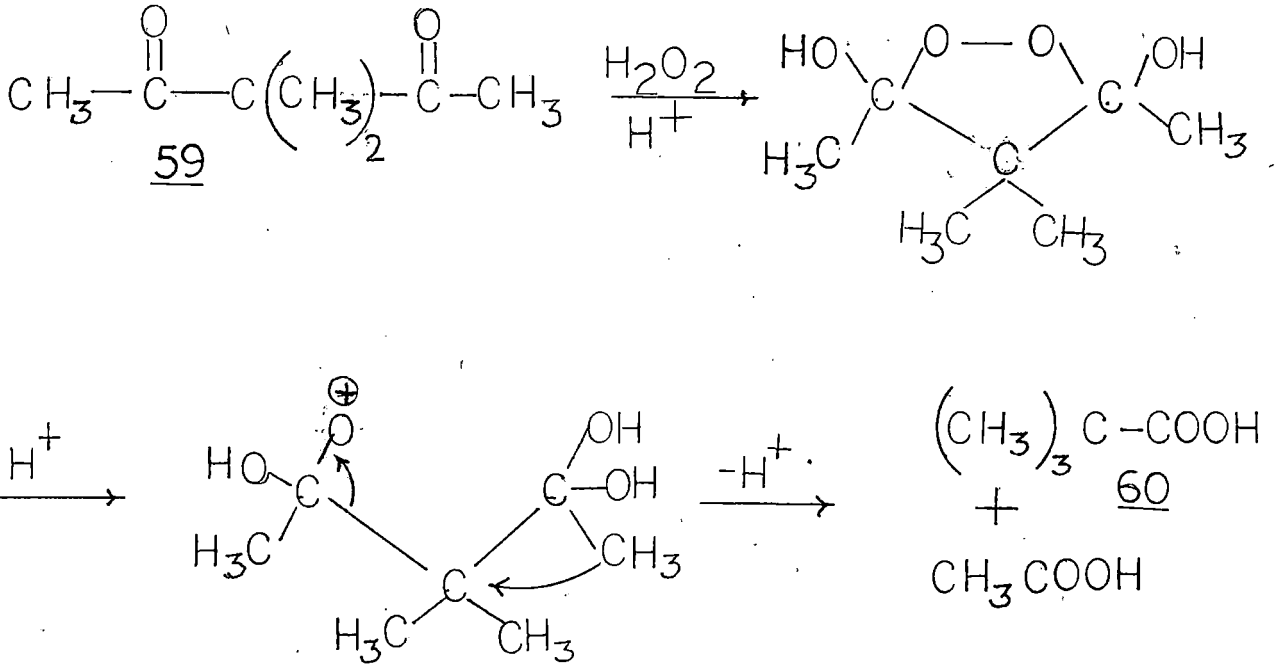
Scheme - VII



54 55 56 56 57 56 58

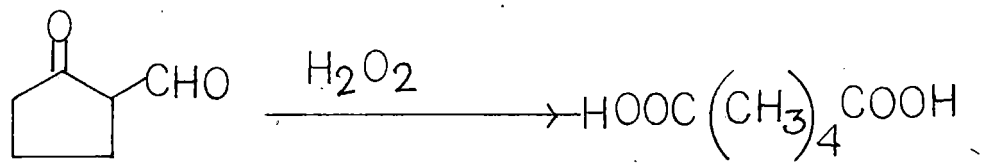
It was found that while 2,4 pentadione (acetyl acetone) did not undergo an oxidative rearrangement under similar conditions of reaction 3,3 dimethyl 2,4 pentadione, 59, behaved differently giving pivalic acid, 60, in 76% yield. The success achieved with 59 is believed to be a consequence of carbonium ion stabilization by the gem-dimethyl groups during breakdown of the cyclic peroxides (Scheme - VIII).

Scheme - VIII

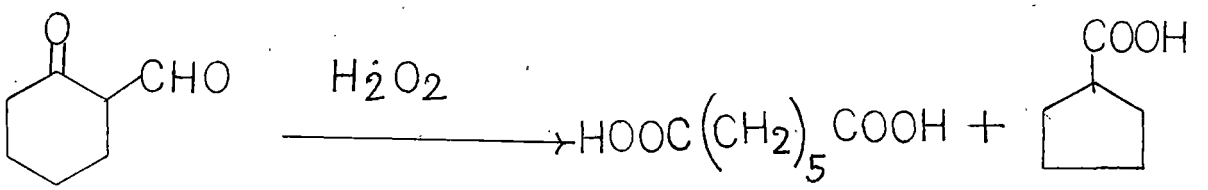


No isobutyric acid was identified as product from the oxidation of the monomethyl compound, 3-methyl 2,4 pentanedione. It was concluded, therefore, that one alkyl substituent does not provide sufficient carbonium ion stabilization to allow the rearrangement to proceed in the acyclic series.

Vinogradova et al[52,53] had shown that 2-formyl cyclopentanone 61, and 2-formyl cyclohexanone, 62, on treatment with aqueous hydrogen peroxide undergo unusual oxidation cleavage to produce dicarboxylic acid containing the same number of carbon atoms in the starting compound. It was also established that the cleavage of the six membered ketone completes with ring contraction to form cyclopentane carboxylic acid.



61



62

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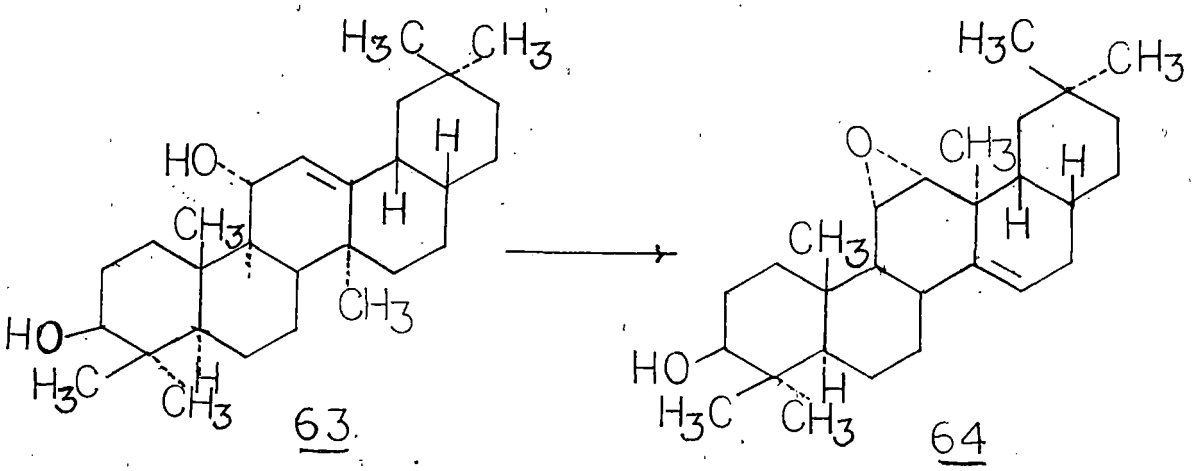
52. L.P. Vinogradova and S.I.Zavialov, Izv. Acad. Nauk SSR, Otd., Chim. Nauk 1717 (1960)

53. L.P.Vinogradova and S.I.Zavialov, Zh. Obsch. Khim., 30, 4110 (1960)

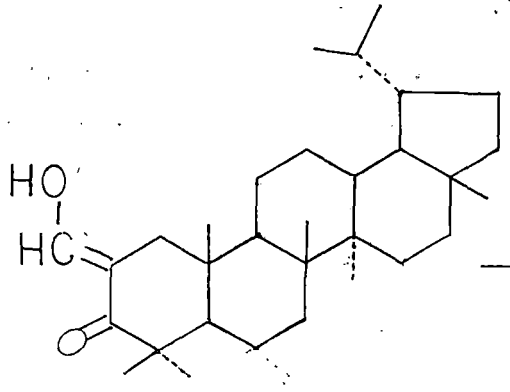
The mechanism of the reaction was considered to be the rearrangement of the corresponding peroxides in two possible directions as discussed under Scheme-VII.

Corey et al[54] made the surprising discovery that the 3β, 11α-dihydroxy- Δ^{12}-pentacyclic triterpenoids, 63, on treatment in methylene chloride with a solution of 30% hydrogen peroxide and p-toluene sulfonic acid in tert-butanol forms an epoxide, the 11α, 12α epoxide and undergoes a skeletal rearrangement by $C_{14} \longrightarrow C_{13}$ methyl migration and shift of the double bond, 64.

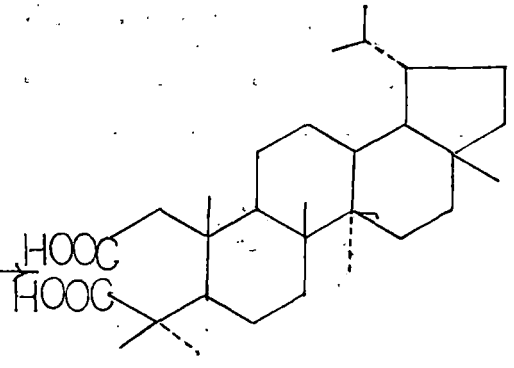


54. I. Agata, E.J. Corey, A.G. Hortnan, J. Khim, S. Proskow and J.J.Ursprung, J. Org. Chem. 30, 1698 (1965)

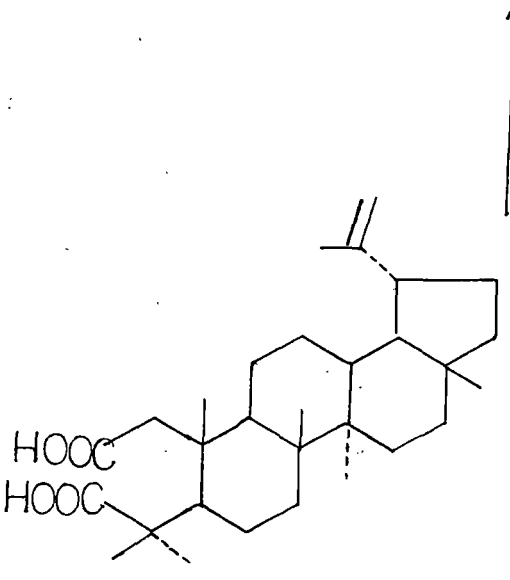
Another example of interest is the action of hydrogen peroxide on triterpenoids containing a hydroxymethylene ketone function. It has been observed that in absence of β,γ unsaturation and especially in alkaline media oxidative cleavage occurs producing 2,3 seco-acids. Thus, the ketone, 65, gave exclusively the diacid, 66, characterised as the ester, 67, which was also obtained from 68 by catalytic hydrogenation.



65

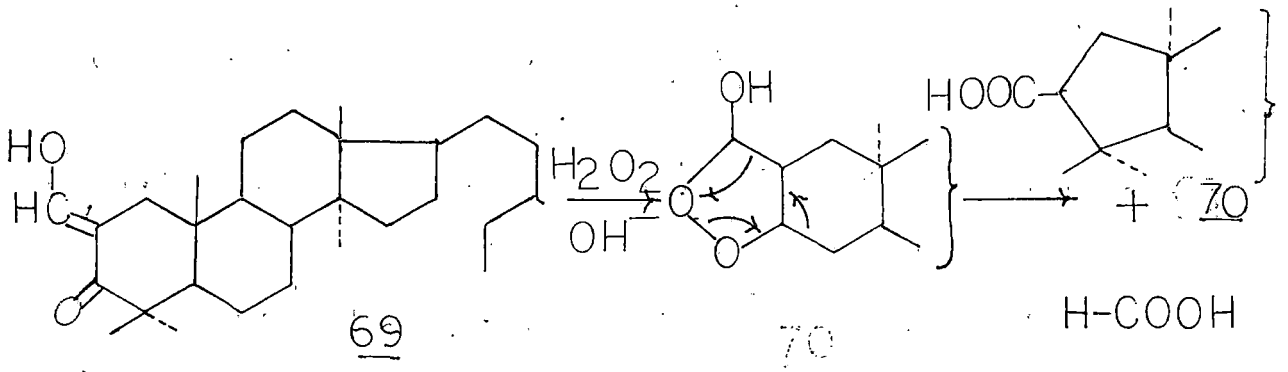


66 R=H
67 R=Me



68

It has been found that in the presence of β,γ unsaturation, ring contraction occurs. Thus, hydroxymethylene anhydrodihydro litsomentone, 69 undergoes a rearrangement[55] in presence of hydrogen peroxide in alkaline media producing 70.



Reactions involving Hydrogen peroxide and Selenium Dioxide.

It transpires from discussions in the preceeding sections that selenium dioxide and hydrogen peroxide have separately found wide application. Not too many reactions using hydrogen peroxide and selenium dioxide together are, however, known. The combination perhaps found application in the oxidation of acrolein to acrylic acid for the first time[56]. In another obviously different case[57],

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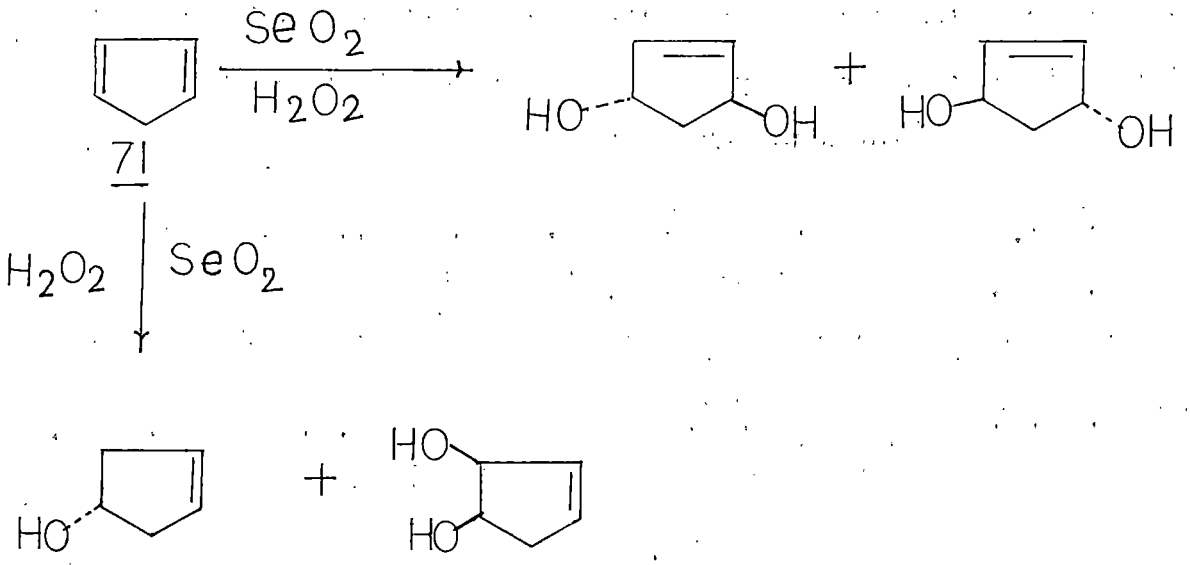
55. T.R.Govindachari, N.Viswanathan and A.R.Sidyaye, Ind. J. Chem., 10, 786 (1972)

56. Ref. 13 of this chapter.

57. L.Stall and H.Jucher, Helv.Chim.Acta., 36, 268 (1953)

the reagents have been used for hydroxylation of cyclopentane and cyclopentadiene, 71. The catalyst in this case is probably perselenic acid.



Oxidation of methylene groups adjacent to carbonyl groups with stoichiometric quantity of selenium dioxide to give α-diketones or keto aldehydes are well known. Payne et al[58] while studying the reactions of hydrogen peroxide in presence of selenium dioxide on cyclopentanone, cyclohexanone and cycloheptanone anticipated that the cyclic ketones might undergo the well known reaction with SeO_2 giving α-diketones, with H_2O_2 serving merely

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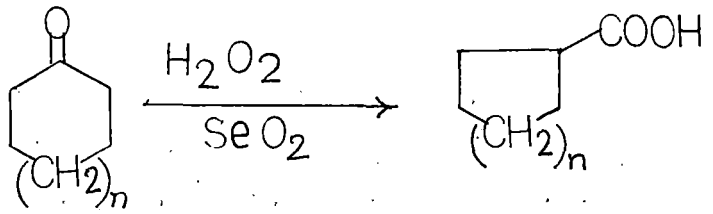
58. G.B.Payne and C.W.Smith, J. Org. Chem., 22, 1680 (1957)

to oxidise Se metal back to the dioxide. It was found, however, that along with other competing reactions all the three ketones underwent oxidative ring contraction to cyclohexane, cyclopentane and cyclobutane carboxylic acids in 34, 32 and 23% yields respectively.



72

n = 2 (34%)
n = 1 (32%)
n = 0 (23%)

Since the discovery that a mixture of SeO_2 and H_2O_2 transforms alicyclic ketones to ring contracted cycloalkane carboxylic acid, the rearrangement was extended to acyclic and alkylphenyl ketones by Sonoda et al[59]. In trying to hydroxylate olefins, 73, with hydrogen peroxide in the presence of selenium dioxide as catalyst and by using a mixed solvent of tert-butyl alcohol and a ketone, it was found by the workers that the oxidation of ketone, used as solvent, proceeded mainly to form carboxylic acid by the following equation;

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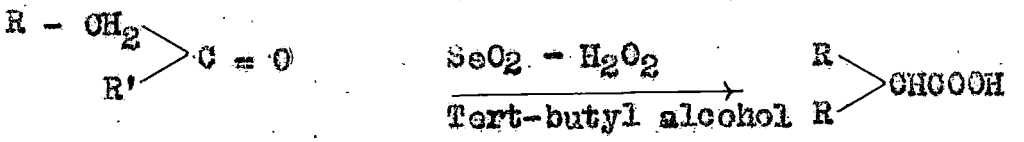
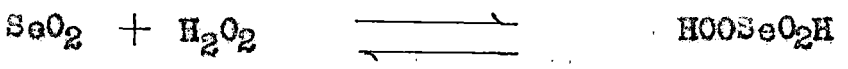
59. N. Sonoda and S. Tsutsumi, J. Org. Chem., 32(5), 505 (1969)



73

Acetone, methyl ethyl ketone, methyl n-propyl ketone and diethyl ketone were selected as starting materials. The main rearrangement observed is due to the migration of the alkyl group having a smaller number of carbon atoms to the α-carbon atom of the larger alkyl group and the migration of the alkyl group with a larger number of carbon atoms to the smaller one also occurs in some degree. The workers shared the view of Hughes and Martin[60] who proposed the formation of peroxyselenious acid, 74, in the course of the oxidation of selenium dioxide to selenic acid as shown below:



74

The following mechanism as shown in Scheme - IX was presumed by the workers.

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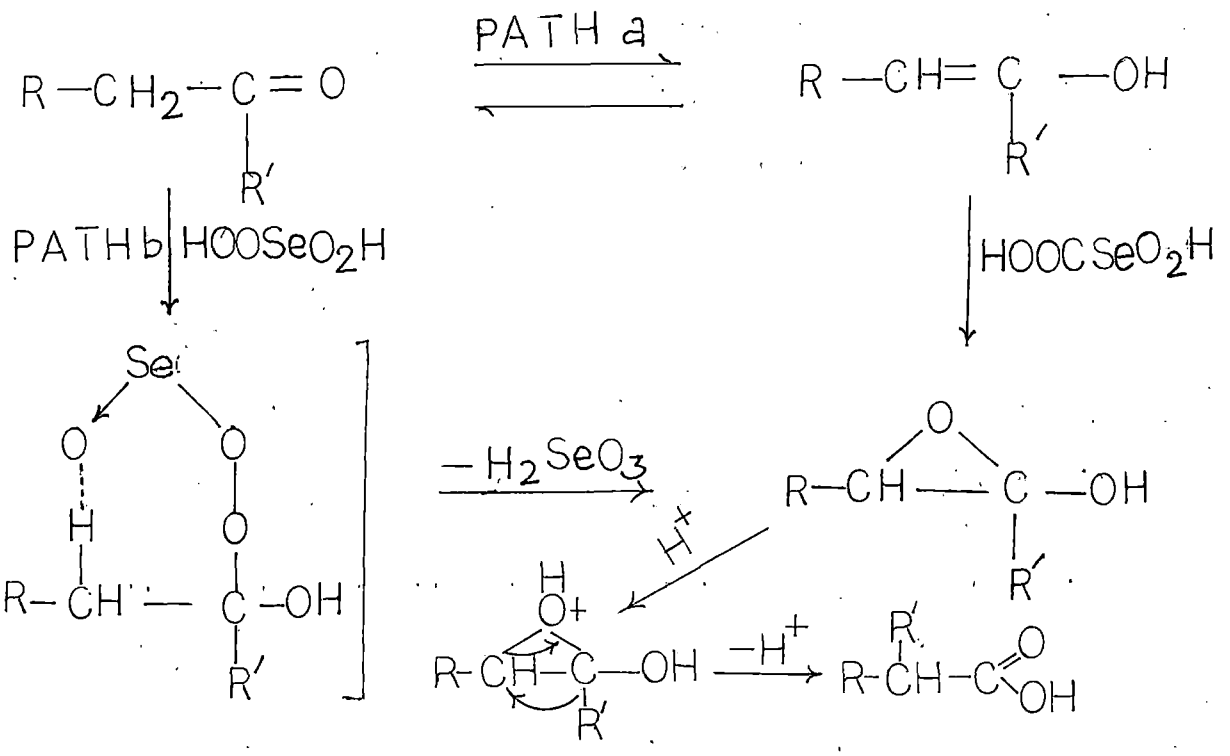
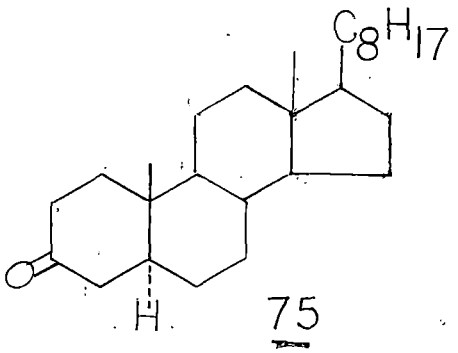
60. F.J. Hughes and D.S. Martin, Jr., J.Phys. Chem., 59 410 (1955)

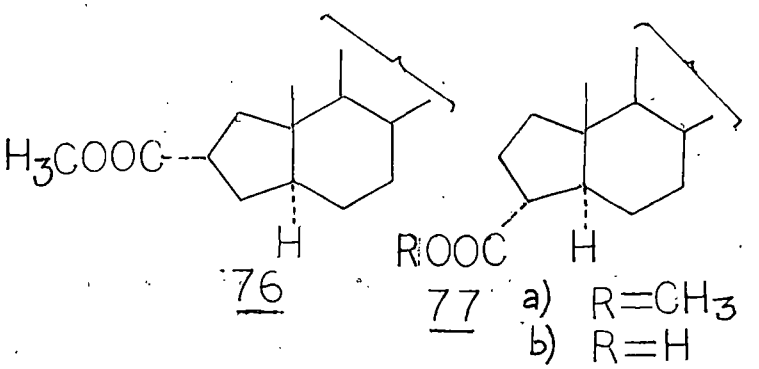
Scheme - IX



The reaction was also applied to several keto steroids. With 5α-cholestan-3-one, 75, a mixture of acid was obtained[61]. The acids after esterification were separated and characterised as 76 and 77 . The yields were 25% and 19.5% respectively.



75



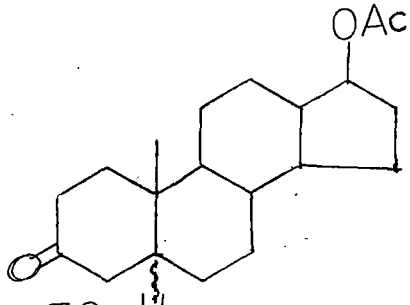
76 77 a) R=CH3 b) R=H

61. E. Caspi and S.N. Balasubramanyam, Tet. Lett., 745 (1963)

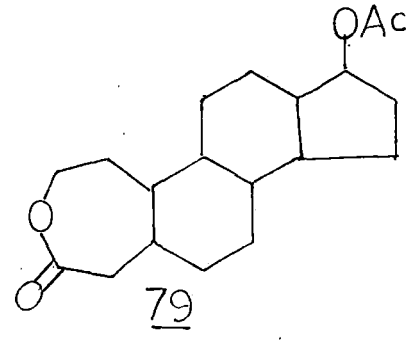
62. E. Caspi, Y. Shimizu and S.N. Balasubramanyam, Tetrahedron. 20, 1271 (1964).

Caspi et al[62] studied the reaction for steroidal 3-ketones of 5α and 5β series and found that the major reaction was not ring contraction but Baeyer-Villiger oxidation.

The compound with A/B trans junction, 17β-acetoxy-5 - α androstan-3-one, 78a, gave a lactone, 79 and two carboxylic acids, 80 and 81. The oxidation of 17β-acetoxy-5β-androstan-3-one, 78b, gave the lactone 82 as a single product.



78



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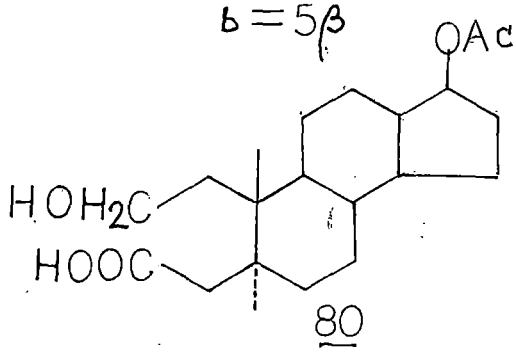
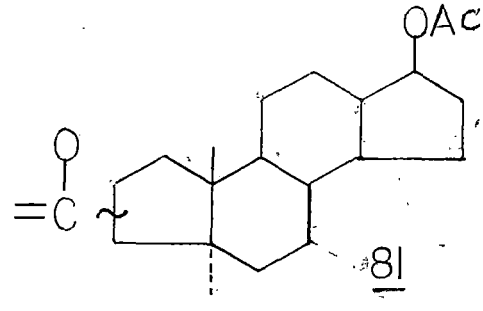


80



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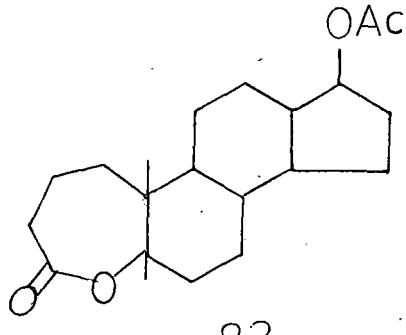

82

Hara et al[63], however, had shown that perbenzoic acid oxidation of 5α and 5β-3-ketones yielded mixture of lactones with an oxygen atom inserted in either side of the 3-oxo group. With the commonly used peracids it would seem that the reaction proceeds in a rather indiscriminate manner[64]. Caspi et al[62] employed nearly neutral condition and concluded that the direction of attack was more substrate dependent, and hence led to the formation mainly of single compound. For example, for A/B trans junction the 2,3 bond and for A/B cis junction the 3,4 bonds are cleaved. In their succeeding experiment Caspi et al[65] observed that no directional influence of ring A/B junction on the course of the reaction occurs.

Jerussi et al[66] studied the same reaction on 17β-acetoxy-5α-cholestan-3-one and reported formation of the products which were different from those previously published[67,68]. They carried out the reaction of 83, with selenic acid and 30% H_2O_2 in tert-butyl alcohol and the reaction yielded a complex mixture of acids. Esterification of the crude product with diazomethane followed by chromatography and several times crystallisation yielded 2α-

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63. S.Hara, N. Matsunoto and M. Tekenchi, Chem. and Ind., 2086(1962)

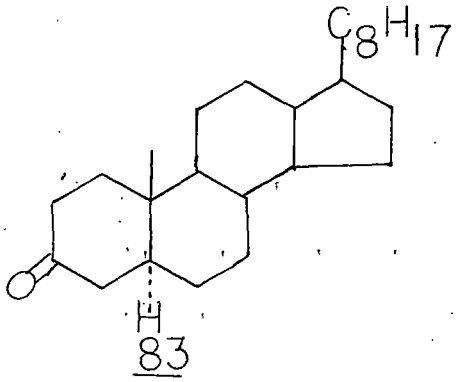
64. V.Prelog, L.Ruzicka, P.Meister and P.Wieland, Helv. Chim.Acta., 28, 618 (1945); 28, 1651 (1945)

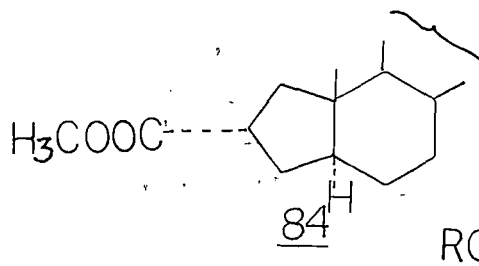
65. E. Caspi, Y.Shimizu and S.N.Balasubramanyam, Tetrahedron 20, 1271 (1964)

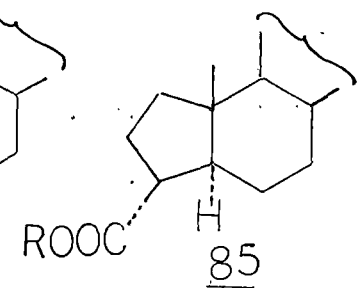
66. H.M.Hellman and R.A.Jerussi, Tetrahedron, 20, 741 (1964)

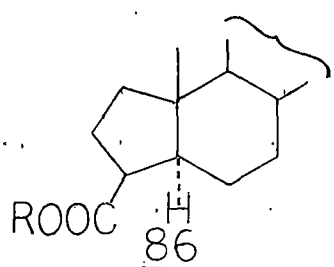
67. C. Biellmann and M.Rajic, Bull.Soc.Chim. Fr., 441 (1962)

carbomethoxy-A-nor-5α-cholestane, 84a, and 2,3-seco-5α-cholestane, 2,3 dioate, 87a and 86a; compound 85 was, however, not found.

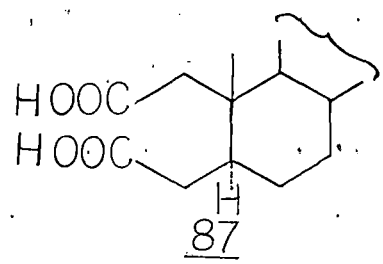








a $R=CH_3$
b $R=H$



a $R=CH_3$
b $R=H$

Hence isolation of 86a, the epimer of, 85, led Jerussi et al questioning the evidence as to the identity of the compound 85 given by the French workers[67]. However, for 85, the m.p. 51° and rotation $[\alpha]_D$ +11° were between those reported[69] for 85, m.p. 45-46°, $[\alpha]_D$ +1°, and for 87a, m.p. 60-63°, $[\alpha]_D$ +19°. Therefore, it was thought that the product assigned

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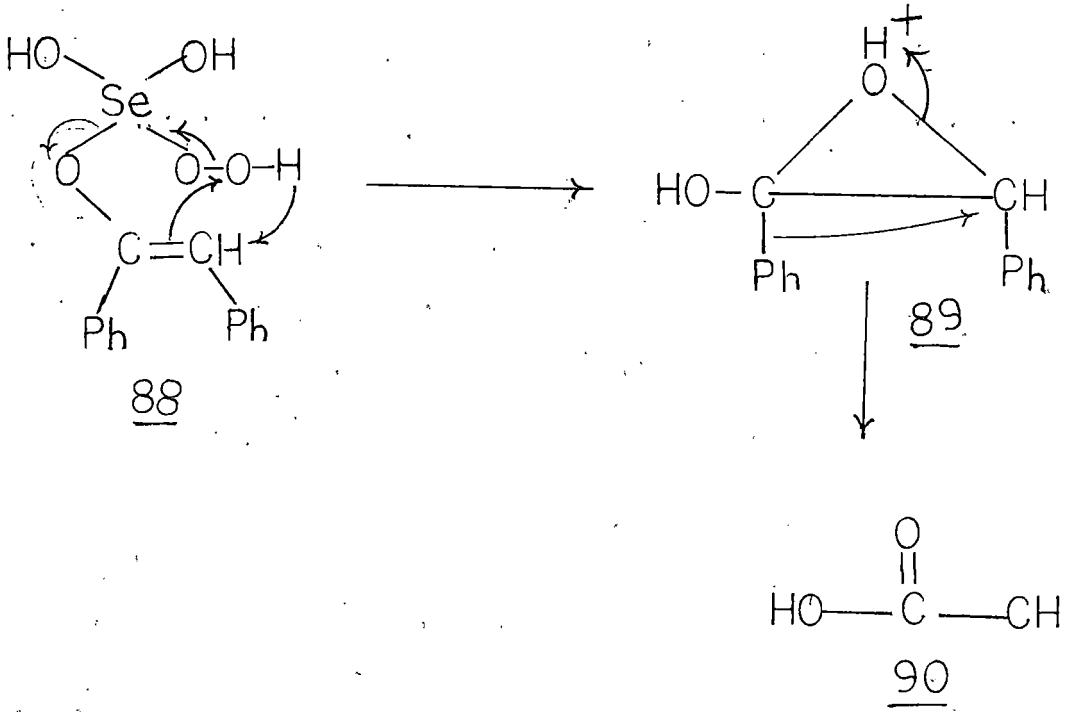
68. E. Caspi and S.N.Balasubramanyam, Tet. Lett., 12, 745 (1963)
69. D.E.Evans, A.C. De Paulet, C.W. Shoppee and F. Winterritz, J.Chem.Soc., 1451 (1957)

structure 85 by them[67] may actually be 87a reported by Jerussi[66].

A mechanism had been proposed by Sonoda and Tsutsumi for the rearrangement of deoxybenzoin[69] in which a peroxyselenious enol ester, 88, was postulated as an intermediate. This then undergoes intramolecular epoxidation to give the enol epoxide, 89, which rearranges as shown to give diphenyl acetic acid, 90. Opening of the epoxide, 89, in the manner proposed appears unlikely in view of the course of epoxide reactions in the acidic solution[71].

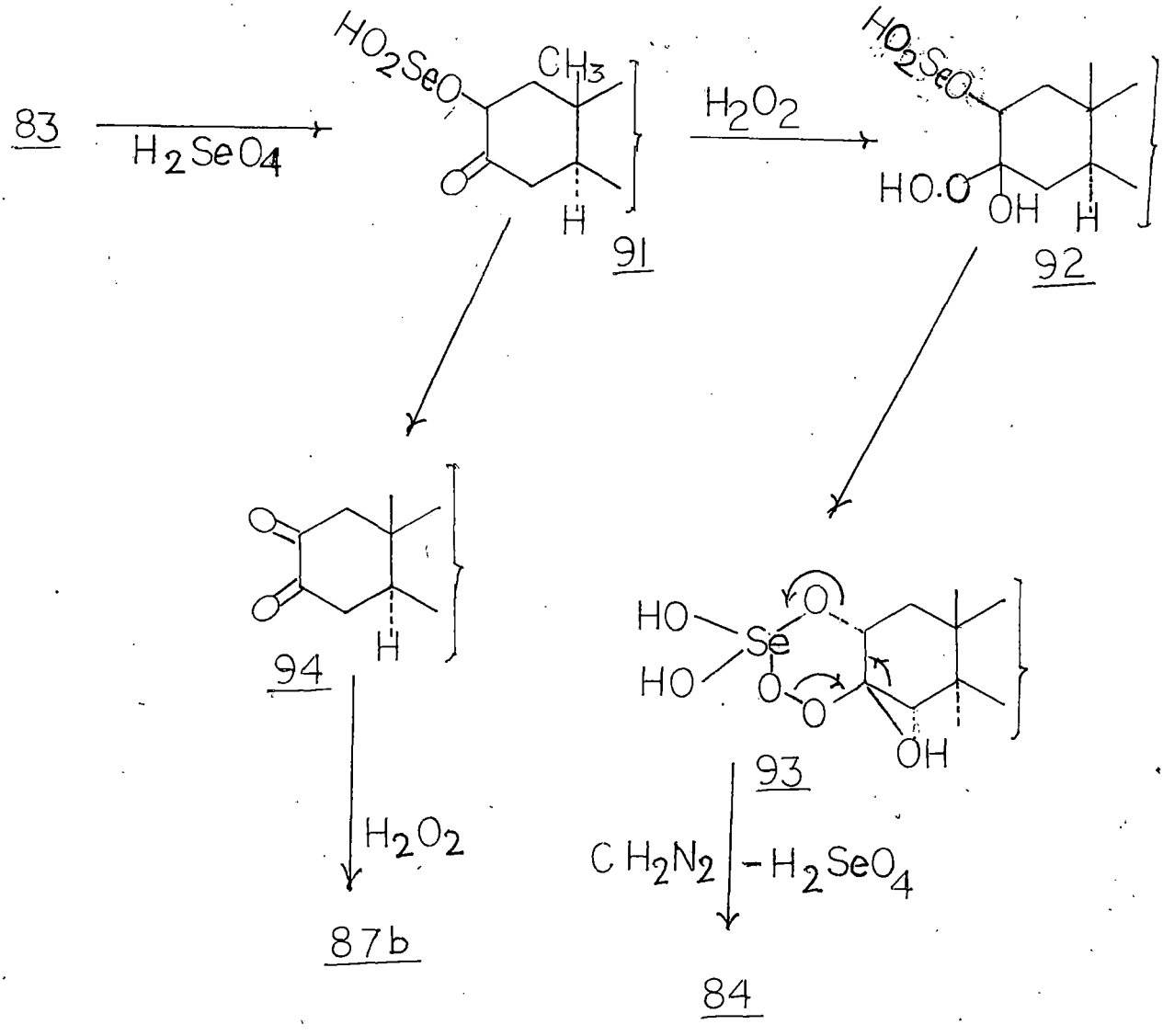


70. N.Sonoda and S.Tsutsumi, Bull. Chem.Soc.Japan, 34, 1006 (1961)

71. R.E.Parker and N.S.Isaacs, Chem.Revs., 59, 737 (1959)

Scheme - X summarizes the mechanism proposed by Jerussi et al[66]. All examples of oxidative rearrangement of ketones using H_2O_2 and selenic acid or SeO_2 have involved enolised ketone. Non-

Scheme - X



enolizable ketones, even those having α-hydrogen atoms fail to give the reaction[72]. Hence, it is plausible to assume that with steroid ketones also enolisation or enol ester formation is an essential step. An enol selenite ester, which rearranges to an α-keto selenium ester, has been proposed by Corey and Schaefer as an intermediate in the selenious acid oxidation of desoxybenzoin[73].

Hence, here the first step involves the interaction of ketone with selenic acid to give an α-keto selenite ester, 91. Attack by H_2O_2 on the carbonyl group of 91 gives 92. α-substituted hydroxy hydroperoxide such as 92 have been isolated by Kharasch and Sosnovsky[74] by treatment with α-bromo and α-chlorocyclohexane with H_2O_2. In the absence of a bulky α-group only dimer is isolated. Cyclisation of 92 gives the peroxide 93, which rearranges as indicated to give product 84. A cyclic peroxide has been proposed by Payne[75] to account for the formation of cyclopentane carboxylic acid from 2-acetylcyclohexanone and hydrogen peroxide. 91 can also go to the diketone, 94, which can be oxidised by H_2O_2 to 2,3 seco acid 87b.

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72. R.A.Jorussi, Ph.D. Diss., N.Y. Univ. (1961)

73. Ref. 43 of this chapter.

74. M.S.Kharasch and G.Sosnovsky, J.Org.Chem., 23, 1322 (1958)

75. G.B.Payne, J.Org.Chem., 26, 4793 (1961)

CHAPTER - II

Section A

This chapter deals with the oxidation of lupanone, taraxerone and friedelin by hydrogen peroxide in the presence of selenium dioxide. The reaction results in the conversion of ring A of the triterpenoids containing a gem dimethyl group alpha to carbonyl group in ring A into lactones by elimination of the gem dimethyl group in the first two cases while in the last case, a compound with a single methyl group in the same position, formation of a lactone results without elimination of a methyl group. The lactones obtained by elimination of gem dimethyl group may be converted to Δ^4-3-one system, characteristic of many physiologically important steroids. Different attempts have been made on this problem[76-79]. The importance of the work lies in the fact

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76. W.Voser, D.E.Heusser and L.Ruzicka, Helv. Chim. Acta., 35, 830 (1952)

77. W.Voser, H.Heusser, O. Jeger and L.Ruzicka, Helv. Chim. Acta., 36, 299 (1953)

78. D.H.R. Barton, D.A.J. Ires and B.R. Thomas, J.Chem.Soc., 903 (1954)

79. P. Crabbe, G. Ourisson and I. Takahashi, Tetrahedron, 3, 279 (1958)

that naturally occurring steroids lack substituents at the C-4 position, but their biogenetic precursors usually possess a 4,4 dimethyl substituted A-ring[80]. It is possible, in principle, to obtain a variety of new and potentially useful steroids by deletion of the 4,4 dimethyl substituents from the readily available tetracyclic triterpenes. It would, therefore, be relevant to discuss some previous works done on bis demethylation reactions using different reagents.

Review of some important works on bis demethylation:

The removal of 4,4 dimethyl substituents from the ring A of the tetracyclic triterpenes was an important step of the classic procedure[81] for terpene steroid transformation; for example, for preparation of 14 -methyl steroids[82]. The removal of the 4,4 dimethyl substituents from the ring A of the tetracyclic triterpenes may be done following a biosynthetic type sequential elimination of 30 and 31-methyl groups or by removing either 30 or 31 methyl group and then the C-3 carbon atom or by removing the isopropyl group followed by readdition of a carbon atom as accomplished by Voser et al[77] (Scheme XI and XII).

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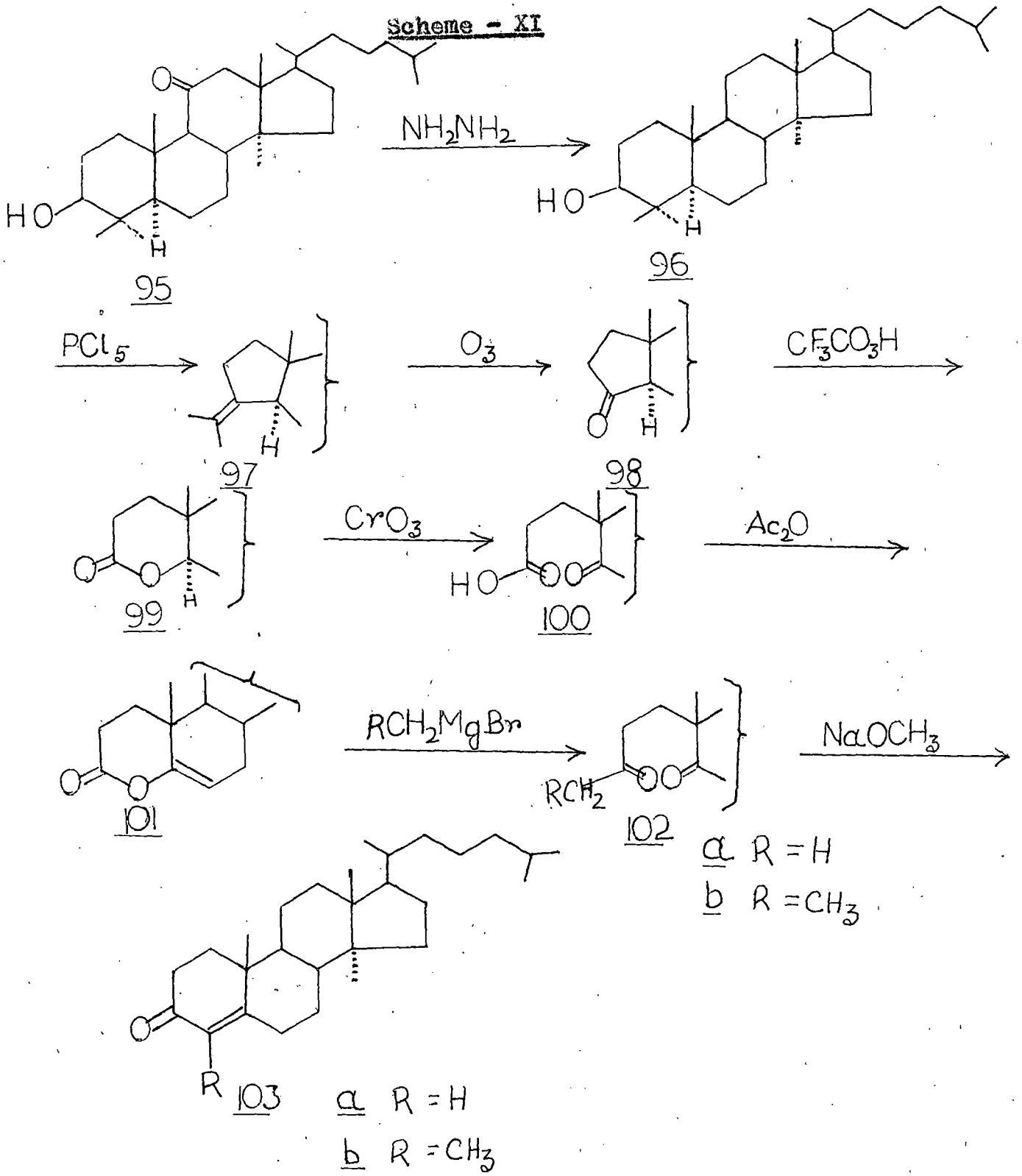
80. G. Ourisson, P. Crabbe and O. Rodig, "Tetracyclic Terpenes", E. Lederer, Ed., Holden-Day, San Francisco, California.

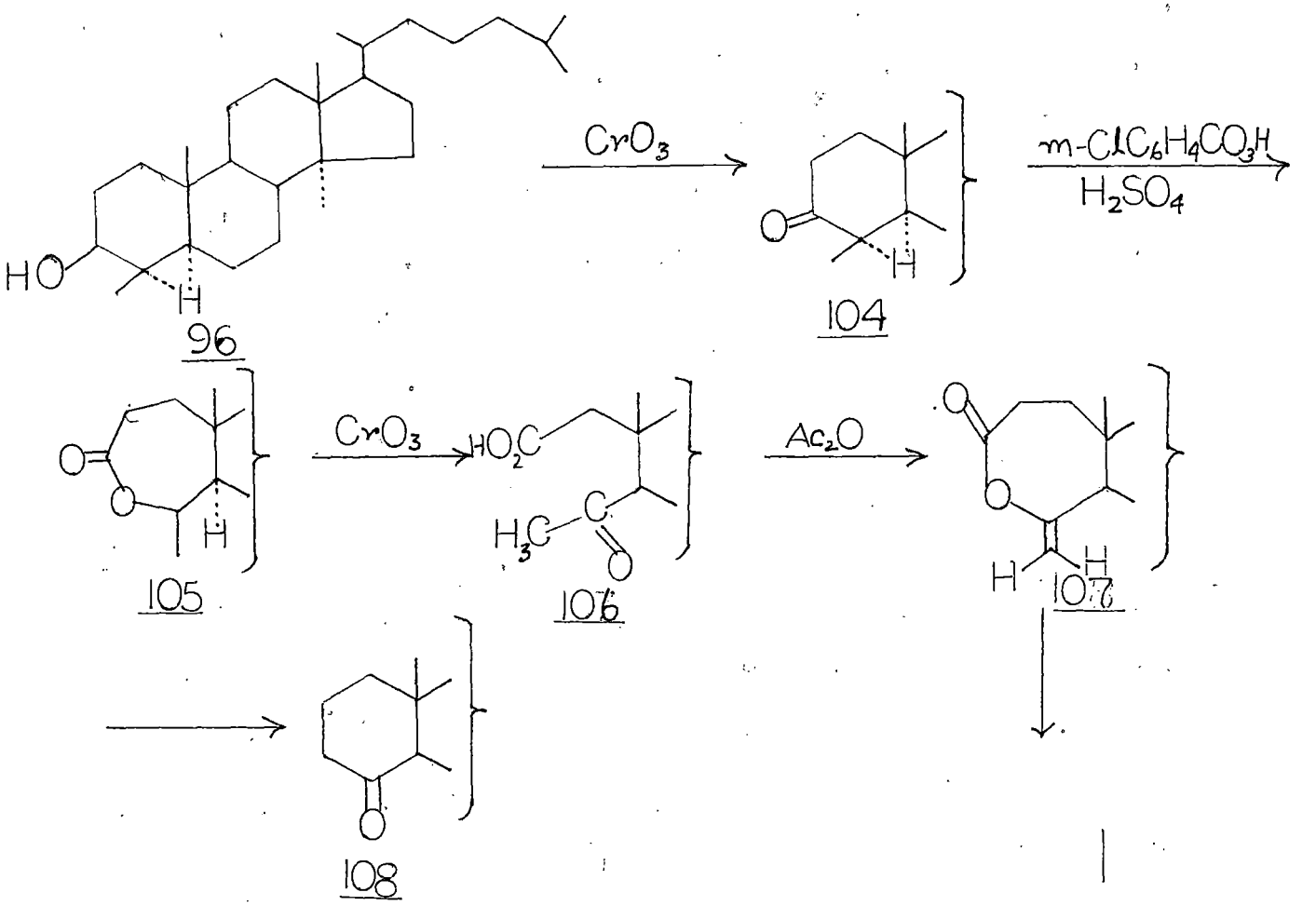
81. G.R. Pettit and P. Hofer, Helv. Chim. Acta., 46, 2142 (1963)

82. G.R. Pettit and P. Hofer, J. Chem. Soc., 4439 (1963)

Scheme - XI


NH2NH2
PCl5
O3
CF3CO3H
CrO3
Ac2O
RCH2MgBr
NaOCH3
HO
95
96
97
98
99
100
101
102
103
a R = H
b R = CH3

Scheme - XII


HO
H
96
CrO_3
104
m-$ClC_6H_4CO_3H$
H_2SO_4
105
CrO_3
HO_2C
H_3C
106
Ac_2O
H
H
107
108

The key step in the Voser method for the elimination of the 4,4 dimethyl groups utilises a 1,3 Wagner-Meerwein rearrangement to transform the 3 β-hydroxy-4,4 dimethyl system into an isopropylidine group (96 to 97). Stereoelectronic requirement make it imperative that the 3-hydroxy group has a β-configuration so that the C-O bond is trans to the approaching 4,5 bond; otherwise, olefins resulting from hydrogen and methyl migrations are obtained (1,2 Namatkin rearrangement). When 1:1 mole ratio of phosphorus pentachloride to triterpene alcohol 96 was allowed to react (ice bath temperature, 1 hr. in benzene-toluene), only a 10% conversion of alcohol to olefin 97 occurred whereas with a 2:1 mole ratio, 100% conversion was realised.

Cleavage of the isopropylidine group by ozone (97 to 98) introduced a 3-oxo-group adjacent to the 5α-hydrogen. The positive cotton effect curve observed for ketone, 98, unequivocally established the 5 β-configuration.

A method for Bdeyer-Villiger oxidation of ketone 98 to lactone, 99, was not realised using m-chlorobenzoic acid, but was easily effected by pertrifluroacetic acid[83]. As Bdeyer-Villiger oxidation is well-known to proceed with retention of configuration (of the migrating group) the lactone would be expected to bear cis A/B ring junctions. Prolonged contact with

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83. W.D. Emmons and G.B. Lucas, J.Am.Chem.Soc. 77

CrO_3 in concentrated sulphuric acid or with excess of Jones reagent in acetone was found most effective for transforming lactone, 99, directly to keto acid, 100.

Enol lactone, 101, was obtained by brief contact of keto-acid, 100, with acetic anhydride-perchloric acid reagent[84]. The enol formed the corresponding ester in methanol containing a trace of pyridine. 1,5 diketone, 102a and 102b was formed in good yield on slow addition of methyl or ethyl Grignard reagent respectively to an ice-cold solution of enol-lactone 101.

The unique loss (in 65% yield) of a 31-methyl group was observed when perbenzoic acid promoted Baeyer-Villiger oxidation of 3-oxo-4, 4 dimethyl 5α -cholestane was explored in the presence of mineral acid[85].

A 3:1 molar ratio of m-chloroperbenzoic acid to 3-oxo-5α -lanostane, 104, in presence of 20% sulphuric acid was found to yield 29% of 3-oxo-4-oxa-4aα , 14αdimethyl-A-homo-5α -cholestane, 105. Prolonged contact of lactone, 105, with Jones reagent in acetone gave keto acid 106 in good yield, thereby demonstrating the utility of this oxidising system for direct conversion of

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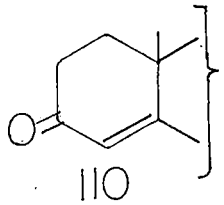
84. B.E. Edwards and P. Narasima Rao, J.Org.Chem., 31, 324 (1966)

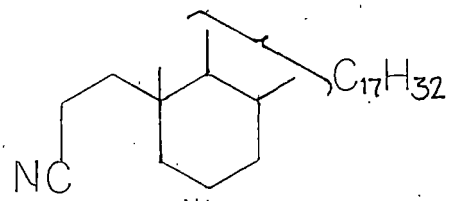
85. J.S.E. Holker, W.R. Jones and P.J. Ramn, Chem. Commun., 435 (1965)

lactones to keto-acids. The double bond in the enol-lactone, 107, was demonstrated by the pair of doublets in a ^{1}H NMR spectrum at δ 5.0 and 4.6.

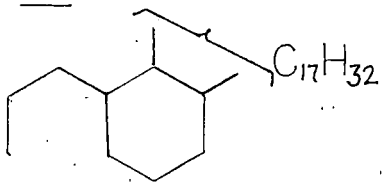
A very efficient among the published 4,4 bis demethylation procedure utilised[86] the second order Beckman oxime cleavage (from 5α H-lanostan-3-one) giving the corresponding 4-en-3-one, 110, in eight steps in 25% yield. The scheme is based on the use of the 3,4-seco-3-nitrile, 111, as the starting material rather than the corresponding Δ^8 carboxylic acid, which was used in parallel work aimed partially at mono demethylation of 4,4 dimethyl steroids[87].



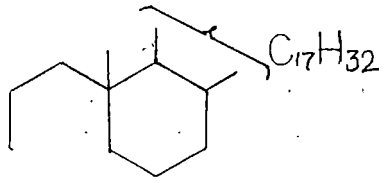
110



111



112



113

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86. O.N. Shoppee, N.W. Hughes, R.E. Lack and J.T. Pinhey, J.Chem.Soc. C 1443 (1970)

87. R. Kazlaukas, J.T. Pinhey, J.J.H. Simes and T.H. Watson, Chem. Commun. 945 (1969)

The main features of the route were the conversion of the 3,4 seco-3-nitrile, 111, into the methyl ketone, 112 by reaction with Grignard reagent and degradation of the 5-isopropenyl group to a carbonyl group to yield the diketone 113, known[76,78,81,82] to cyclise with the base to give the ^{4}-3-oxo-system, characteristic of many steroid system. The attempt to use the sequence of reaction on compounds containing an 8,9 double bond failed; conditions for selective oxidation of the 4(30) double bond in the ^{8} 3,4 seco nitrile could not be found. The ^{8} 3,4 seco-3-nitrile the preparation of which had been briefly reported[88,89] was formed by abnormal "second order" Beckman cleavage[90,91] in about 60% yield from 3-hydroxyimino-5 -lanost-8-ene[92].

During an investigation into the oxidation of 4,4, dimethyl-3-oxosteroids and related compounds with peroxyacid, it was found[93] that treatment of 4, 4 dimethyl cholestan-3-one, 114, with m-chlorobenzoic acid or perbenzoic acid in the presence of mineral acid gave a product (65%) identical with 4a -methyl-4-oxa-A-

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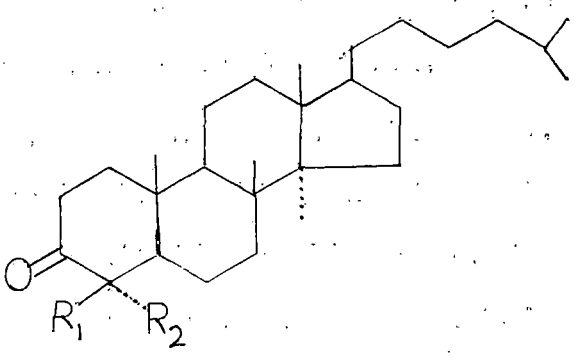
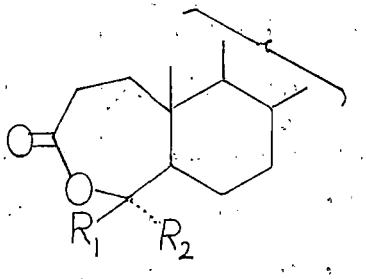
88. G. Quinkert and H.G. Heine, Tet. Lett., 1659 (1963)
89. G.P. Moss and S.A. Nicolaides, Chem. Commun. 1072 (1969)
90. C.W. Shoppee, R.E. Lack and S.K. Roy, J.Chem.Soc., 3767(1963)
91. C.W. Shoppee and S.K.Roy, J.Chem.Soc., 3774 (1963)
92. L. Ruzicka, R. Denss and O. Jeger, Helv.Chim.Acta., 28, 759 (1945)
93. G.H. Whittam, J. Chem. Soc., 2016 (1960)

homocholestan-3-one, 117. This apparently unique loss of a methyl group in a Baeyer-Villiger oxidation merited a careful investigation of the reaction.





114 $R_1 = R_2 = Me$

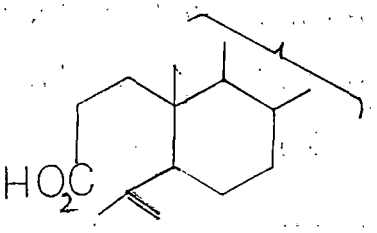
115 $R_1 = H$, $R_2 = Me$

116 R_1 or $R_2 = Me$
R_2 or $R_1 = CHO$

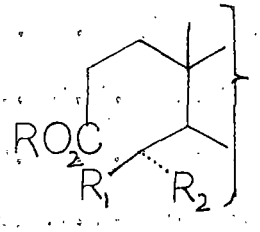
117 $R_1 = H$, $R_2 = Me$

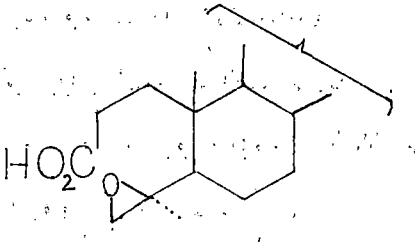
118 $R_1 = R_2 = Me$

119 $R_1 = Me$; $R_2 = H$



120





121

122 $R_1 = Me$; $R_2 = CHO$

123 $R_1 = H$; $R_2 = CHO$

124 $R_1 = H$; $R_2 = CO_3H$

125 $R_1 = H$; $R_2 = OCHO$

In the absence of mineral acid, oxidation of 4,4 dimethyl cholestan-3-one, 114, with m-chloroperbenzoic acid gave the product 4a, 4a dimethyl 4-oxa-A-homo cholestan-3-one[94] 118. Hence, at the outset it seemed likely that this might be an intermediate in the original reaction. Furthermore, treatment of dimethyl lactone, 118, with 10% sulphuric acid or hydrochloric acid in acetic acid under conditions of acidity similar to those used in the original oxidation gave in high yield 4-methyl-4-methylene-3, 4 seco-cholestan-3-oic acid, 120, identical with the product obtained by pyrolysis of the dimethyl lactones, 118. Since oxidation of either the dimethyl lactone 118 or the unsaturated acid, 120, under the conditions of the original acid-catalyzed oxidation of 114, gave monomethyl lactone 117, in similar yields to that of the original reaction, compound 118, and 120, are probably intermediates in the reaction sequence. When the epoxy-acid 121 reacted with acid in the presence of air, the monomethyl lactone, 117 was obtained as a major product together with reduced amounts of the 4α-methyl ketone 115 and the acid mixture, 123. The lactone, 117, was formed likely through aerial oxidation of the oxoacid 123 to the peroxy-acid, 121, a well-known type of autoxidation[95], followed by this peroxy acid on the

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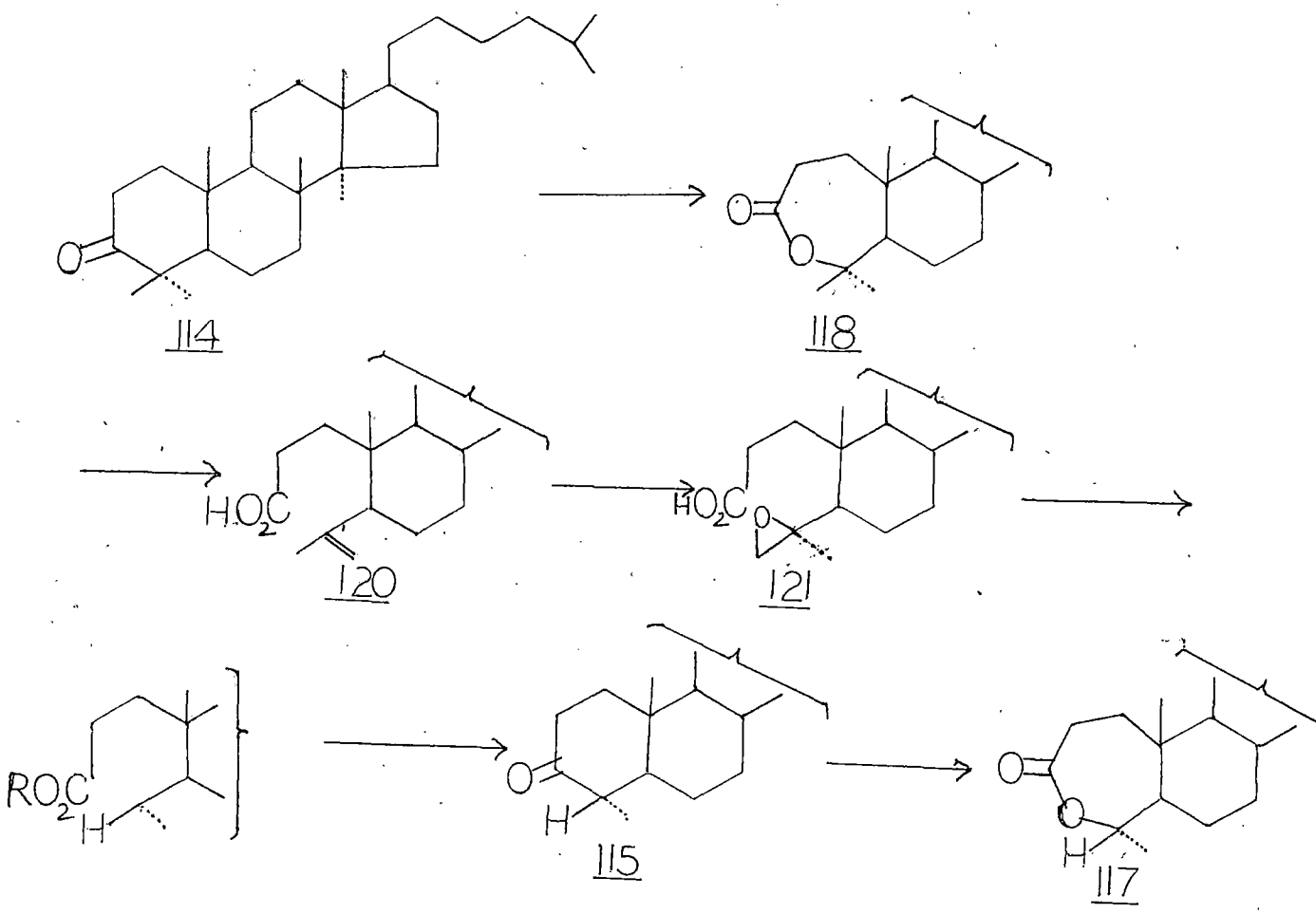
94. D. Rosenthal, A.O. Niedermeyer and J. Fried, J. Org. Chem. 30, 510 (1965)

95. T.A. Turney, "Oxidation Mechanism", Butterworths, London, 1965, p. 171.

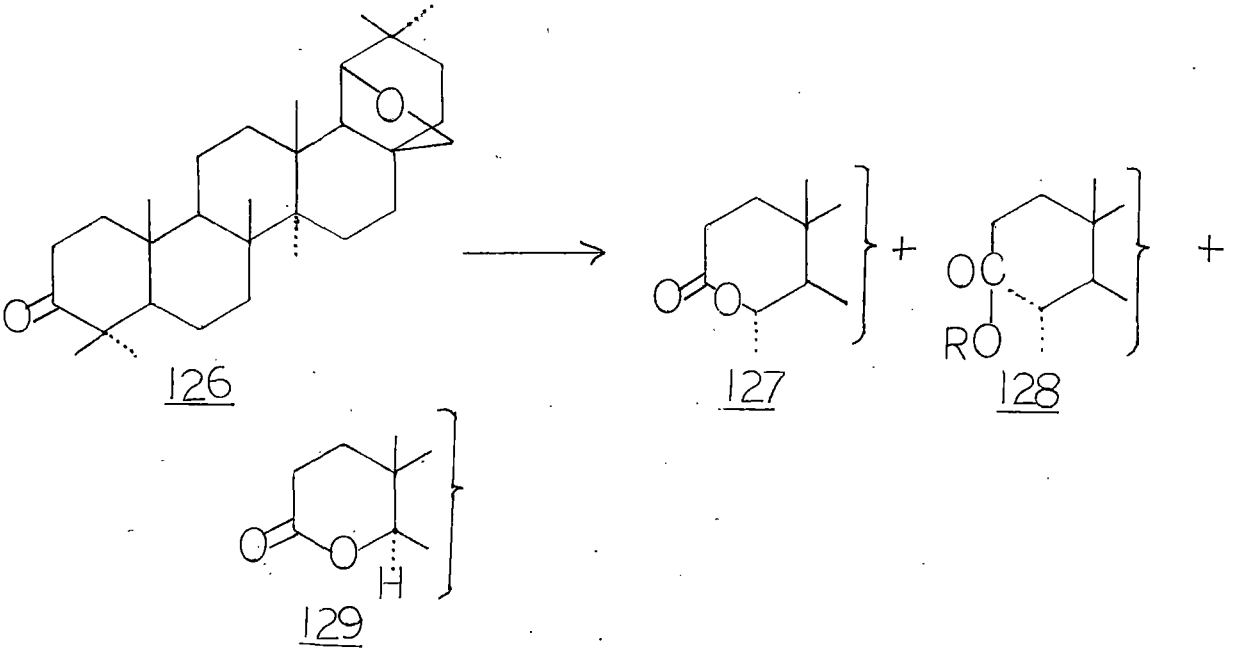
4α-methyl ketone, 115. It was, therefore, proposed that in the original acid-catalyzed Baeyer-Villiger oxidation the probable sequence of the reaction intermediate as (Scheme-XIII) follows:

Scheme - XIII



Bachhawat et al[96] reported epo-oxidation and trans-hydroxylation of olefins with O - sulphoperbenzoic acid prepared by reaction between O-sulphobenzoic anhydride (1.0 mole) and hydrogen peroxide (30%; 1.3 mole) in acetone solution at -4° to 0° . Baeyer-Villiger oxidation of cyclic ketones was reported by the authors with the reagent. But Hase[97] did not find the reagent to react with ketones of lupane and cholestane series.

Hase[98] reported a case of exhaustive Baeyer-Villiger oxidation of the penta cyclic triterpene, allo-betulone, 126, giving, 129, in 50% yield.



126 127 128 129

96. J.M. Bachhawat and N.K. Mathur, Tet. Let., 691 (1971)

97. T. Hase, Chem. Commun., 755 (1972)

98. T. Hase and R. Huikko, Acta. Chem. Scand., B32, 6, 467-8 (1978)

Concerning the overall reaction pathway they were of the opinion that normal Baeyer-Villiger product, 127, and its ring opened form, 128, were likely intermediates as they were oxidised with the paracetic acid/$BF_3.Et_2O$ conditions to the same lactone, 117, as discussed earlier in the case of m-chloroperbenzoic acid/H_2SO_4 oxidation of 4,4 dimethyl-3-oxosteroids.

A survey of literature revealed that various attempts have been made with a view to transforming triterpenoids to the structurally related steroids. Such transformations involve a number of steps. The main objective of such processes were to eliminate the C-4 gem dimethyl groups of triterpenoids. From the above review it is evident that per acids are good reagents in causing exhaustive Baeyer-Villiger oxidations, but there is no previous report on the application of hydrogen peroxide-selenium dioxide mixture in affecting such an oxidation.

A mixture of hydrogen peroxide-selenium dioxide as the oxidizing agent was chosen for two reasons. Firstly, hydrogen peroxide reacts as any peracid in presence of acids causing Baeyer-Villiger oxidation. Secondly, selenium dioxide acts both as an oxidizing agent and as a Lewis acid in the form of seleneous acid.

Two types of triterpenoids were studied: (a) Lupanone and Taraxerone with gem dimethyl substituents at the C-4 position, and (b) Friedelin, which contains only one methyl group vicinal to the C-3 oxo group.

Section B.

Oxidation of Lupanone

Lupanone 130, m.p. 210°, $[\alpha]_D$ 16.2° was refluxed with molar proportion of hydrogen peroxide and catalytic amount of selenium dioxide in tert-butanol on water bath for 35 hours. The completion of the reaction was indicated by the precipitation of black selenium metal. The reaction mixture was then diluted with water and the liberated solid extracted with ether. This was then separated into neutral and acid parts.

The acid part showed two spots on the chromatoplate. In order to separate the two components the total mass was esterified with diazomethane followed by chromatography on a deactivated alumina column. Petroleum ether - benzene (4:1) eluate gave a solid designated as L_1 . The solid L_1 was crystallised thrice from chloroform-methanol and showed m.p. 174-77°. Elemental analysis showed the molecular formula as $C_{31}H_{52}O_2$. Elution with petroleum ether - benzene (3:2) afforded solid L_2. On crystallisation from chloroform - methanol mixture, the compound showed m.p. 116-18°. The compound was analysed for $C_{32}H_{54}O_4$.

The neutral part was chromatographed on a neutral alumina column. Elution of the column with petroleum ether - benzene (2:3) afforded solid L_3, which on crystallisation from chloroform-methanol mixture showed m.p. 175-77°.

In another experiment, when lupanone was oxidised with excess amount of hydrogen peroxide in presence of selenium

dioxide in tert-butanol, it afforded a compound, marked as L_4, in the neutral part, which on crystallisation from chloroform - methanol mixture showed m.p. 252°. The acid part after esterification followed by chromatography yielded a compound which was found to be identical with L_2 by comparison of their mixed m.p. and co- t.l.c.

All the products obtained from the reactions were further purified and subjected to detailed spectral studies for elucidating the structures.

Structure of L_1 as 2α -carbomethoxy-A-nor lupanane, 131

The infrared absorption spectrum of L_1 (Fig. 1) has important peak absorptions as recorded in Table - 1.

Table - 1

Infrared absorption peaks of L_1 in KBr

Position of absorption peak in cm^{-1}	Intensity	Probable assignment
1740	strong	$\rangle C = O$ stretching vibration of an ester group.
1434	medium strong	δ -CH_3 vibration of the ester group.
1170	strong	-C - O stretching vibration of the ester function.

It is evident that $>C = O$ frequency is in the expected range of 1735 to 1740 cm^{-1}, commonly found for a strain free ring and in the steroidal series[99]. It is also known that infrared spectra of esters show a strong supporting band in the range of 1150 to 1280 cm^{-1}[100], accompanied by one or several bands of variable intensity between 1100 to 1300 cm^{-1}. These bands have been associated with various modes of coupled C - O and O - R' vibrations of the COOR' group[101]. The band at 1434 cm^{-1} may be assigned to δ -CH_3 vibration of the ester group in I_1.

The ester formulation of I_1 is also found to be tenable from a careful examination of the 60 MHz ^1H NMR spectrum of the compound (Fig. 2). The signals for the various protons and their probable assignments as recorded in Table - 2 clearly indicate the presence of eight methyl groups on saturated carbon atoms (six tertiary and one isopropyl, δ 0.72 to 1.04)and one carbomethoxy function.

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99. H.W. Thompson, P. Torkington, J.Chem.Soc., 640 (1945)

100. L.J. Bellamy, "Infrared Spectra of Complex Molecules", London, Methuen, 380-89 (1959)

101. R.A. Russel, H.W. Thompson, J.Chem.Soc., 479 (1955)

Fig.1 IR Spectrum of 2α- Carbomethoxy-A-nor-lupane, 121.

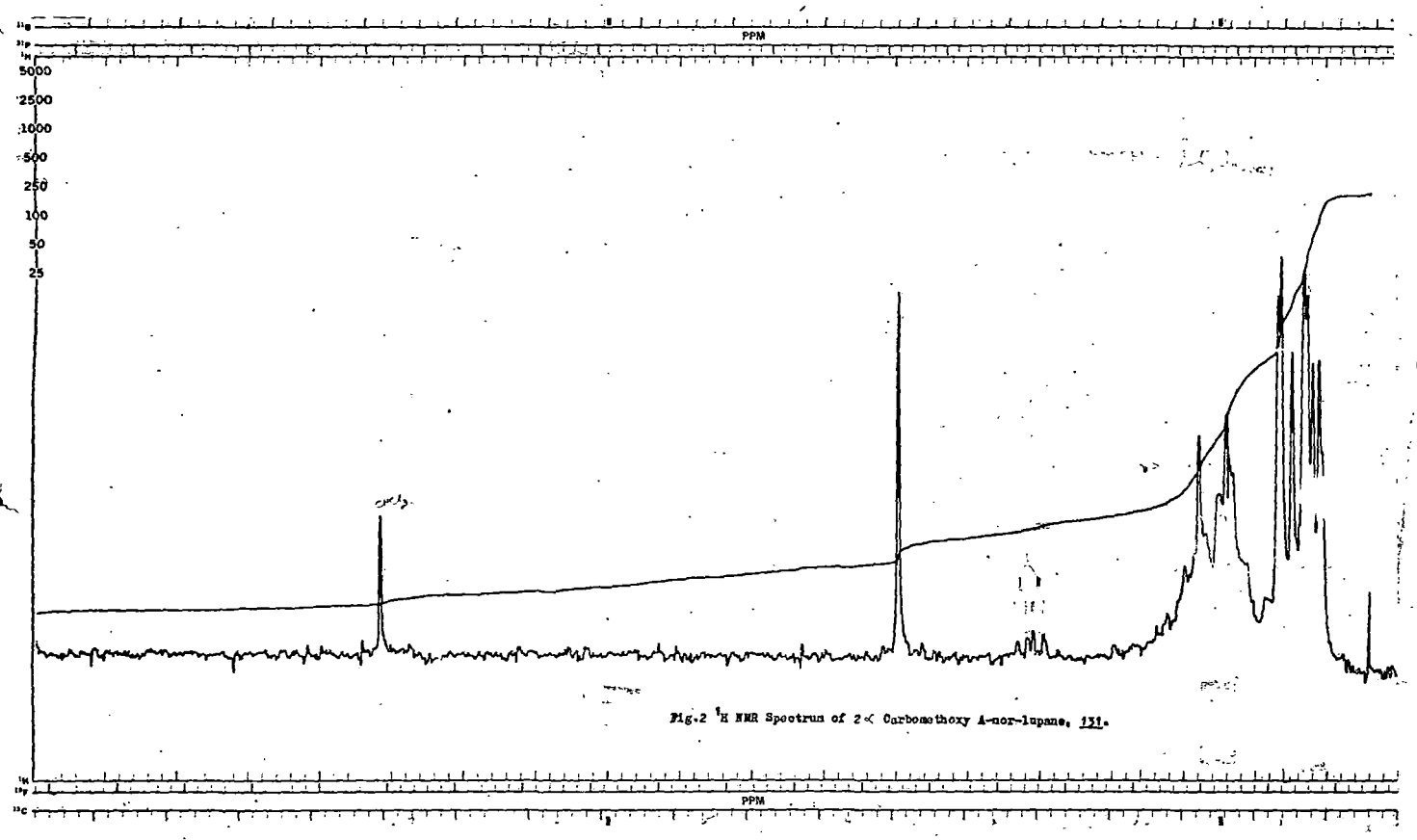


Fig.2 ^{1}H NMR Spectrum of 2< Carbomethoxy A-nor-lupane, 131.

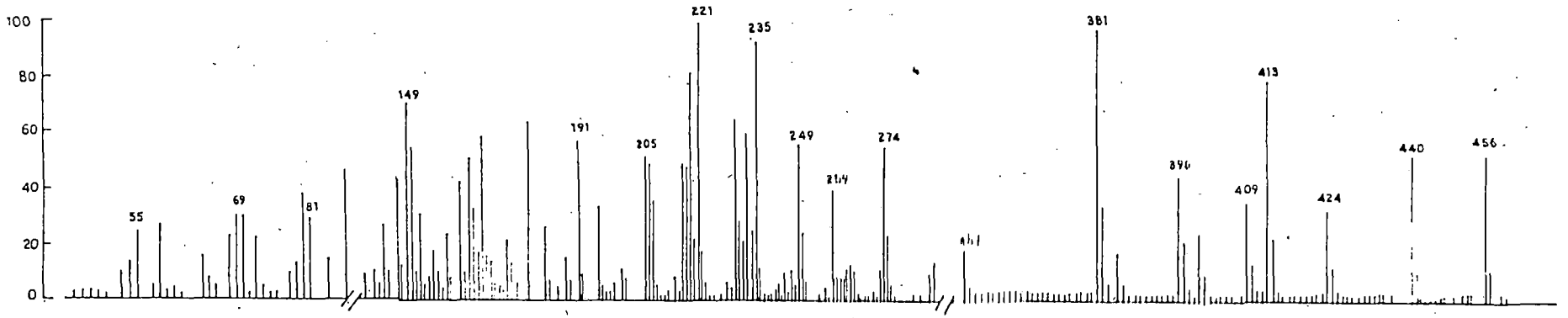
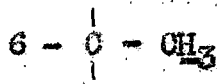
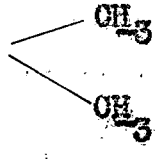
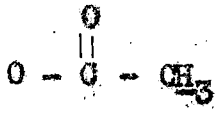
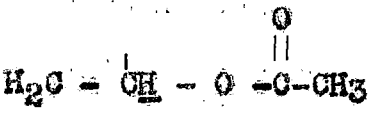


Fig.3 Mass Spectrum of 2α Carbomethoxy-A-nor-lupane, 131

Table - 2

^1H NMR signals of I_1

Chemical shift δ(ppm)	Number of protons	Multiplicity of signals	Probable assignments
1.04 1.02 0.94 0.83 0.80 0.72	3 3 3 3 3 3	singlet singlet singlet singlet singlet singlet	
0.85 0.75	3 3	doublet J = 7 Hz	
3.7	3	singlet	
2.77	1	quartet J_{aa} = 12 Hz J_{ae} = 6 Hz	

(δ 3.7, 3H, s). The methine proton attached to the carbon atom bearing the carbomethoxy group appears in the usual region (δ 2.77) as a quartet (J_{aa} = 12 Hz, J_{ae} =6Hz). The J values indicate the proton to be axial with one axial and another equatorial neighbouring protons and hence the carbomethoxy group is equatorial.

The structure of L_1 is further supported by the mass spectal analysis of the compound (Fig. 3). The mass spectrum shows characteristic peaks at m/e 456 (M^+), 440, 424, 413, 409, 396, 381, 357, 274, 259, 249, 235, 221, 205, 191 and 149.

As in the case of typical saturated lupane derivatives[102,103], L_1 also exhibits peaks at m/e 413 due to loss of isopropyl group from the molecular ion M^+. The presence of peaks at m/e 221, 205 and 191 are probably due to fragments II, III and IV respectively, II being the base peak in this case (Scheme-XIV). The peaks at m/e 249 and 235 are due to formation of fragments V and VI, which are accompanied by peaks at m/e 175 and 121 formed by fragments following the loss of acetic acid group from species V and VI. The other fragments may be explained as follows: 440 ($M^+ - CH_4$), 424 [$M^+ - CH_3OH$], 396 [$M^+ - CH_3COOH$], 381 [396 - CH_3]. Normally, lupane-3-one exhibits most abundant fragment at m/e 205, the only fragment comprising ring A, which corresponds to species I. For compound L_1, IR and NMR spectra indicate the presence of a carbomethoxy group and with the help of mass fragment this group can be most suitably placed at C-2 in ring A.

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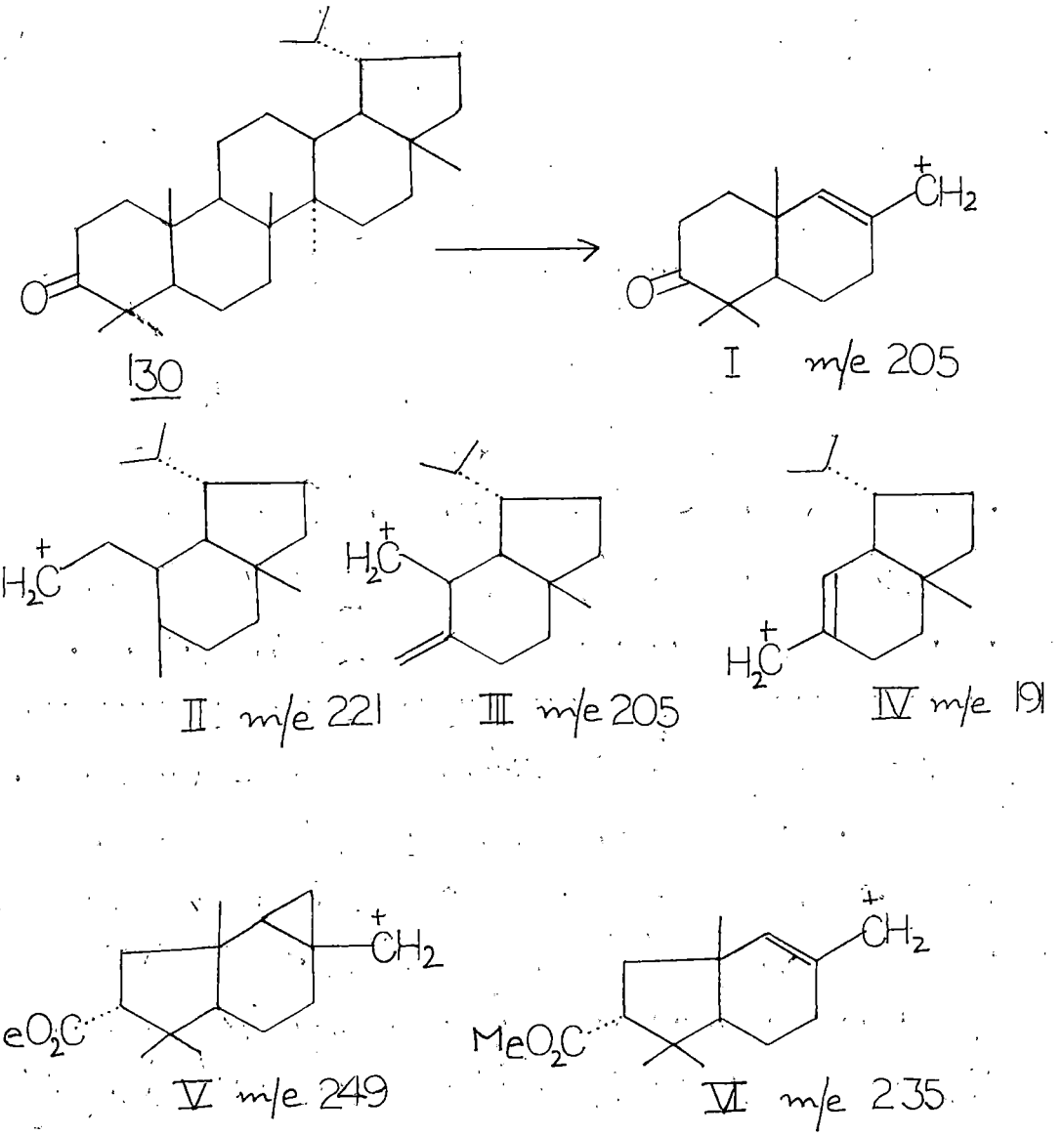
102. H. Budzikiewicz, J.M. Wilson and Djerassi, J.Am.Chem.Soc., 85, 3698 (1963)

103. L. Ogunkoya, Phytochemistry, 20, 121 (1981)

Scheme - XIV



Thus, all the spectral data support the structure of I_1 to be 2α-carbomethoxy-A-nor-lupane, 131[104].

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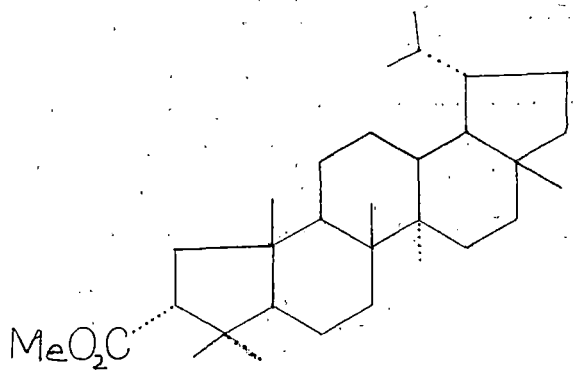
104. S. Kundu, A. Chatterjee and A.S. Rao, Chem. Ber., 101, 3255 (1968)



131

Structure of L_2 as 2,3 -seco methyl lupane dicarboxylate, 132

The molecular formula of L_2 as $C_{32}H_{54}O_4$ was confirmed by combination of its mass spectrum that determined the molecular weight as 502 and the independent elemental analysis.

The IR spectrum (Fig. 4), recorded in Table - 3, discloses the presence in its molecule two ester functions. The absorption band at 1735 and 1740 cm^{-1} are normal νCO frequency in ester of dicarboxylic acid[105]. The bands are split due to either coupling of the symmetrical or asymmetrical vibrations. The supporting bands appear at 1160, 1140 and 1120 cm^{-1}. The band at 1435 cm^{-1} is due to δCH_3 vibration.

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105. W.L. Walton, R.B. Hughes, J.Am.Chem.Soc., 79, 3985 (1957)

Table - 3

Infrared spectrum of L_2 in KBr

Position of peak absorption cm^{-1}	Intensity	Probable assignment
1735 1740	strong	$>C = O$ stretching vibration of ester group.
1160	strong	-C-O stretching vibration of the ester group.
1140	strong	
1120	medium	
1435	medium	δCH_3 vibration of ester group.

The signal of 60 MHz ^1H NMR spectrum (Fig. 5) for various protons together with their probable assignments are recorded in Table - 4.

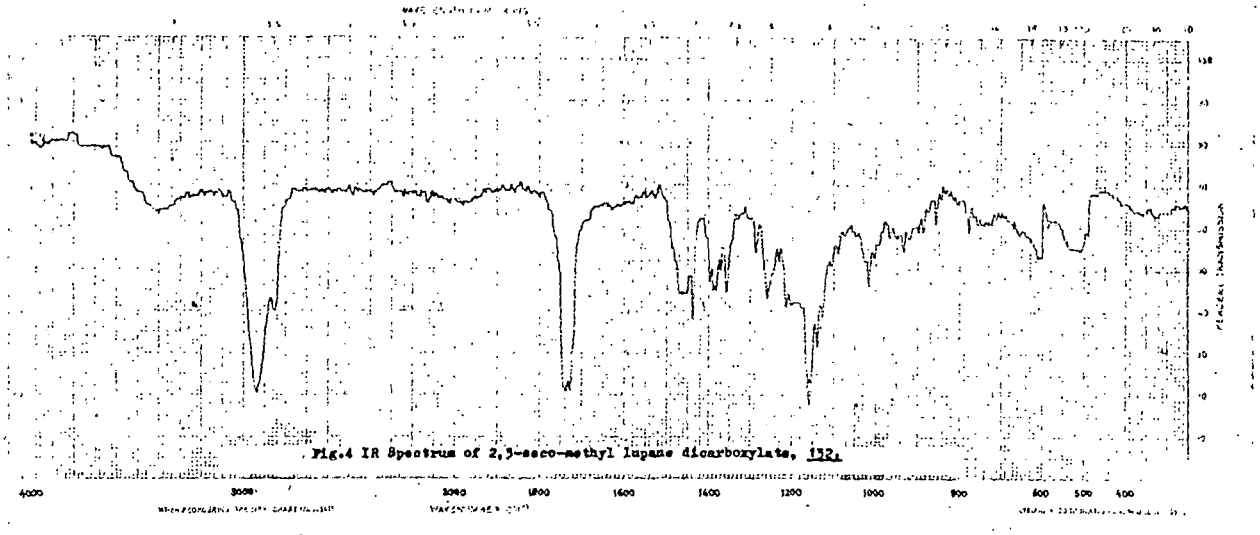


Fig.4 IR Spectrum of 2,3-seco-methyl lupane dicarboxylate, 12.

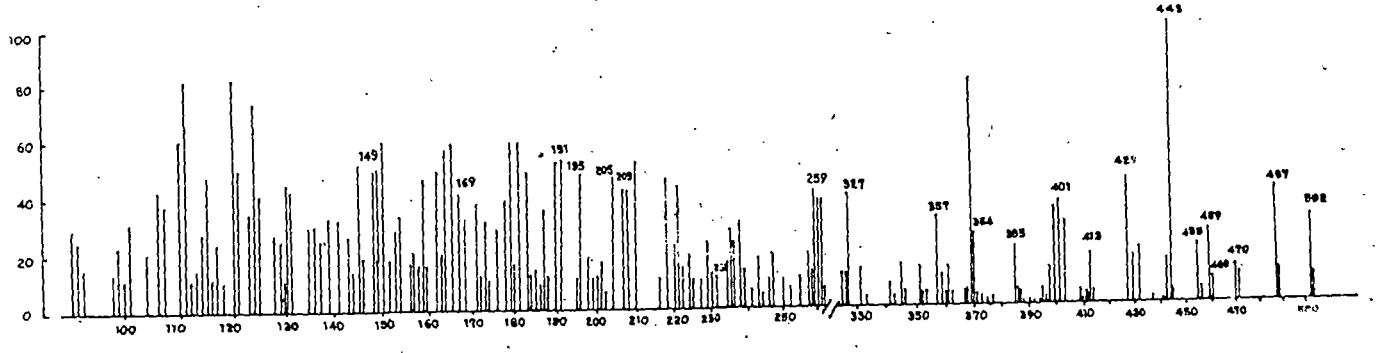


Fig.6 Mass spectrum of 2,3-seco methyl lupane dicarboxylate, 1.

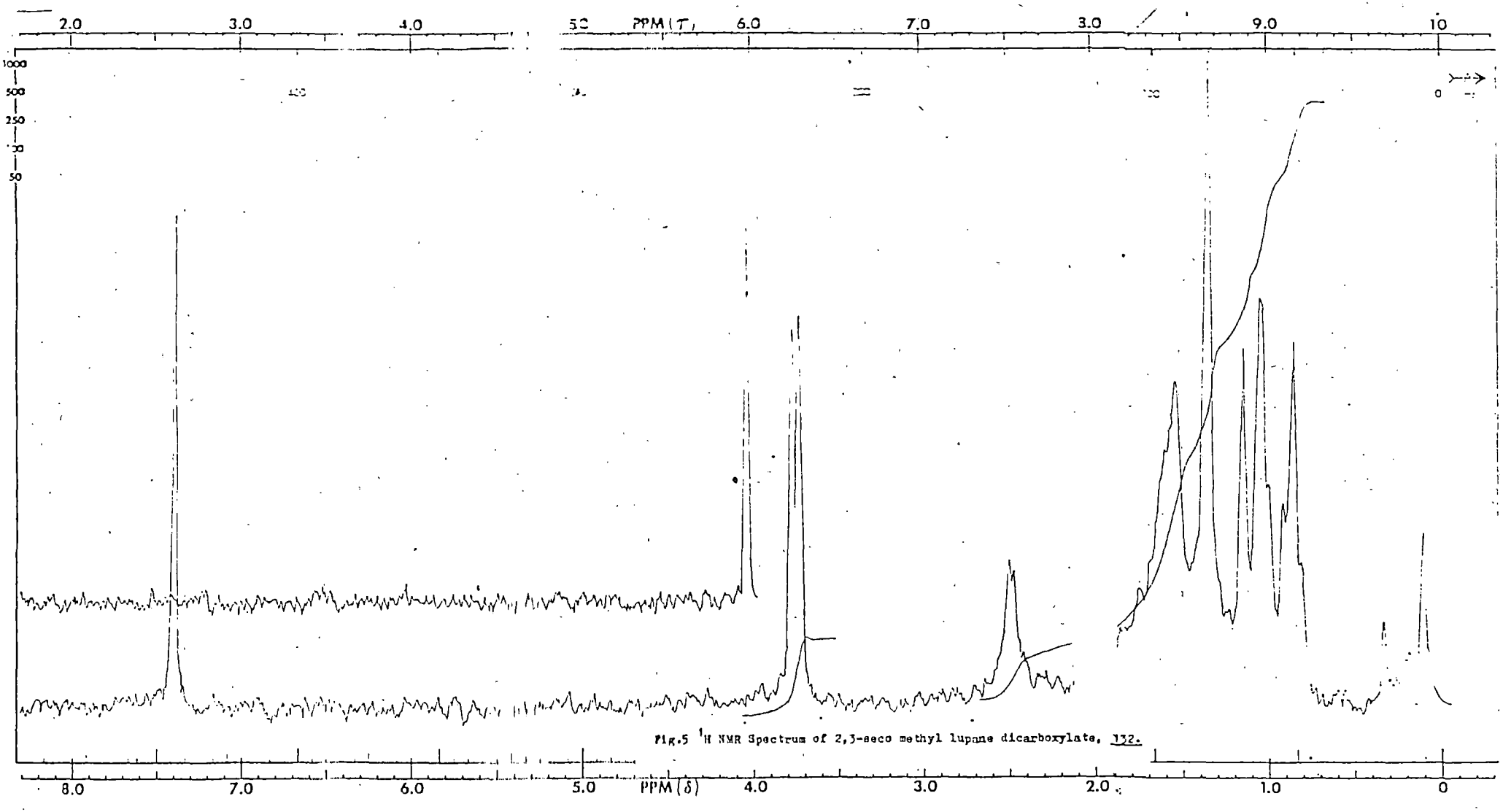


Fig.5 ^{1}H NMR Spectrum of 2,3-seco methyl lupane dicarboxylate, 132.

Table - 4

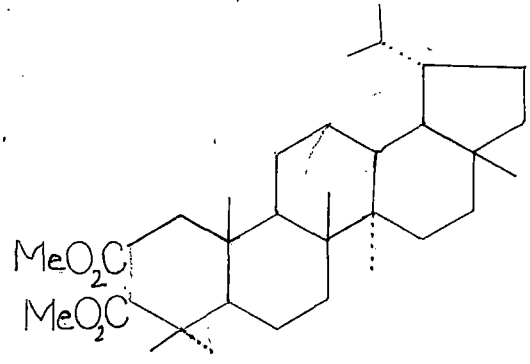
^{1}H NMR signals of L_2

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignment
0.92	3	singlet	
0.96	3	singlet	6 - C - CH_3
1.06	6	singlet	
1.22	6	singlet	
0.75	3	doublets	HC(CH_3)(CH_3)
0.85	3	J = 7 Hz	
3.68	3	singlet	2 - C - $COOCH_3$
3.64	3	singlet	
2.45	1	singlet	H_3COOC - CH_2
2.48	1	singlet	

The signals at δ 0.92 to 1.22 are integrated for 18 protons corresponding to six C - methyl functions. The doublets centered at δ 0.85 and 0.75 with a J value of 7 Hz indicate the presence of isopropyl group on a carbon atom bearing a hydrogen atom which is perhaps responsible for the splitting as doublets for the C-29 and C-30 methyl groups. Two three-proton singlets each at δ 3.68 and at δ 3.64 indicate the presence of two carbomethoxy groups. The appearance of two one proton singlets at δ 2.45 and δ 2.48 indicate that one carbomethoxy group is accompanied by a methylene

group in its alpha position. Also, the signals speak of the presence of methylene group on a prochiral centre[106].

The mass spectrum of L_2 (Fig. 6) gives further insight regarding its structure. It exhibits characteristic peaks at m/e 502 (M^+), 443, 429, 413, 400, 385, 369, 321, 259, 205, 191. The genesis of these fragments may be best rationalised if structure, 132 be formulated for compound L_2 .



132

m/e 502 (M^+)

→ m/e 443 (M^+ - $COOCH_3$)

→ m/e 429 (M^+ - H_2C - $COOCH_3$)

→ m/e 400 (443 — $HC(CH_3)_2$)

→ m/e 369 (429 - $HCCOOCH_3$)

Thus, compound L_2 has been established as 2,3-seco methyl lupane dicarboxylate. Compound, 132, was hydrolysed with methanolic KOH to afford lupane dicarboxylic acid[107], 133, $C_{30}H_{50}O_4$, m.p. 270-71°, which also confirmed the structure of L_2 as 132.

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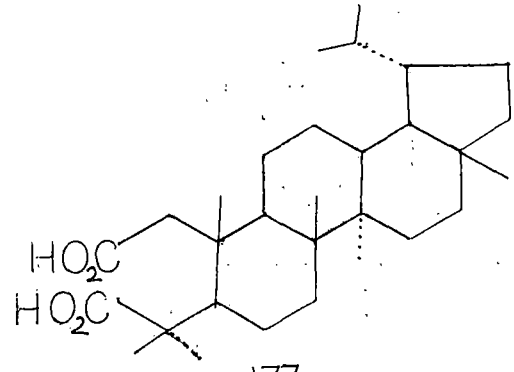
106. Chemical Revies, 75, 307 (1975)

107. Simonsen and Ross, "The Terpenes", Volm. IV, p. 336.



133

Structure of I_3 as lup-1-ene-3-one, 134.

Elemental analysis of the compound was in good agreement with the molecular formula $C_{30}H_{48}O$.

The infrared spectrum of the compound I_3 (Fig. 7) is recorded in Table - 5.

Table - 5

IR absorption peaks of compound I_3 in Nujol Mull

Position of absorption peaks cm^{-1}	Intensity	Probable assignment
1675	strong	α,β unsaturated ketone
1650	weak	$-\overset{|}{C} = \overset{|}{C}$ - frequency

The absorption band at 1675 cm^{-1} is indicative of α,β unsaturated ketone as it is well known that conjugation of the carbonyl group with a double bond results in a decrease in >CO frequency by about 40 cm^{-1} and that, the frequency generally lies within the range of 1665 - 1695 cm^{-1}[108]. The >C = C< frequency in α,β unsaturated carbonyl compound is lower than in non-conjugated compound and appears at 1650 cm^{-1}, but the band intensity is small as $C_1 - C_2$ double bond is flanked by a carbonyl group and a methyl group. For the same reason, the degree of polarisation is low and, therefore, the band is weak.

The ultraviolet spectrum of L_3 shows maxima at 228 nm in methanol.

That the compound L_3 is an α,β unsaturated compound is evident from IR and UV spectra and is further confirmed by its 60 MHz ^1H NMR spectrum (Fig. 8). The chemical shifts, multiplicity and probable assignments of the signals are recorded in Table -6.

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108. R.S. Rasmussen, D.D. Tuncliff, R.R. Brattain, J.Am.Chem.Soc., 71, 1068 (1949)

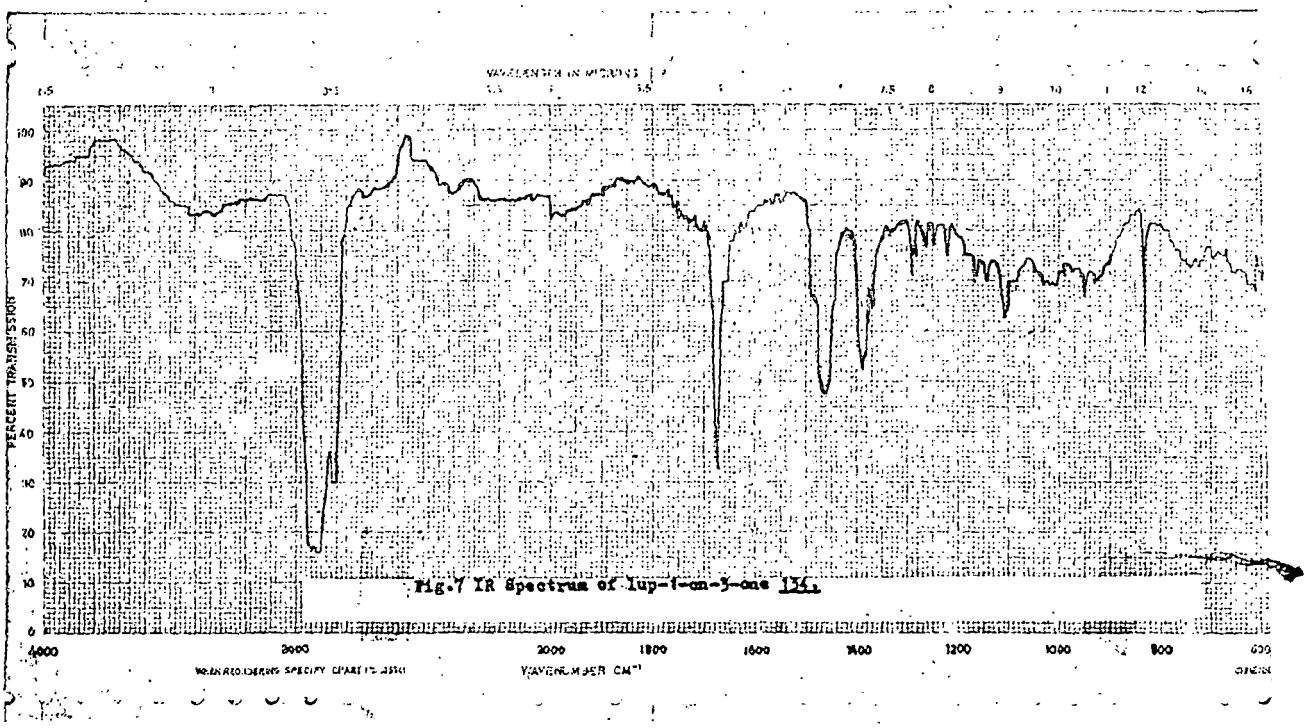


Fig.7 IR Spectrum of lup-1-en-3-one 134

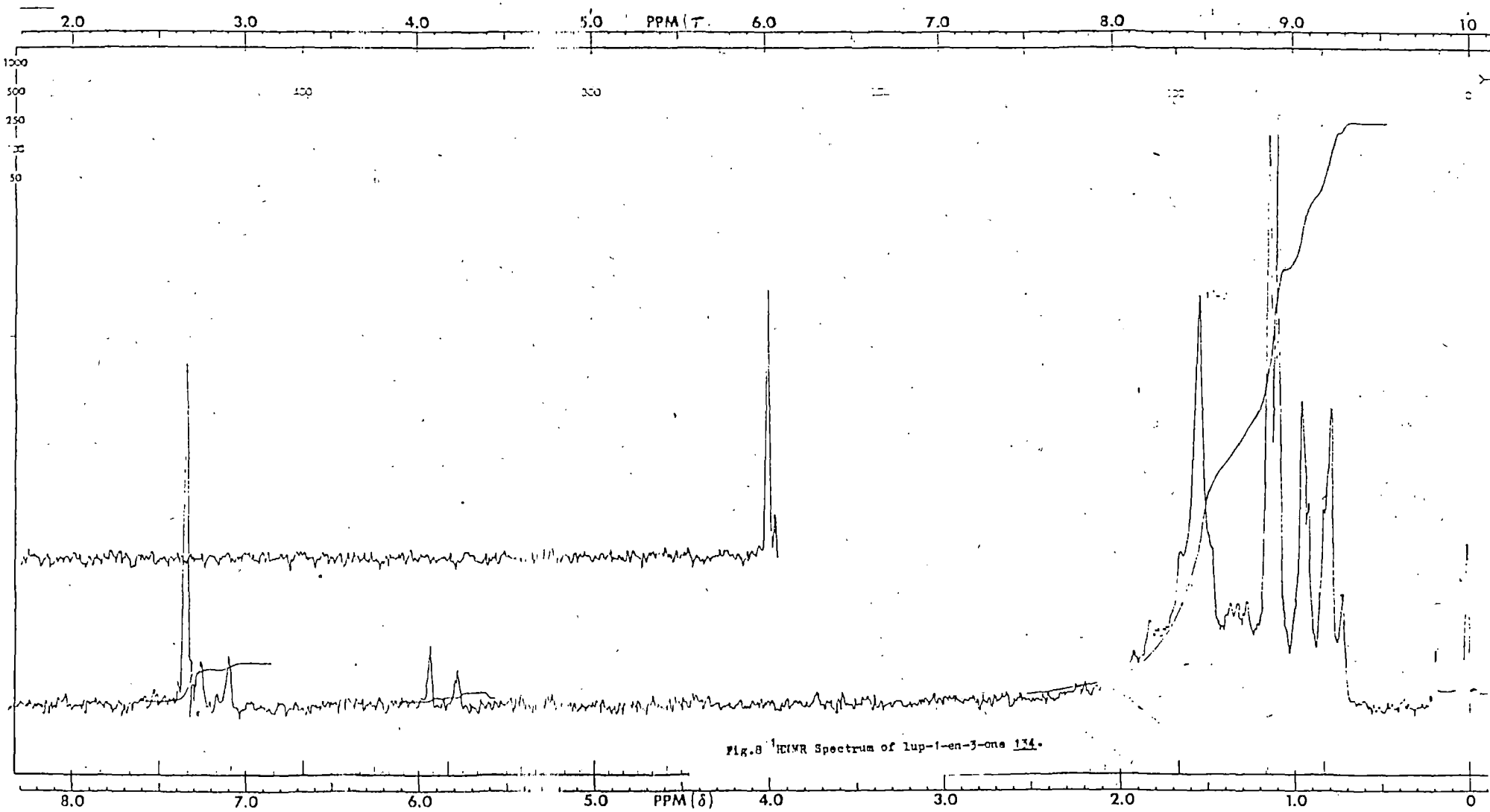
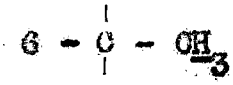
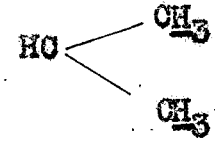
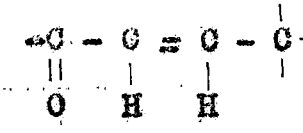


Fig.8 ^{1}HNMR Spectrum of lup-1-en-3-one 134.

Table - 6

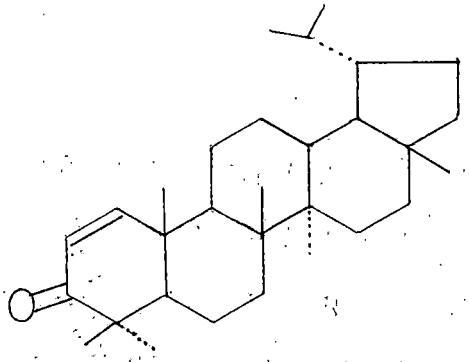
^1H NMR signals of L_3

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignment
0.78	3	singlet	
0.96	3	singlet	
1.06	6	singlet	
1.08	6	singlet	
0.75	3	doublet	
0.80	3	J = 6.8 Hz	
5.85	1	doublet J = 10 Hz	
7.19	1	doublet J = 10 Hz	

The most interesting observation here is the appearance of two one-proton doublets each at δ 5.85 and at δ 7.19 with a coupling constant 10 Hz. In α,β unsaturated ketone the hydrogen on β -carbon atom appears at lower field than the α -proton due to polarisation of α,β unsaturated carbonyl chromophore, which causes a reduction in the electron density at the β -carbon atom and hence decreases the effective shielding of the β-proton. These facts are reflected in the ^1H NMR spectrum of L_3 with

appearance of signals at δ 5.85 and 7.19. Also, the high J value indicates that the orientation of the two hydrogen atoms are cis.

From all these considerations of UV, IR and ^1H NMR spectral analysis, compound, I_3 has been assigned structure 134 as lup-1-ene-3-one. It was confirmed by mixed m.p. and spectral comparison studies with an authentic sample of dihydro glochidone[109].



134

Structure of I_4 as 4, 23, 24-tri-nor lupane 3 → 5 olide, 135:

The most interesting aspect of the reaction was the isolation of compound I_4. Its structure was determined from spectral studies. Elemental analysis and mass spectrum of the compound show its molecular formula to be $C_{27}H_{44}O_2$.

The important absorption bands of IR spectrum of I_4 (Fig. 9) are recorded in Table - 7.

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109. A.K.Ganguly, T.R. Govindachari, P.A. Mohamed, A.D. Rahimtulla and N. Viswanathan, Tetrahedron, 22, 1513 (1966)

Table - 7

Infrared Absorption peaks of L_4 in Nujol Mull.

Position of Absorption peak ν_{max} cm^{-1}	Intensity	Probable assignment
1748	strong	δ- lactone
1420	weak	$-CH_2$ group alpha to the $>C=O$ group
1250	strong	$-\overset{|}{C}-O$ vibration

The absorption band at 1743 cm^{-1} indicates the presence of δ-lactone[110]. Deformation vibration of the CH_2 group alpha to the $>C=O$ group is indicated by the small absorption band at 1420 cm^{-1} [110]. The frequency of absorption of -C-O vibration occurs at 1250 cm^{-1}[111].

The ^1H NMR spectrum of L_4 (Fig. 10) was studied in $CDCl_3$ in 360 MHz instrument using TMS as the internal standard. The signals for various protons and their probable assignments are recorded in Table - 8.

110. R.N. Jones and B.S. Gallapher, J.Am.Chem.Soc., 81, 5242 (1959)

111. R.H. Wiley, J.G. Esterle, J.Org.Chem., 22, 1257 (1957)

Table - 8

^{1}H NMR signals of L_4 in $CDCl_3$

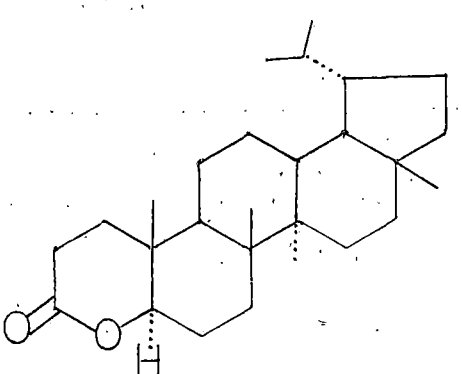
Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
0.74 0.87 0.91 1.07	3 3 3 3	singlet singlet singlet singlet	4 - C - CH_3
0.82 0.73	3 3	doublets (J = 7 Hz)	HC(CH_3)(CH_3)
3.9	1	multiplet ($W_{½}$ = 18 Hz)	-C(=O)-O-CH -CH_2
2.6	2	multiplet	H_2C-CH_2 -C(=O)-O-CH

It may be seen from Table - 8 that there are six C-methyl groups in L_4 resonating in the region from δ 0.74 to 1.07 instead of eight in lupanone i.e. there is loss of two C-methyl groups. The appearance of a multiplet at δ 3.9 is assignable to a lactonic proton[112a,b].

112(a) G.V.D. Tiers, J.Phys.Chem., 62, 1151 (1958)

The half width value (sum of J) of 18 Hz indicates that the lactonic proton is axially oriented with one axial and one equatorial neighbours[113]. The multiplet centred at δ 2.6 integrable for two protons is indicative of the presence of methylene protons alpha to the carbonyl group.

From IR and ^{1}H NMR spectral data analysis it is evident that ring A of lupanone is lacking three carbon atoms and the tentative structure that may be assigned to L_4 is 4, 23, 24-tri-nor-lupane-3 $\longrightarrow$ 5 olide, a δ-lactone, 135.



135

Further information as to the structure of 135 comes out from a study of the fragmentation pattern in the mass spectrum (Fig. 11). The mass spectrum by chemical ionisation method shows

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112(b) "Characteristic NMR Shielding values for hydrogen in Organic Structures" (Minnesota Mining and Manufacturing Company, 1958)

113. K.L. Williamsons and W.S. Johnson, J.Am.Chem.Soc., 83, 4629 (1961)

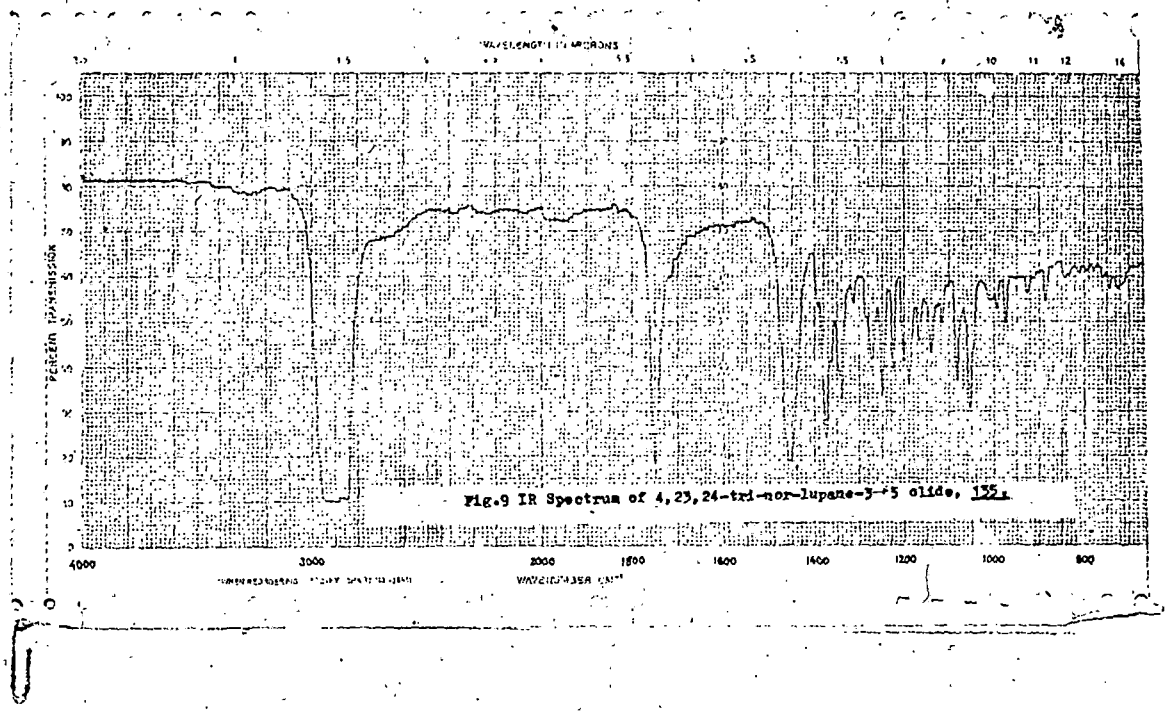


Fig.9 IR Spectrum of 4,23,24-tri-nor-lupane-3-*5 olide, 155.

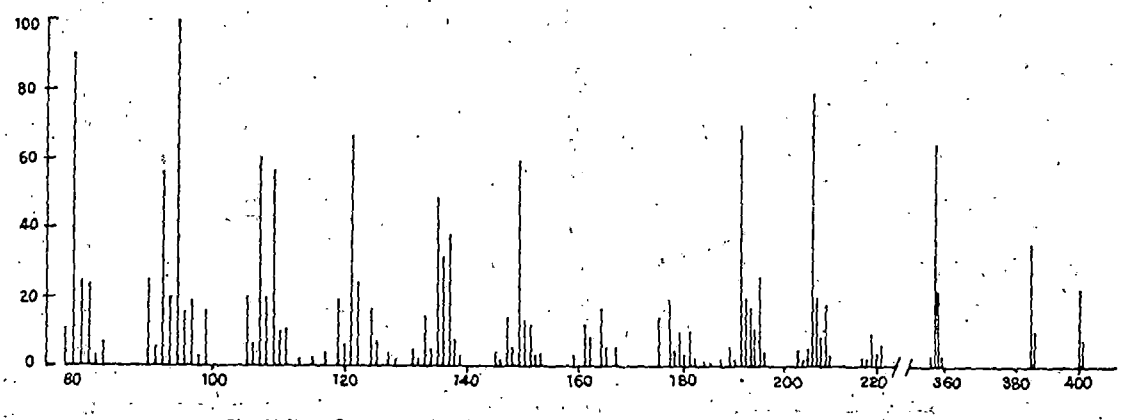


Fig.11 Mass Spectrum of 4,23,24-tri-nor-lupane-3--5 olide 155.

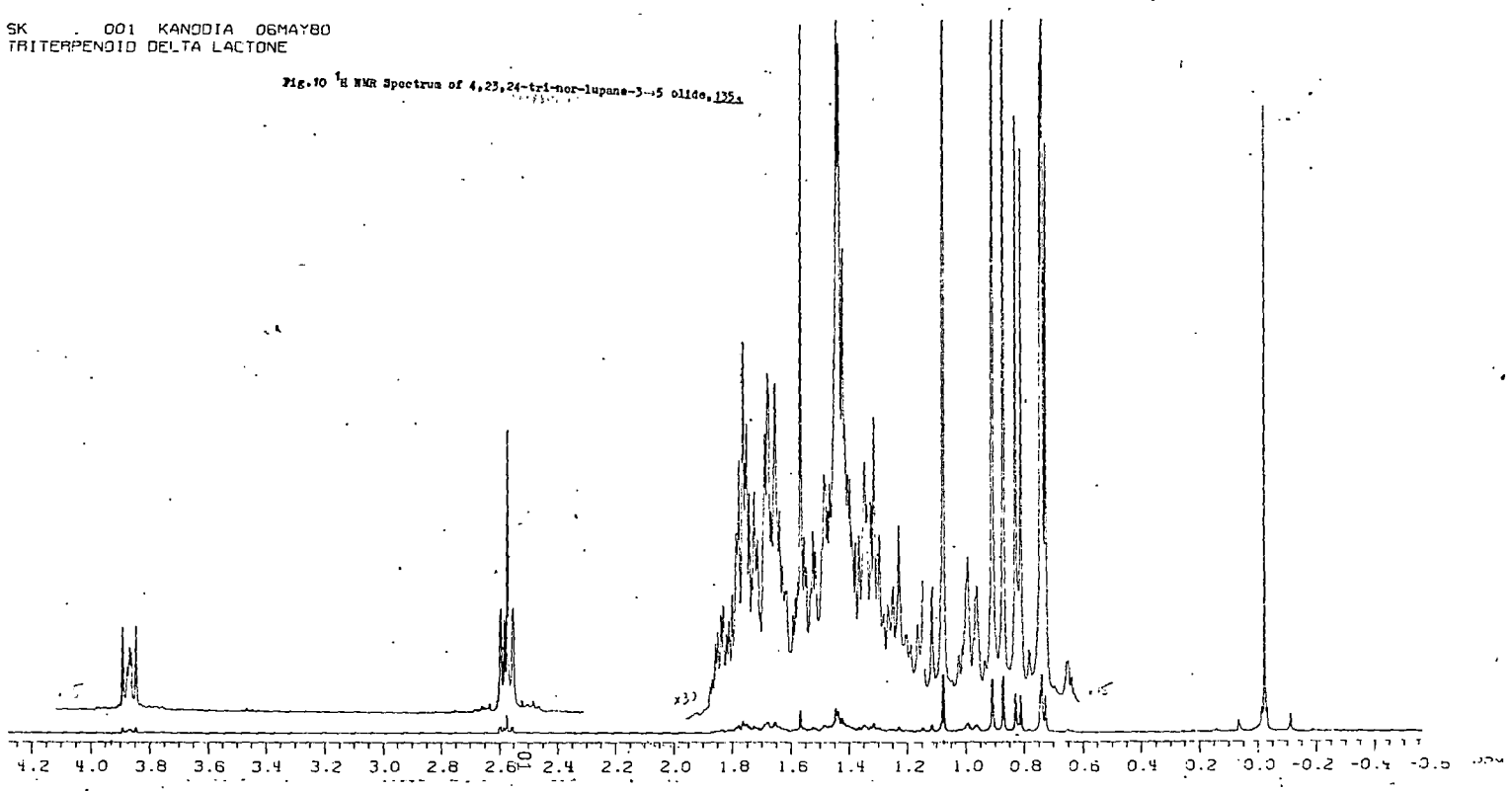
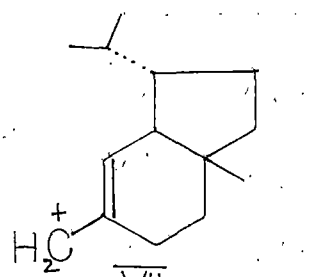


Fig.10 ^{1}H NMR Spectrum of 4,23,24-tri-nor-lupane-3→5 olide, 135a

molecular ion M^+ at 400. The peaks at m/e 357 and 385 are due to the fragments formed from the molecular ion by the loss of isopropyl and methyl units respectively. The most abundant fragment at m/e 191, characteristic of lupane series[102,114a,b] is due to the fragment VII.



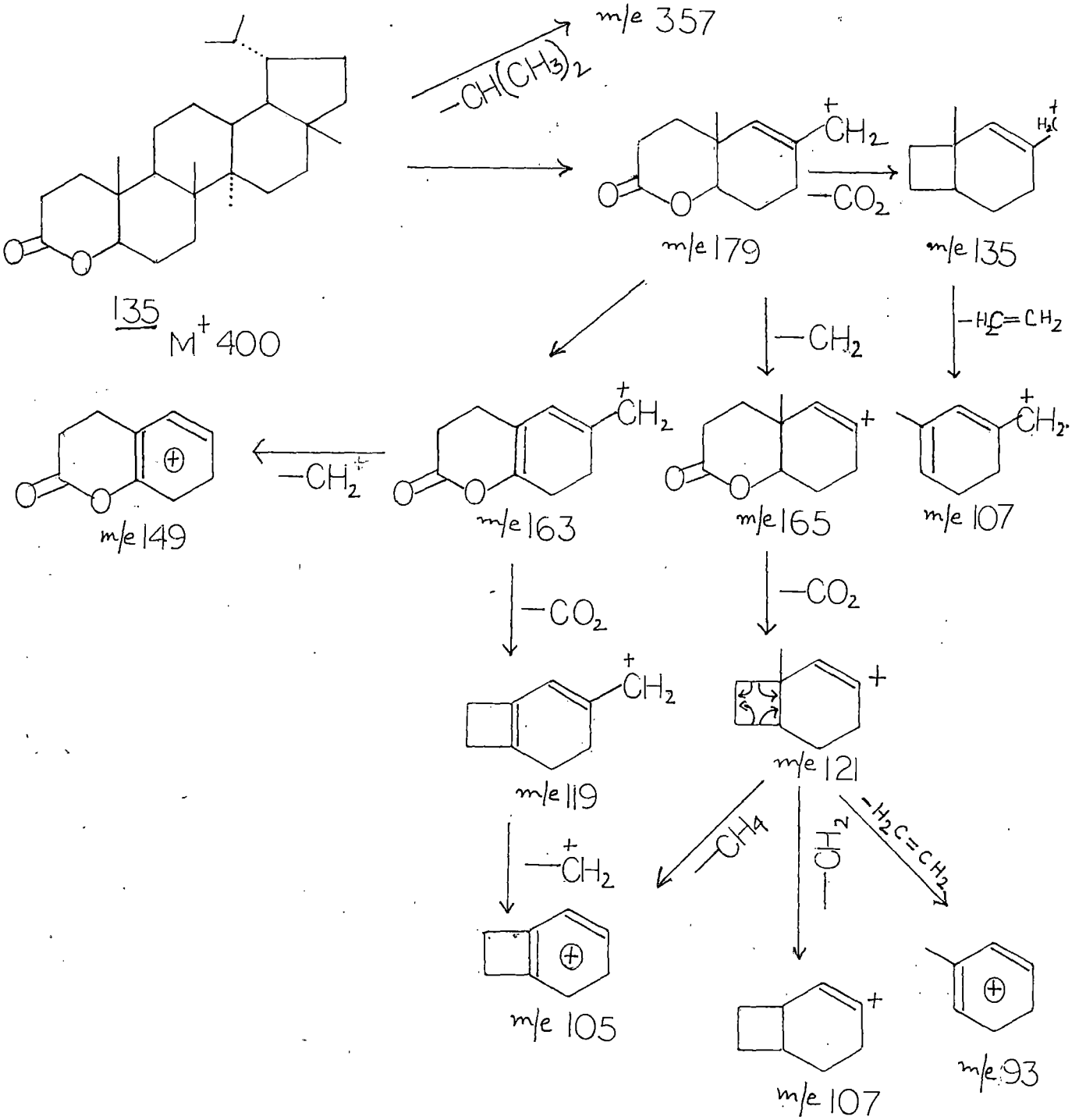
VII m/e 191

The other characteristic peaks are at m/e 400 (M^+), 384, 357, 219, 209, 206, 195, 179, 165, 163 (base peak), 149, 135, 123, 121, 119, 109, 107, 95, 93, 81. A probable fragmentation pattern is shown in the Scheme- XV assuming structure 135 for compound L_4.

114(a) H. Budzikiewcz, C. Djerassi and D.H.William, "Structure Elucidation of Natural Products by Mass Spectrometry", Volm. II, Holden-Day, Sanfrancisco, 1964.

(b) J. Kartiner and C. Djerassi, J.Org.Chem., 31, 1945 (1966)

Scheme - XV


m/e 357
$-CH(CH_3)_2$
135
M^+ 400
m/e 179
$-CO_2$
m/e 135
$-H_2C=CH_2$
$-CH_2$
m/e 149
$-CH_2$
m/e 163
m/e 165
m/e 107
$-CO_2$
$-CO_2$
m/e 119
m/e 121
$-CH_2$
$-CH_4$
$-CH_2$
$-H_2C=CH_2$
m/e 105
m/e 107
m/e 93

Section C

Oxidation of Friedelin

We have discussed the reaction of lupanone with hydrogen peroxide in presence of selenium dioxide in Section B. The reaction led to the formation of a δ lactone 135 with demethylation of 23 and 24 methyl groups present as gem dimethyl, group along with C-4 carbon atom.

With a view to examine what happens in the case of a compound which possesses only one secondary methyl group in C-4 position, we studied the same reaction on friedelin, 136, the results of which are discussed here in sequence.

Friedelin, 136 in tert-butanol was refluxed on water bath for 60 hours with hydrogen peroxide and selenium dioxide. Precipitation of black selenium metal marked the completion of the reaction. The t.l.c. of the reaction mixture indicated the absence of friedelin. In order to separate the products formed, the reaction mixture was diluted with water and extracted with solvent ether followed by separation into neutral and acid parts as usual.

It appeared from the t.l.c. of the neutral part that only one compound was present in neutral part. It was then subjected to chromatography in a deactivated alumina column. Elution of the column with petroleum-ether-benzene (2:3) yielded a solid, F_1 . This was crystallised three times from chloroform-methanol to afford crystals of F_1, m.p. 262°.

The acid part showed the presence of two compounds on t.l.c. plate. It was esterified with diazomethane and was subjected to chromatographic separation over a deactivated alumina column. Elution of the column with pet. ether-benzene (4:1) afforded solid F_2 and was crystallised three times to give fine needle shaped crystals, m.p. 263-65° and showed single spot on chromatoplate. Another compound, F_3, was obtained from the column on elution with petroleum ether-benzene (2:3). The compound was crystallized three times from chloroform-methanol and showed its m.p. to be 167-69°. Its t.l.c. indicated the presence of a single compound.

All the three compounds, i.e., F_1, F_2 and F_3 were subjected to IR, ^1H NMR and mass spectral studies, interpretation of which led to the establishment of structures of the compounds.

Characterisation of F_1 as 2-nor-friedelin 3 ⟶ 4 olide, 137:

The molecular formula of F_1 was established as $C_{29}H_{48}O_2$ considering together the mass spectrometrically derived molecular weight 428 and the independent elemental analysis.

The infrared spectrum (Fig. 12) of compound F_1 unfolds some information regarding its structure. The important peak absorptions and their probable interpretations are recorded in Table - 9.

Table - 9

Infrared Absorption Peaks of F_1 in Nujol Mull

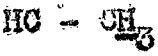
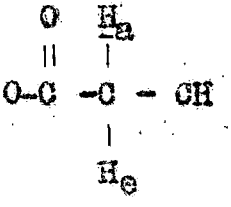
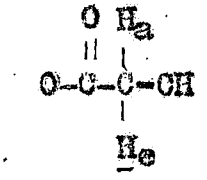
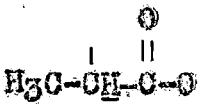
Position of absorption peak in cm^{-1}	Intensity	Probable assignment
1730	strong	δ-lactone
1410	weak	$-CH_2$ group alpha to the $>C=O$ group
1245	medium strong	$-\overset{|}{C}-O-$ vibration

The strong absorption band at 1730 cm^{-1} demonstrate the presence of a δ-lactone moiety[110]. The $>CO$ vibration occur at 1245 cm^{-1}[111]. The weak absorption band at 1410 cm^{-1} is due to the deformation vibration of the CH_2 group in the position alpha to the $>C=O$ group. Thus, the infrared absorption spectrum indicates that F_1 is possibly a δ-lactone. This is supported by its proton magnetic resonance spectrum (Fig. 13) studied in $CDCl_3$ in 360 MHz instrument using TMS as internal standard. The signals for various protons and their assignments are recorded in Table-10.

The appearance of singlets in the region δ 0.88 to δ 0.94 and δ 1.14 to δ 1.21 indicated the presence of seven tertiary methyl groups in compound F_1. The doublet at δ 1.18 with a coupling

Table - 10

PMR signals of F_1

Chemical shift (ppm)	Number of protons	Multiplicity of signals	Probable Assignments
0.88 0.90 0.91 0.94 1.14 1.18 1.21	3 3 3 3 3 3 3	singlet singlet singlet singlet singlet singlet singlet	
0.99 1.01	3	doublet J = 6.5 Hz	
2.4	1	Double doublet J_{gem} = 13 Hz J_{aa} = 13 Hz	
2.6	1	Double doublet J_{gem} = 13 Hz J_{ae} = 4 Hz	
4.02	1	quartet J = 10 Hz	

constant 6.5 Hz indicates the presence of a secondary methyl group. This shows that all the methyl groups of friedelin is present in compound F_1 . The nature of the multiplet centred at δ 2.48 indicates it to be of AMX pattern[115]. The chemical shift

115. Norman S. Bhacca and Dudley A. Williams, "Application of NMR spectroscopy in Organic Chemistry", Holden-Day Inc, 47 (1964)

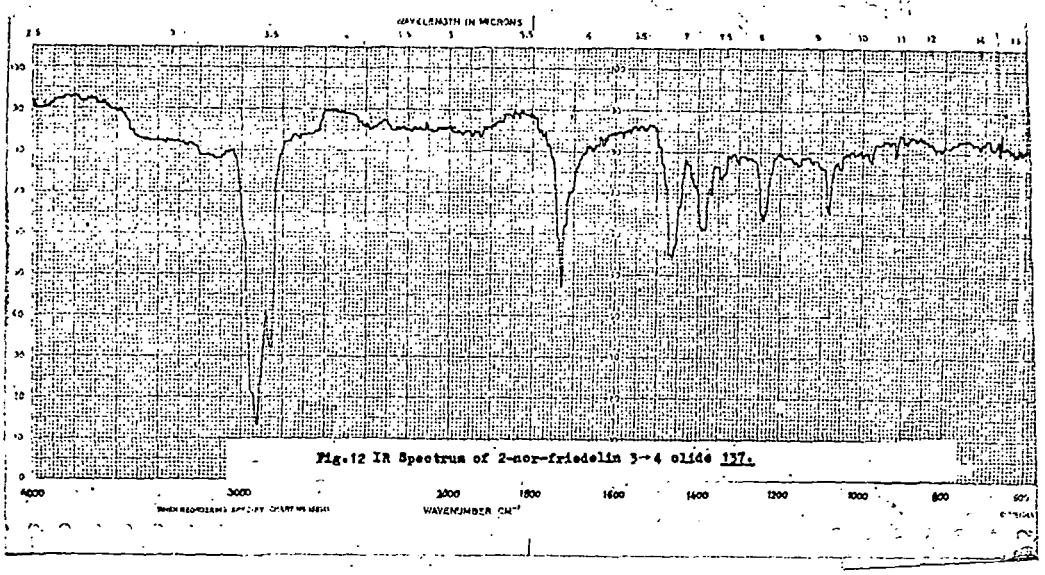


Fig.12 IR Spectrum of 2-nor-friedelin 3→4 olide 137.

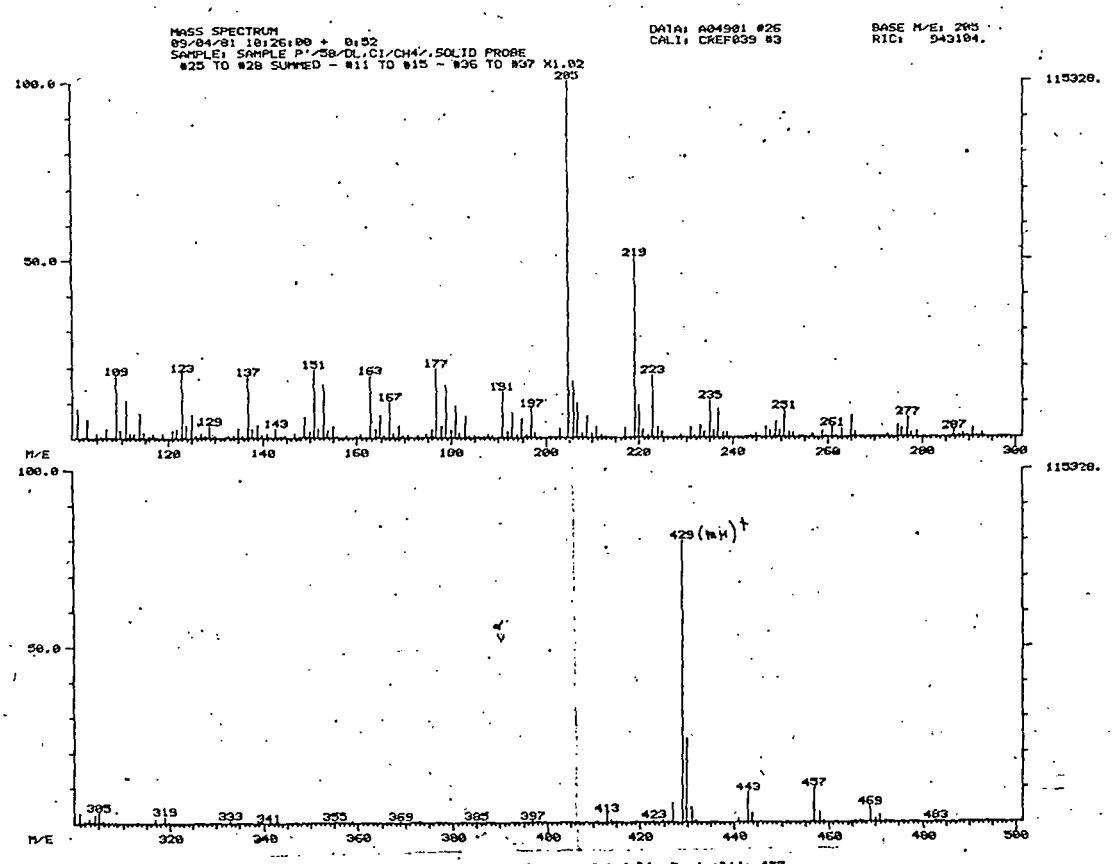


Fig.14 Mass spec of 2-nor-friedelin 3→4 olide 137a.

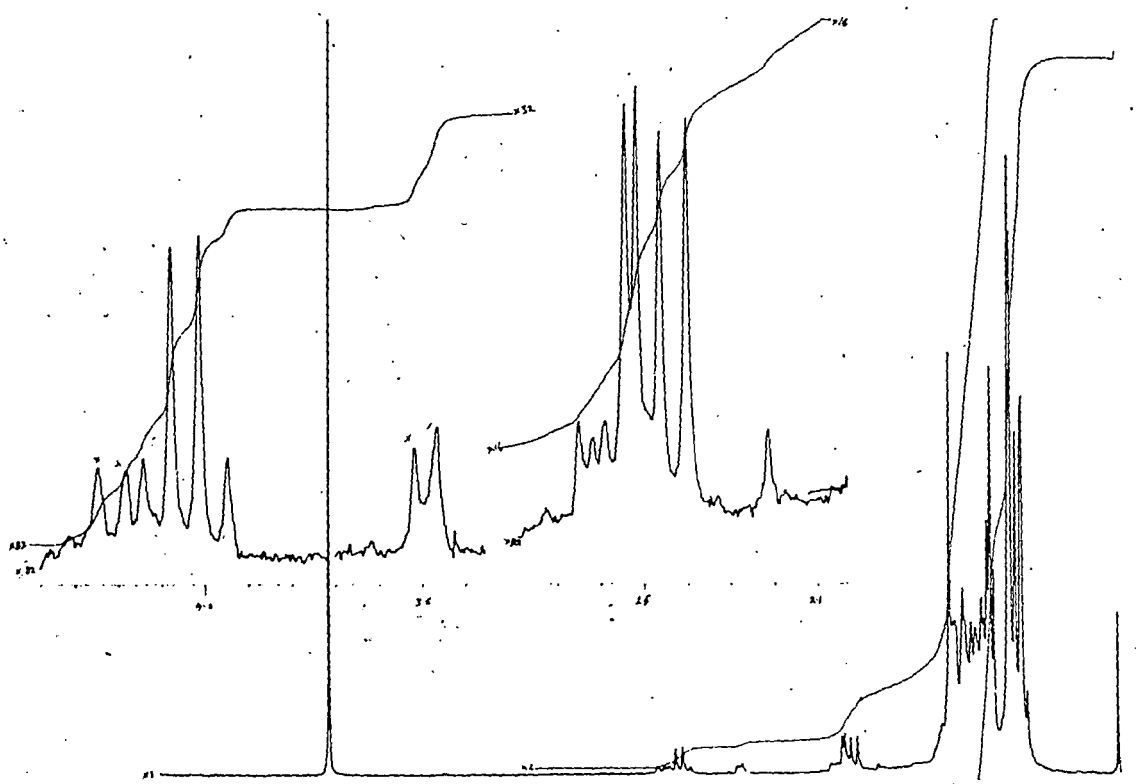
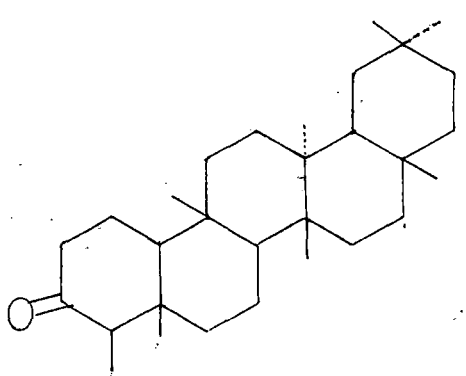
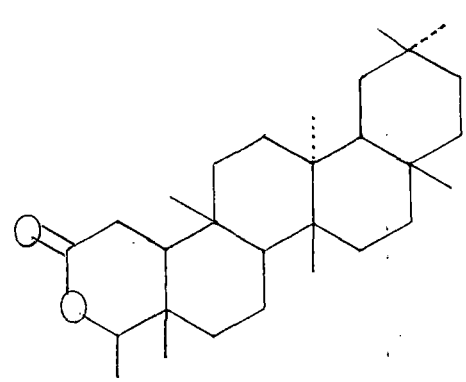


Fig:13 ^{1}HNMR Spectrum of 2-oxo-friedelin 3→4 olide 13a

value of the multiplet is indicative of the presence of methylene group alpha to the carbonyl group. Also the nature of the multiplet indicates the presence of an axial proton vicinal to the methylene group. The axial proton of the methylene group appears as a triplet centred at δ 2.4 (J_{gem} = 13 Hz, J_{aa} = 13 Hz) and the equatorial proton as a quartet centred at δ 2.61 (J_{gem} = 13 Hz, J_{ae} = 4 Hz). The appearance of a quartet at δ 4.02 (J = 10 Hz) shows the presence of a lactonic group[112] and the quartet indicates the proton to be vicinal to a methyl group. Thus, it is evident from ^{1}H NMR spectrum that the C-4 of friedelin is attached to the lactonic oxygen and the secondary methyl group is still attached to it which is responsible for the one proton quartet at δ 4.02. It is also clear that the methylene group present at C-1 is alpha to a carbonyl group that appears as a multiplet at δ 2.61. On the basis of the IR and ^{1}H NMR spectral data, structure 137 is attributed to F_1 . Mass fragmentation pattern (Fig. 14) confirms structure 137.

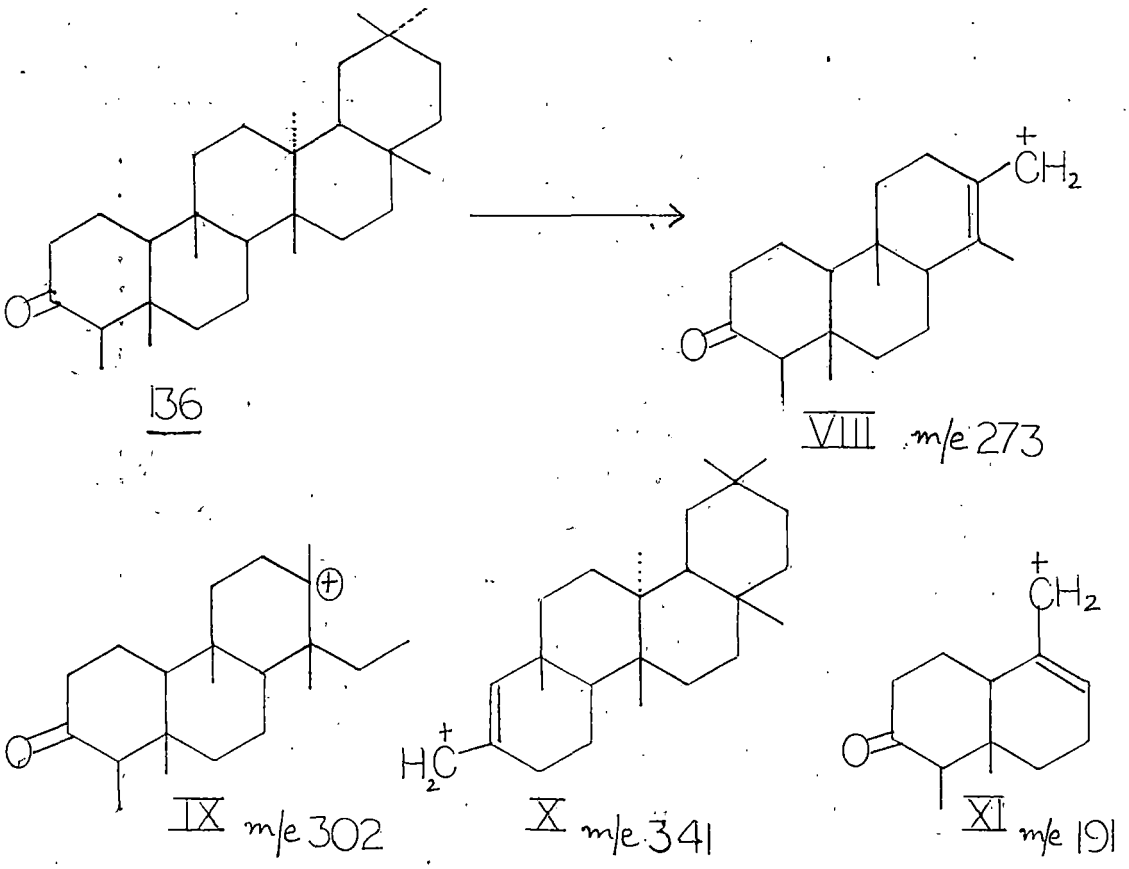


136



137

Djerassi et al[102] and Courtney et al[116] reported the following mass fragmentation pattern for friedelin



Now as the fragments VIII to XI are the diagnostic of structure 136, it is expected that F_1 would exhibit peaks at 275, 305, 341 and 193 corresponding to the following fragments if structure 137 assigned to it is the correct one.

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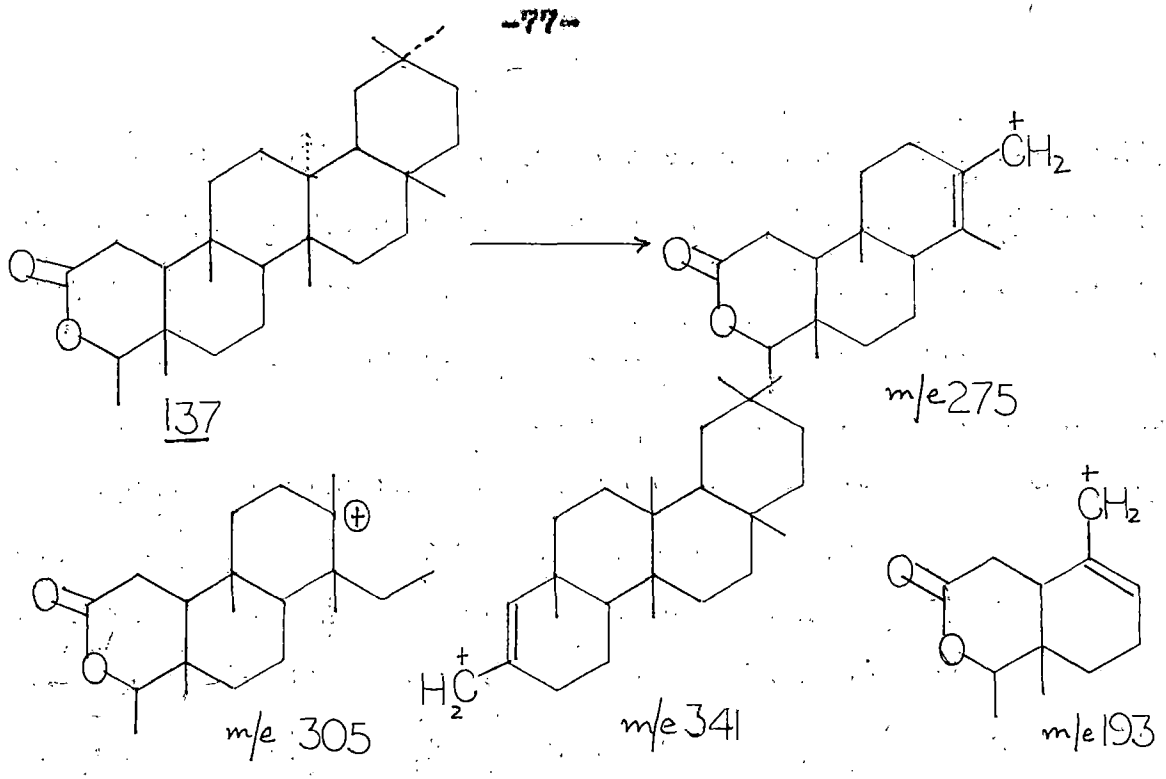
116. J.L. Courtney and J.S. Shannon, Tet. Letters, 13, 173 (1963)



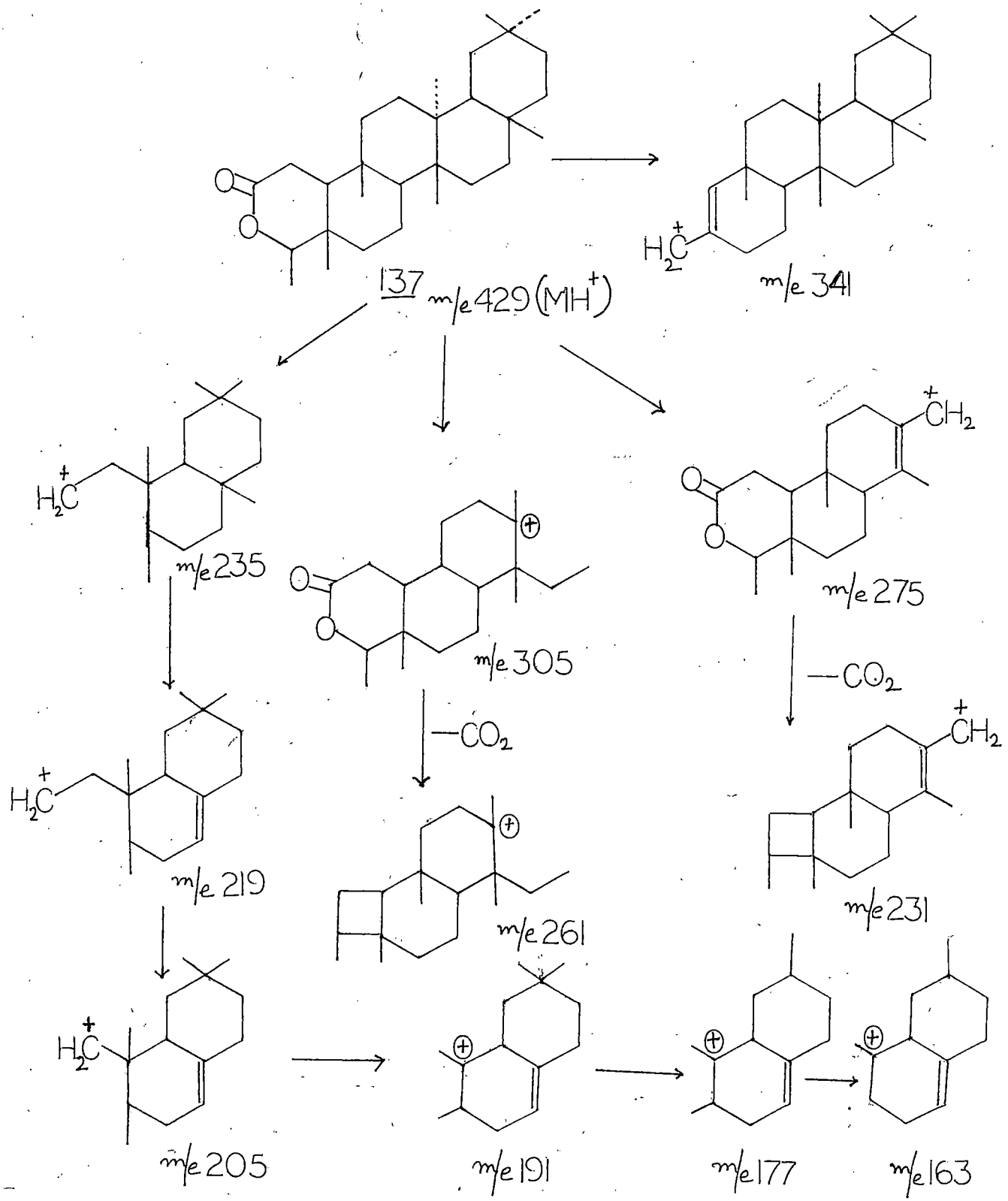
In accordance with the above expectation, the mass spectrum of 137 (Fig. 14) shows prominent peaks at m/e 429 (MH^+), 341, 305, 275, 261, 235, 231, 219, 205 (base peak), 191, 177 and 163. The genesis of the ion fragments corresponding to the above peaks could be best rationalised in terms of the structure 137 as shown in Scheme - XVI.

Structure of F_2 as 2α-carbomethoxy-A-nor-Friedelin, 138:

Elemental analysis and molecular weight determination by mass spectrum showed the molecular formula of F_2 to be $C_{31}H_{52}O_2$.

The infrared spectrum (Fig. 15) of F_2 indicates the presence of an ester group in the compound. The important peak absorption and their probable assignments are recorded in Table-11. The strong absorption band at 1730 cm^{-1} is due to the $>C=O$

Scheme - XVI


137 m/e 429 (MH+)
m/e 341
m/e 235
m/e 305
m/e 275
—CO2
—CO2
m/e 219
m/e 261
m/e 231
m/e 205
m/e 191
m/e 177
m/e 163

stretching vibration of an ester group in strain free saturated ring. The supporting band for the ester appears at 1165 cm^{-1} as a band of strong intensity assignable to -C-O stretching vibration of the ester group. The band at 1430 cm^{-1} may be attributed to δ $-CH_3$ vibration of the ester group. Thus, it is apparent from the IR spectrum that compound F_2 had an ester group as its functionality.

Table - 11

Inrared absorption peak of F_2 in Nujol Mull

Position of absorption peak in cm^{-1}	Intensity	Probable assignment
1730	strong	$>C = O$ stretching vibration of an ester group.
1430	medium	δ $-CH_3$ vibration of an ester group
1165	strong	-C-O stretching vibration of the ester group

This formulation of F_2 is further supported by its 360 MHz ^1H NMR spectrum (Fig. 16). The signals for various protons together with their probable assignments are recorded in Table - 12.

Table - 12

^1H NMR signals of F_2

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
0.77 0.78 0.91 0.94 1.17 1.24 1.28	3 3 3 3 3 3 3	singlet singlet singlet singlet singlet singlet singlet	7-C(CH$_3$)-
0.99 1.01	3	doublet J = 6 Hz	HC(CH$_3$)-
3.64	3	singlet	HC(COOCH$_3$)-
2.90	1	multiplet $W_{\frac{1}{2}}$ = 14 Hz	-CH(COOCH$_3$)-

The appearance of singlets from δ 0.77 to 0.94 and from δ 1.17 to 1.28 indicate the presence of seven tertiary methyl groups; a three proton doublet centred at δ 0.9 with J = 6 Hz indicates the presence of one secondary methyl group in compound F_2 . The the proton singlet at δ 3.64 is assigned to an ester group. One proton multiplet that appeared as a very broad signal (half band

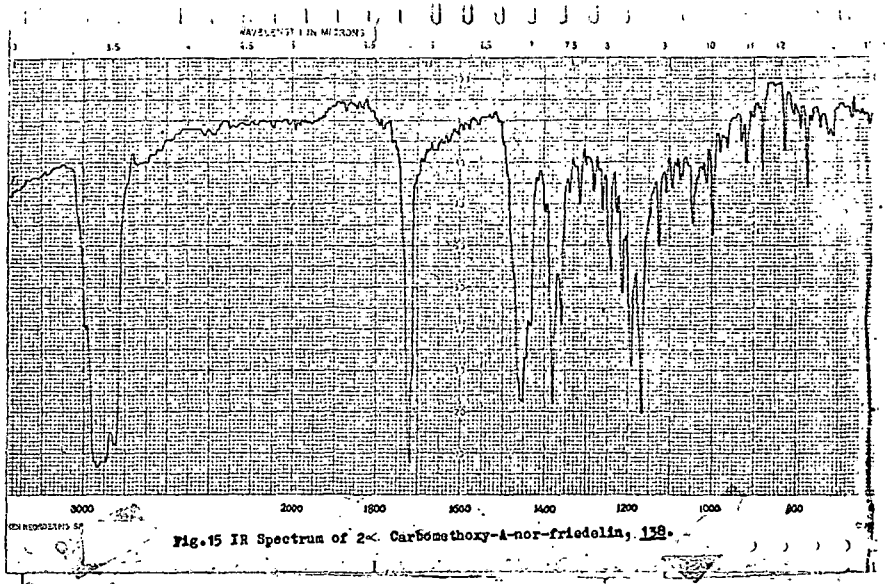


Fig.15 IR Spectrum of 2< Carbomethoxy-A-nor-friedelin, 138.

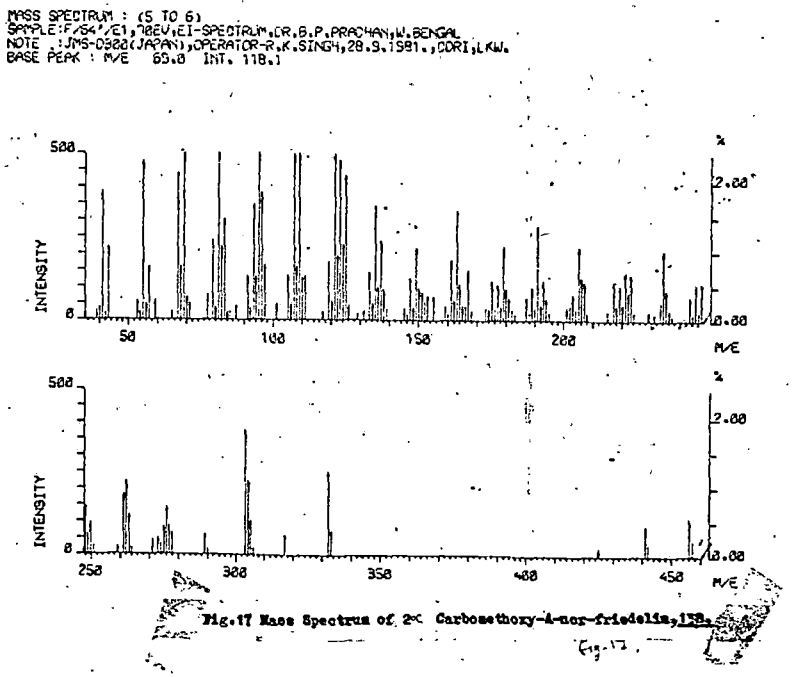
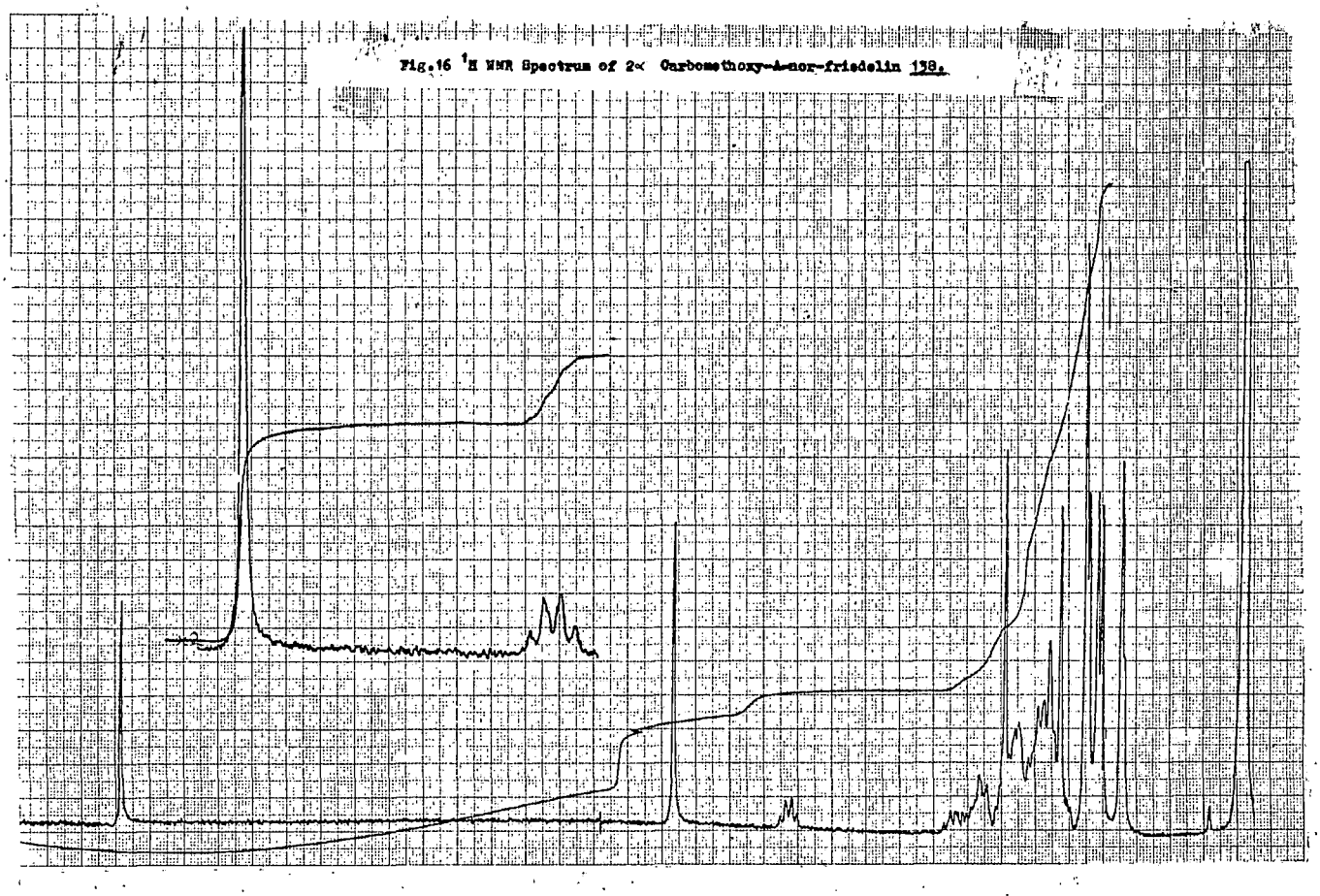


Fig.17 Mass Spectrum of 2< Carbomethoxy-A-nor-friedelin, 138.

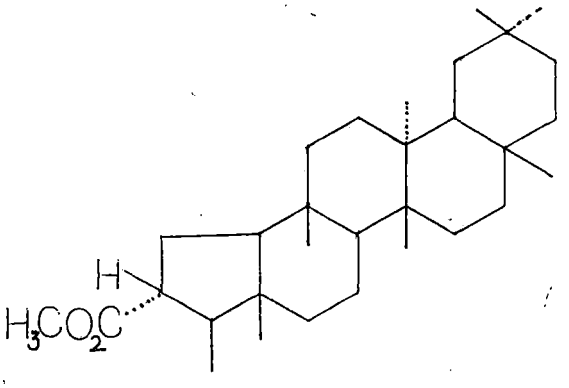
Fig.17

Fig.16 ^{1}H NMR Spectrum of 2α Carbomethoxy-A-nor-friedelin 138.



width $\simeq$ 14 Hz) at δ 2.9 indicates the presence of an axial proton geminal to the carbomethoxy group. This inference exactitudes the equatorial orientation of the carbomethoxy group. Again, the multiplet also shows the presence of methylene group alpha to the carbomethoxy function.

Finally, the mass spectrum (Fig. 17) analysis gives complete support for the formulation of F_2 . The total mass 456 (M^+) may be attributed to F_2 if it has one carbon less than friedelin, 136. Again, from its ^1H NMR data analysis it is clear that F_2 contains all the seven tertiary and one secondary methyl group of friedelin. Also, the ^1H NMR spectrum shows that the carbomethoxy group is alpha to a methylene group. Hence, the tentative structure that may be assigned to F_2 is 138, which satisfies all the above arguments.

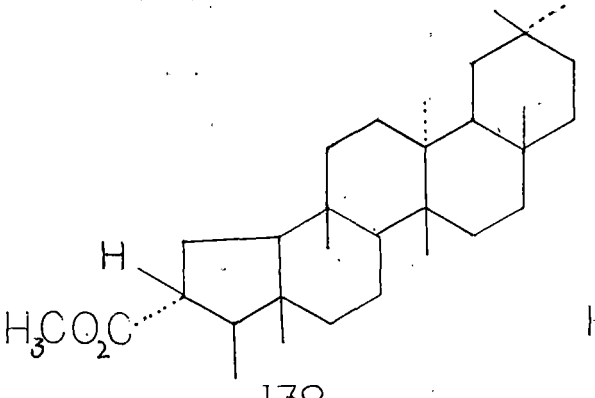


138

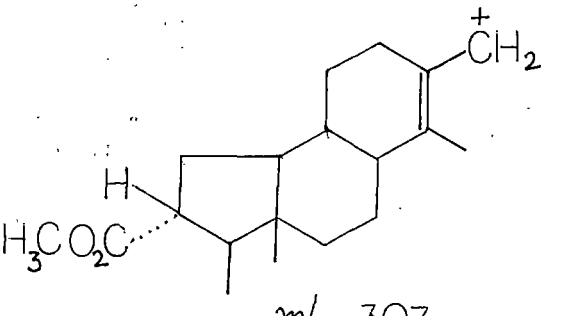
Thus, compound, 138, is 2α-carbomethoxy A-nor friedelin.

From the discussion of the mass spectrum of 137 it is apparent that if, 138, is the formulation for compound F_2, it should exhibit fragments at m/e 303, 323, 221 corresponding to fragments VIII, IX and XI for friedelin. Compound F_2 exhibits ion fragments at m/e 303, 332 and 221, which may be rationalised if structure, 138, is formulated for F_2. The fragmentation pattern is represented as below (Scheme - XVII).

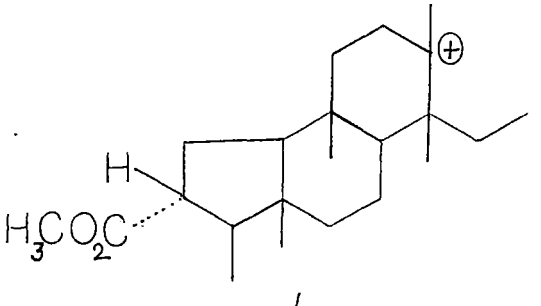
Scheme - XVII



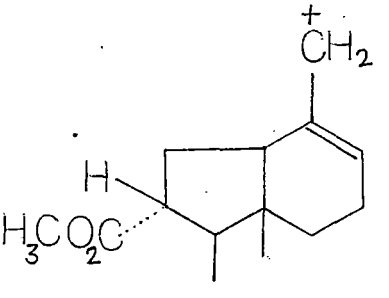
138



m/e 303



m/e 332



m/e 221

Structure of F_3 as 2,3 seco methyl Friedelin dicarboxylate.

Elemental analysis of compound F_3 along with mass spectrum established its molecular formula as $C_{32}H_{54}O_4$.

The infrared spectrum (Fig. 18) of F_3 initially discloses some information regarding its structure . The important peak absorption and their probable assignments are recorded in Table-13.

Table - 13

Infrared Absorption Peak of F_3 in Nujol Mull.

Position of peak absorption in cm^{-1}	Intensity	Probable interpretation
1730 1720	strong shoulder	>C = O stretching vibration of ester group.
1440	medium	δ-CH_3 vibration of ester group
1120 1110	strong strong	-C-O-stretching vibration of the ester group

From its IR spectrum, it is apparent that compound F_3 is an ester.

The 360 MHz ^1H NMR spectrum (Fig. 19) of F_3 is also informative. The signals for various protons together with their probable assignments are recorded in Table - 14.

The appearance of peaks from δ 0.88 to δ 1.03 and from δ 1.19 to 1.25 indicate the presence of seven tertiary methyl groups in the compound.

Table - 14

^{1}H NMR signals of F_3

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
0.88 0.93 0.97 1.03 1.19 1.20 1.25	3 3 3 3 3 3 3	singlet singlet singlet singlet singlet singlet singlet	7 - C - CH_3
1.13 1.16	3	doublet J = 8 Hz	HC - CH_3
3.62	3	singlet	-C - $COCH_3$
3.65	3	singlet	-C- $COOCH_3$
2.3	1	quartet J = 10 Hz	HC - CH_3

The doublet (J = 8 Hz) centred at δ 1.14 assignable for three protons shows the presence of one secondary methyl group. The one proton quartet at δ 2.3 (J = 10 Hz) is probably due to the methine proton geminal to the secondary methyl group. Two singlets

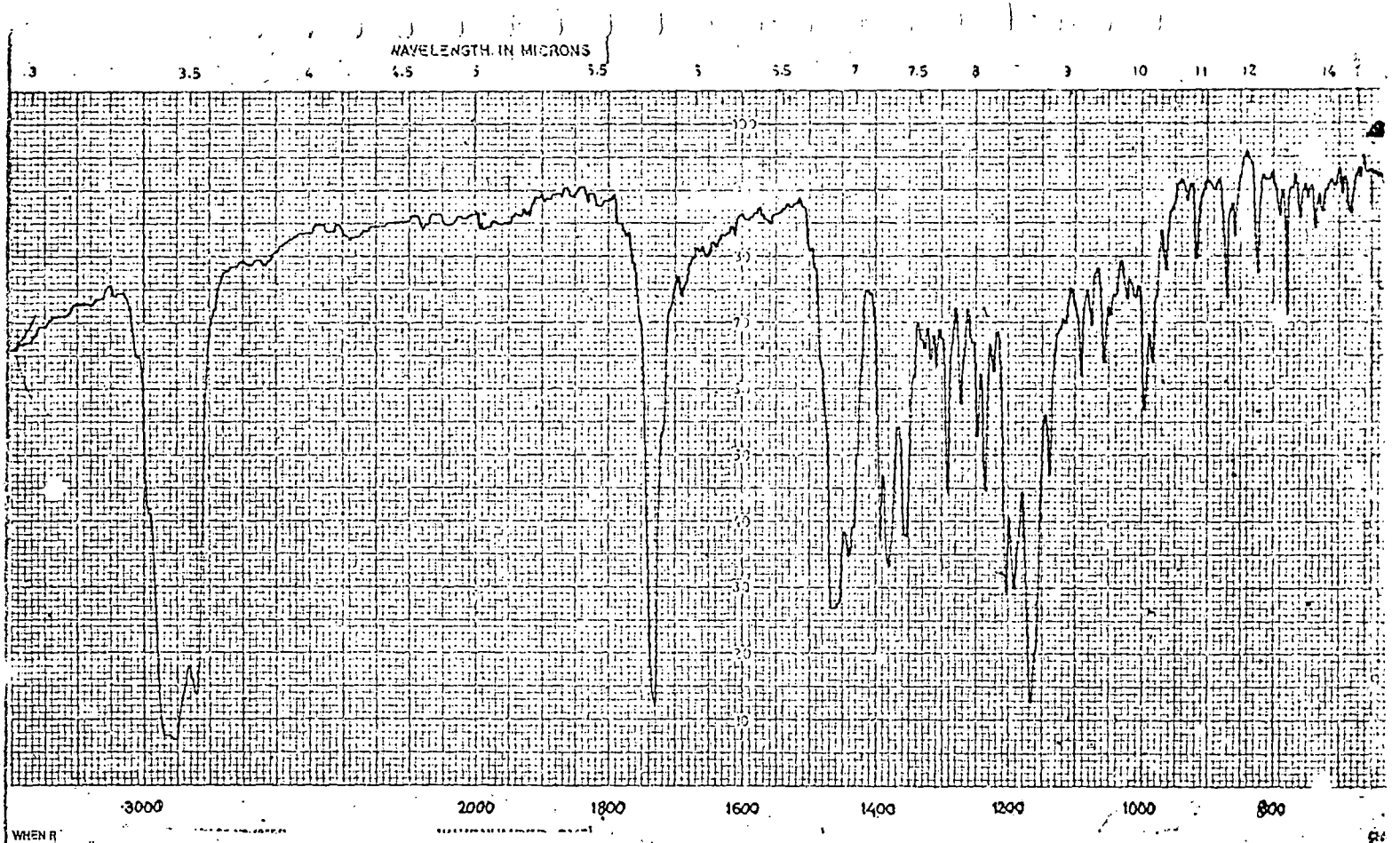
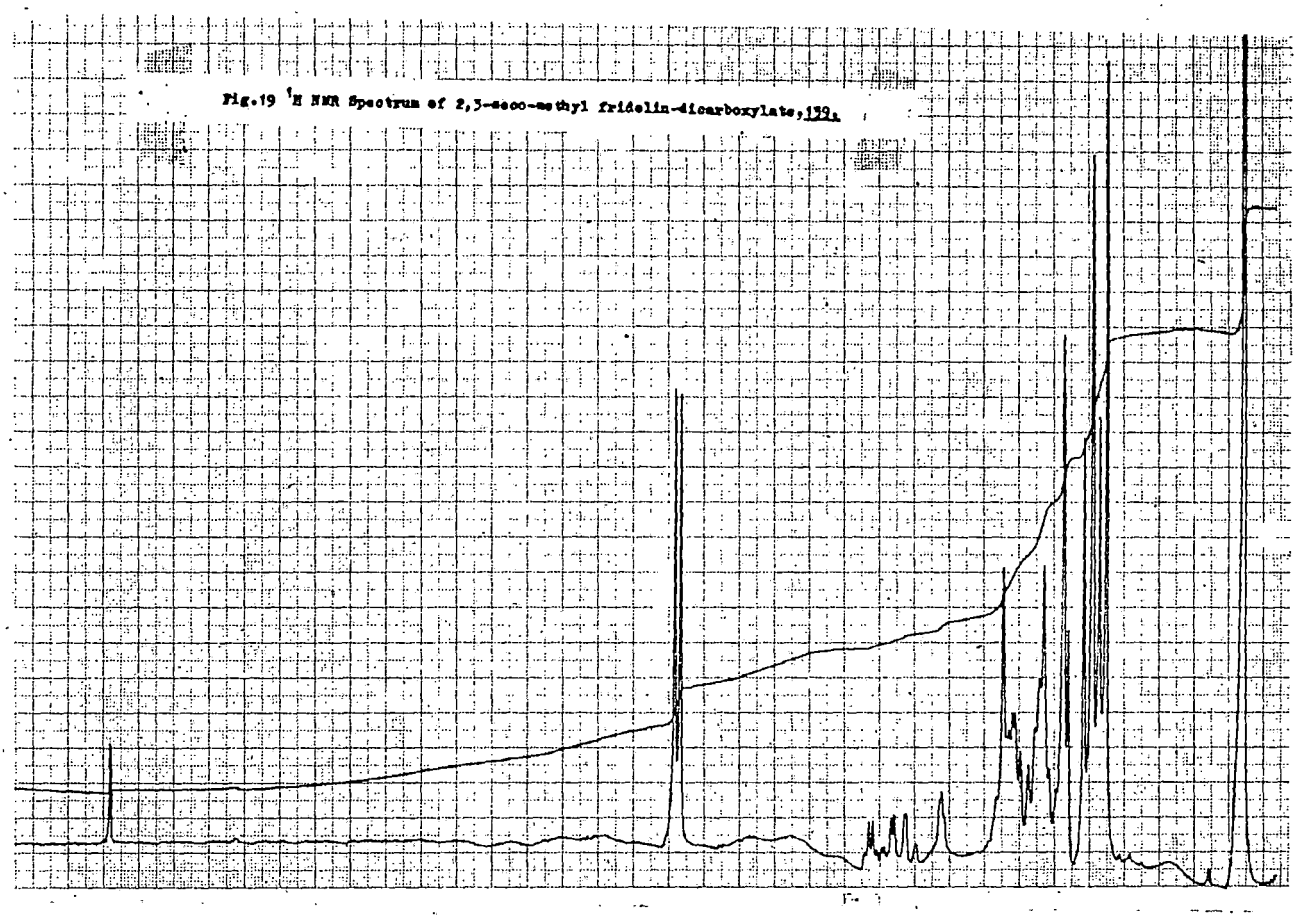
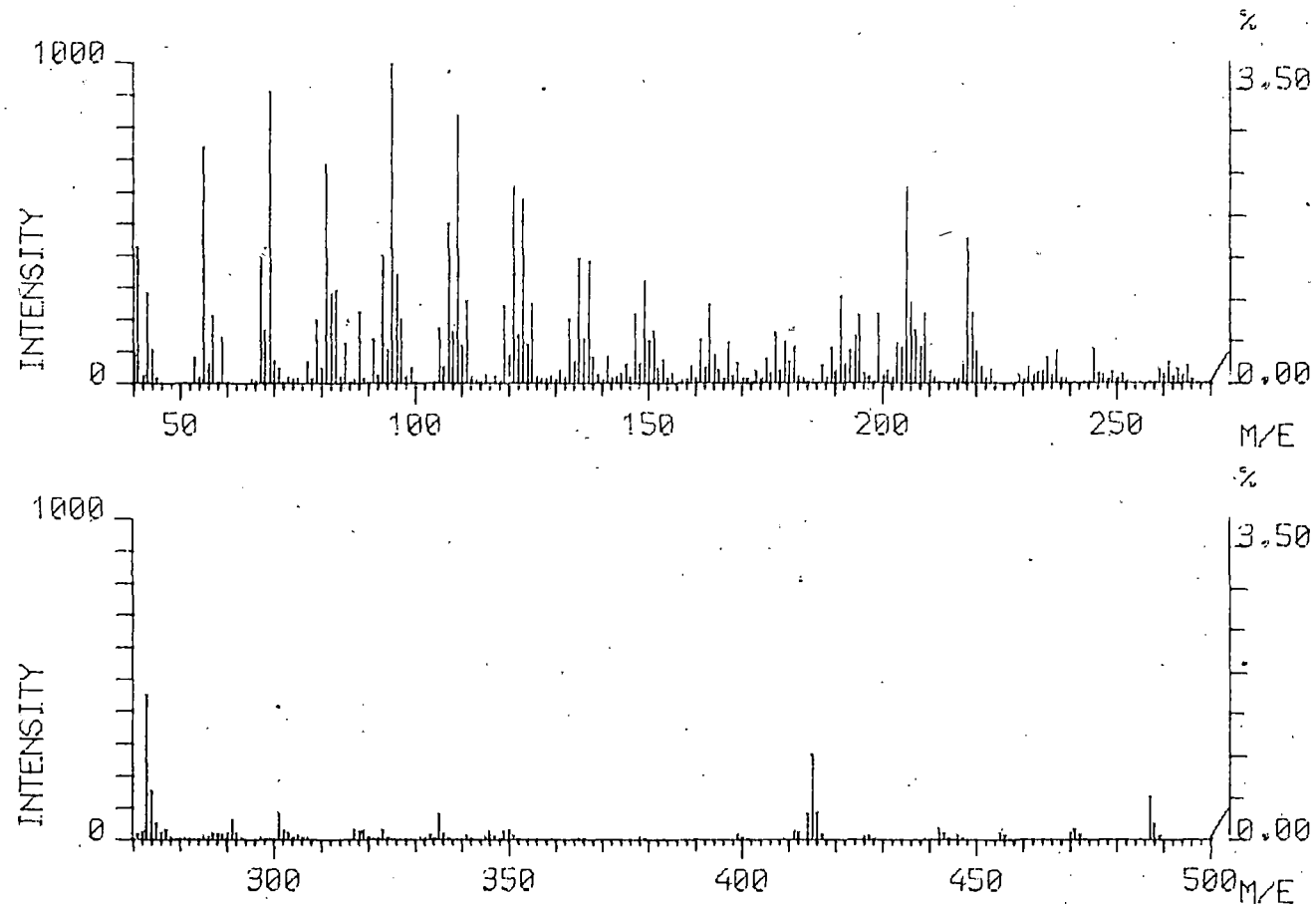


Fig.18 IR Spectrum of 2,3-seco-methyl friedelin dicarboxylate, 139.

Fig.19 ^{1}H NMR Spectrum of 2,3-seco-methyl fridelin-dicarboxylate,139.



MASS SPECTRUM : (4 TO 5)
SAMPLE:F/65'/E-2,DR.A.K.GHOSH,N.W.UNIVERSITY.
NOTE :2ND AUG.82
BASE PEAK : M/E 95.0 INT. 151.6



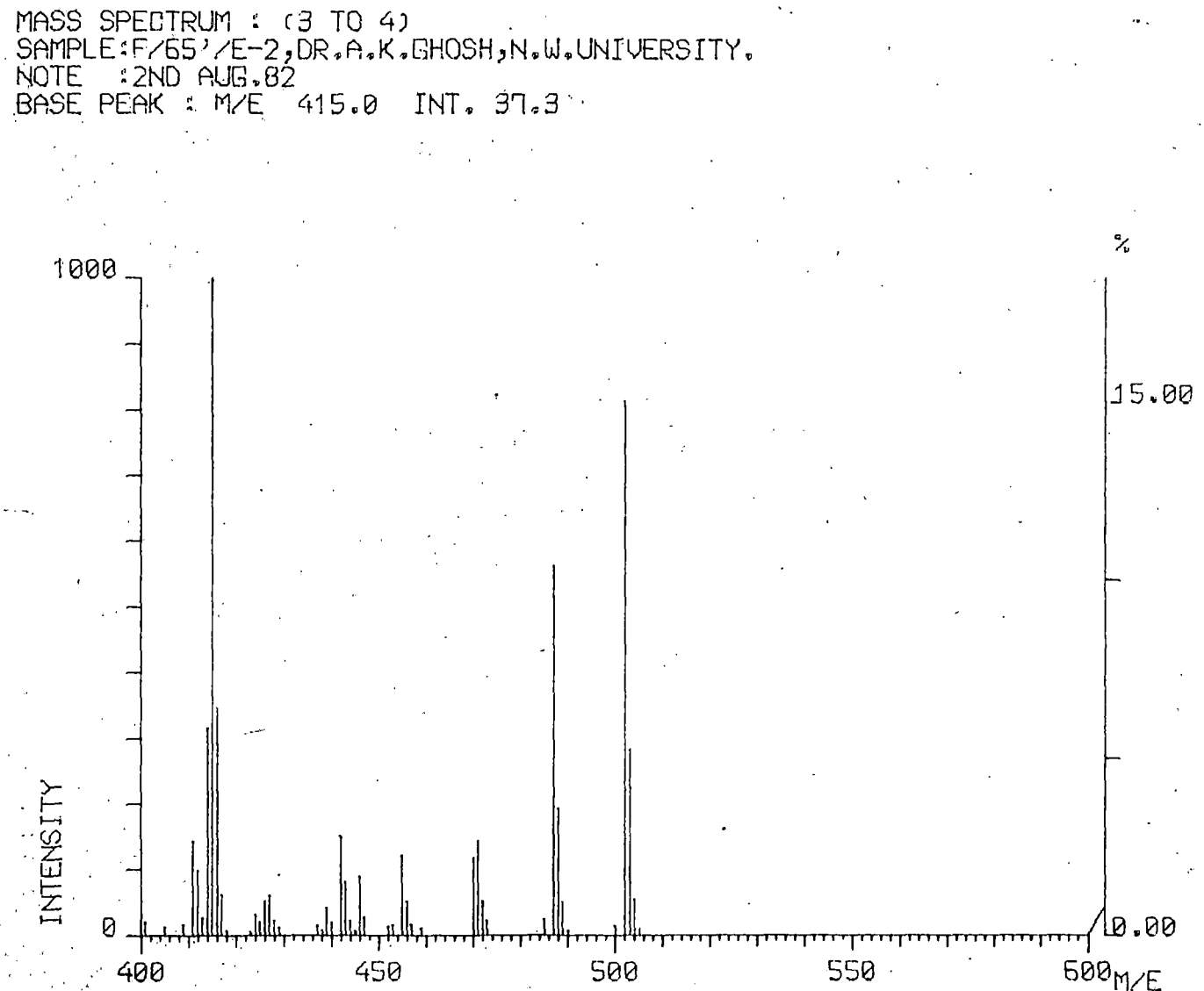


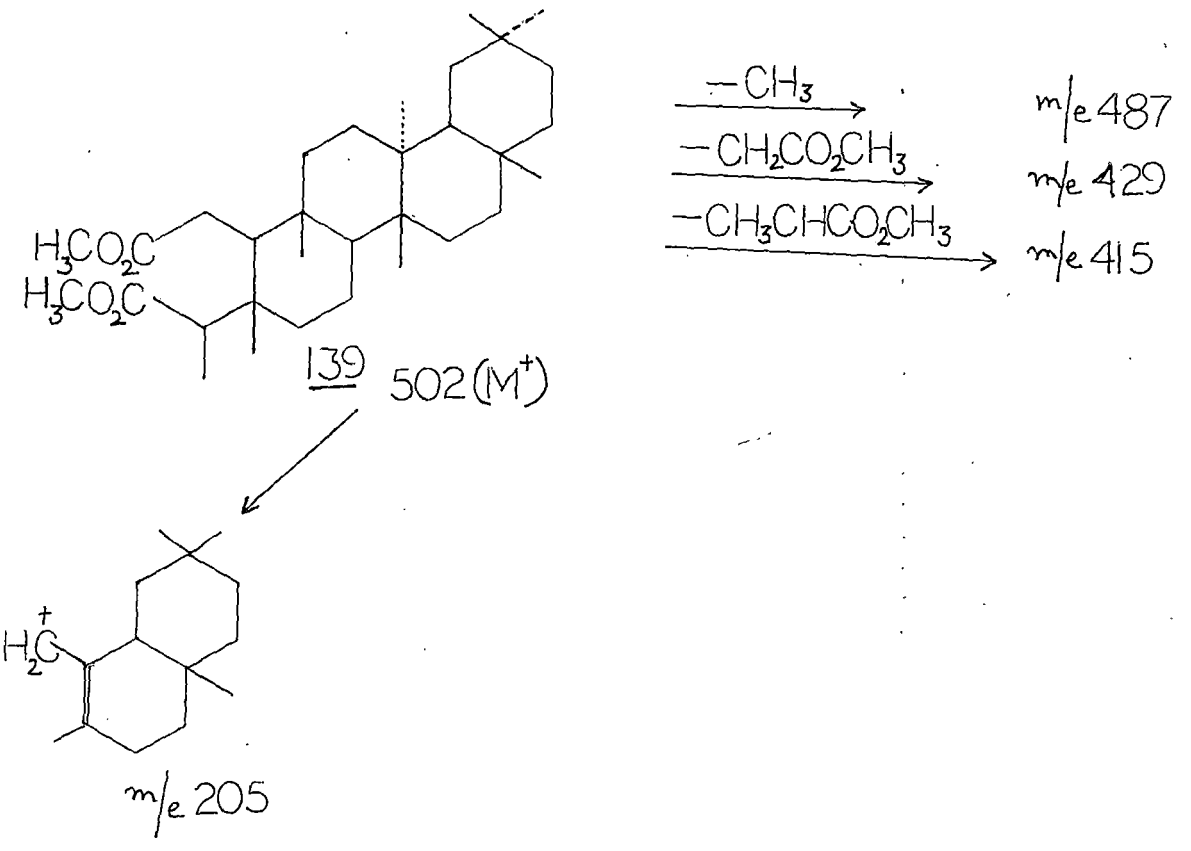
Fig.20 Mass Spectrum of 2,3-seco-methyl-friedelin-dicarboxylate, 139.

each assignable for three protons at δ 3.62 and δ 3.65 indicate the presence of two ester functionalities in the compound.

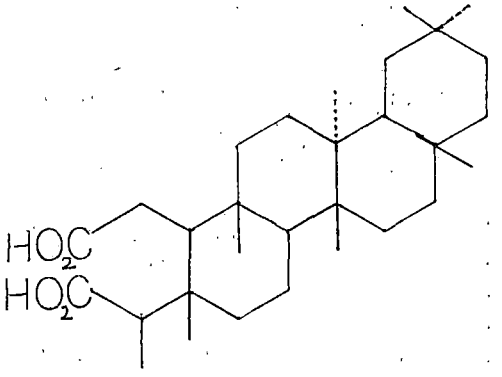
Thus, on the basis of ^1H NMR spectrum it is possible to infer that F_3 is a diester and contains all the seven tertiary and one secondary methyl groups of friedelin.

Finally, mass spectrum of F_3 (Fig. 20) helps to formulate its structure. The spectrum shows prominent peaks at m/e 502 (M^+), 487, 471, 455, 442, 429, 415, 335, 301, 273, 245, 219, 205 and 191.

The genesis of these fragments may be rationalised if structure 139 is formulated for F_3 .



In order to ensure the above structure, 139, for F_3, it is hydrolysed with methanolic potassium hydroxide. The compound that resulted thereof, showed m.p. 280° (d) which has similar physical data as that of 2,3 seco friedelinic acid, 140[117].



140

Thus, the structure of F_3 is assigned as methyl ester of friedelin 2,3 seco dicarboxylic acid, 139.

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117. E.J. Corey and J.J. Ursprung, J.Am.Chem.Soc., 78, 5041 (1956)

Section D

Oxidation of Taraxerone

Oxidation of Lupanone, 130 and Friedelin, 136, with hydrogen peroxide and selenium dioxide resulted in the formation of δ-lactones. In the case of lupanone, elimination of gem dimethyl group alpha to the carbonyl group was found to take place, whereas, in the case of friedelin, which contains a secondary methyl group in the same position, no demethylation was found.

In this section the results of the reaction of hydrogen peroxide and selenium dioxide on Taraxerone, 141, a 3-keto triterpenoid having a trisubstituted double bond in $C_{14} - C_{15}$ position under the same reaction condition has been reported. The characterisation and identification of the compounds obtained as a result of the reaction are discussed in sequence.

Taraxerone, m.p. 238-40° was refluxed in tert-butanol with hydrogen peroxide in presence of selenium dioxide on water bath for 20 hours. The black selenium metal precipitated out indicating completion of the reaction. The reaction mixture was then diluted with water and the liberated solid extracted with ether. It was then separated into neutral and acid parts.

The neutral fraction showed two spots on chromatoplate. In order to separate the components, the total mass was

chromatographed over a deactivated alumina column. Elution of the column with pet. ether-benzene (4:1) gave a solid T_1 , which was crystallised from chloroform-methanol and analysed for $C_{30}H_{46}O_2$, m.p. 188°-90°. Further, elution of the column with pet. ether-benzene (2:3) afforded a solid, which on fractional crystallisation from chloroform - methanol yielded solid T_2 , $C_{27}H_{42}O_2$, m.p. 228-30° and solid T_3, $C_{30}H_{48}O_2$, m.p. 218-20°.

The acid part showed two spots on chromatoplate. The gummy mass was esterified with diazomethane and the products were separated by column chromatography on a deactivated alumina column. Petroleum ether eluate furnished solid T_4, m.p. 161-63°, which was crystallised from chloroform-methanol and analysed for $C_{31}H_{50}O_2$. Elution of the column with pet. ether-benzene (1:1) gave solid T_5, m.p. 149-51°, which was crystallised from chloroform-methanol and analysed for $C_{32}H_{52}O_4$.

All the products of the reaction were then subjected to detail spectral studies. The analysis of all the spectra are discussed below and the structures of the compounds determined.

Structure of T_1 as 1α , 2α -epoxy-Taraxerone, 142:

The molecular formula of the compound T_1 was assigned as $C_{30}H_{46}O_2$ from mass spectrometric data (M^+ 438) as well as from elemental analysis.

The infrared spectrum (Fig. 21) of T_1 with important peak absorptions and probable interpretation are recorded in Table - 15.

Table - 15

Infrared Absorption peak of T_1 in Nujol Mull.

Position of absorption peak cm^{-1}	Intensity	Probable assignment
1705	strong	$>C=O$ stretching vibration
1255 905 830	strong weak medium	Ring vibration characteristic of epoxide.
820	medium strong	Trisubstituted double bond.

The infrared spectrum indicates that the compound T_1 has got an epoxide functional group together with the carbonyl group and trisubstituted double bond already present in taraxerone, 141. It is known that substituted epoxides have three characteristic bands in the range of 750-1280 cm^{-1} assigned to ring vibrations. The bands are generally found around 750-875 cm^{-1}, 810-950 cm^{-1} and 1230-1280 cm^{-1}. The 1230-1280 cm^{-1} band has been reported to

be approximately constant for epoxide with different substitutions[118]. In the present case, therefore, bands at 1255, 905 and 830 cm^{-1} are indicative of epoxide functionality. The band at 1705 cm^{-1} indicates the presence of a carbonyl group and that at 820 cm^{-1} is due to the presence of a trisubstituted double bond.

That the compound T_1 is an epoxide is evident from its ^1H NMR spectrum (Fig. 22) analysis. The spectrum was recorded in 360 MHz instrument using TMS as internal standard. The signals for various protons and their probable assignments are recorded in Table - 16.

Table -16

^1H NMR signals of T_1

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
0.83	3	singlet	
0.92	3	singlet	
0.96	3	singlet	
1.00	3	singlet	
1.02	3	singlet	
1.10	3	singlet	
1.13	3	singlet	
1.25	3	singlet	
3.35	1	doublet J = 4.5 Hz	
3.52	1	doublet J = 4 Hz	
5.56	1 multiplet		

118(a) W.A. Patterson, Anal. Chem., 26, 823 (1954)

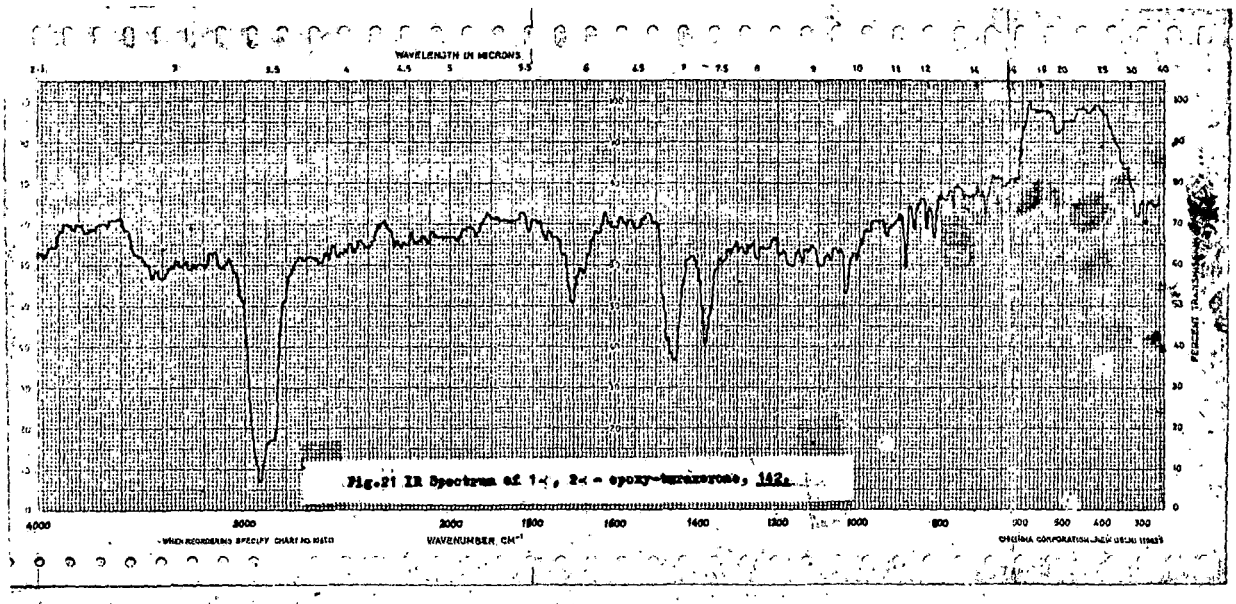


Fig.21 IR Spectrum of 1-, 2- - epoxy-turmerone, 142.

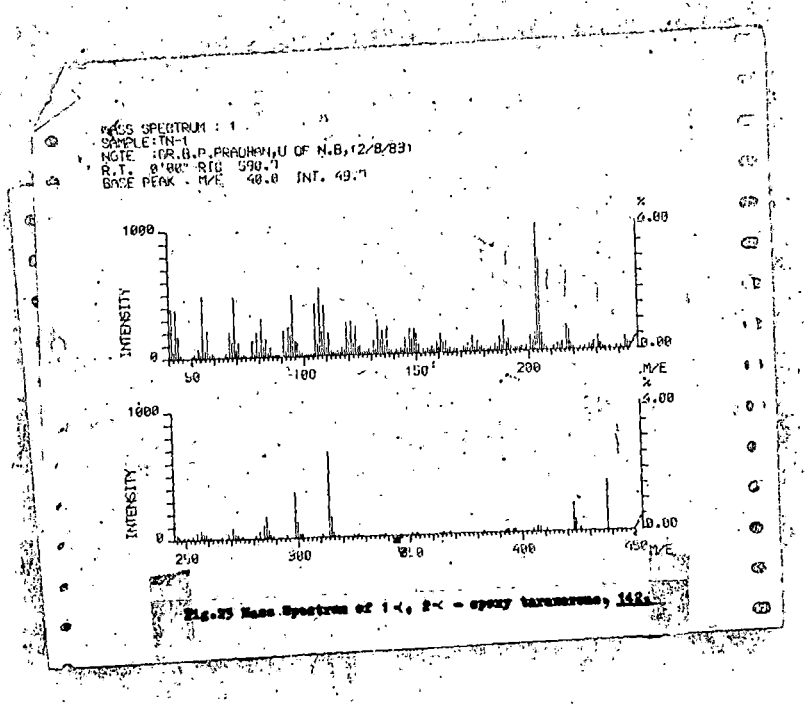


Fig.22 Mass Spectrum of 1-, 2- - epoxy turmerone, 142.

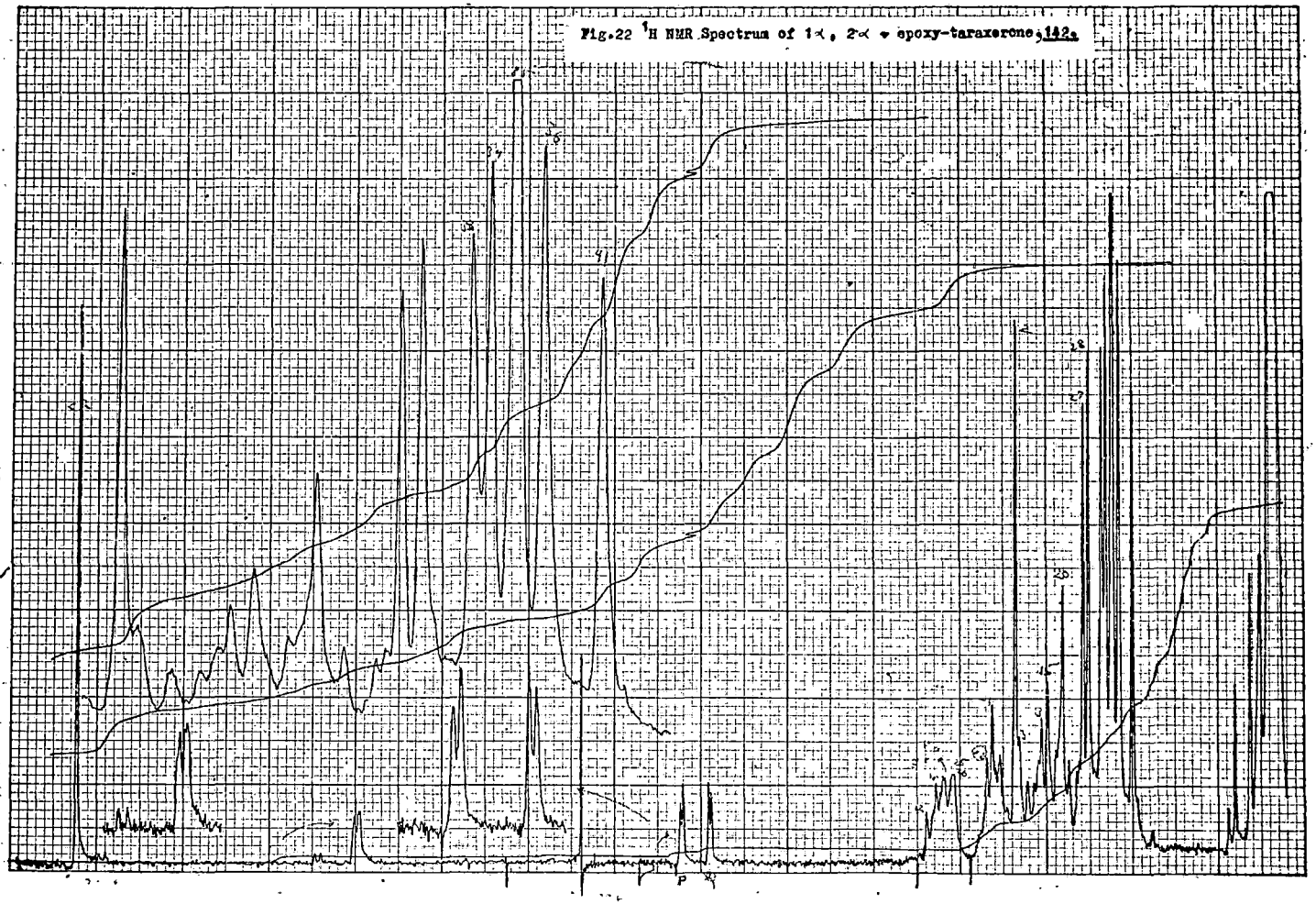
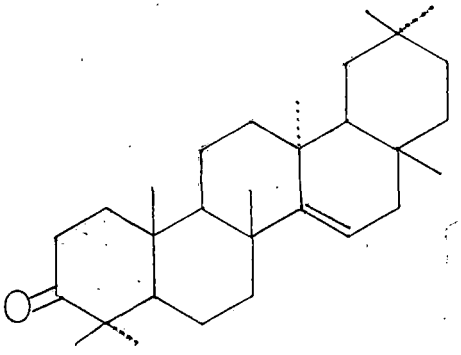
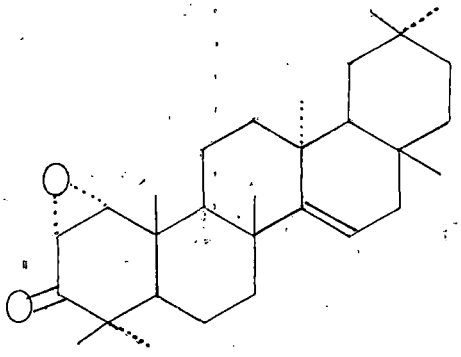


Fig.22 ^{1}H NMR Spectrum of 1α, 2α - epoxy-taraxerone, 142a

The singlets from δ 0.83 to 1.25 indicate the presence of eight tertiary methyl groups in T_1 . The one proton multiplet at δ 5.56 shows the presence of an olefinic proton in the compound, which may be associated with the $C_{14} - C_{15}$ double bond of Taraxerone skeleton. A pair of doublets each at δ 3.35 (J = 4.5 Hz) and at δ 3.52 (J = 4 Hz) are indicative of an alpha epoxide moiety[119]. That the epoxide group is present in 1,2 position of the taraxerone is evident from the fact that the ^1H NMR spectrum does not show the presence of any methylene protons adjacent to the carbonyl group. The structure of T_1 is therefore, formulated as 142.



141



142

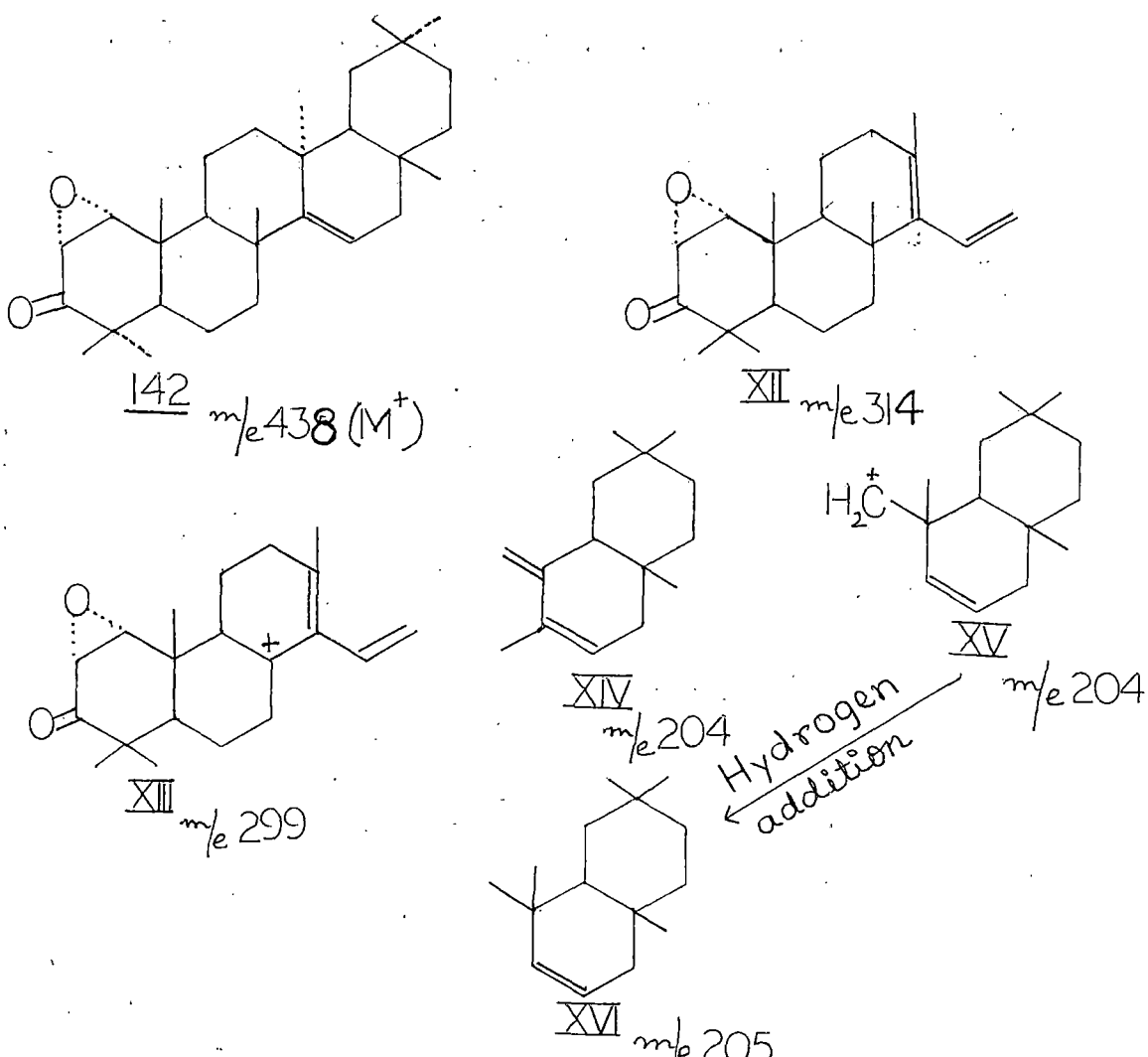
118(b) J.E. Field, J.O. Cole, D.E. Woodfor, J.Chem.Phys., 18, 1298 (1950)

119. N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day Inc., 101 (1964)

The formulation of structure 142 for compound T_1 was finally proved by its mass spectrum (Fig. 23). The spectrum shows characteristic peaks at m/e 438 (M^+), 423, 314, 299, 205, 204 and 189. The presence of the peaks at m/e 314, 299, and 204 may be assigned to the formation of fragments XII, XIII and XIV that arises from a typical taraxerone skeleton[102], thereby confirming the existence of the double bond at $C_{14} - C_{15}$ position.

The genesis of the ion fragments are recorded in Scheme - XVIII.

Scheme - XVIII



From the combined results of the physical data, namely, IR, ^1H NMR and Mass spectra, the structure of T_1 is assigned as 1α, 2α epoxy taraxerone 142.

Structure of T_2 as 4, 23, 24 tri-nor-Taraxerene-3 ⟶ 5 α H - olide, 144.

Mass spectrum and independent elemental analysis established the molecular formula of T_2 as $C_{27}H_{42}O_2$.

Some important information regarding the structure of T_2 come from its infrared spectrum (Fig. 24). The prominent absorption bands and their probable assignments are recorded in Table - 17.

Table - 17

Infrared spectrum of T_3 in Nujol Mull

Position of absorption peak cm^{-1}	Intensity	Probable assignment
1750	strong	δ-lactone
1260	medium strong	-C-O vibration
810	medium	Trisubstituted double bond.

The band at 1750 cm^{-1} may be attributed to the presence of a δ-lactone functionality in T_2[110]. The >CO vibration occurs at 1260 cm^{-1}[111]. Appearance of band at 810 cm^{-1} demonstrates the presence of a trisubstituted double bond.

The 360 MHz ^1H NMR spectrum of T_2 (Fig. 25) studied in $CDCl_3$ taking TMS as internal standard is very informative. The signals for various protons and their probable assignments are recorded in Table - 18.

Table - 18

^1H NMR signals of T_2 in $CDCl_3$

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
0.83	3	singlet	
0.91	3	singlet	
0.95	3	singlet	6 - C - CH_3
1.00	3	singlet	
1.10	3	singlet	
1.12	3	singlet	
2.26	2	multiplet	$-H_2C - CH_2 - C = O$
3.92	1	quartet J_{ae} = 5 Hz J_{aa} = 12 Hz	$-CO-O-CH-CH_2$
5.57	1	multiplet	$>C = CH - CH_2$

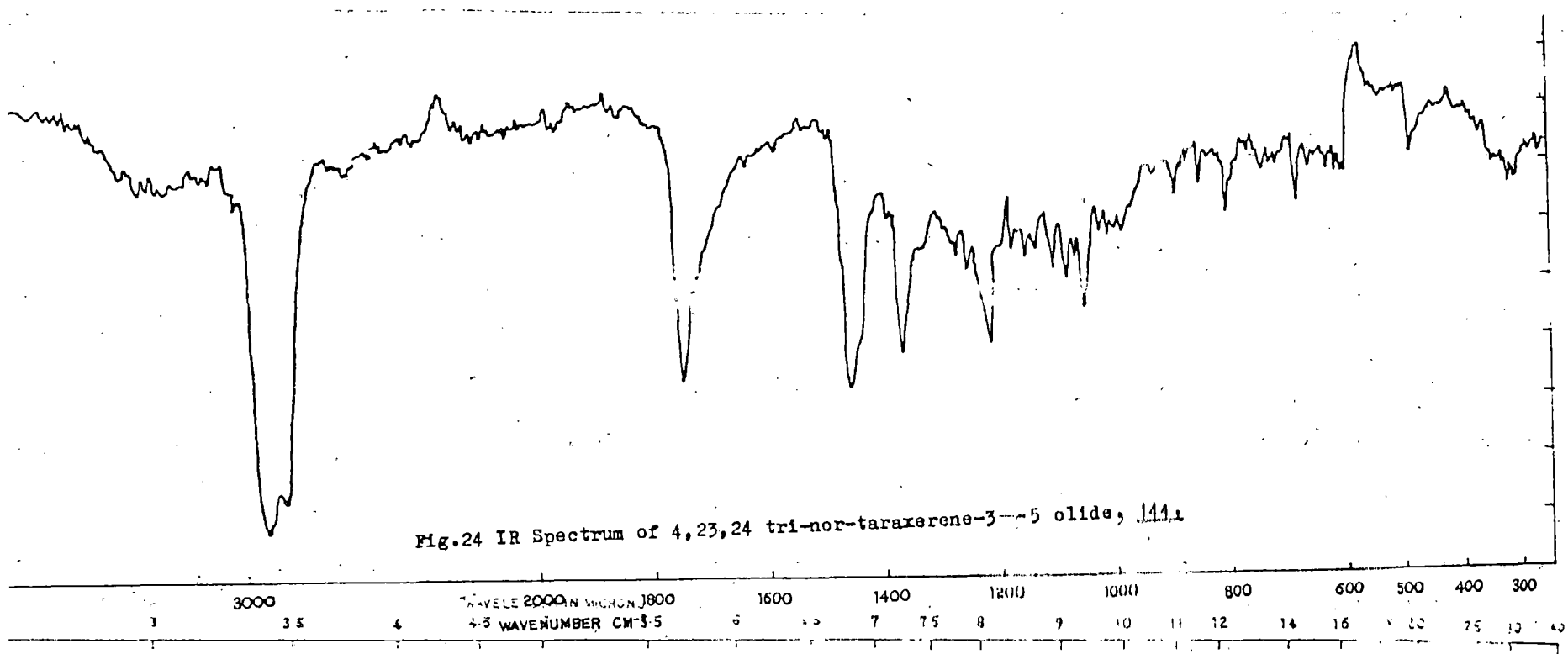


Fig.24 IR Spectrum of 4,23,24 tri-nor-taraxerene-3--5 olide, 141.

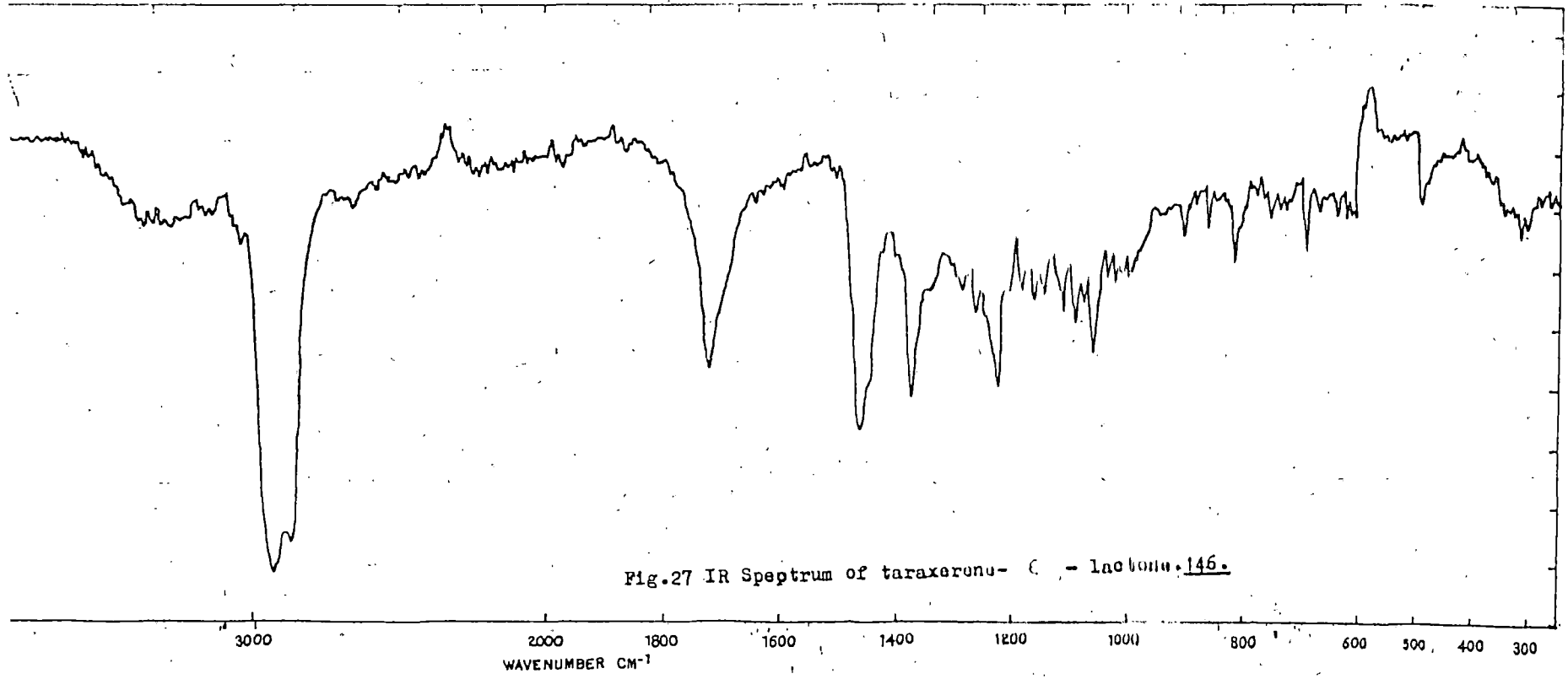
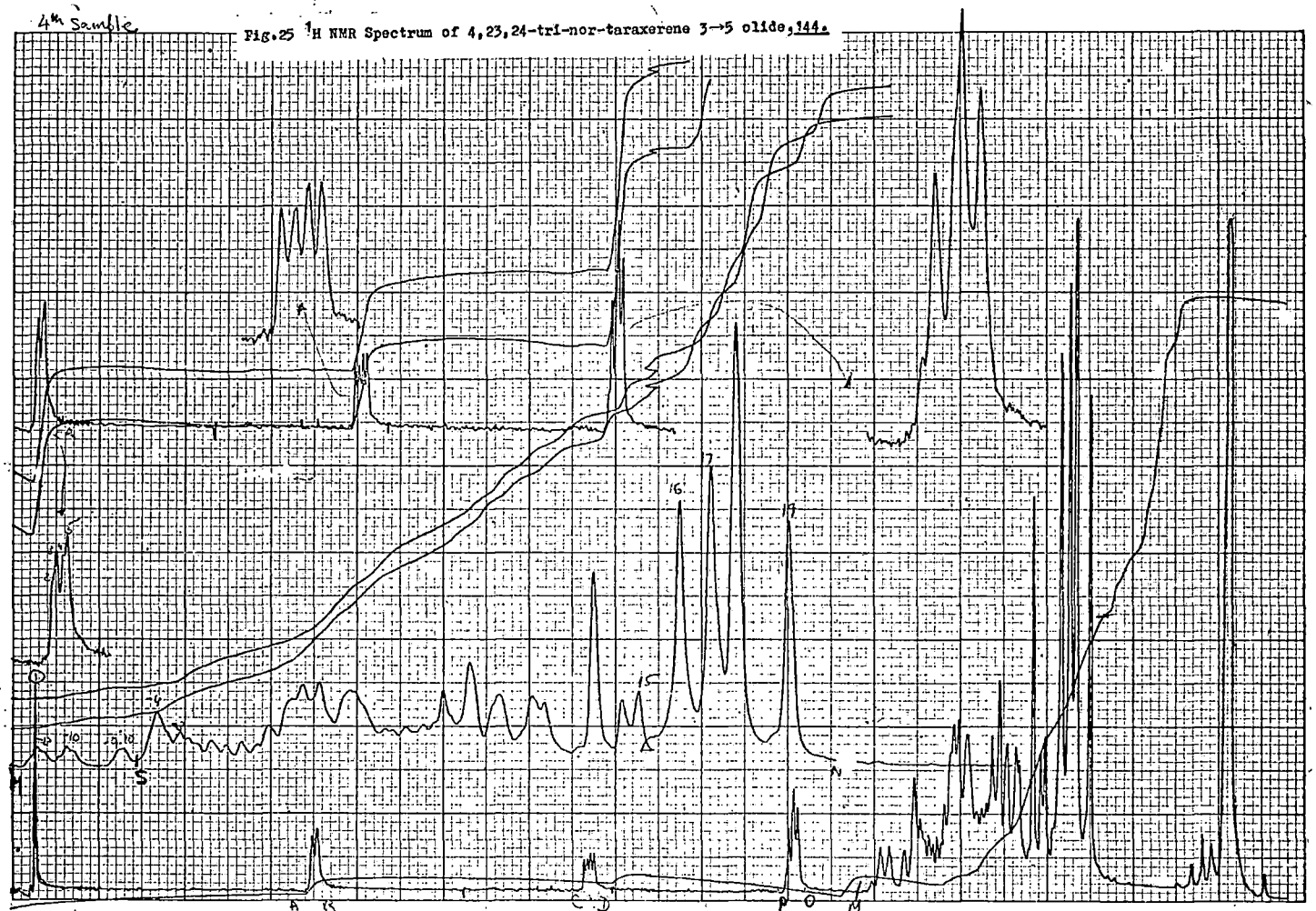


Fig.27 IR Spectrum of taraxerone- C - lactone. 146.

4th Sample.

Fig.25 ^{1}H NMR Spectrum of 4,23,24-tri-nor-taraxerene 3→5 olide, 144.



MASS SPECTRUM : (5 TO 6)
SAMPLE:TN-2
NOTE :DR.B.P.PRADHAN,U OF N.B,(2/8/83)
BASE PEAK : M/E 274.0 INT. 282.6

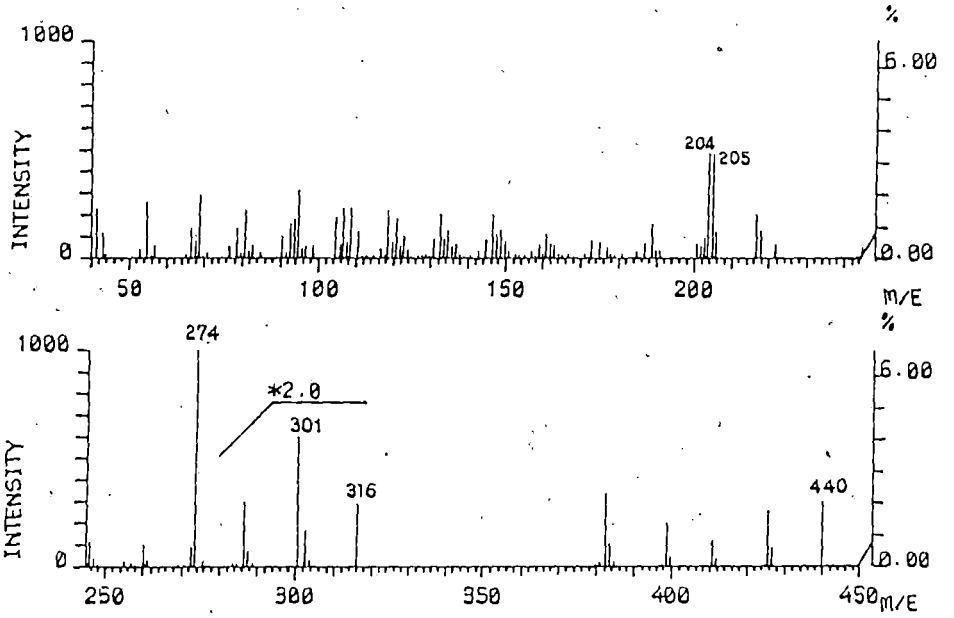


Fig.28 Mass Spectrum of taraxerene- ϵ - lactone,146.

MASS SPECTRUM : (5 TO 6)
NOTE :DR.B.P.PRADHAN,U OF N.B,(2/8/83)
BASE PEAK : M/E 274.0 INT. 2[illegible]5

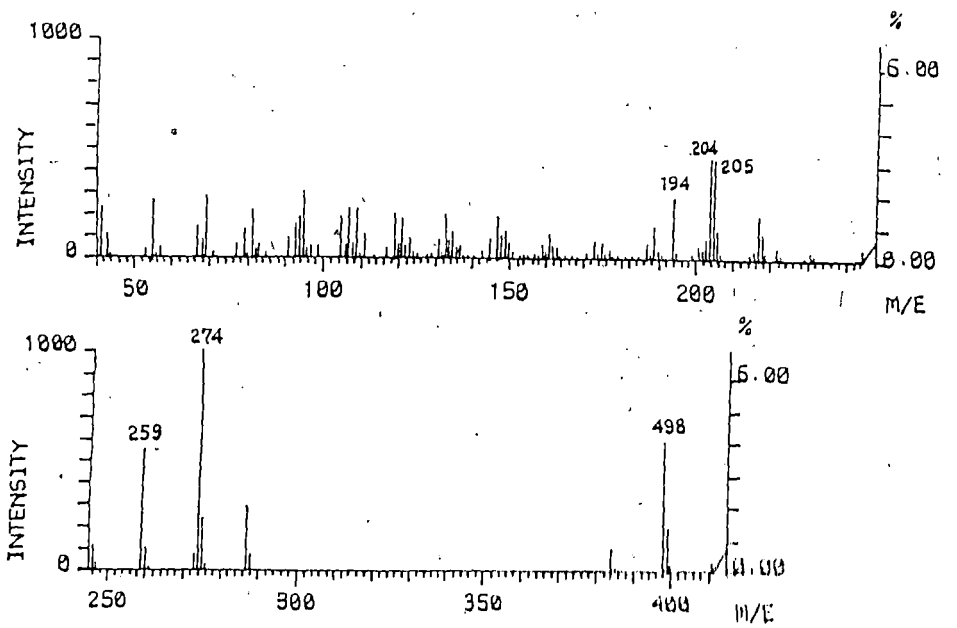
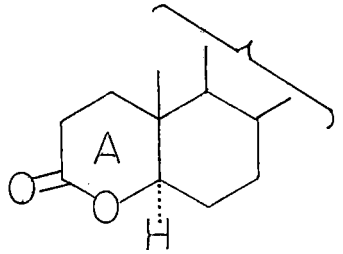


Fig.26 Mass spectrum of 4 23,24-tri-nor taraxerene 3→5 olide,144.

The appearance of singlets from δ 0.83 to 1.12 integrable for eighteen protons indicates the presence of six tertiary methyl groups in compound T_2. A two proton multiplet centered at δ 2.26 is assigned to a methylene group alpha to carbonyl group. The quartet at δ 3.92 (J_{ae} = 5 Hz, J_{aa} = 12 Hz) shows the presence of a lactonic proton[112]. The J values indicate the axial orientation of the proton having one axial and one equatorial neighbours. These peaks appear to be very similar to those of 4, 23, 24- trinor lupane 3 $\longrightarrow$ 5 olide, 135, mentioned earlier thus indicating the formation of similar δ-lactone in ring A of taraxerone formed by elimination of three carbon atoms 4, 23 and 24. Thus, ring A may be represented as 143. The one proton multiplet centred

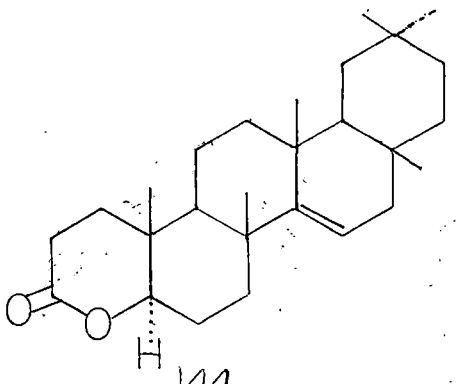


143

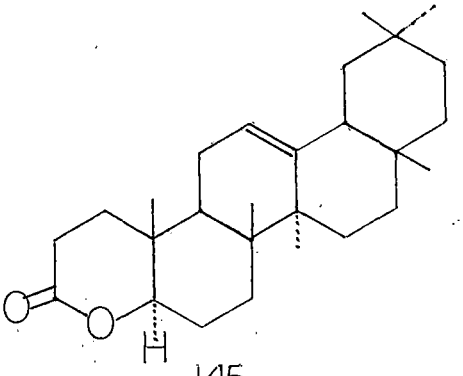
at δ 5.57 is due to an olefinic proton.

From the IR and ^{1}H NMR data analysis, it appears that compound T_2 has a trisubstituted double bond which is either at C_{14} - C_{15} position, that is, the double bond is retained as in the case of taraxerone, or it is due to C_{12} - C_{13} double bond formed by isomerization of C_{14} - C_{15} double bond during the course

of the reaction. From these observations two structures 144 and 145 may be assigned for T_2 . The structure of T_2 is finally



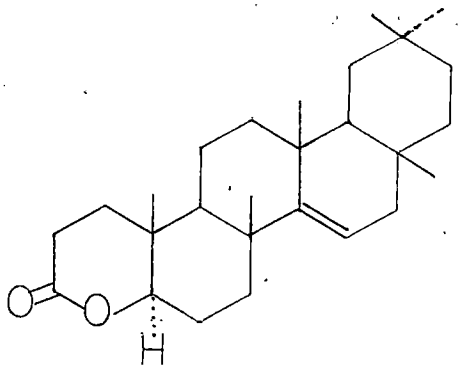
144



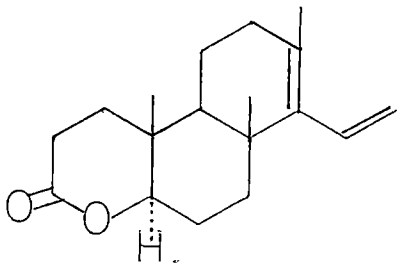
145

established as 144 from its mass fragmentation pattern (Fig. 26). The molecular ion of T_2 is found to be (M^+ 398) by the chemical ionisation method. The ion peak at m/e 274, XVII probably arises due to retro-Diels-Alder decomposition of ring D, the charge remaining with the diene portion comprising the ring A, B and C as was in the case of taraxerone[102]. The fragment XVII, undergoes the loss of allylically activated methyl group at C-8 and thus the ion peak at m/e 259 results due to fragment XVIII. The ion peak at m/e 204 is due to fragment XV. Hydrogen addition to the fragment XV results in the formation of the fragment XVI responsible for ion peak at m/e 205. Fragment XIX is due to loss of a methyl group . Fragment XIV is also responsible for ion peak at m/e 204, which is characteristic of taraxerone skeleton. Thus, the ion peaks at m/e 274 and m/e 259 suitably support the formulation of T_2 as 144. The fragmentation pattern is shown in Scheme - XIX.

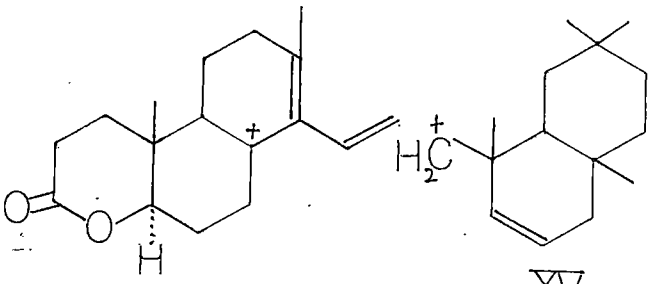
Scheme - XIX



144 m/e 398 (M^+)

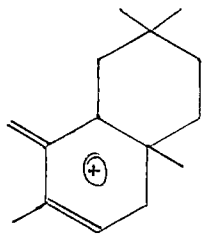


XVII m/e 274

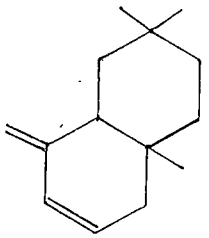


XVIII m/e 259

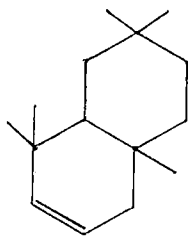
XV m/e 204



XIV m/e 204



XIX m/e 189



XVI m/e 205

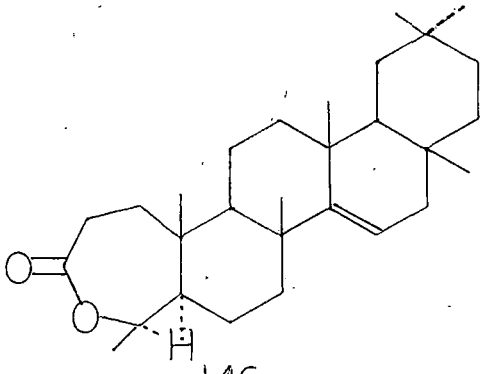
Thus the structure of T_2 is confirmed from mass spectrum as 4, 23, 24 tri-nor-Taraxerene-3 $\longrightarrow$ 5αH -olide, 144.

Structure of T_3 as taraxerene-ϵ-lactone, 146:

Molecular weight determination by mass spectrometric method and independent elemental analysis of T_3 showed the molecular formula of T_3 as $C_{30}H_{48}O_2$ (M^+ 440).

The infrared spectrum (Fig. 27) of T_3 showed a sharp band at 1720 cm^{-1}, which may be due to the presence of a carbonyl function or ϵ lactone moiety. If one of the oxygen atoms is present as keto or aldehyde group, the other oxygen atom should be present as hydroxy or epoxy or ether functional group. Since the IR spectrum does not show any peak that are generally shown by these functions, the probability of the presence of ϵ lactone could be inferred from IR spectrum. The peak at 810 cm^{-1} is, as usual, attributed to a trisubstituted double bond.

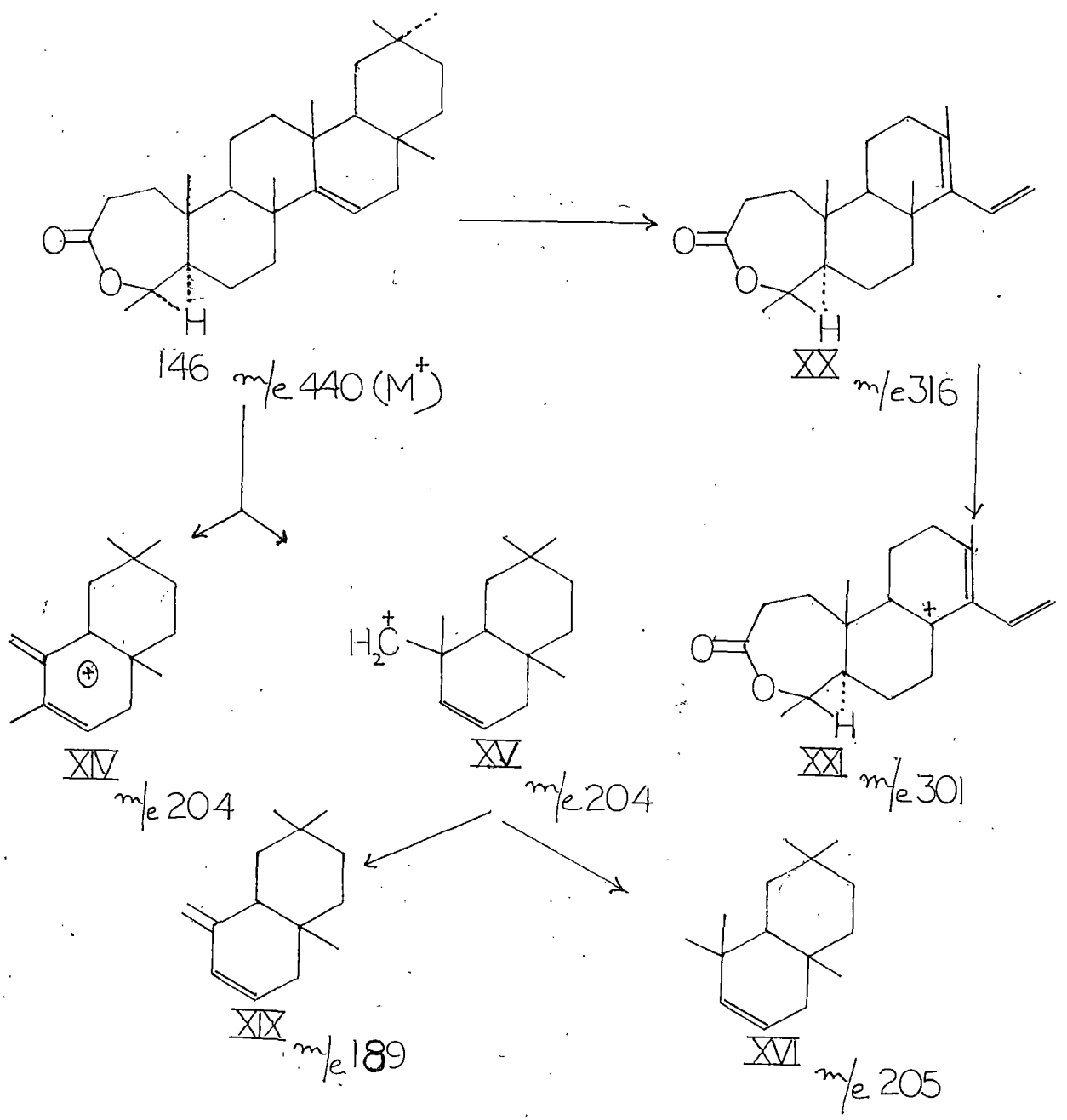
The mass spectrum of T_3 (Fig. 28) shows characteristic peaks at m/e 440 (M^+), 316, 301, 204, 205 and 189. The appearance of these fragments may be explained if structure 146 is formulated for T_3.



146

The genesis of the ion fragments m/e 316 and m/e 301 is similar to fragments XVII and XVIII as in the case of compound 144 and 146 can be explained by structure 146 as is given below in Scheme - XX.

Scheme - XX



Thus, the structure of T_3 is confirmed by IR, PMR and Mass Spectral analysis as taraxerene-ϵ-lactone, 146.

Structure of T_4 as 2α-Carbomethoxy-A-nor-taraxerene, 147:

Elemental analysis and mass spectral data indicate the molecular formula of T_4 to be $C_{31}H_{52}O_2$.

The infrared spectrum (Fig. 29) of T_4 is recorded in Table - 19 with its important peak absorptions and their probable assignment.

Table - 19

IR spectrum of T_4 in Nujol Mull

Position of peak absorption cm^{-1}	Intensity	Probable assignment
1735	strong	>C = O stretching vibration of an ester group
1155	strong	-C-O stretching vibration of the ester group
815	strong	trisubstituted double bond

It, therefore, appears from infrared spectrum of T_4 that the compound is probably an ester with a trisubstituted double bond.

The information regarding the structure of T_4 as obtained from its IR spectrum gets further support from its 360 MHz ^1H NMR spectrum (Fig. 30). The spectrum is recorded in Table - 20 with its chemical shift and their probable assignment.

Table - 20

^1H NMR signals of Compound T_4

Chemical shift in δ (ppm)	Number of protons	Multiplicity of signals	Probable assignment
0.82	3	singlet	
0.85	3	singlet	
0.90	3	singlet	
0.92	3	singlet	$\delta - \overset{|}{C} - CH_3$
0.95	3	singlet	
0.99	3	singlet	
1.08	3	singlet	
1.12	3	singlet	
2.75	1	quartet $J_{aa} = 11$ Hz $J_{ae} = 5$ Hz	$\underline{H} - \overset{|}{C} - COOCH_3$
3.6	3	singlet	$H - \overset{|}{C} - COOCH_3$
5.54	1	multiplet	$\underline{H} - \overset{|}{C} = CH_2 -$

Appearance of eight singlets from δ 0.82 to δ 1.12 integrable for twenty four protons demonstrate the presence of eight tertiary methyl groups in T_4 . A three proton singlet at δ 3.6 shows the presence of a carbomethoxy group in the compound. A quartet

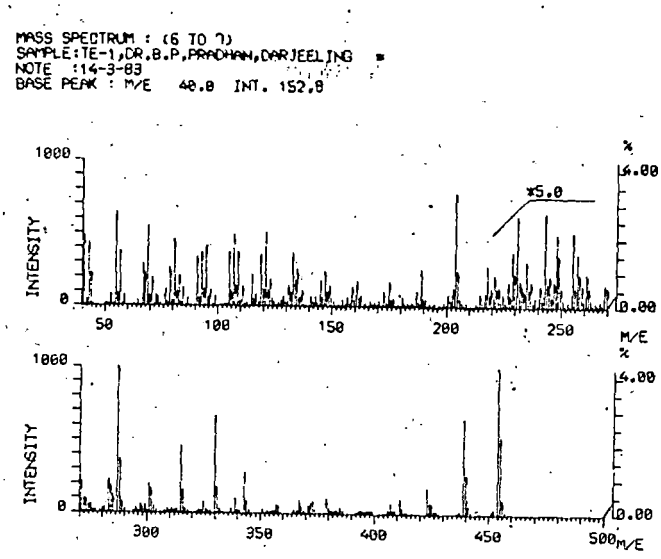


Fig.31 Mass Spectrum of 2∝ -carbomethoxy-A-nor-taraxerene, 147.

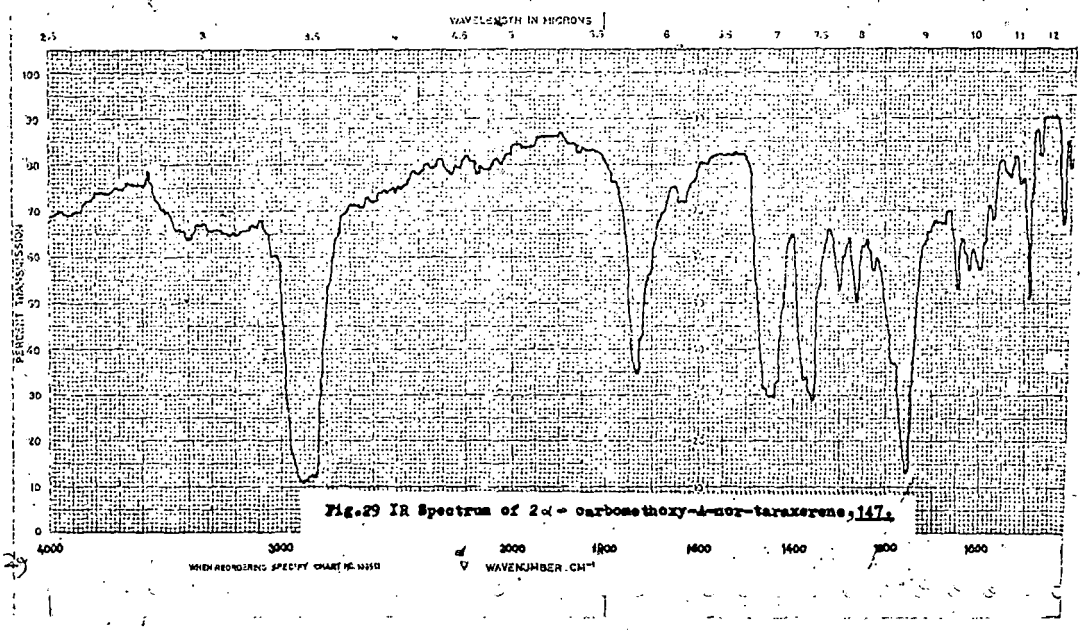


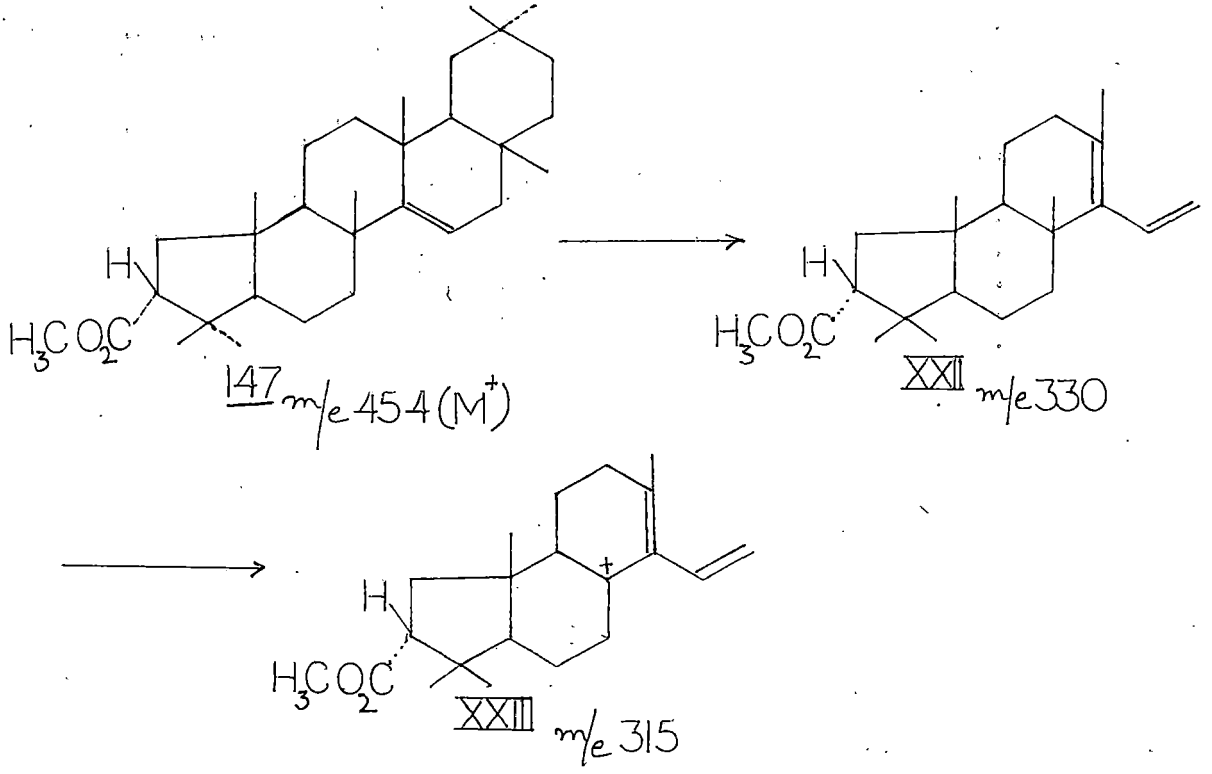
Fig.29 IR Spectrum of 2∝ - carbomethoxy-A-nor-taraxerene, 147.

Fig 29

Fig.30 ^{1}H NMR Spectrum of 2α - carbomethoxy-4-nor-tarraxerane,147a.

centred at δ 2.75 integrable for one proton may be assigned to the hydrogen atom geminal to the carbomethoxy group. The J values also indicate that the proton is axially oriented with one axial and one equatorial neighbours. The multiplet at δ 5.54 integrable for one proton indicates the presence of a trisubstituted olefinic proton.

The mass spectrum of T_4 (Fig. 31) finally establishes its structure. It shows characteristic peaks at m/e 454 (M^+), 439, 330, 315, 204, 189. From our previous discussion on mass spectrum of taraxerone, **141**, and compounds T_1, T_2 and T_3, it is evident that fragments at m/e 204 and 189 are due to species XIV, XV and XIX. Fragments at m/e 454, 330 and 315 may be explained if structure **147** is formulated for T_4 , which also satisfies the ^{1}H NMR and IR spectral analyses.



Hence, on the basis of spectral data the structure of T_4 has been assigned as 2α-carbomethoxy-A-nor-taraxerone, 147.

Structure of T_5 as Taraxerene 2,3 seco-methyl dicarboxylate, 148 :

Elemental analysis and mass spectrum of T_5 show its molecular formula to be $C_{32}H_{52}O_4$.

The important peak absorption and their probable assignment of infrared spectrum of T_5 (Fig. 32) is recorded in Table - 21.

Table - 21

Infrared spectrum of T_5 in Nujol Mull

Position of peak absorption cm^{-1}	Intensity	Probable assignment
1730 1720	strong strong	>C = O stretching vibration of ester group
1440	medium	δ-CH_3 vibration of ester group
1140	weak	-C-O stretching vibration of the ester group.
810	weak	Trisubstituted double bond

The infrared spectrum is indicative of two ester groups and a trisubstituted double bond as functionalities in T_5 .

The inference gets support from its ^1H NMR spectrum (Fig. 33). The spectrum is studied in 360 MHz instrument using TMS as internal standard. The signals for various protons and their probable assignments are recorded in Table - 22.

Table - 22

Chemical shift δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
0.81	3	singlet	
0.87	3	singlet	
0.91	3	singlet	
0.95	3	singlet	$\delta - \overset{\vert}{\underset{\vert}{C}} - CH_3$
0.98	3	singlet	
1.01	3	singlet	
1.09	3	singlet	
1.25	3	singlet	
3.60	3	singlet	$-\overset{\vert}{C} - COOCH_3$
3.65	3	singlet	$-\overset{\vert}{C}-COOCH_3$
2.30	2	multiplet	$-CH_2 - COOCH_3$
5.54	1	multiplet	$>C = CH - CH_2$

The appearance of eight singlets from δ 0.81 to δ 1.25 integrable for twenty four protons may be accounted for the presence of eight tertiary methyl groups in compound T_5. Two three proton singlets each at δ 3.60 and δ 3.65 indicate the presence of

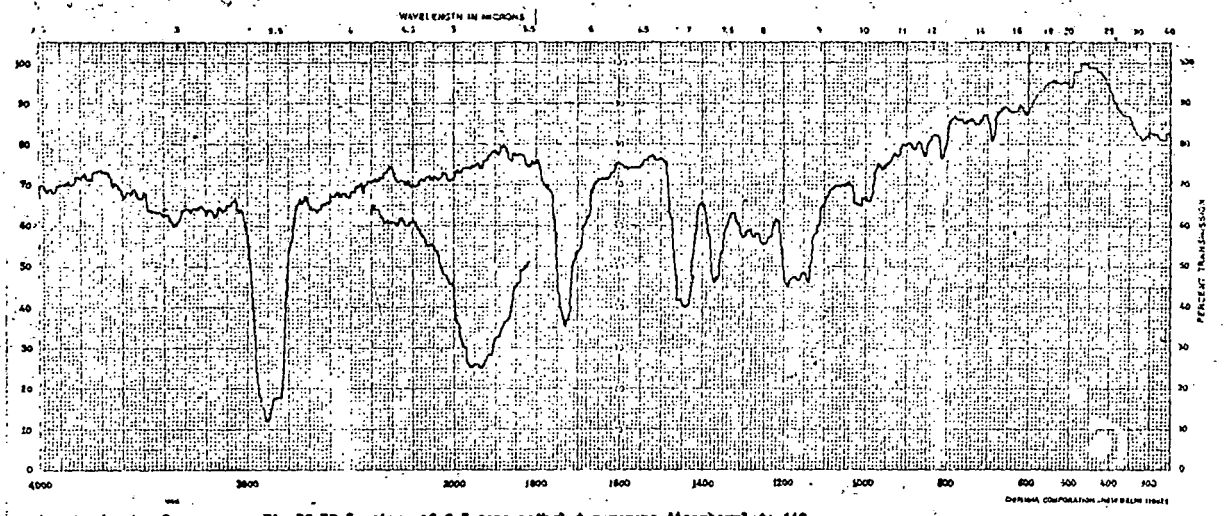


Fig.32 IR Spectrum of 2,3-exo-methyl taraxerene dicarboxylate,148.

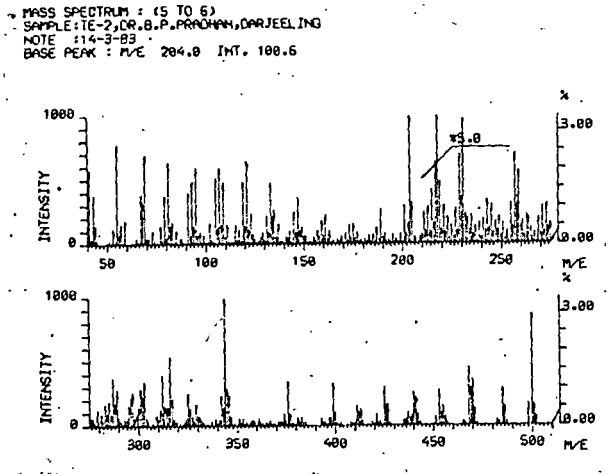
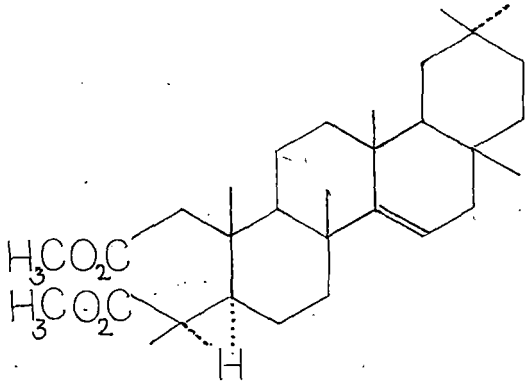


Fig.34 Mass Spectrum of 2,3-exo-methyl taraxerene dicarboxylate,148.

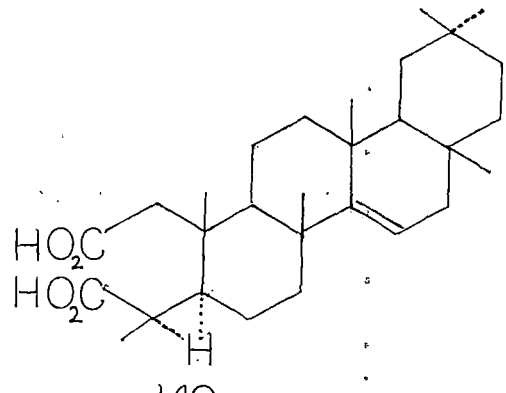
Fig.33 ^{1}H NMR Spectrum of 2,5-exo-exo-dimethyl tetracyclo[4.2.0.0^{2,5}.0^{3,7}]octane-4,8-dicarboxylate, 148a.

two carbomethoxy groups in the compound. The two proton multiplet centred at δ 2.3 is attributed to a methylene group alpha to a carbomethoxy group. The multiplet centred at δ 5.54 is due to a trisubstituted double bond. Thus, from IR and ^{1}H NMR spectral data, it is found that compound T_5 contained two carbomethoxy group along with eight tertiary methyl groups and the trisubstituted double bond that is present in taraxerone.

Hydrolysis of T_5 with methanolic KOH gave a compound identical with taraxadioic acid[120], 149. Compound T_5 is, therefore, assigned structure 148.



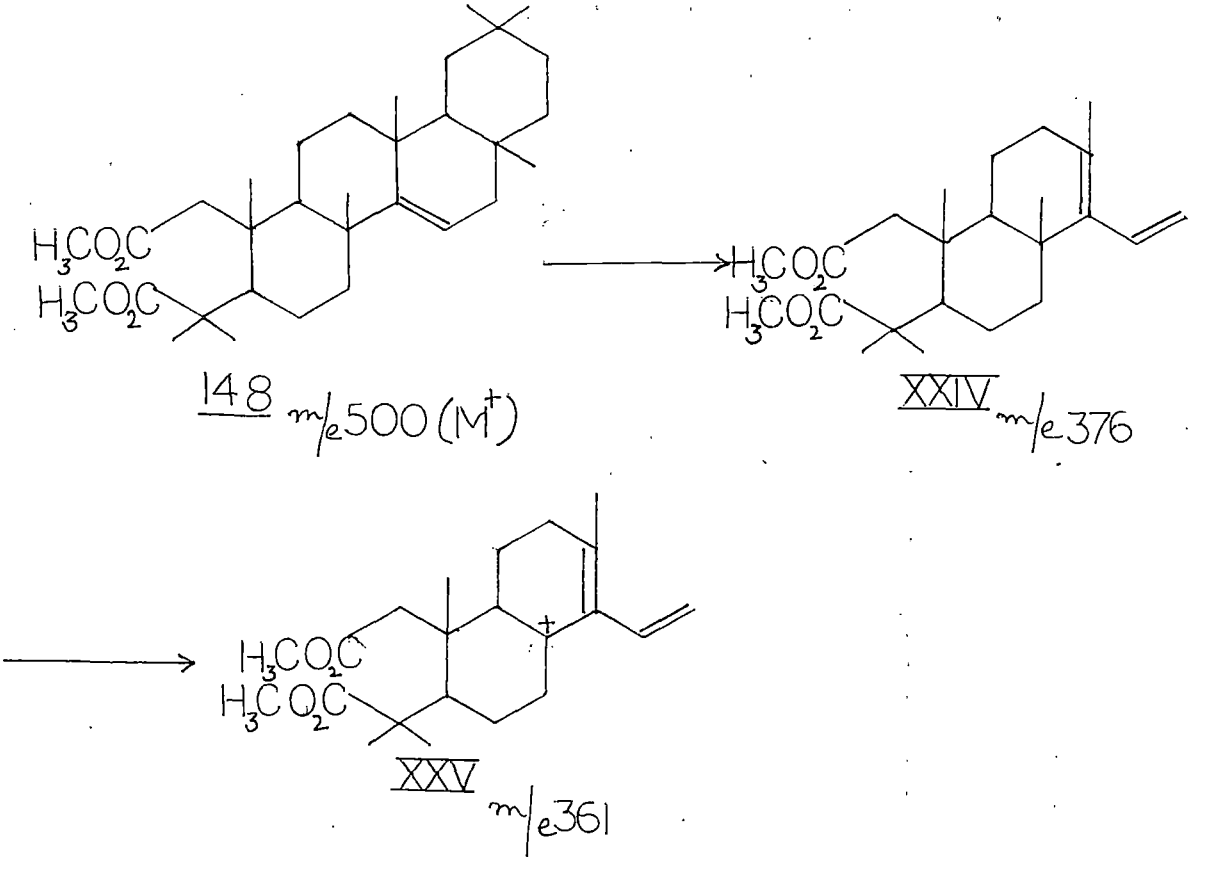
148



149

120. J. Simonson and W.C.J. Ross, "The terpene", Volm. IV (Cambridge University Press, Lond), 283 (1957)

The formulation of T_5 as taraxerone 2,3 seco methyl dicarboxylate gets further support from its mass spectrum (Fig. 34). It shows characteristic peaks at m/e 500 (M^+), 485, 470, 468, 440, 399, 376, 361, 204. These ion fragments may be rationalised if structure 148 is assigned to T_5. Moreover, peaks at m/e 376, XXIV and m/e 361 XXV stand as support for the structure 148.



All these spectral data analysis of the compound suggest the structure of T_5 as Taraxerone 2,3 seco-methyl dicarboxylate.

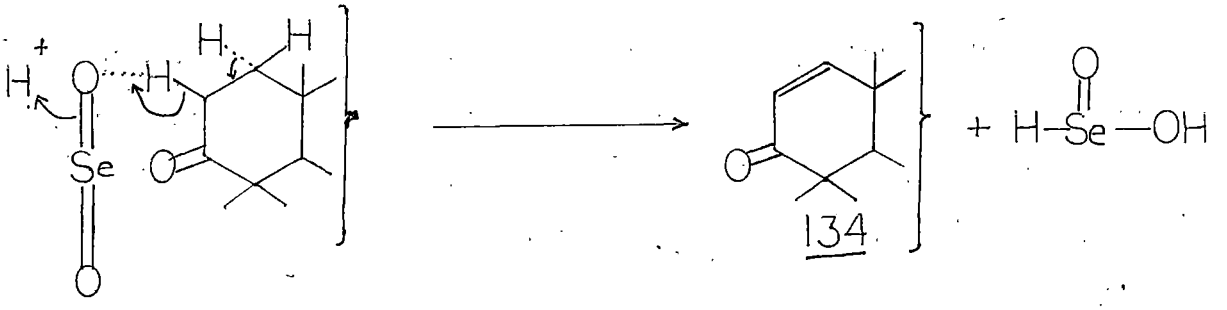
Section E

Proposed mechanism of the reaction

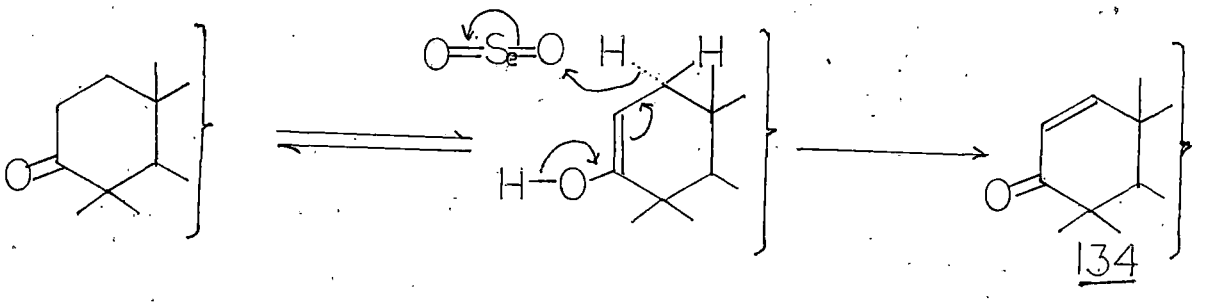
Formation of α, β unsaturated ketones:

While reviewing the works on oxidative transformations by selenium dioxide (Chapter I), it has been discussed that selenium dioxide acts as a dehydrogenating agent if hydrogen atoms are available at positions α and β to the carbonyl group. In the case of triterpenoids, the formation of 1, 2-ene-3-one seems to be rather restricted due to steric hindrance by the methyl groups present at the four position and at the A/B ring juncture. Lupanone, 130, yielded dihydro glochidone (lup-1-ene-3-one), 134, in small amount when hydrogen peroxide was present in negligible proportion, while in presence of higher amount of hydrogen peroxide, 3 keto 1α, 2α epoxide, 142, was obtained from taraxerone, 141. The products indicate that dehydrogenation reactions take place even if there are gem dimethyl group at the four position. The same reaction when carried out with friedelin, 136, did not yield 1, 2-ene-3-one or 4, 23-ene-3-one or their corresponding epoxides. It may, therefore, be concluded that the twisted boat structure of friedelin, 136, causes hindrance to the formation of α, β unsaturated ketone by sterical interference. Thus, we may propose the formation of α, β unsaturated ketones in the case of triterpenoids containing gem dimethyl group at the four position in two different pathways[46] as follows:

Path a

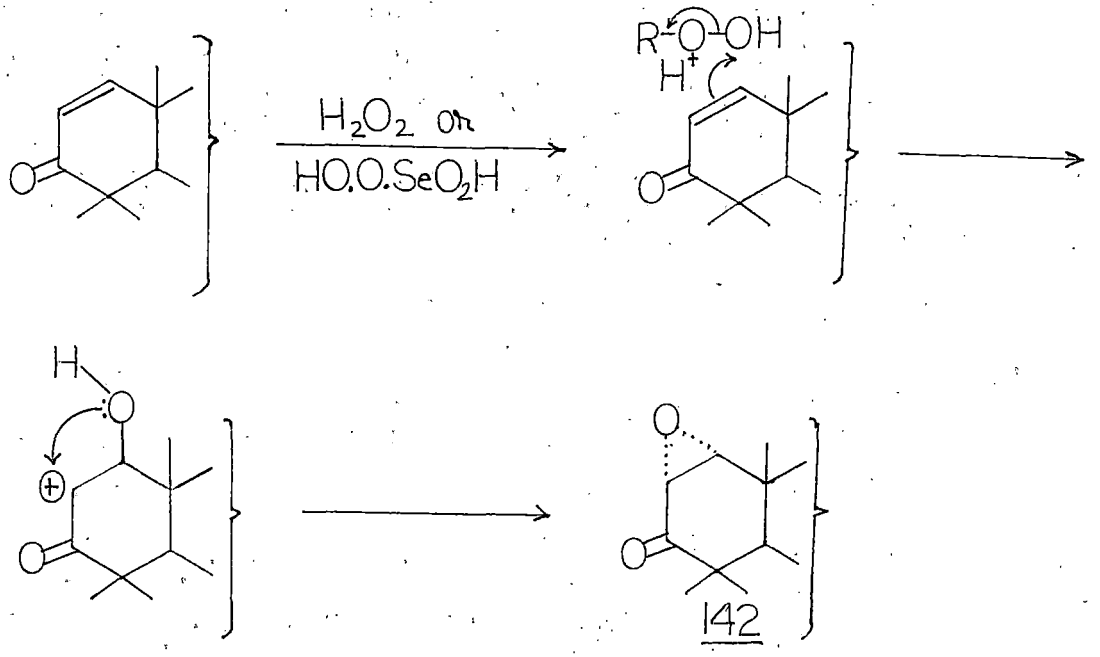


Path b



The probable mechanism of formation of the epoxide may be by the action of H_2O_2 or peroxy selenious acid[60], which proceeds as given below in Scheme XXI.

Scheme XXI

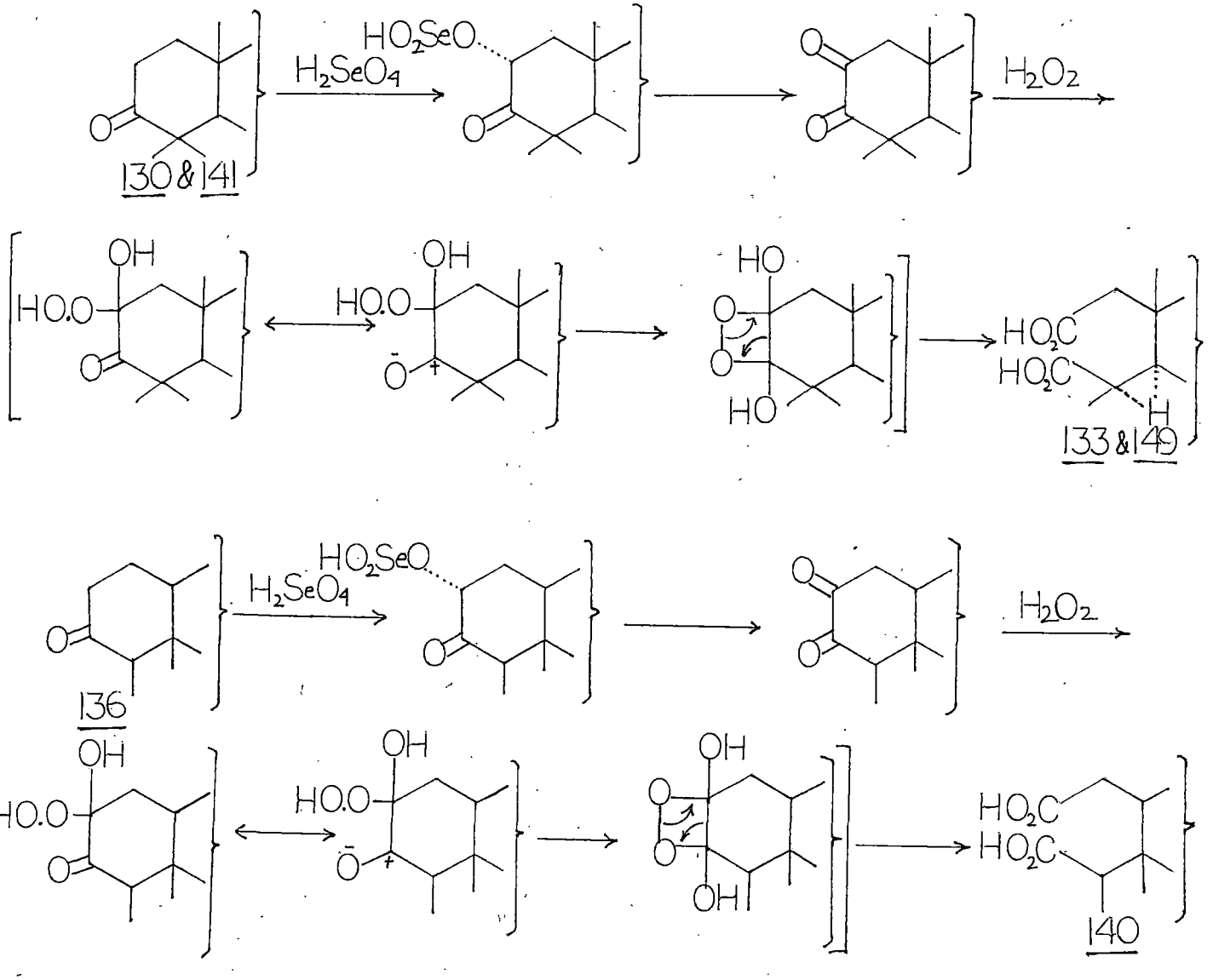


Formation of dicarboxylic acids:

It has been observed experimentally that triterpenoid 3-ketones with gem dimethyl or monomethyl group at C-4 position give dicarboxylic acids by cleavage of 2, 3 carbon-carbon bond during the reaction with hydrogen peroxide - selenium dioxide in appreciable amount. The formation of carboxylic acids, 133, 140 and 149 from lupanone 130, friedelin 136 and taraxerone 141 respectively can be explained via the intermediate stage of 2, 3-

diketones, which in turn is further oxidised by hydrogen peroxide to carboxylic acids. As it is well known that selenium dioxide is a good oxidising agent of the methylene group α to the oxo group, it is obvious that the high temperature and prolonged reaction time cause complete oxidation of the 3-keto triterpenoids to the diketone. The steps involved in the conversion of 3-keto triterpenoids to seco-dicarboxylic acids are given below[66] in Scheme -XXII.

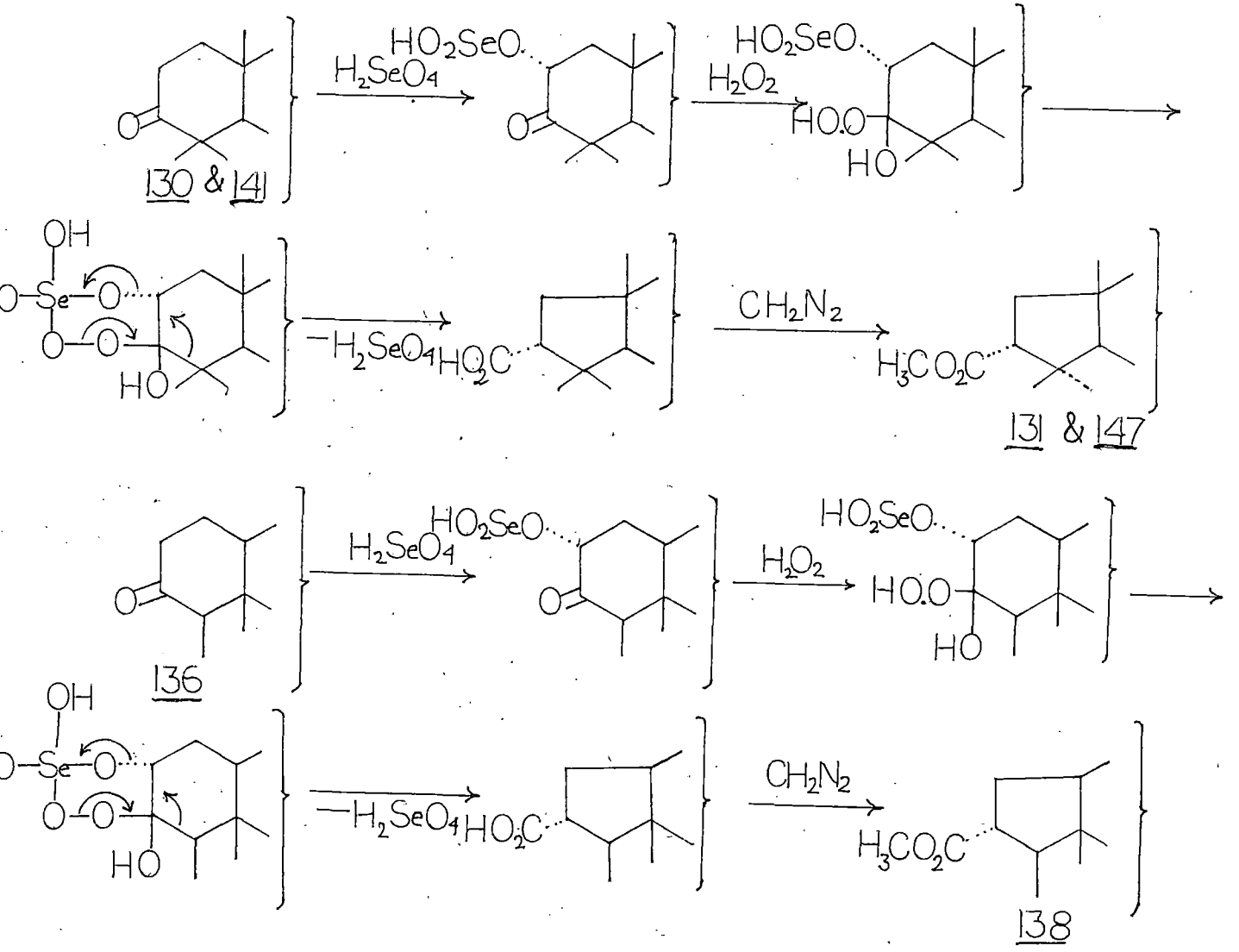
Scheme - XXII



Formation of A-nor-carboxylic acid:

Lupanone and taraxerone both with gem dimethyl group at C-4 position and friedelin having one methyl group at C-4 position furnished A-nor-carboxylic acid in poor yield. The proposed mechanism for the formation of these type of monocarboxylic acids by the oxidation of 3-ketones by selenic acid followed by attack with hydrogen peroxide and rearrangement[66] is proposed in Scheme -XXIII.

Scheme - XXIII



Formation of δ-lactones:

We have observed in Section B of this chapter that lupanone, 130, forms a δ-lactone, 135, along with other products when oxidised with hydrogen peroxide-selenium dioxide. The same type of δ-lactone, 144, was obtained from taraxerone, 141. It is surprising to note that in the case of taraxerone when the refluxing period was only 20 hours, a second lactone, 146, with the same number of carbon atoms as in the original ketone, 141, was isolated. In our first paper[121] in the series of oxidation reaction with hydrogen peroxide-selenium dioxide we had proposed the formation of δ-lactone via the intermediate ε lactone. It may be noted that in the case of lupanone, 130, the reaction period was 30 hours, while in case of taraxerone, 141, it was 20 hours. It is, therefore, possible that in the fomrer case, the ε-lactone which is formed first, undergoes hydrolysis and by Baeyer-Villiger oxidation results in the formation of δ-lactone, 135. The isolation of ε-lactone, 146, in the case of taraxerone, 141, has confirmed our mechanism proposed earlier. Thus, we may write the mechanism of formation of 4, 23, 24 tri-nor-3 → 5 olide as shown in Scheme - XXIV.

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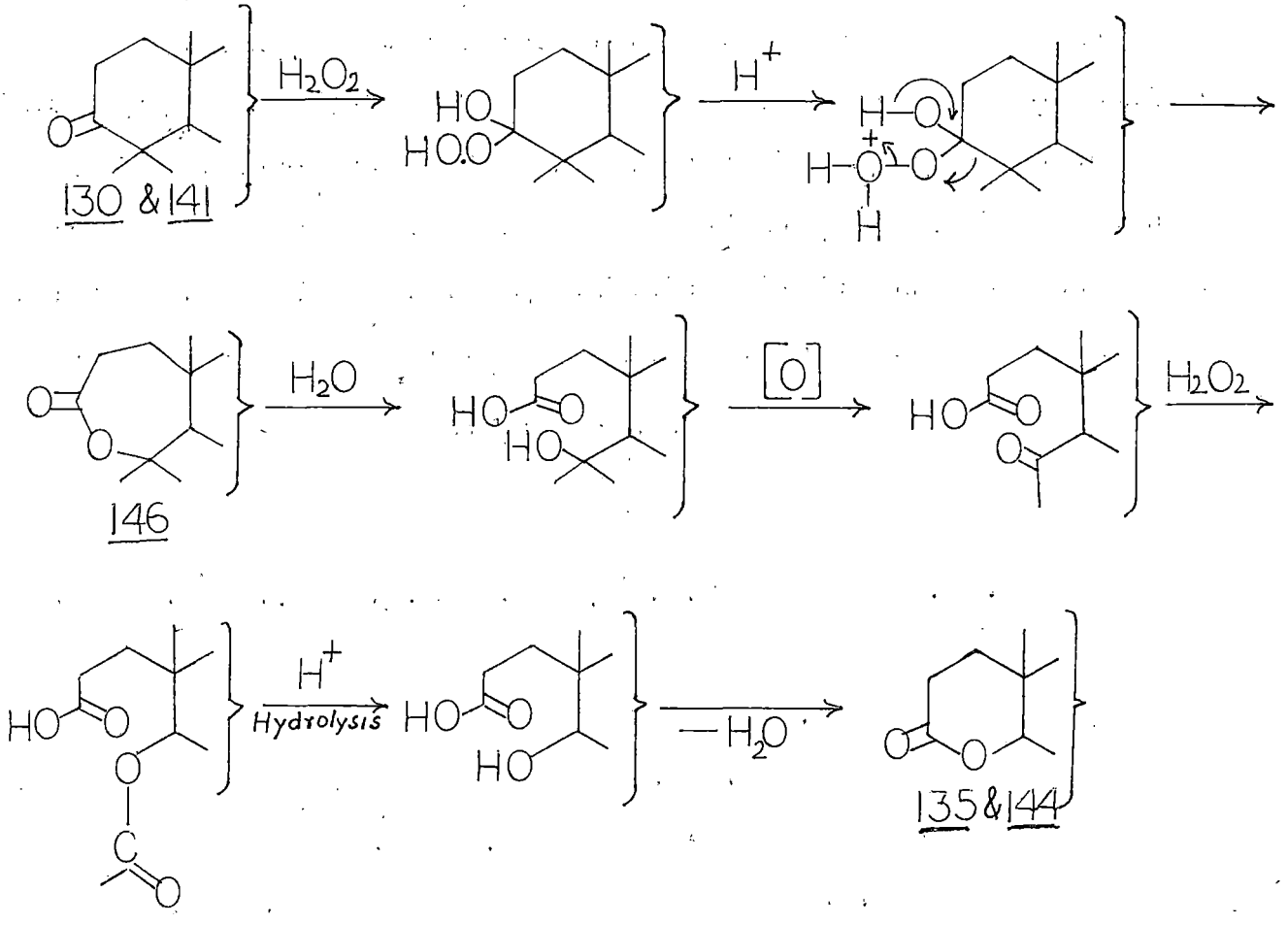
121. S. Dutta and B.P.Pradhan, Ind.J.Chem., 21B, 575 (1982)

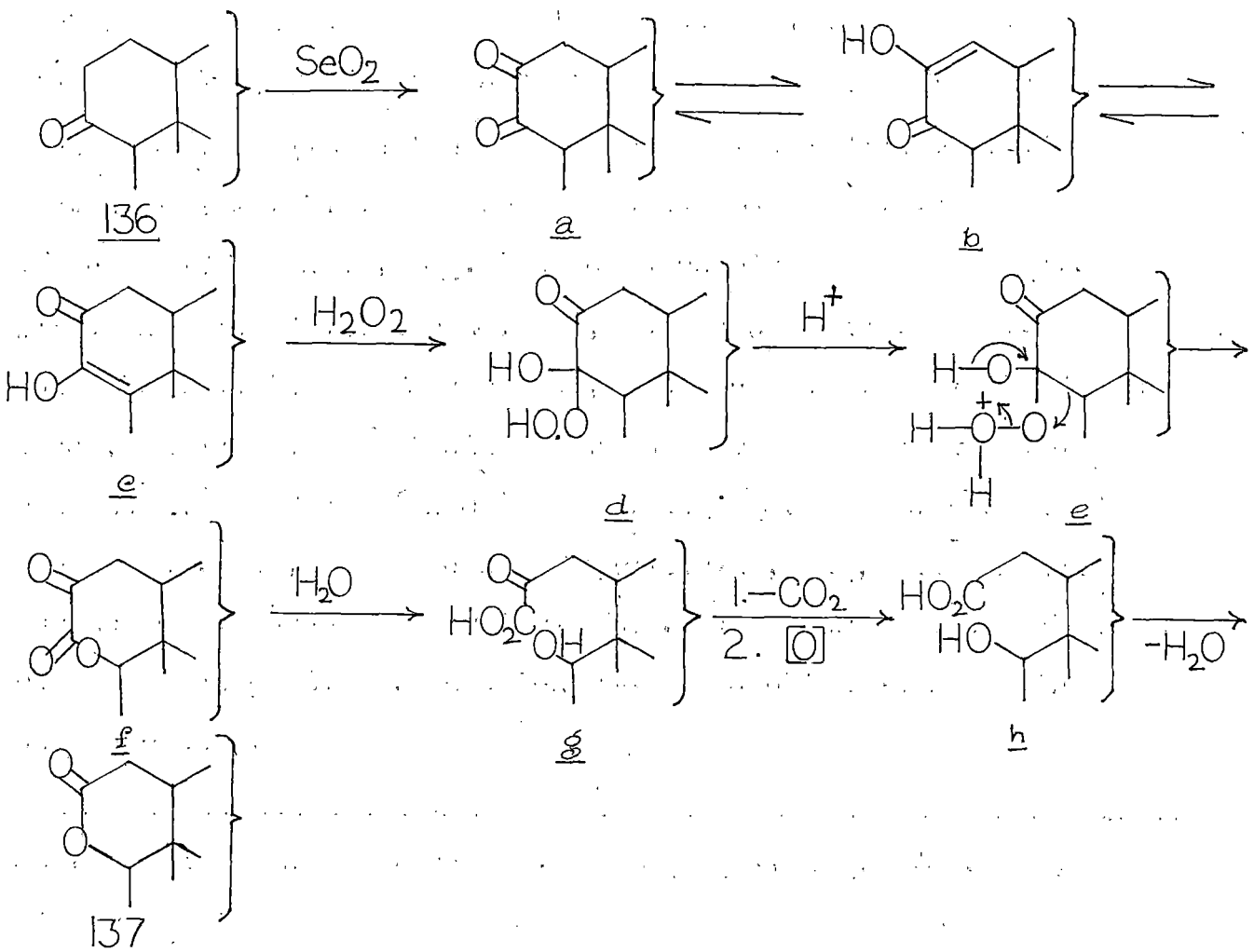
Scheme - XXIV



In the case of friedelin, 136, where there is one methyl group at C-4 position, it was expected that a δ lactone with the loss of 4, 23 carbon atoms would be formed as in the case reported

by Corey et al[122]. To our surprise the δ-lactone, 137, isolated from friedelin contains one atom less than friedelin. It was characterised as 3-nor-friedelin 2 → 4 olide. The mechanism for the formation of this lactone possibly follows a completely different path way as shown in Scheme - XXV.

Scheme - XXV



122. E.J. Corey and J.J. Irsprung, J.Am.Chem.Soc., 5041 (1956)

It is probable that selenium dioxide converts friedelin to 2, 3-diketone a ⟨⇌ diosphenol b ⇌ c ⟩. One mole of hydrogen peroxide may attack c to give the intermediate α-keto-ϵ-lactone, f, which may undergo hydrolysis to furnish the α-keto acid g. The acid g on decarboxylation furnishes 3, 4-seco-C-3-nor-4-hydroxy-friedelin-2-carboxylic acid h, which undergoes lactonization to form the δ-lactone 137. All the above intermediates are formed during the reaction conditions in situ. The formation of a similar lactone in the oxidation of lupanone and taraxerone by H_2O_2 - SeO_2 is not possible due to the presence of gem dimethyl group at C-4, which hinders the formation of a diosphenol similar to c from lupanone and taraxerone.

Section F

Experimental:

Melting points are uncorrected. The petroleum ether used throughout the investigation had b.p. in the range of 60-80°C. The infrared spectra were recorded in Beckman IR-20 Spectrophotometer. The UV absorption spectra were taken in Beckman DU-2 Spectrophotometer. Mass spectra were recorded by electron impact method in MS 300 spectrometer. Silica gel used for column chromatography was of 60-120 mesh (B.D.H) and alumina used for column chromatography was of active basic grade (B.D.H). TLC were performed in chromatoplates prepared on glass strips with Silica gel G (B.D.H).

Isolation of lupeol from Xanthoxylum budrunga.

Six kilo grams of air dried finely powdered bark of Xanthoxylum budrunga[123] was soxhletted for 48 hours with benzene. The extract was cooled and then solvent was distilled off. The residue left was dissolved in minimum volume of benzene, chromatographed over deactivated alumina column and the petroleum-ether eluent collected. Petroleum-ether was distilled off and a solid (14 g) was obtained. The solid on rechromatography over deactivated

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123(a) Dieterle, Arch. Pharm., 257 (1919), 260 (1921)

(b) Ultee, Bull. Jardinbot. Buitenzorg, 1922(iii), 4, 315.

alumina afforded lupenone on petroleum-ether elution and lupeol on petroleum ether-benzene (4:1) elution. The latter was further purified by repeated crystallisations from chloroform-methanol mixture. 12 g of lupeol, m.p. 215-16°, $[\alpha]_D$ 33°, was obtained and found to be identical with authentic sample of lupeol (co-t.l.c. ; m.m.p. and co- IR).

Hydrogenation of Lupeol to Lupanol

7.0 gm of lupeol in glacial acetic acid (150 ml) and ethyl acetate (150 ml) was reduced with hydrogen at atmospheric pressure in presence of Adam's catalyst (200 mg). The catalyst was filtered off, the solvent evaporated in vaccum and the residue on recrystallisation from chloroform-methanol mixture afforded fine crystals of lupanol (6 gm), m.p. 206°, $[\alpha]_D$ + 17.8° identical with authentic sample of lupanol (co-IR, m.m.p).

Oxidation of Lupanol to Lupanone.

Dry chromium trioxide (6g) was added to a magnetically stirred solution of 9.6g of dry pyridine in 150 ml dry methylene chloride. The flask was stoppered with fused calcium chloride and the deep burgandy solution was stirred for 15 minutes at room temperature. At the end of this period, a solution of lupanol (4g) in a small volume of methylene chloride was added in one portion. A tarry black deposit separated immediately. After stirring for an additional 15 minutes at room temperature, the

solution was decanted from the residue . The decanted methylene chloride solution was condensed in vaccuo and then the residue was taken up with ether and filtered to remove insoluble chromium salts. The ether solution was washed with dilute aqueous base and with a saturated brine solution and dried over anhydrous sodium sulphate.

Evaporation of the solvent yielded the crude ketone (3.8g). The crude ketone dissolved in minimum volume of benzene was chromatographed over active alumina column (100 g). The chromatogram was developed in petroleum-ether and eluted with the following solvents.

Table - 23

Eluent	Fractions 50 ml each	Residue on evaporation	Melting point ^{0}C
Petroleum-ether	1-4	Oil	-
Petroleum-ether	5-30	Solid (3.5g)	200-203^{0}

Further elution with more polar solvents did not afford any solid material.

Fractions 5-30, Table - 23 were combined. This on repeated crystallisation from chloroform-methanol mixture afforded needle-shaped crystals of lupanone, m.p. 209-10^{0}, $[\alpha]_{D}$ 16.2^{0} identical

with authentic specimen of lupanone (m.m.p. showed no depression); IR : ν_{max} (nujol 1690 cm^{-1}) (>C = O).

Oxidation of Lupanone with Selenium dioxide and hydrogen peroxide

A solution of lupanone, (1.2 g) dissolved in tert-butanol (60 ml) containing selenium dioxide (0.008 g) and hydrogen peroxide (17%, 0.2 ml) was refluxed on water bath. After 32 hours black selenium metal precipitated out indicating the completion of reaction. It was cooled and poured in ice-cold water when a white solid appeared. This was taken in ether and the ether solution was washed first with 10% Na_2CO_3 solution (three times, 200 ml) and then with 5% Na_2CO_3 solution (three times, 200 ml). The ether layer which now contained neutral part only, was washed three times with dil. HCl (200 ml), then with water and finally dried over anhydrous Na_2SO_4. The filtered solution on evaporation to dryness yielded a gummy residue (0.5 g). The alkali-wash was kept aside for further treatment.

Isolation of Lup-1-ene-3-one

The gummy neutral mass was dissolved in minimum volume of benzene and chromatographed over a deactivated alumina column (40 g). The chromatogram was developed with petroleum ether and eluted with the solvents stated in Table - 24.

Table - 24

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum ether	1-2	Traces of oil
Petroleum ether and benzene (4:1)	3-6	Solid, (80 mg) m.p. 150-52°

Further elution with more polar solvents did not afford any solid material.

Fractions 3-6, Table - 24 were combined (80 mg) and on crystallisation from a mixture of chloroform and methanol afforded colourless crystals of lup-1-ene-3-one 134.

Analysis:

		%C	% H
$C_{30}H_{48}O$ required		84.84	11.39
Found		84.71	11.43
IR : ν_{max}^{Nujol}	1675 cm^{-1} (-C(=O)-C=C-)		
	1650 cm^{-1} (>C=C<)		
		(Fig. 7)	
UV : λ_{max}^{MeOH}	228 nm		

^1H NMR : 0.78 to 1.08 (6s, 18H, 6t-CH_3),

(δ, $CDCl_3$) 0.75 + 0.80 (d, J = 6.8 Hz, 6H, HC<$^{CH_3}_{CH_3}$),

5.85 (d, J = 10 Hz, 1H, $-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{C}=\overset{\overset{\underline{H}}{|}}{C}-$),

7.19 (d, J = 10 Hz, 1H, $-\overset{\overset{O}{\|}}{C}-\overset{\overset{\underline{H}}{|}}{C}=\overset{\overset{H}{|}}{C}-C-$)

(Fig. 8)

Treatment of the alkali wash.

The alkali wash that remained after separation of neutral part was treated with 20% HCl till the whole solution was acidic. White precipitate that separated out was taken in ether. The ether-solution was washed with water & dried over anhyd. Na_2SO_4 . After recovery of ether, a coloured gummy mass (550 mg) was obtained. It showed two spots on chromatoplate. The mass was then subjected to esterification.

Esterification of acid part. Isolation of 2$^{\alpha}$-carbomethoxy-A-nor-lupane , and 2,3-seco-methyl lupane dicarboxylate.

The gummy mass (550 mg) was dissolved in ether and cooled to 5°. To this solution was added well cooled ethereal solution of diazomethane prepared from 1 gm of nitrosomethyl urea and was kept overnight. Next day, excess of diazomethane was destroyed with acetic acid. The ether solution was washed with water, 10% sodium bicarbonate solution and again with water till neutral and then dried over anhyd. Na_2SO_4. Evaporation of ether yielded a gummy residue (535 mg).

Chromatography of the above gummy residue:

The gummy residue (535 mg) was dissolved in minimum volume of benzene and was placed over a column of alumina (60 g) deactivated with 2.5 ml of 10% aqueous acetic acid. The chromatogram, was developed with petroleum ether and eluted with the following solvents.

Table - 25

Eluent	Fraction 50 ml each	Residue on evaporation	Melting point ^{o}C
Petroleum ether	1-2	Nil	-
Petroleum ether-benzene (4:1)	3-8	Solid (100 mg)	162^{o}
Petroleum ether -benzene (3:2)	9-10	Nil	-
Petroleum ether -benzene (2:3)	11-20	Solid (140 mg)	102^{o}

Further elution with more polar solvents did not furnish any solid material.

TLC of fractions 3-8, Table- 25, showed homogenity hence, they were combined (100 mg) and crystallised from chloroform-methanol mixture to furnish fine crystals of 2α-carbomethoxy-A-nor-lupane, 131, m.p. $174-77^{o}$.

Analysis:	% C	% H
$C_{31}H_{50}O_2$ required	81.52	11.42
Found	81.41	11.38

IR : ν_{max}^{KBr} 1740, 1434 and 1170 cm^{-1} ($-COOCH_3$) (Fig. 1)

^1H NMR : 0.72 to 1.04 (6s, 18H, 6-C-CH_3), ($\delta CDCl_3$) 0.75 + 0.85 (d, J = 7 Hz, 6H, HC$\langle^{CH_3}_{CH_3}$), 2.77 (q, J_{aa} = 12 Hz, J_{ae} = 6 Hz, 1H, H_2C -C(H_a)-$COOCH_3$), 3.7 (s, 3H, $-COOCH_3$) (Fig. 2)

Mass : M (456), m/e 440, 424, 413, 409, 396, 381, 357, 274, 259, 249, 235, 221, 205, 191 and 149. (Fig. 3)

Fractions 11-20 (Table 25) were found to be identical from examination of TLC and therefore, combined (140 mg). This after crystallisation from chloroform-methanol mixture afforded needle-shaped crystals of 2, 3 seco methyl lupane dicarboxylate, 132, m.p. 116-18°.

Analysis:	% C	% H
$C_{32}H_{54}O_4$ Required	76.45	10.83
Found	76.32	10.92

IR : ν_{max}^{KBr} 1735, 1740 cm^{-1} ($-COOCH_3$) (Fig. 4)

^{1}H NMR : 0.92 to 1.22 (6s, 18H, 6-C-CH_3)

(δ, $CDCl_3$) 0.85+0.75 (d, J = 7 Hz, 6H, HC$\langle^{CH_3}_{CH_3}$),

2.45 and 2.48 (2s, 2H, H_2C -$COOCH_3$)

3.68 and 3.64 (2s, 6H, 2- $COOCH_3$)

(Fig. 5)

Mass: m/e 502 (M^+), 443, 429, 413, 400, 385, 369, 321, 259, 205, 191.

(Fig. 6)

Hydrolysis of methyl lupane dicarboxylate.

Methyl lupane dicarboxylate, 132, (0.100g) dissolved in benzene (2 ml) was refluxed in 10% methanolic KOH (15 ml) for 4 hours. The mixture was cooled, acidified with dil. HCl (20 ml) and extracted with ether. Removal of the solvent afforded a solid, which on repeated crystallisations from methanol furnished lupane dicarboxylic acid, 133, $C_{30}H_{50}O_4$, m.p. 270-71°.

Analysis:	% C	% H
$C_{30}H_{50}O_4$ Required	75.90	10.62
Found	75.42	10.79

Oxidation of lupanone with H_2O_2 - SeO_2 under drastic condition: Preparation of 4, 23, 24 tri-nor-lupane 3 → 5 olide and lupane dicarboxylic acid

A solution of lupanone, 130, (2g) in tert-butanol (150 ml) containing H_2O_2 (17%, 30 ml) and SeO_2 (0.5 g) was refluxed for

30 hours. The reaction mixture was separated into neutral and acid parts as usual. The acid part ($\simeq$ 600 mg) on repeated crystallisations from methanol furnished a crystalline solid, m.p. 265-66°, identical with lupane dicarboxylic acid.

The neutral part (0.5 g) was chromatographed over deactivated alumina (20 g). The column was developed with petroleum ether and eluted with the following solvents.

Table -26

Eluent	Fractions 50 ml each	Residue on evaporation	Melting point °C
Petroleum ether	1-2	Oil	-
Petroleum ether-benzene (4:4)	3-4	Nil	-
Petroleum ether-benzene (3:2)	5-6	Nil	-
Petroleum ether-benzene (2:3)	7-8	Nil	-
Petroleum ether-benzene (4:4)	9-11	Oil	-
Benzene	12-21	White solid (300 mg)	243-46°

Further elution with more polar solvents did not yield any solid material.

TLC of compound 12-21 (Table - 26) showed homogenity and, therefore, they were combined (360 mg) and crystallised from chloroform-methanol to furnish colourless crystals of 4, 23, 24-tri-nor lupane 3 $\longrightarrow$ 5 olide, 135, m.p. 252°.

Analysis:

	% C	% H
$C_{27}H_{44}O_3$ required	77.84	10.64
found	77.62	10.58

IR : ν_{max}^{Nujol} 1743 (δ-lactone) cm^{-1}

(Fig. 9)

^1H NMR : 0.74 to 1.07 (4s, 12H, 4t-CH_3)

(δ, $CDCl_3$) 0.82 0.73 (d, J = 7 Hz, 6H, H$\begin{cases} CH_3 \\ CH_3 \end{cases}$)

3.9 (m, $W_{\frac{1}{2}}$ = 18 Hz, 1H, -COO-CH -)

2.6 (m, 2H, H_2C - COO-)

(Fig. 10)

Mass : M/e 400 (M^+), 385, 384, 357, 219, 209, 206, 195, 191, 165, 163, (base peak), 149, 135, 123, 121, 119, 109, 107, 95, 93, 81

(Fig. 11)

Isolation of Friedelin from Cork:

2 kgs of finely powdered cork was extracted with petroleum ether in a Soxhlet apparatus for 18 hours. After removal of the solvent, a white solid separated out. The solid was dissolved in

minimum volume of benzene and chromatographed over deactivated alumina column. Elution of the column with petroleum ether gave shining crystals of friedelin[124], m.p. 262-63, $[\alpha]_D$ -48.7^0

Oxidation of friedelin with selenium dioxide and hydrogen peroxide

A solution of friedelin, 136, (0.9g) in tert-butanol was refluxed on a water bath for 60 hours in presence of hydrogen peroxide (15 ml, 22%) and selenium dioxide (0.225g). The completion of the reaction was indicated by precipitation of black selenium metal. The reaction mixture was then cooled and poured on ice cold water when a white solid separated out. The mass was taken in ether and the ethereal layer was washed successively three times with 10% Na_2CO_3 (260 ml) and then with 5% Na_2CO_3 (200 ml). The ether layer was then washed three times with 200 ml dil. HCl and then with water and finally dried over anhyd. Na_2SO_4 . On evaporation to dryness, a gummy solid ($\simeq$250 mg) was obtained and designated as part A.

The Na_2CO_3 extract was acidified with dil HCl when a white solid appeared thereof. The solid was taken in ether and the ethereal solution was washed with water till neutral. It was then dried over anhyd. Na_2SO_4 and after evaporation to dryness a gummy mass ($\simeq$ 400 mg) designated as Part B was obtained.

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124. J.L. Simonsen and W.C.J. Ross, "The Terpenes", Volm. IV, 408.

Chromatography of Part A : Isolation of 3-nor-friedelin 2 → 4 olide

Part A was dissolved in minimum volume of benzene and chromatographed over a deactivated alumina column (25 g). The chromatogram was developed with petroleum ether and eluted with the following solvents.

Table - 27

Eluent	Fractions 50 ml each	Residue after evaporation	Melting point ^{o}C
Petroleum ether	1-4	Oil	-
Petroleum ether-benzene (4:1)	5-6	Nil	-
Petroleum ether-benzene (3:2)	7-8	Nil	-
Petroleum ether-benzene (2:3)	9-20	White Solid (120 mg)	251-53^{o}

Further elution with more polar solvents did not yield any solid material.

TLC of fractions 9-20, (Table - 27) showed homogenity and, hence, these were combined ($\simeq$ 120 mg) and crystallised three times from a mixture of chloroform-methanol when it yielded needle shaped crystals of 3-nor-friedelin 2 ⟶ 4 olied, 137, m.p. 262^{o}.

		% C	% H
Analysis :			
$C_{29}H_{48}O_2$	Required	81.25	11.29
	Found	80.98	11.03

IR : ν_{max}^{Nujol} 1740 cm^{-1} (δ-lactone)

(Fig. 12)

^1H NMR (δ, $CDCl_3$) : 0.88 to 1.21 (7s, 21H, 7t- CH_3)
0.99+1.01 (d, J = 6.5 Hz, 3H, HC-CH_3)
2.4 (dd, J_{gem} = 13 Hz, J_{aa} = 13 Hz, 1H, -COO- $\overset{H}{\underset{|}{C}}H_a$ -),
2.6 (dd, J_{gem} = 13 Hz, J_{ae} = 4 Hz, 1H, -COO-$\overset{H}{\underset{|}{C}}$-$H_e$),
4.02 (q, J = 10 Hz, 1H, $H\overset{|}{\underset{|}{C}}$-COO-)

(Fig. 13)

Mass : m/e 429 (MH^+), 341, 305, 275, 261, 235, 231, 219, 205 (base peak), 191, 177, and 163.

(Fig. 14)

Esterification of part B.

Part B (400 mg) was dissolved in ether and cooled to 5°. To this was added well cooled solution of diazomethane prepared from 1g of nitrosomethyl urea and was kept over night. On the following day excess of diazomethane was destroyed with acetic acid. The ether solution was washed with water, 10% sodium

bicarbonate solution and again with water till neutral and then dried over anhyd. Na_2SO_4. Evaporation of ether yielded a gummy residue ($\simeq$ 350 mg).

Chromatography of the esterified mass. Isolation of 2α-carbomethoxy-A-nor friedelin, 138, and 2,3 seco methyl-friedelinate

The esterified mass showed the presence of two different compounds on chromatoglate. The compounds were separated by column chromatography over a deactivated alumina column (30 g). The column was developed with petroleum ether and then eluted with the following solvents.

Table - 23

Eluent	Fractions 50 ml each	Residue on evaporation	Melting point ^oC
Petroleum ether	1-2	Nil	-
Petroleum-ether-benzene (4:1)	3-7	White solid ($\simeq$ 20 mg)	252-54^o
Petroleum ether-benzene (3:2)	8-9	Nil	Nil
Petroleum ether-benzene (2:3)	10-18	White solid ($\simeq$ 50 mg)	168-70^o

Elution with solvents of higher polarity did not afford any solid material.

Compounds of flask 3-7 (Table - 23) showed homogenity on TLC and, therefore, these were combined ($\simeq$ 20 mg). These on crystallisation from chloroform-methanol yielded shining crystals

of 2 α carbomethoxy-A-nor-friedelane, 138, m.p. 263-65°.

Analysis:		% C	% H
$C_{31}H_{52}O_2$	Required	81.52	11.48
	Found	81.12	11.43

IR : ν_{max}^{Nujol} 1730, 1165 ($-COOCH_3$) cm^{-1}

(Fig. 15)

^1H NMR (δ, $CDCl_3$) : 0.77 to 0.94 (4s, 12H, 4t-CH_3)

0.99 + 1.01 (d, J = 6 Hz, 3H, $CH - CH_3$)

1.17 to 1.28 (3s, 9H, 3t - CH_3)

2.90 (m, $W_{\frac{1}{2}}$ = 14 Hz, 1H, $H\overset{|}{C}-COOCH_3$)

3.64 (s, 3H, $-COOCH_3$)

(Fig. 16)

Mass: m/e 456 (M^+), 332, 303, 221, 219, 205, 191, 177 and 163

(Fig. 17)

The fractions 10-18 (Table -28) were found homogeneous and hence were combined ($\simeq$ 50 mg). This on crystallisation from a mixture of chloroform and methanol yielded white crystals of 2,3 seco methyl friedelinate, 139, m.p. 175-77°.

Analys:		% C	% H
$C_{32}H_{54}O_4$	Required	76.83	10.36
	Found	76.45	10.83

IR : $\overset{Nujol}{max}$ 1730, 1720, 1120, 1110 (2-COOCH_3) cm^{-1}

(Fig. 18)

^{1}H NMR : 0.88 to 1.03 (4s, 12H, 4t-CH_3)

(,CDCl_3) 1.13 1.16 (d, J = 8 Hz, 3H, HC-CH_3)

1.19 to 1.25 (3s, 9H, 3t-CH_3)

2.3 (q, J = 10 Hz, 1H, H-C-CH_3)

3.62 and 3.65 (2s, 6H, 2-OOCCH_3)

(Fig. 19)

Mass : m/e 502 (M), 487, 471, 455, 442, 429, 415, 335, 301, 273, 245, 219, 205 and 191

(Fig. 20)

Hydrolysis of 2,3 seco-methyl friedelinate, 139, : Isolation of 2, 3-seco-friedelinic acid

2, 3 seco-methyl friedelinate, 139, (25 mg) dissolved in benzene (2 ml) was refluxed in 10% methanolic KOH (6 ml) for 4 hours. The mixture was cooled, acidified with dil. HCl and extracted with ether. Removal of the solvent afforded a solid, which on repeated crystallisation from methanol furnished 2, 3 seco-friedelinic acid, 140, m.p. 280° (d).

Analysis		% C	% H
$C_{30}H_{50}O_4$	Required	75.90	10.62
	Found	75.89	10.66

Isolation of taraxerone , 141 ,from the neutral part of the benzene extract of Sapium baccatum Roxb.[125]

Dried and powdered stem bark of Sapium baccatum Roxb (2 kg) was extracted with benzene in a Soxhlet apparatus for twenty hours. On cooling the benzene extract, a yellow insoluble compound separated out, which was collected by filtration and was kept aside (identified as 3, 5'-di-O-methyl ellagic acid)[126]. From the clear filtrate, benzene was distilled off and the residual gummy solid (30 g) was taken up in ether (2 lts). A cloudy precipitate, which remained in ether extract was separated by filtration. The clear ether solution was washed with 10% aqueous sodium hydroxide solution (4 x 200 ml) and then washed with cold water till washings were neutral and dried over anhyd. Na_2SO_4.

The solvent was evaporated when the neutral material (10.6 g) was obtained as a yellow gummy solid, which after chromatography and crystallisation from chloroform-methanol

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125. H.N. Khastgir, B.P. Pradhan and D.R. Misra, J. Ind.Chem.Soc., 46(7), 663 (1969)

126. D.R. Misra, B.P. Pradhan and H.N. Khastgir, J.Ind.Chem.Soc., 46(9), 485 (1969)

mixture gave shining crystals (1.3 g), m.p. 238-40, $[\alpha]_D$ 10.8° identical in all respects with authentic sample of taraxerone (mixed m.p., co-TLC, co-IR).

Other compounds isolated were 1-hexacosanol, taraxerol and baccatin.

Oxidation of taraxerone with Hydrogen peroxide in presence of selenium dioxide.

To a solution of taraxerone, 141, (0.9 g) in tert-butanol (80 ml) was added hydrogen peroxide (15 ml, 17%) and selenium dioxide (0.225 g). It was then refluxed on water bath for 20 hours when precipitated black selenium metal indicated completion of the reaction. The reaction mixture was separated into neutral and acid parts following the methods stated in the case of lupanone, 130, and friedelin, 136.

Chromatography of neutral part : Isolation of taraxerone 1 , 2 epoxide, 142; 4, 23, 24-tri-nor-taraxene 3 5 H olide 144 and taraxerone - -lactone 146.

The gummy residue (200 mg) obtained in neutral part was chromatographed over a deactivated alumina column (20 g). The mass was dissolved in minimum volume of benzene and the column developed with petroleum ether followed by elution with the following solvents.

Table - 28

Eluent	Fractions 50 ml each	Residue on evaporation	Melting point ^{o}C
Petroleum ether	1-2	Nil	-
Petroleum ether-benzene (4:1)	3-11	White solid ($\simeq$ 25 mg)	m.p. 179^{o}
Petroleum ether-benzene (3:2)	12-13	Nil	-
Petroleum ether-benzene (2:3)	14-24	White solid ($\simeq$ 180 mg)	m.p. 212^{o}

Further elution with higher polar solvents did not afford any solid material.

Compound in fraction 3-11 (Table - 28) showed homogenity on t.l.c. plate and hence were combined. After crystallisations from chloroform-methanol, shining crystals of taraxerone 1α, 2α epoxide, 142, m.p. 188-90^{o} was obtained.

Analysis:		% C	% H
$C_{30}H_{46}O_2$	Required	82.14	10.57
	Found	82.19	10.51

IR : ν_{max}^{Nujol} 1705, 1255 (epoxide)

and 820 (trisubstituted double bond) cm^{-1}

(Fig. 21)

^{1}H NMR : 0.83 to 1.25 (8s, 24H, 8t-C<u>H</u>$_3$)
(δ, $CDCl_3$) 3.35 and 3.52 (2d, J = 4.5 Hz.
and 4Hz, 2H, <u>H</u>C(O)C<u>H</u>)
5.52 (m, 1H, >C = C <u>H</u>-)

(Fig. 22)

Mass : m/e 438 (M^+), 423, 314, 299, 205, 204 and 189.

(Fig. 23)

Compound in fractions 14-24 (Table - 28) were combined, which on fractional crystallisations yielded 4, 23, 24 tri-nor taraxene 3 ⟶ 5 αH olide, <u>144</u>, m.p. 228-30^0 and taraxerone 3 ⟶ 4 olide, <u>146</u>, a ϵ-lactone, m.p. 218-20^0.

Analysis:		% C	% H
$C_{27}H_{42}O_2$	Required	81.35	10.62
	Found	80.98	10.69

IR : ν_{max}^{Nujol} 1750 cm^{-1} (δ-lactone)
810 cm^{-1} (trisubstituted double bond)

(Fig. 24)

^{1}H NMR : 0.83 to 1.12 (6s, 18H, 6t-C<u>H</u>$_3$)

(δ, $CDCl_3$) 2.26 (m, 2H, -C<u>H</u>$_2$ - C(=O) -),

3.92 (q, J_{aa} = 12 Hz, J_{ae} = 5 Hz,

1H, -COO - C<u>H</u> - CH_2)

5.57 (m, 1H, $>C=CH-$)

(Fig. 25)

Mass : m/e 398 (M^+), 384, 274, 259, 205, 204, 194 and 189.

(Fig. 26)

For compound taraxerone ϵ-lactone, <u>146</u> :

Analysis:		% C	% H
$C_{30}H_{48}O_2$	Required	81.76	10.98
	Found	81.22	10.89

IR : ν_{max}^{Nujol} 1720 (ϵ-lactone) and 810 (trisubstituted double bond) cm^{-1}

(Fig. 27)

Mass : m/e 440 (M^+), 316, 301, 205, 204 and 189.

<u>Esterification of acid part:</u>

The acid part ($\simeq$ 450 mg) was esterified in the same way as was done in the case of lupanone and friedelin.

The ester ($\simeq$ 400 mg) obtained as a yellow gummy mass showed presence of two compounds on chromatoplate. In order to separate the compounds, the mass was chromatographed.

Chromatography of esterified product: Isolation of 2 methoxy carbonyl-A-nor taraxerene and 2,3-seco methyl taraxene dicarboxylate , 148

The chromatography of the esterified product was carried out on a deactivated alumina column (25 g). The mass was dissolved in minimum volume of benzene and poured on the column, and was developed with petroleum ether and eluted with following solvents:

Table - 29

Eluent	Fractions 50 ml each	Residue on evaporation	Melting point ^{o}C
Petroleum ether	1	Nil	-
	2-10	White solid (80 mg)	148°
Petroleum ether: benzene (4:1)	11-12	Nil	-
Petroleum ether : benzene (3:2)	13-14	Nil	-
Petroleum ether: benzene (1:1)	15-25	White solid ($\simeq$ 140 mg)	135°

Further elution with more polar solvent did not yield any solid material.

Compound in flask 2-10 (Table - 29) showed homogenity on the plate, hence, these were combined. After repeated crystallisations from chloroform-methanol shining crystals of 2α-methoxy carboxyl-A-nor-taraxerene, 147, was obtained with unchanged m.p. 161-63°.

Analysis :		% C	% H
$C_{31}H_{50}O_2$	Required	81.52	11.48
	Found	80.98	11.62

IR : ν_{max}^{Nujol} 1735, 1155 ($COOCH_3$), 815 (trisubstituted double bond) cm^{-1}.

(Fig. 29)

^1H NMR (δ, $CDCl_3$) : 0.82 to 1.12 (8s, 24H, 8t-CH_3), 2.75 (q, J_{aa} = 11 Hz, J_{ae} = 5 Hz, 1H, H-C-$COOCH_3$), 3.6 (s, 3H, -$COOCH_3$), 5.54 (m, 1H, H-C = CH_2)

(Fig. 30)

Mass : m/e 454 (M^+), 439, 343, 330, 315, 301, 277, 204 and 189.

(Fig. 31)

TLC of compounds in flasks 15-25 (Table - 29) indicated homogenity and, hence, were combined. After crystallisation from a mixture of chloroform-methanol, it yielded white crystals, m.p. 149-51° and characterised as 2,3 seco-methyl taraxene dicarboxylate, 148.

Analysis :		% C	% H
$C_{32}H_{54}O_4$	Required	76.45	10.83
	Found	75.92	10.92

IR : ν_{max}^{Nujol} 1730, 1720 (2-$COOCH_3$), 810 (trisubstituted double bond) cm^{-1}

(Fig. 32)

^1H NMR (δ, $CDCl_3$) : 0.81 to 1.25 (8s, 24H, 8t-CH_3)
2.30 (m, 2H, H_2C-$COOCH_3$)
3.60 and 3.65 (2s, 6H, 2-$COOCH_3$)
5.54 (m, 1H, $>C=CH-CH_2$)

(Fig. 33)

Mass : m/e 500 (M^+), 485, 470, 468, 440, 425, 399, 376, 361, 344, 316, 257, 204, 189.

(Fig. 34)

Hydrolysis of seco-diester, 148 : Isolation of taraxadioic acid

The seco-diester, 148 (20 mg) was hydrolysed with methanolic KOH following the method stated for seco-diesters of lupanone and friedelin. The mass obtained after hydrolysis ($\simeq$ 15 mg) was crystallised from methanol to afford crystals of taraxadioic acid, 149, m.p. 276-78°.

Analysis :		%C	% H
$C_{30}H_{50}O_4$	Required	75.90	10.62
	Found	75.82	10.69

CHAPTER - III

Section A

A Short review of reactions of N-bromosuccinimide

N-bromosuccinimide (NBS) has been in use for allylic bromination since 1919, when Wohl and then Zeigler made detailed studies on application of the reagent for allylic bromination. The reagent also reacts with olefins to add bromine to the double bond or act as a source of hypohalous acid in aqueous solution.

The reagent is also in extensive use since 1969 as an effective reagent for oxidation of allylic methylene to carbonyl function[127-129].

In the following some applications of N-bromosuccinimide is discussed in order to explain formation of the products of reaction between lupenyl acetate and N-bromosuccinimide.

Bromination and Dehydrobromination.

The ability of NBS to act as a specific reagent for allylic brominations has been used to great advantage for the introduction of supplementary double bonds, particularly in cyclic systems. In this way, a large number of monosaturated compounds have been converted to conjugated dienes and trienes, including the aromatization of substituted cyclohexenes and cyclohexadienes.

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127. B.W. Finucane and J.B. Thomson, Chem.Comm., 1220 (1969)
128. B.W. Finucane and J.B. Thomson, J.Chem.Soc., (Parkin I), 1856 (1972)

The method involves a two-step bromination-dehydrobromination process. In many cases, the intermediate bromocompound is isolable and the second step proceeds only after treatment with a base. There are numerous examples, however, in which the bromo-intermediate is unstable under the reaction conditions and spontaneously loses the element of hydrogen bromide to form the final product. There appears to be no definite structural guide, which can be used to predict in advance whether dehydrogenation will occur without the use of a base. Out of a wide variety of substances which have been used as base to effect the second step of the process, tertiary amines, namely, pyridine, quinoline and γ-collidine etc. have found wide application.

While a number of relatively simple olefins have been converted to dienes in this manner, the method has found wide application in a wide range of natural products such as terpenes, steroids, alkaloids etc.

Allylic bromination of Δ^4-cholesten-3-one, 150 by NBS[130] gave the 6-bromocompound 151, which on heating with collidine readily formed $\Delta^{4,5,6,7}$-cholestadien-3-one, 152 . In a similar fashion $\Delta^{1,2,4,5}$-cholestadien-3-one was converted to $\Delta^{1,2,4,5,6,7}$ - cholestatrien-3-one.

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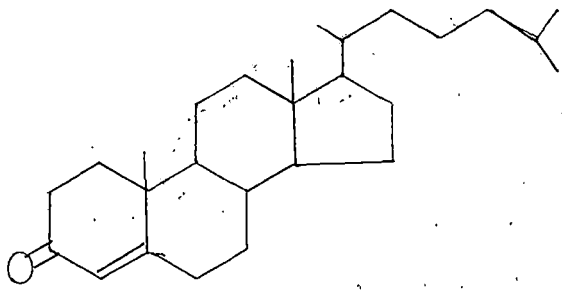
129. S. Corsano and G. Piancatelli, Ann. Chem. (Italy), 55, 742 (1965)

130. H.H. Inhoffen, G. Stoeck and H. Martens, Ann., 563, 131 (1949)



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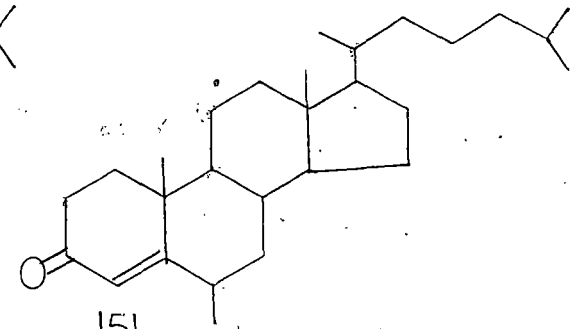

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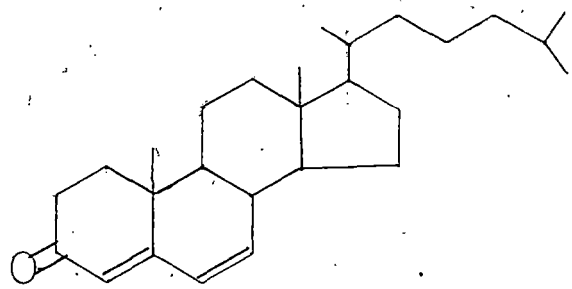

152

An interesting example of allylic bromination with subsequent spontaneous dehydrobromination is provided[131] by the reaction of NBS with Δ^2 - 3-acetoxy-cholestene 153. This enol acetate of cholestanone 154 (ring A/B trans) reacted with NBS in CCl_4 to give a mixture of Δ^1 and Δ^4 -Cholesten-3-one 155 and 156 and 2-bromocholestan-3-one 157, the amount of which increased with reaction time at the expense of 155.

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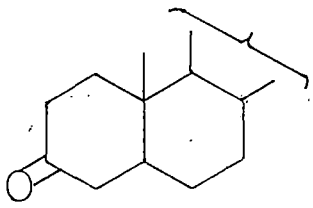
131. M. Rubin and B.H. Armbrecht, J.Am.Chem.Soc., 75, 3573 (1953)



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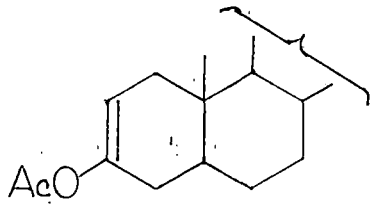

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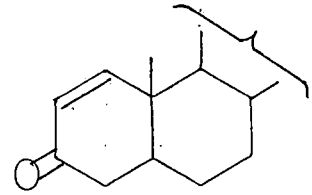

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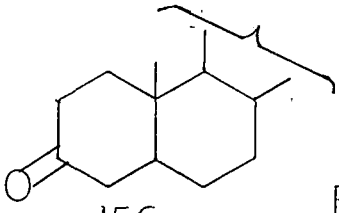

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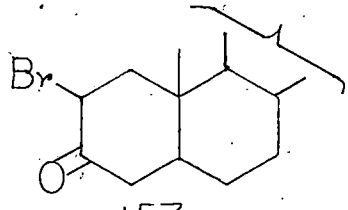

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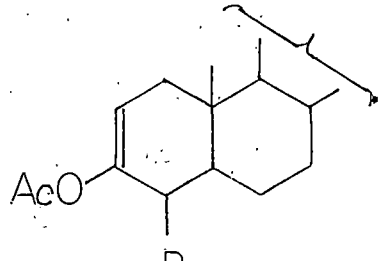

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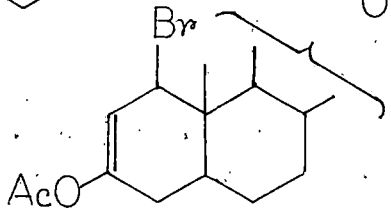


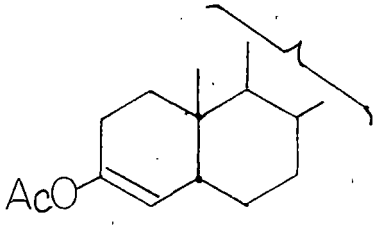
159

The origin of the reaction products has been attributed to the thermal and acid instability of the intermediate allylic bromination products, 153 and 159 . The formation of the compound, 156 has been explained on the basis of spontaneous loss of hydrogen bromide from, 158, and then acid catalyzed cleavage of the resulting enol acetate. Owing to absence of an available hydrogen for spontaneous dehydrogenation, 159 is more stable than 158. However, the rapid formation of 155 suggests the acid cleavage of 159 and ketonisation of the resulting enol to produce a β-bromoketone, which does possess a hydrogen atom on an adjacent carbon.

The reaction becomes complex as time increases because of the formation of hydrogen bromide in the reaction mixture, which

catalyzes the regeneration of 154 from 153 and results in the formation of free bromine by reaction with NBS. Bromine and 154 react to form compound 157. This compound was obtained[132] from NBS and 154.

The reaction of NBS with Δ^3-3-acetoxycoprostene 160 (rings A/B cis) indicated that in 160, the activation energy of both allylic position (C_2 and C_5) was of similar order of magnitude. The attack at the tertiary C_5 position was somewhat unexpected since it was anticipated that more vigorous activation would be required for this type of substitution by NBS.



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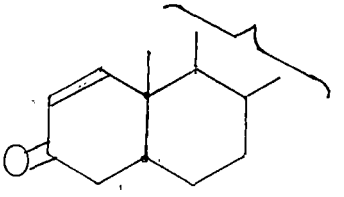

161

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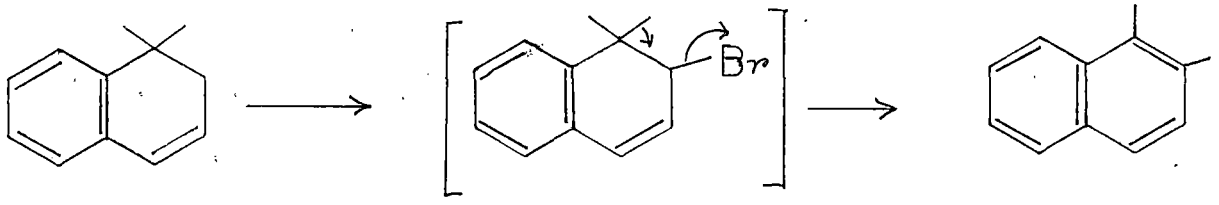
132. C. Djerassi and C.R. Scholz, Experimentia, 3, 107 (1947)

Steroid sapogenins containing the Δ^5-3-OH group and a spiroketal side chain in the 16, 17 position are selectively brominated in the 7-position with NBS under irradiation with artificial light. Dehydrobromination with collidine gives $\Delta^{5,7}$-sapogenins, useful as intermediates for synthetic hormones or after irradiation, as products with antirachritic activity[133]. The method has also been used in structural studies of the terpenoids[134]. Similar action of NBS on friedelin and bromofriedelin has also been reported[135].

Barnes et al[136] has shown that treatment of 1,1, 6-trimethyl 1, 2 dihydronaphthalene with NBS gave an allylic bromide which aromatized to 1, 2, 6-trimethyl naphthalene by silver ion or heat (temperature of refluxing carbon tetrachloride).



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133. G. Rosenkranz, J. Pataki and C. Djerassi, Chemical Abstract, 52, 14721 (1958)

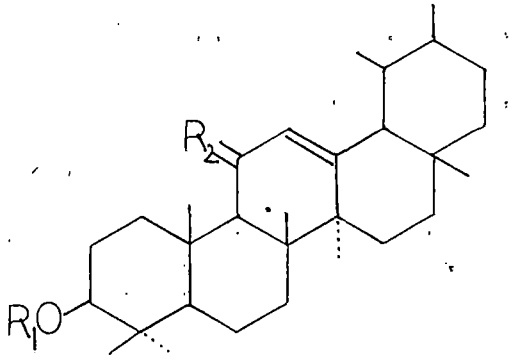
134. D. Lavie and Y. Shvo, Chem. and Ind., 403 (1960)

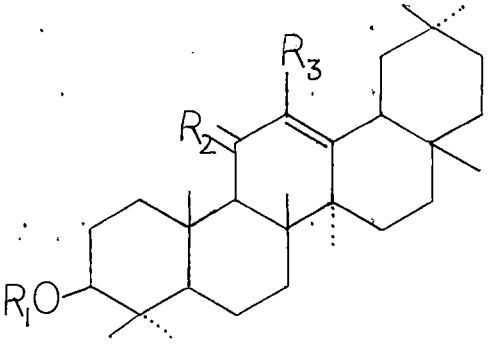
135. V.V. Kane and R. Stevenson, Chem. and Ind., 1243 (1960)

136. R.A. Barnes and G.R. Buckwatter, J.Am.Chem.Soc., 73, 3858 (1951)

Oxidation of allylic methylene to carbonyl group

N-bromosuccinimide is in extensive use since 1969 as an effective reagent for oxidation of allylic methylenes to carbonyl function. Corsano et al[137] reported direct oxidation of the allylic methylene to carbonyl group with NBS in aqueous dioxane solution. Thus, 3β-acetoxy-urs-12-ene-11-one 163 was formed in 80% yield from α-amyrin acetate 162.





162 R_1 = Ac, R_2 = H

163 R_1 = Ac, R_2 = O

164 R_1 = Ac, R_2 = H_2, R_3 = H

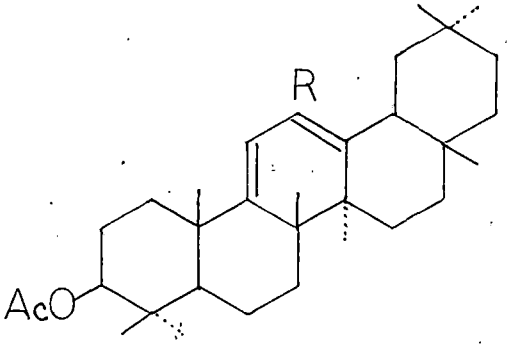
165 R_1 = Ac, R_2 = O, R_3 = H

166 R_1 = Ac, R_2 = OH, R_3 = H

167 R_1 = Ac, R_2 = OMe, R_3 = H

168 R_1 = Ac, R_2 = OAc, R_3 = H

169 R_1 = Ac, R_2 = OH, R_3 = Br



170 R = H

137. S. Corsano and G. Piancatelli, Ann. Chem. (Italy), 55, 742 (1965)

Finucane et al[138,139] reported an improved method for the direct oxidation of the allylic methylene to carbonyl by the action of NBS and simultaneous irradiation with visible light. They claimed that when trisubstituted olefins containing an allylic methylene groups were treated with NBS in aqueous dioxane followed by irradiation with visible light, α,β unsaturated ketones were formed in near quantitative yield. Finucane et al treated β-amyrin acetate 164 with NBS in aqueous dioxane in a typical ambient light experiment as described by Corsano et al[137]. They isolated starting material (ca 50%), 3 β-acetoxy-olean-12-ene-11-one (ca 40%), bromocompound (ca 8%) and 3 -acetoxy-olean-12-ene-11-α-ol, 166 (ca 2%), Oxidation of the latter, 166, with CrO_3 in acetone afforded 3β-acetoxy-olean-12-ene-11-one 165.

In another experiment the products were isolated by chromatography over alumina and yielded β-amyrin acetate 164 (35%), 3β-acetoxy-olean-12-ene-11-one 165 (ca 40%), bromocompounds (ca 10%) and polar materials (ca 10%). The polar fraction on elution with methanol was acetylated and on rechromatography gave 11α-methoxy-olean-12-ene-3β-yl-acetate, 167, together with smaller amounts of 11α ol 166 and olean-9(11), 12 diene-3β-yl-acetate 170 and a trace of 3β, 11α-diacetate 168.

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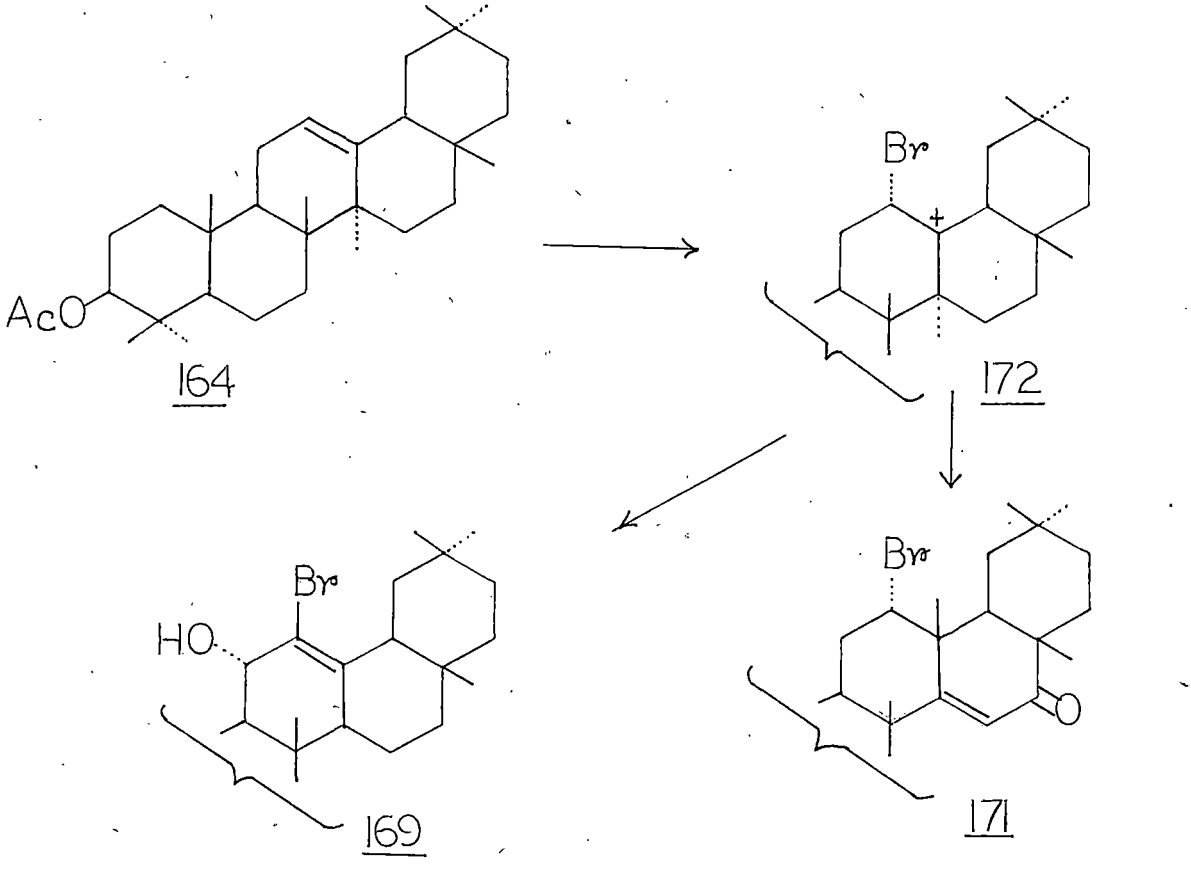
138. B.W. Finucane and J.B. Thomson, Chem. Comm., 1220 (1969)

139. B.W. Finucane and J.B. Thomson, J.Chem.Soc. (Perkin I) 1856 (1972)

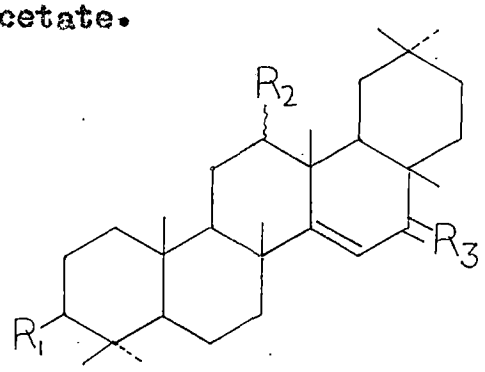
The fraction containing the bromocompounds was resolved by chromatography over alumina and fractionally crystallised into two components. The major product was identified as 3β-acetoxy-12-bromo-olean-12-ene-11-ol 169. The minor component of the mixture of bromocompounds was identified as 12α-bromo - 16-one 171. The mechanism proposed for the formation of 169 and 171 suggested that the initial α-face attack on β-amyrin acetate 164 at C-12 would lead to a carbonium ion, 172. Elimination of a proton from C-12, followed by allylic hydroxylation would then lead to 169. Alternatively, migration of 14α-methyl group to C-13, elimination of a proton from C-15 and subsequently allylic oxidation would give 171 (Scheme - XXVI).

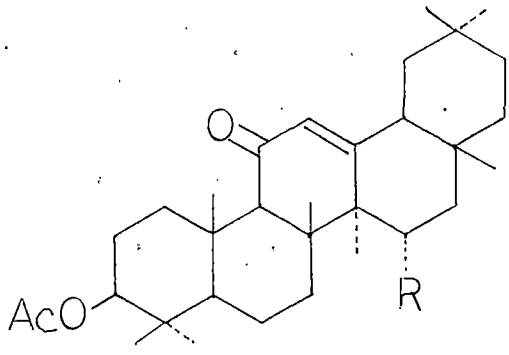
Scheme - XXVI



164 172 169 171

Thomson et al[140] carried out oxidation of taraxeryl acetate 173 by following the method of Corsano et al[137] and obtained two major products to which they assigned structure of 16-oxo taraxeryl acetate 174 (ca 30%) and 16 β-hydroxy taraxeryl acetate 175 (ca 30%). Treatment of 175 with chromic acid in acetone gave the unsaturated ketone 174. The workers also carried out the reaction on 173 by the method described for β-amyrin acetate, which resulted in the formation of 12α-bromo-taraxer-14-ene-16-one 176. Oxidation of taraxeryl acetate with NBS in aqueous dioxane[138] for five and one half hours in presence of $CaCO_3$ in visible light gave a compound 177 the structure of which was established as 11-keto-15-bromo-β-amyrin acetate, which in turn yielded a halogen free compound 178 on treatment with Zn-dust in acetic acid. Its structure was established as β-amyrenonyl acetate.





173 R_1 = OAc R_2 = H, R_3 = H_2

174 R_1 = OAc, R_2 = H, R_3 = O

175 R_1 = OAc, R_2 = H, R_3 = -OH, H

176 R_1 = OAc, R_2 = Br, R_3 = O

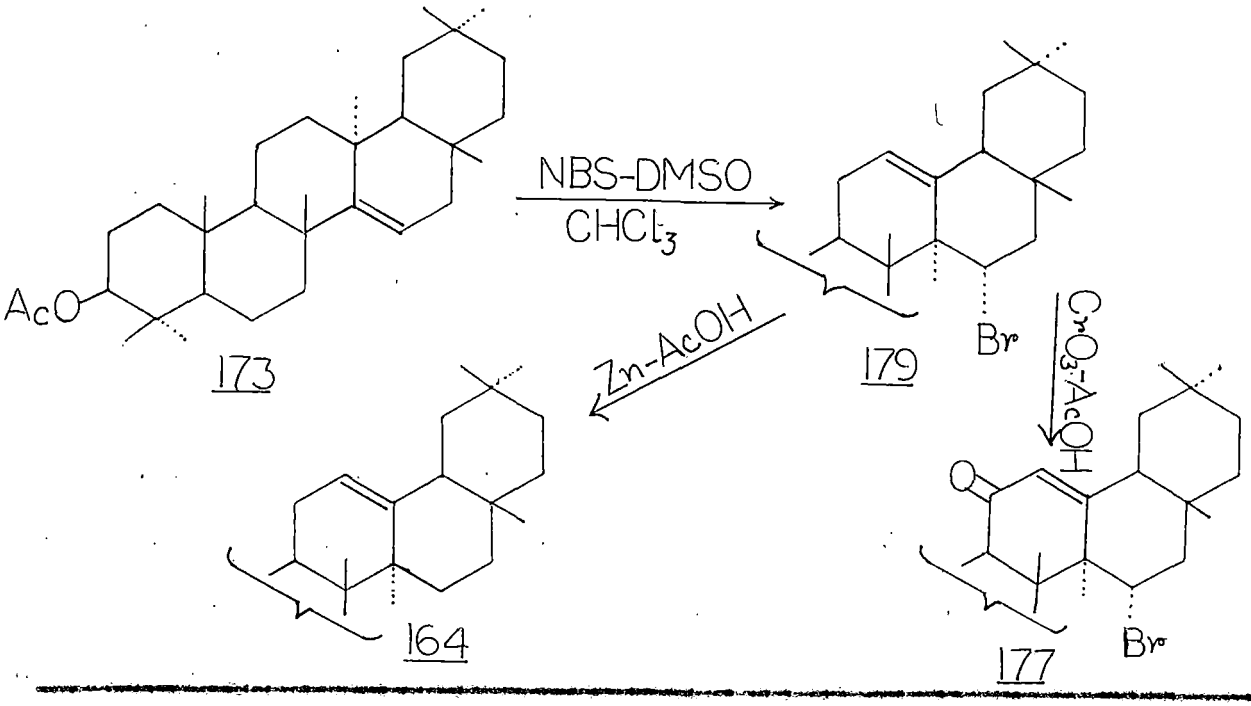
177 R = Br

178 R = H

---

140. Ref. 128 of this chapter.

Khastgir et al[141] carried out the oxidation of taraxeryl acetate, 173 by the method of Dalton[142] using NBS in DMSO solvent.[143] Treatment of taraxeryl acetate 173, with aqueous dimethyl sulphoxide in chloroform and NBS in dark afforded a solid 179. The compound 179 on treatment with zinc-acetic acid yielded β-amyrin acetate 164. The bromine atom at 15 position of 179 would be expected to have the same stereochemistry as in the case of product from NBS - aqueous dioxane oxidation method. Compound 179 on oxidation with chromium trioxide - acetic acid[144] gave 177 identical with the product obtained from NBS-aqueous dioxane oxidation method.



173 179 164 177

141. K. Chattopadhaya, D.R. Misra and H.N. Khastgir, Ind.J.Chem. 14B, 403 (1976)

142. D.R. Dalton and V.G. Jones, Chem.Comm., 2875 (1967)

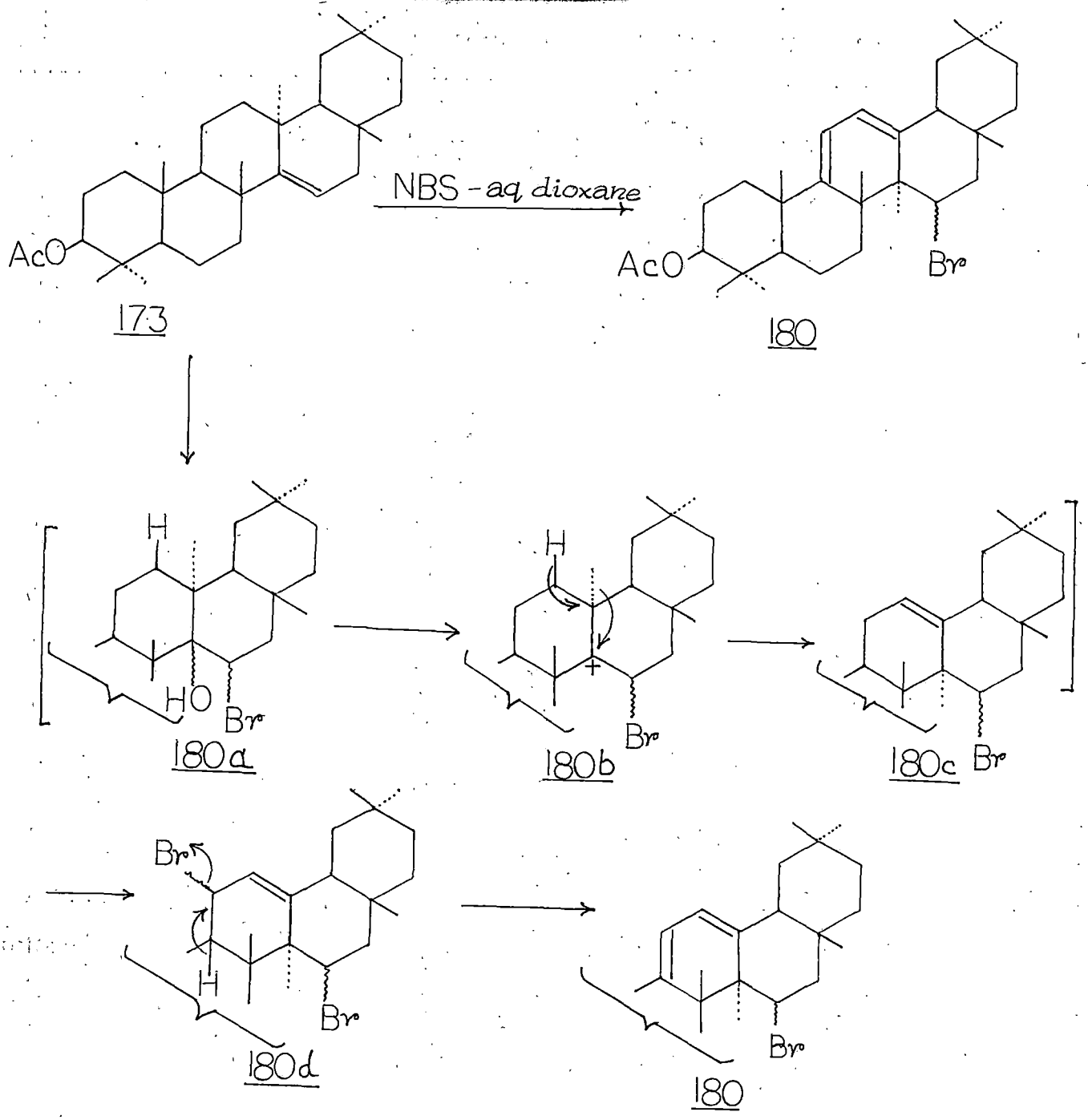
143. J. Klinot, K. Waisser, L. Streinz and A. Vystreil, Coll. Czech. Chem. Comm. 35, 3610 (1970)

144. Ruzicka and Muller, Helv. Chem. Acta, 22, 758 (1939)

The second compound devoid of bromine was identified as 16-oxo-taraxeryl acetate 174.

The third product was found to be 180. The mechanism for the formation of 179 was proposed as in Scheme - XXVII.

Scheme - XXVII

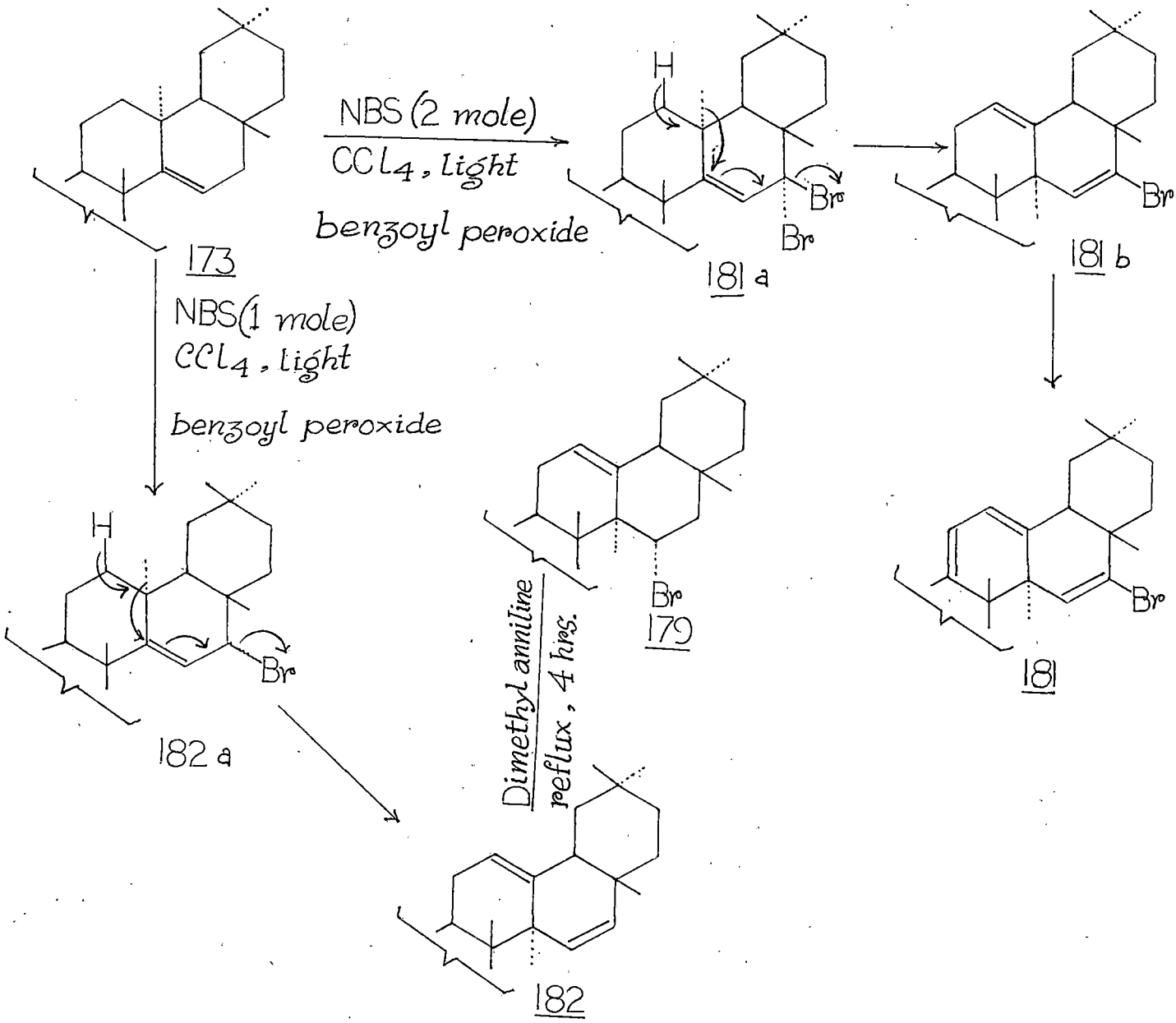


Khastgir et al[141] also studied the reaction of taraxeryl acetate 173 with 2 moles equivalent of NBS in carbon tetrachloride using visible light for three hours and isolated a product, which was assigned the structure 181.

When the same reaction was carried out with one mole equivalent of NBS, it afforded a halogen free product of structure 182, identical to that obtained by dehydrobromination of 179.

The mechanism for the formation of 180 and 181 was proposed as shown in Scheme - XXVIII.

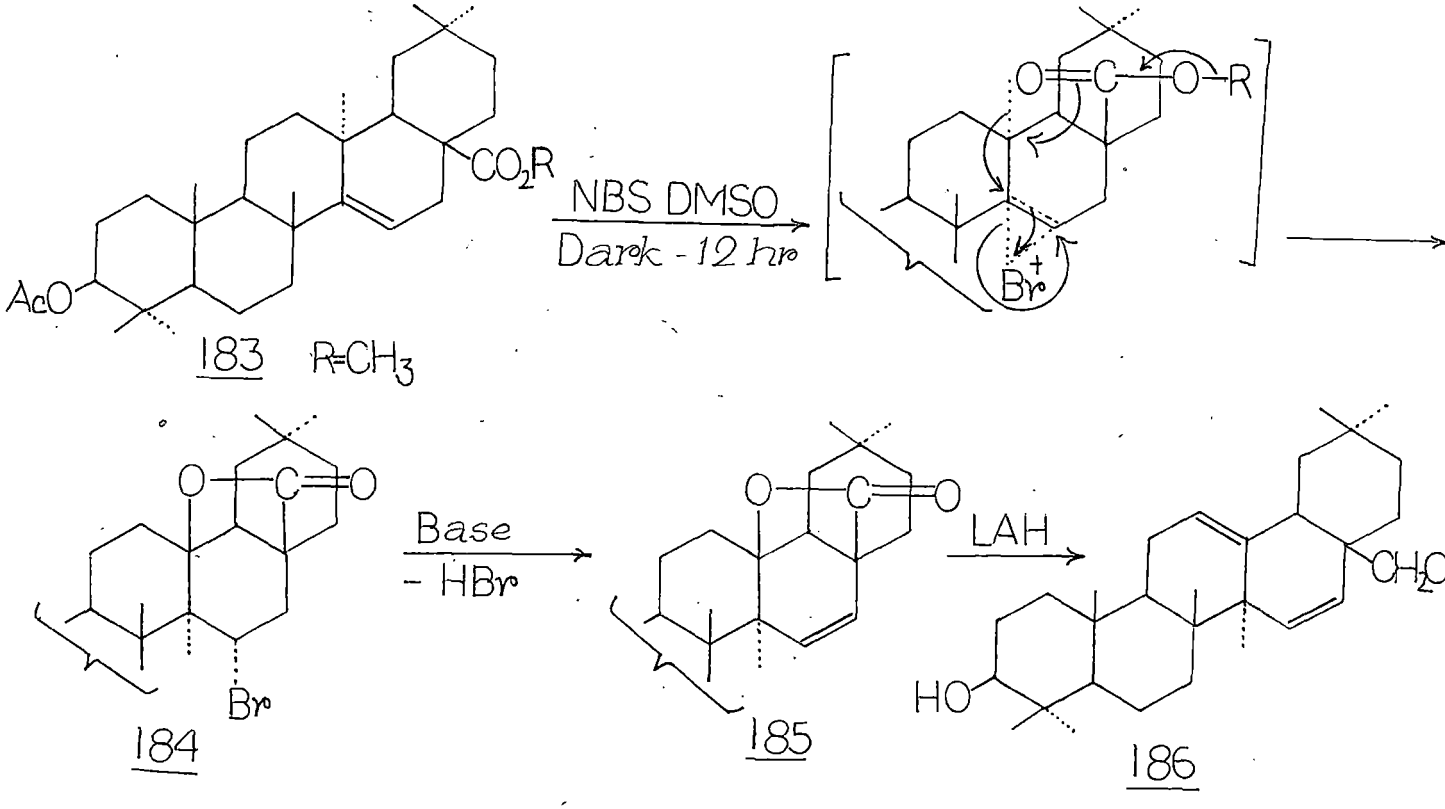
Scheme - XXVIII



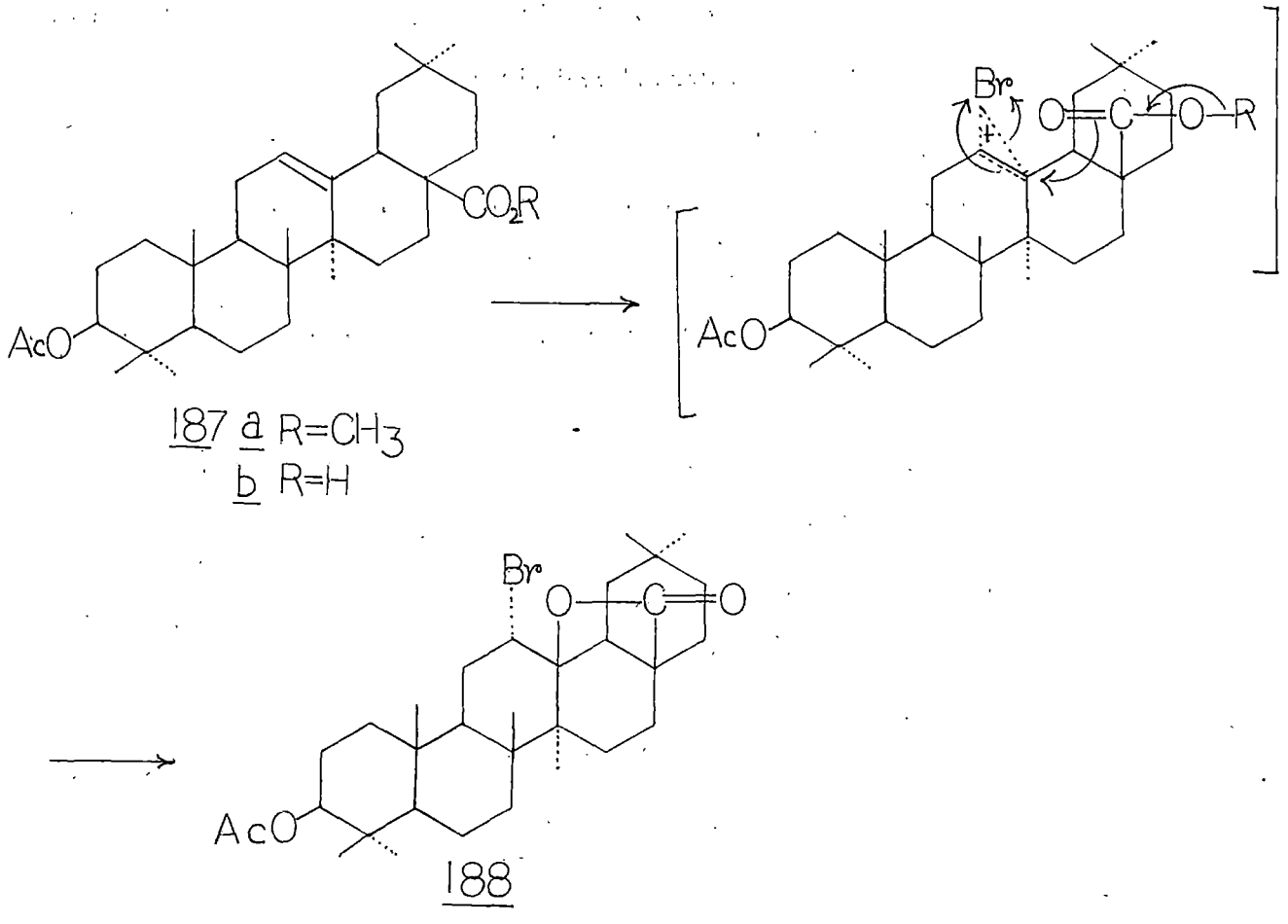
Pradhan et al[145] carried out the reaction of NBS on triterpene acids and esters. They studied the reaction of methyl acetyl aleuritolate 183 with NBS in DMSO in the dark for 12 hours and isolated a bromo-lactone 184. The structure of the bromo-lactone was confirmed from the fact that dehydrobromination with dimethyl aniline afforded 15, 16 -dehydrolactone 185 which on LAH reduction furnished aegiceradiol 186.

The mechanism of formation of 184 involved the attack of bromonium ion from NBS in DMSO at the double bond. Bromine being a bulky atom ultimately assumed the equitorial position so as to have the minimum strain and steric interaction. The next step involved concerted migration of the C-13 methyl to the C-14 position and elimination of the methoxy methyl to form the 28 → 13-olide 184.

Scheme - XXIX



Methyl acetyl oleanolate 187a and 3β-acetyl oleanolic acid 187b under the same condition afforded the bromolactone 188, which was found to be identical with 12α-bromo-oleanan-28 ⟶ 13 olide[146].

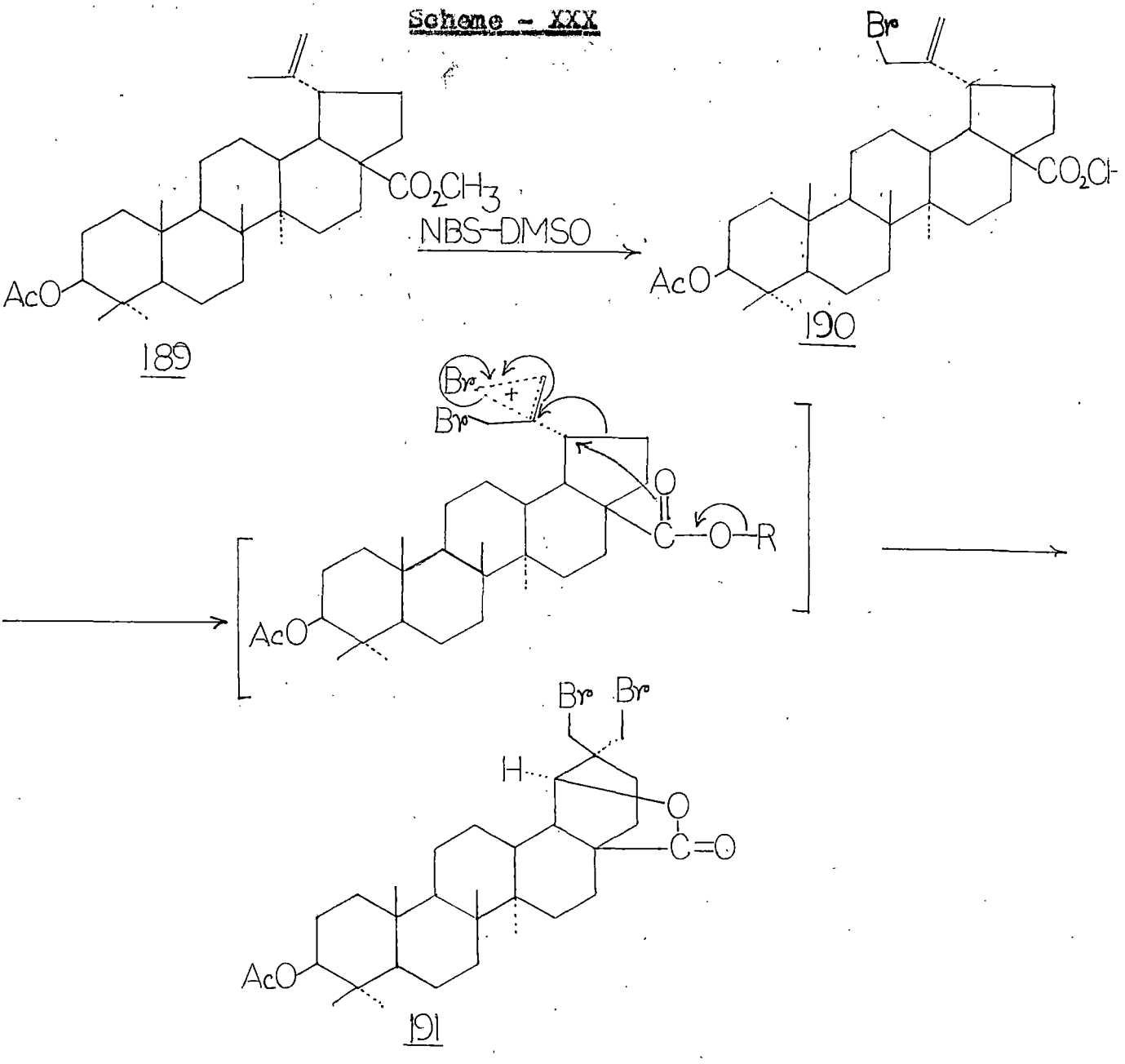


145. B.P. Pradhan, M.M. Mukherjee, D.K. Chakrabarti and J.N. Shoolery, Ind. J. Chem., 22B, 12 (1983).

146. D.H.R. Barton and N.J. Holeness, J.Chem.Soc., 78 (1952)

Methyl 3 β-acetylbetulenate 189 on similar reaction with NBS in DMSO afforded two different bromo-compounds. The less polar one was identified as methyl-30-bromo-3 β-acetyl betulenate 190. The more polar fraction was dibromolactone, 191. The proposed mechanism of formation of 189 and 191 is shown in Scheme - XXX below.

Scheme - XXX



191

Allylic hydroxylation by N-bromosuccinimide:

The N-bromosuccinimide may be used for the introduction of an allylic hydroxyl group. The method is indirect and usually involves allylic bromination and the conversion of the resulting bromide into alcohol via the formation of formate or acetate. Thus, 3-p-menthene-5yl bromide was prepared from 3-p-menthene using NBS in chloroform and UV light. The bromide was converted to 3-p-menthene-5yl formate by sodium formate and the crude ester on treatment with methanolic sodium carbonate gave dl-trans-3-p-menthene-5-ol[147].

A mixture of cis (38%) and trans (62%) cyclodecene formed the bromide, which on reaction with silver acetate in glacial acetic acid gave the crude acetate from which 2-cyclodecen-1-ol was obtained on treatment with methanolic hydroxide[148].

An example of the hydroxylation of steroids is illustrated by the transformation of 11-dihydro progesterone 192 to give $\Delta^{4,9(11)}$ pregenadien-12α-ol-3, 20 dione 193[149].

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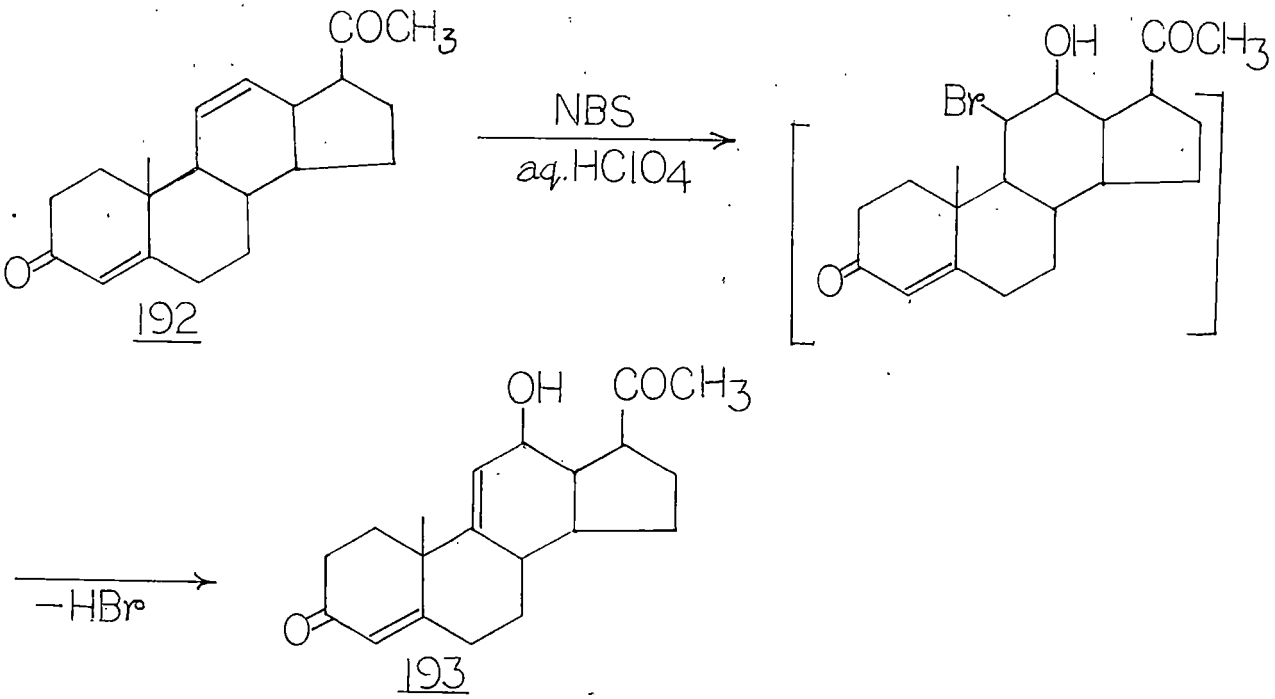
147. J. Fried and J.E. Herz, Chem. Abst., 52, 5491 (1958)

148. A.K. Macbeth, B. Milligon and J.S. Shannon, J.Chem.Soc. 2674 (1953)

149. A.C. Cope, M. Brown and H.H. Lee, J.Am.Chem.Soc., 80, 2855 (1958)

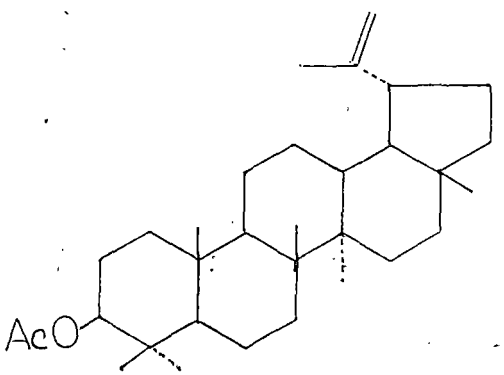

COCH3
NBS
aq.HClO4
OH
COCH3
Br
192
OH
COCH3
−HBr
193

SECTION - B

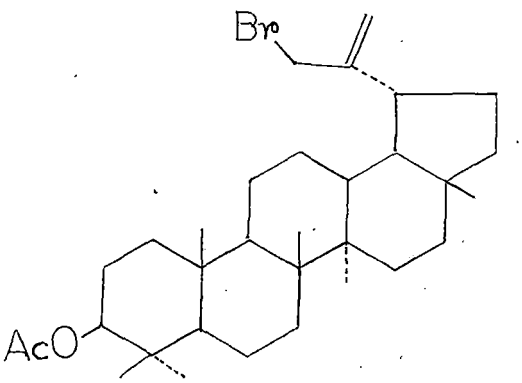
Studies on the action of NBS on lupenyl acetate:

The versatility of NBS is reflected in the review of different reactions involving the reagent. A number of compounds may be formed depending on the nature of the reactants and the reaction condition.

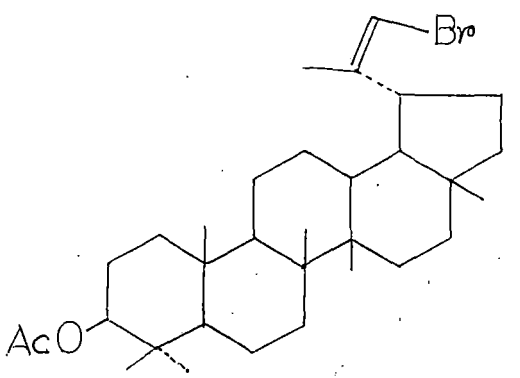
Ramachandra Rao et al[150] studied the oxidation of lupenyl acetate 194 with NBS in CCl_4 and exclusively isolated a product identified as 30-bromo-lupenyl acetate 195. They isomerised the



194



195

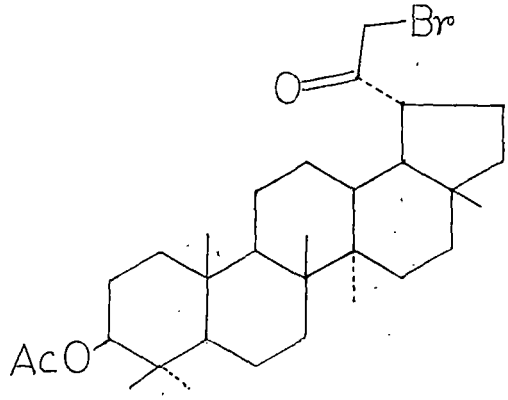


196

150. L.Ramachandra Rao, C.Shankara Rao and T. Sundara Ramaiah, Ind. J. Chem., 6, 16 (1968)

compound 195 with hydrobormic acid (60%, 1 ml) in acetic acid - chloroform (1:1, 10 ml) and isolated 3β-acetoxy-29-bromo-lup 20(29)-en 196.

Halsall et al[151d] studied the bromination of 194 with bromine in acetic acid at 0° and reported the isolation of 29 bromo-20(29) en-3β-yl-acetate 196, m.p. 196-98°, $[\alpha]_D$ 30°, $C_{32}H_{51}BrO_2$, together with an inhomogenous tribromo compound $C_{32}H_{51}Br3O_2$, m.p. 250-52° whose structure was not determined by them. When the same reaction was carried out by Halsall et al at -78°, they isolated 30-bromo-lup-20(29)-en-3β-yl-acetate 195, m.p. 235-36°, $C_{32}H_{51}BrO_2$. Ozonolysis of both 29 and 30 bromo compounds gave 3β-acetoxy-30-nor-lupan-20-one 197.



197

151a T.G. Halsall, S.R. Gupta and E.H.R. Jones, J.Chem.Soc., 5353 (1961)

Although the previous workers reported the reaction of lupenyl acetate with NBS, there is no report that the reaction has been studied in DMSO in the condition reported by Pradhan et al[145] in the case of 3β-acetylbetulinate 189. The isolation of the rearranged dibromolactone 191 besides 3β-acetyl-30-bromo-betulenate 190 prompted the present worker to explore the applicability of the reaction on lupenyl acetate 194.

Lupenyl acetate on oxidation with NBS in DMSO in dark for 24 hrs gave a mixture of compounds which on the examination showed the presence of at least three compounds. These compounds were separated by chromatography over silica gel column. The fraction eluted with petroleum-ether gave a solid (N_1) which showed positive Beilstein test for halogen and indicated the presence of two compounds on tlc experiment. Hence, that fraction was set aside for further treatment.

The fraction eluted with petroleum-ether : benzene (4:1) afforded solid (N_2) which also gave positive Beilstein test for halogen and existence of single compound was obvious from tlc experiment. The compound was crystallised from chloroform-methanol to afford fine crystals of m.p. 236-37°.

Further elution of the column with petroleum-ether : benzene (2:3) afforded an amorphous solid (N_3) by crystallisation from chloroform-methanol and showed m.p. 258-60°.

Characterisation of N_2 :

Elemental analysis established the molecular formula of N_2 as $C_{32}H_{51}O_2Br$, $[\alpha]_D$ 12°. Its IR spectrum (Fig. 35) shows the appearance of sharp peaks at 1725 and 1255 cm^{-1} assignable to an acetoxy moiety and peaks at 3015, 1640 and 880 cm^{-1} indicate the presence of a double bond in compound N_2. The signals of ^1H NMR spectrum (Fig. 36) for various protons and their probable assignments has been recorded in Table -30.

Table - 30

^1H NMR signals of N_2 in $CDCl_3$

Chemical shift, δ, ppm	Number of protons	Multiplicity of signals	Probable assignment
0.79	3	Singlet	
0.84	3	Singlet	6-C-CH_3
0.85	6	Singlet	
0.95	3	Singlet	
1.04	3	Singlet	
2.04	3	Singlet	-O-CO-CH_3
3.99	2	Singlet	H_2C - Br
4.48	1	Multiplet $W_{\frac{1}{2}}$ = 16 Hz	HC - O - O-
5.04	1	Singlet	H_2C = C
5.12	1	Singlet	

Fig.35 IR spectrum of 30-bromo-lup-20(29)-ene-3β-acetate,135.

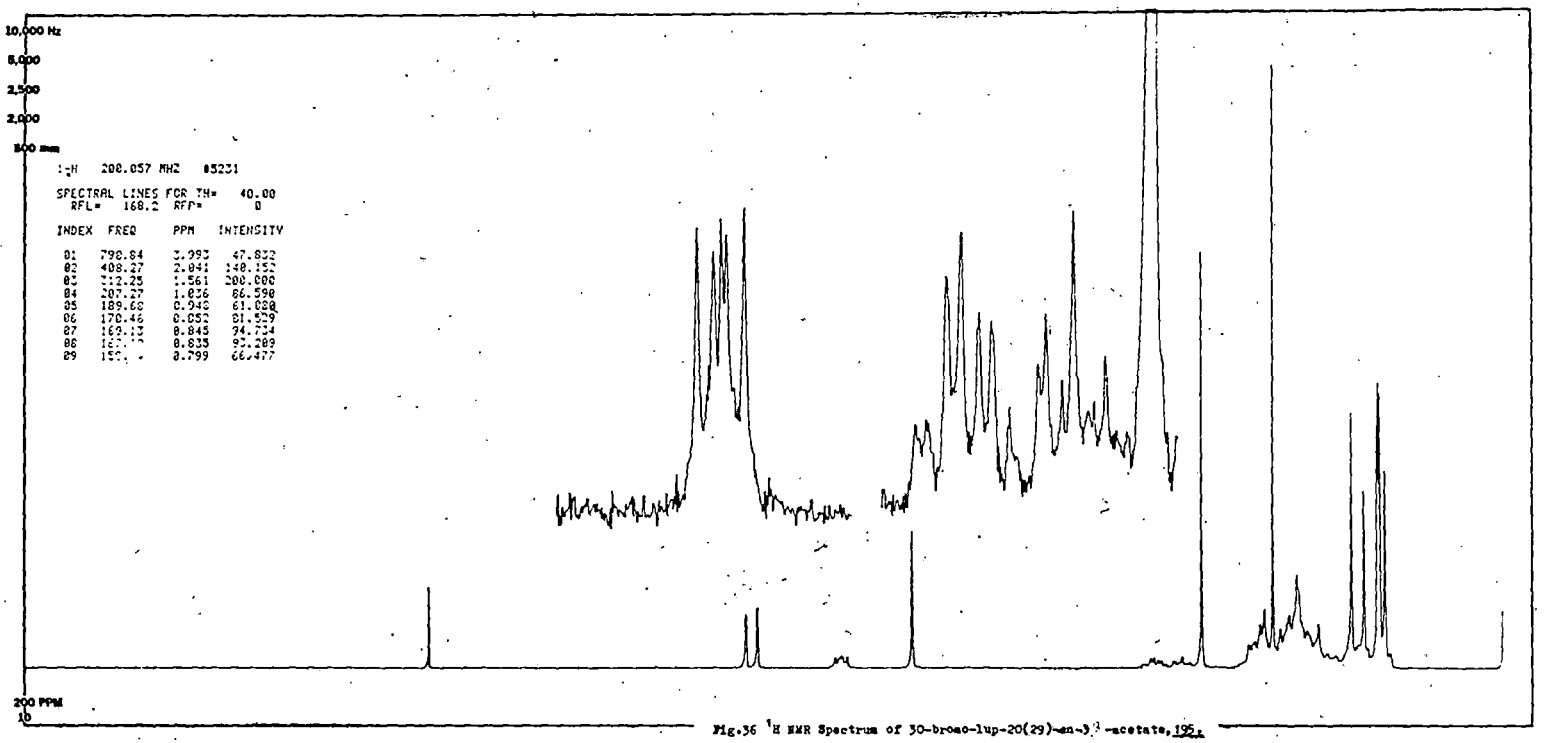


Fig.36 ^{1}H NMR Spectrum of 30-bromo-lup-20(29)-en-3β-acetate, 19$_{a}$

The appearance of singlets at δ 0.79, 0.84, 0.85, 0.95 and 1.04, assignable to eighteen protons indicate the presence of six tertiary methyl groups in compound N_2 instead of seven present in the starting material compound 194. Two singlets in the downfield region at δ 5.04 and 5.12 for one proton each indicate the presence of an end methylene group. The two proton singlet at δ 3.99 is due to a methylene group containing electronegative bromine atom which is responsible for large downfield shift of the methylene protons. Its appearance as singlet indicates free rotation of CH_2Br group in the molecule. The three proton singlet at δ 2.04 is due to the acetoxy methyl group. The multiplet centred at δ 4.48 assignable to one proton is due to the proton geminal to the acetoxy group. The high half width value ($W_{\frac{1}{2}}$ = 16 Hz) indicates the axial orientation of the proton with one axial and one equatorial neighbours. The ^1H NMR data thus support the observation of IR spectrum that the compound N_2 possess acetoxy and end methylene functionalities as was the case for its starting compound. Moreover, ^1H NMR data shows the presence of five tertiary methyl and one CH_2Br group in compound N_2. All these observations are satisfied by assuming structure 30-bromo-lup-20(29)-en-3β-yl acetate 195 for compound N_2.

Characterisation of N_3

Elemental analysis and mass spectrum indicated the molecular formula of the compound as $C_{32}H_{52}O_3Br$. On several crystallisations from a mixture of chloroform-methanol, it afforded

crystals of m.p. 258-60°. It gave positive Beilstein test for the presence of halogen but did not respond to TNM test showing the absence of unsaturation in the compound.

IR spectrum (Fig. 37) of the compound exhibits peaks at 3330 (-OH), 1732, 1250 (-O-CO-CH_3) and 1270-80 (CH_2Br) cm^{-1}. Thus, it indicates that the compound contains a hydroxy group and no double bond is present. It also indicates the presence of CH_2Br group in the compound. These observations from IR spectrum of N_3 is also found to be tenable from a careful examination of the 200 MHz ^1H NMR spectrum of the compound (Fig. 38). The signals for various protons together with their probable assignments as recorded in Table - 31 clearly indicate the presence of

Table - 31

^1H NMR signals of N_3 in $CDCl_3$

Chemical Shift, δ (ppm)	Number of Protons	Multiplicity of signals	Probable assignments
0.84	3	Singlet	
0.85	3	Singlet	6 - C - CH_3
0.87	3	Singlet	
0.89	3	Singlet	
0.95	3	Singlet	
1.06	3	Singlet	
3.53			
3.58	2	AB quartet	
3.72		J = 10 Hz	2 - CH_2Br
3.77			
3.74	2	AB quartet	
3.78		J = 6 Hz	
3.85			
3.89			

Contd..

Fig.57 IR Spectrum of 5β,5α-dibromo-cholestan-2β-hydroxy-3β-methoate,1984

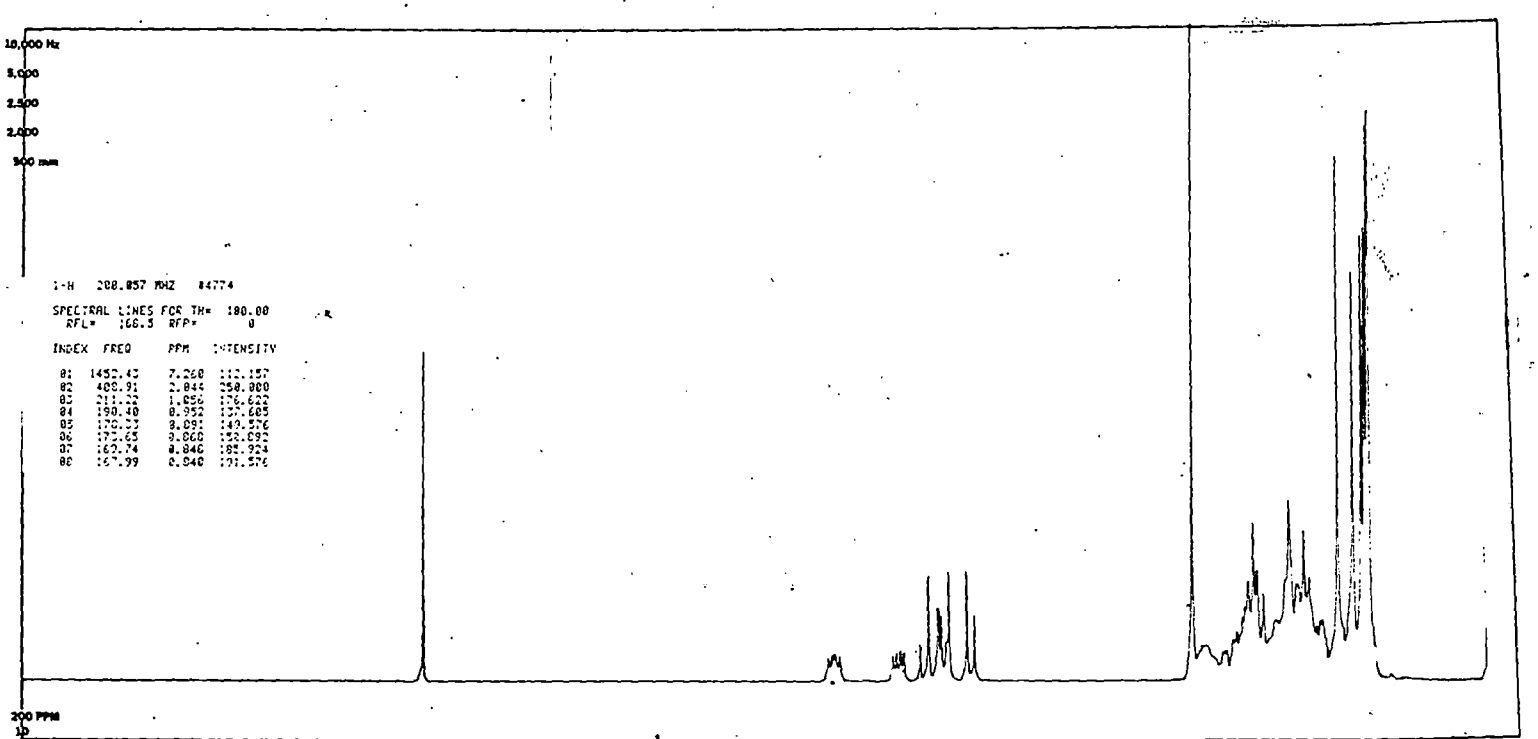


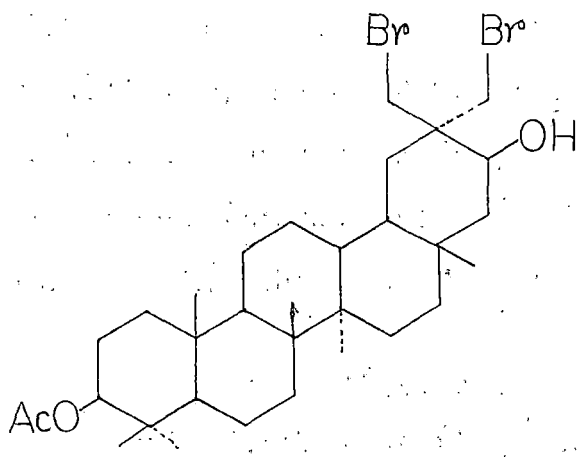
Fig.38 ^{1}H NMR Spectrum of 29,30-dibromo-21 ? -hydroxy-oleanan-3 ? -acetate,198.

Table - 31 (Contd..)

Chemical shift, δ (ppm)	Number of protons	Multiplicity of signals	Probable assignments
2.04	3	Singlet	$-O-CO-\underline{C}H_3$
4.48	1	Multiplet $W_{\frac{1}{2}}$ = 18 Hz	$\underline{H}-C-O-COCH_3$
4.01	1	Quartet J_{aa} = 12 Hz J_{ae} = 6 Hz	$-H_2C - C\underline{H}OH$

six tertiary C-methyl groups (δ 0.84 to 1.06) in N_3. Appearance of four doublets each at δ 3.56 (J = 10 Hz), δ 3.72 (J = 10 Hz), δ 3.81 (J = 12 Hz) and δ 3.87 (J = 12 Hz) for one proton each are due to two non-equivalent $C\underline{H}_2Br$ groups. The downfield shift of the methylene protons also support their attachment with electronegative bromine atom. Appearance of a quartet at δ 4.01 integrable for one proton is due to the hydrogen atom geminal to hydroxyl group. Also, the J values (J_{aa} = 12 Hz, J_{ae} = 6 Hz) indicate that the hydroxyl group is equatorially oriented with a gem axial proton which has one axial and one equatorial neighbouring protons. A three proton singlet at δ 2.04 is due to acetoxy methyl and an one proton multiplet at δ 4.01 ($W_{\frac{1}{2}}$ = 18 Hz) is due to the axial orientation of the proton geminal to acetoxy group. Now, these spectral evidences can be best fitted in a

rearranged lupane skeleton as was in the case of betulinic acid discussed in the review[145]. Also the nature and chemical shift values of dibromolactone 191 were comparable to those of compound N_3. Hence, structure 198 has been depicted for compound N_3.



198

In an effort to arrive at a conclusive evidence for assigning the structure 198 for the dibromo hydroxyl compound, its ^{13}C NMR spectrum (Fig. 39) was of immense help. The spectrum displays 32 resolved lines thus confirming the presence of 32 carbon atoms as found by elemental analysis. The APT spectrum (Fig. 40) represented in Table - 32 shows the presence of 7 CH_3, 12 CH_2 and 6 CH in compound N_3.

Table - 32

Number of different groups and their ^{13}C shift values in APT spectrum

Different groups	Number	^{13}C shift values, (ppm)
$-CH_3$	7	14.40, 15.95, 16.16, 16.51, 18.29, 21.32, 27.91.
$>CH_2$	12	18.15, 21.14, 23.61, 25.00, 26.36, 28.29, 34.12, 36.54, 37.68, 38.07, 38.29, 43.02
$\rightarrow CH$	6	37.78, 45.54, 49.12, 55.18, 73.05, 80.92

Total no. of carbon = 25

Thus, the APT spectrum accounts for 25 carbon atoms. The nature of the seven other carbon atoms are to be assigned to account for 32 carbon atoms of compound N_3. From ^{13}C NMR spectrum (Fig. 39), it is clear that the peak at 171.025 (s) ppm is inconsistent with the presence of one acetate carbonyl group. Appearance of peaks at 36.33, 36.87, 37.74, 41.17, 42.80, 44.44 ppm as singlets indicate the presence of six tertiary carbon atoms. The peaks at 80.92 and 73.05 ppm are due to CH carbons attached to the acetate and hydroxyl group respectively. Thus, the ^{13}C and APT spectra help to account for the number and nature of the carbon atoms of compound N_3. Table - 33 represents the number of different groups and their ^{13}C shift values.

Fig-39 ^{13}C NMR Spectrum of 29,30-dibromo-21β-hydroxy-oleanan-3β-acetate.IIB

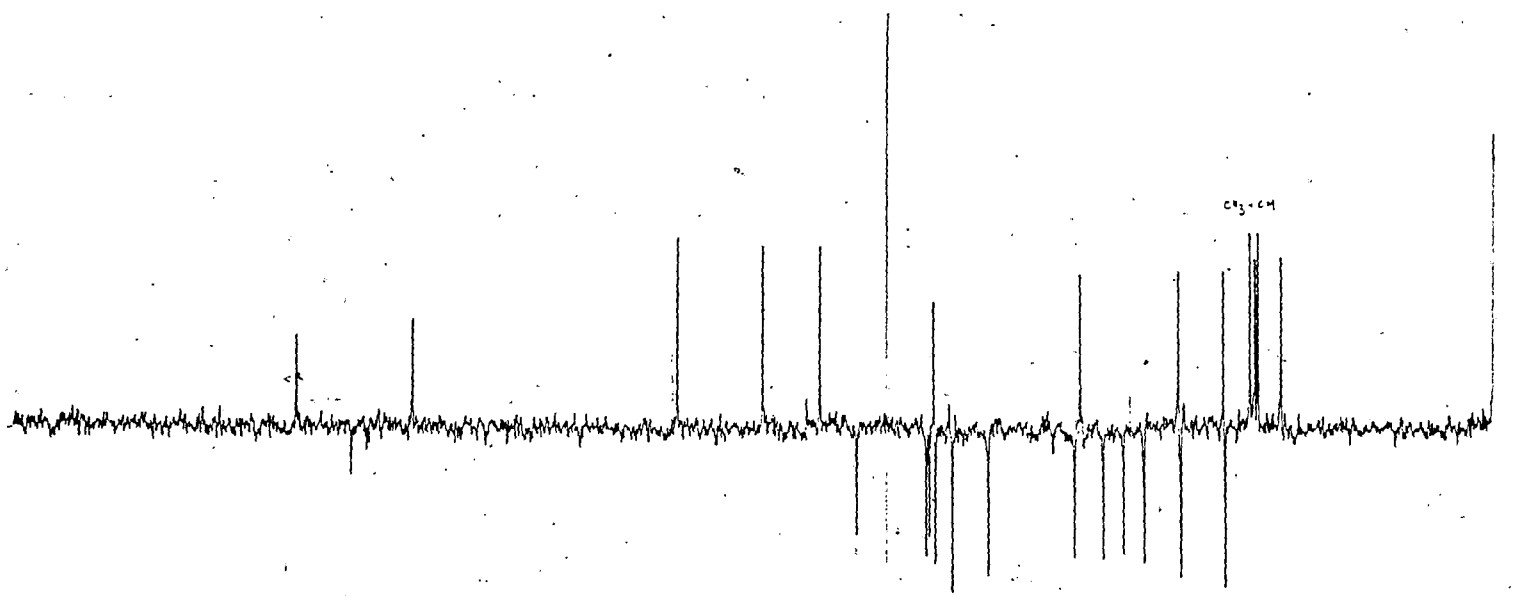


Fig.40 APT Spectrum of 29,30-dibromo-21β-hydroxy-oleanan-3β-acetate, 19Ba

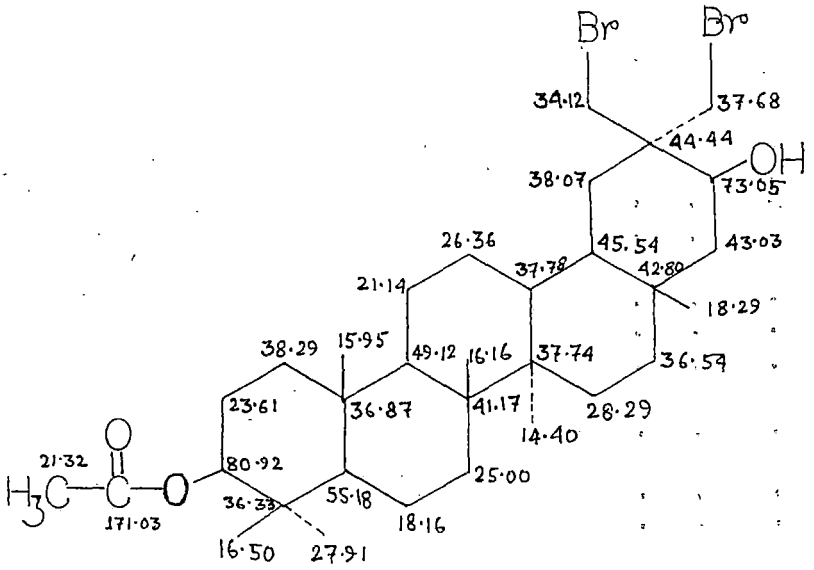
Table - 33

No. of different groups of compound N_3 with their ^{13}C NMR shift values.

Different groups	Number	^{13}C shift values (ppm)
$-CH_3$	7	14.40, 15.95, 16.16, 16.50, 18.29, 21.32, 27.91
$>CH_2$	12	18.16, 21.14, 23.61, 25.00, 26.36, 28.29, 34.12, 36.54, 37.68, 38.07, 38.29, 43.02
$\rightarrow CH$	4	37.78, 45.54, 49.12, 55.18
$\rightarrow C-$	6	36.33, 36.87, 37.74, 41.17, 42.80, 44.44
$>CHOH$	1	73.05
$>CH-OAc$	1	80.92
$-O-\overset{O}{\overset{\|\|}{C}}-CH_3$	1	171.03

Total number of Carbon = 32 ; M.Formula: $C_{32}H_{52}O_3Br_2$

The total carbon shift assignment could be portrayed if structure 198 given below be depicted for compound N_3.



198

It is to be noted here that the position of ^{13}C shift values for different carbon atoms has been assigned by comparison with ^{13}C NMR spectrum of lupenyl acetate[151b].

Mass spectrum of the compound (Fig. 41) exhibits peaks at m/e 646 (M^+), 628, 626, 624, 586, 584, 565, 547, 504, 483, 466, 453, 423, 297, 283, 269, 189 (base peak). In a series of fourteen mass spectra, the molecular ion at 646 has been observed only in two cases. This may be due to easy elimination of a

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151b. Ernest Wenkert, G. Vernon Baddley, I.R. Burfitt and L.N. Moreno, Org. Magne. Reson., 11, 7 (1978)

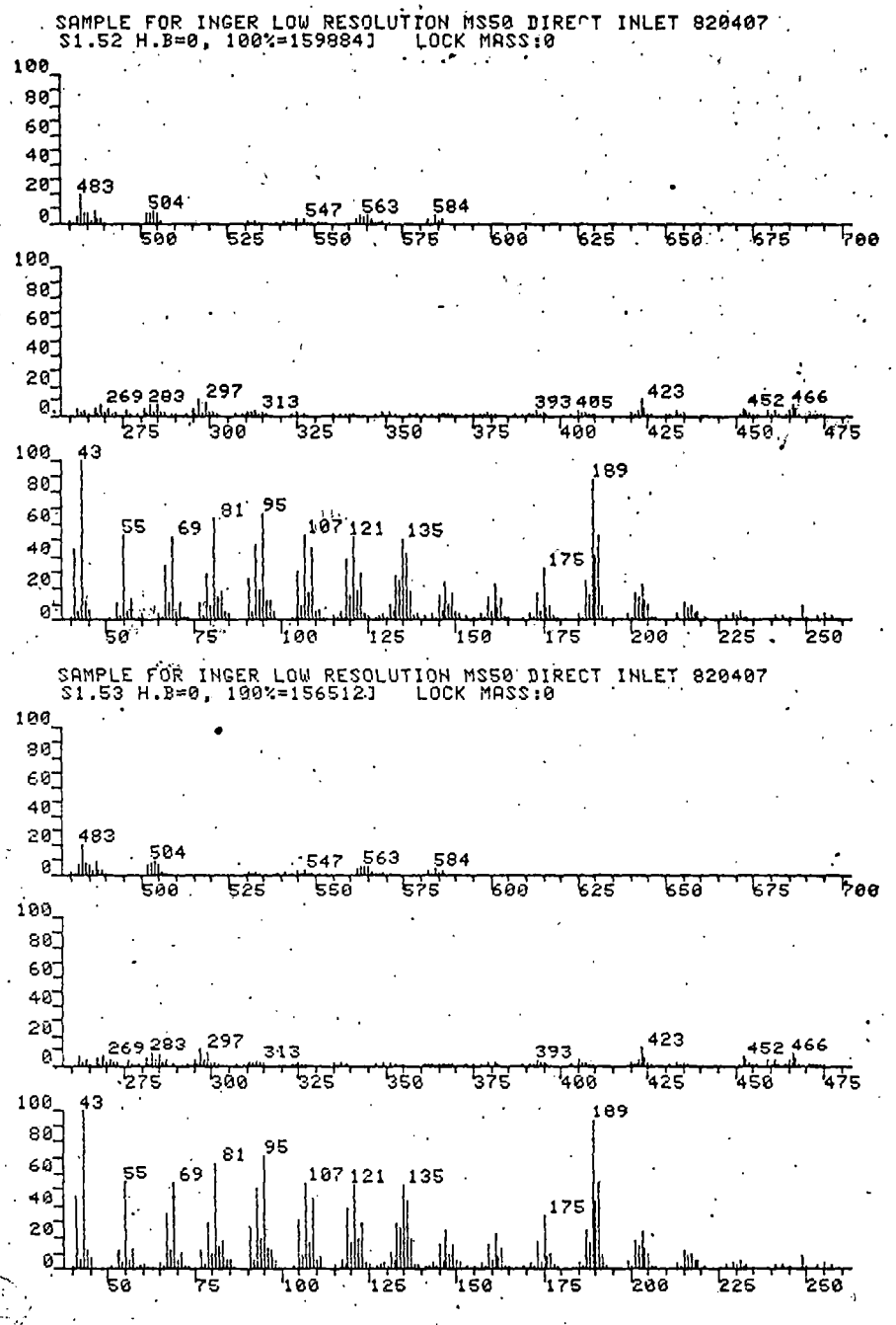
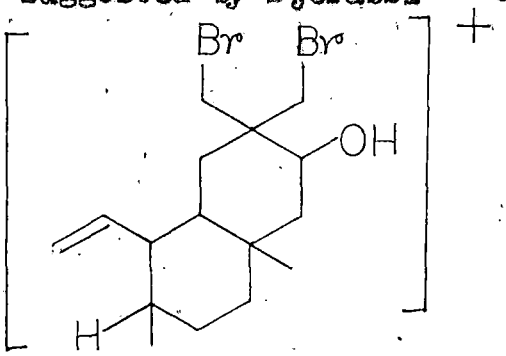
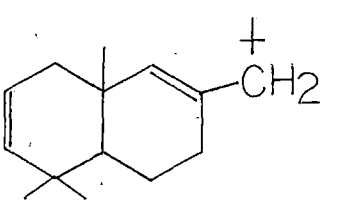


Fig.41 Mass Spectrum of 29,30-dibromo-21β-hydroxy-oleanan-3β-acetate, 198.

molecule of water from C-21 position. Thus, the peaks at 628, 626, 624 are due to loss of a molecule of water from the molecular ion. The existence of these three peaks in 1:2:1 ratio definitely shows that two bromine atoms are present in the molecule. The peaks at 586, 584 and 582 are due to loss of acetic acid and the peaks at 565, 564, 563 are due to loss of one bromine atom from the molecular ion. The peaks at 505, 504, 503 may be due to loss of a bromine atom from the ions m/e 586, 584 and 582 respectively. The peak at 483 is due to loss of another bromine atom from the fragment m/e 564. The existence of peak at 393 may be due to the fragment XXVI formed by the cleavage of ring C of the oleanane skeleton. The base peak at 189 exclusively proves that this fragment comes from the species XXVII as suggested by Djerassi[152] and Ogunkoya[153].



XXVI m/e 393



XXVII m/e 189

152. H. Budzikiewicz, J.M. Wilson and C. Djerassi, J.Amer.Chem. Soc., 85, 3698 (1963)

153. L. Ogunkoya, Phytochemistry, 20, 121 (1981)

Thus, the structure of N_3 has been established as oleanan-29, 30-dibromo-21 β -hydroxy-3 β -acetate 193. But the compound was isolated in a very low yield, hence, it was not possible to confirm the structure chemically.

Characterisation of N_1

The solid N_1 was found to be a mixture of two compounds and it showed positive Beilstein test for bromine. The compound, however, was poured on an active alumina column and was allowed to stand for three days.

Elution of the column with petroleum ether afforded small amount of white solid which on crystallisation from chloroform-methanol yielded needle shaped solid, m.p. 186-88°, $[\alpha]_D$ 32°. IR spectrum (Fig. 42) of the compound shows peaks at 1735, 1240 (O-CO-CH_3), and at 1265 (=CHBr) cm^{-1}. The compound responded to TNM test and also responded to Beilstein test for halogen. Elemental analysis established its molecular formula as $C_{32}H_{51}BrO_2$. Comparison of physical data of the compound with those reported by Halsall et al[151d] revealed that the compound was 29-bromo lupenyl acetate 196.

Elution of the column with petroleum-ether : benzene (4:1) yielded a solid which on crystallisation from chloroform-methanol afforded a crystalline solid, m.p. 235-37°. The compound responded to Beilstein test for bromine. The compound, however, was found identical with 30-bromo-lup-20(29)-en-3 β -acetate 195

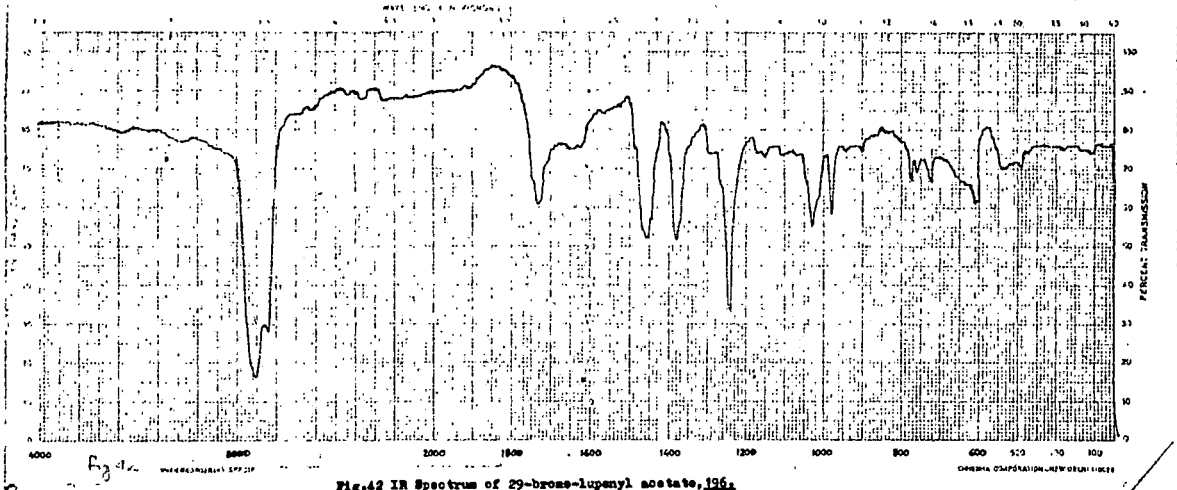


Fig.42 IR Spectrum of 29-brome-lupenyl acetate, 196.

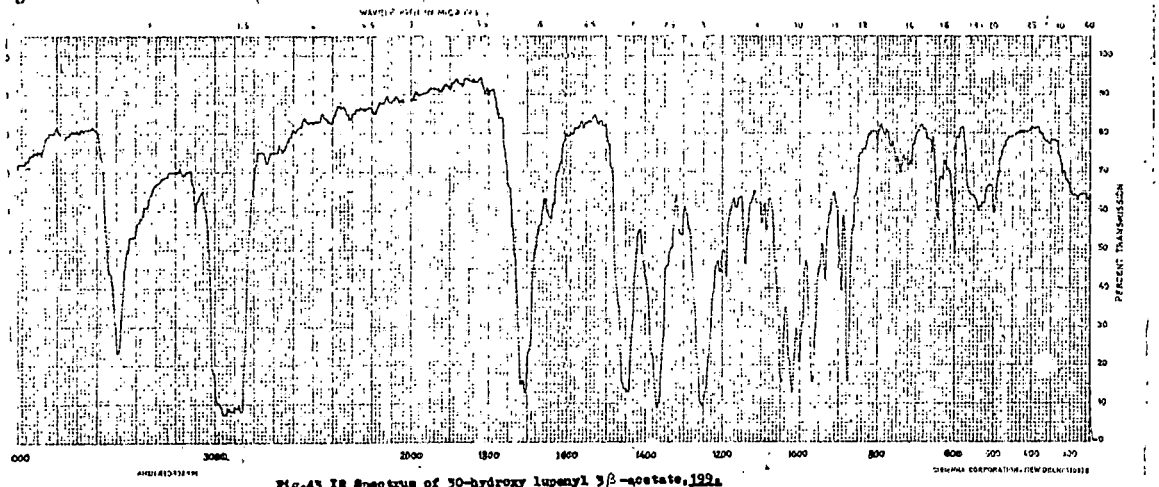


Fig.43 IR Spectrum of 30-hydroxy lupenyl 3β-acetate, 199.

from IR comparison and m.m.p data[150].

Elution of the column with benzene afforded a solid (N_4) which was crystallised from chloroform-methanol and analysed for $C_{32}H_{52}O_3$ (M^+ 484), m.p. 248-49°, $[\alpha]_D \pm 0°$. It did respond to TNM test but gave a negative test for halogen in the Beilstein. Its IR spectrum (Fig. 43) shows peaks at 3500 (-OH), 1715, 1250 (-O-CO-CH_3), 3100, 1640 and 890 (>C = CH_2) cm^{-1}. The ^1H NMR spectrum has been recorded in Table - 34. The spectrum shows appearance of six singlets between δ 0.78 to δ 1.03 accountable

Table - 34

^1H NMR spectrum of N_4 in $CDCl_3$

Chemical shift δ, ppm	Number of protons	Multiplicity of signals	Probable assignment
0.78	3	Singlet	6-C(CH$_3$)-
0.83	3	Singlet	
0.84	3	Singlet	
0.86	3	Singlet	
0.94	3	Singlet	
1.03	3	Singlet	
2.04	3	Singlet	-O-CO-CH_3
4.48	1	Multiplet ($W_{\frac{1}{2}}$ = 18 Hz)	HC(-OCOCH$_3$)-
4.94	2	Multiplet	>C = CH_2
4.15	2	Quartet J_{AB} = 6 Hz	H_2C -OH

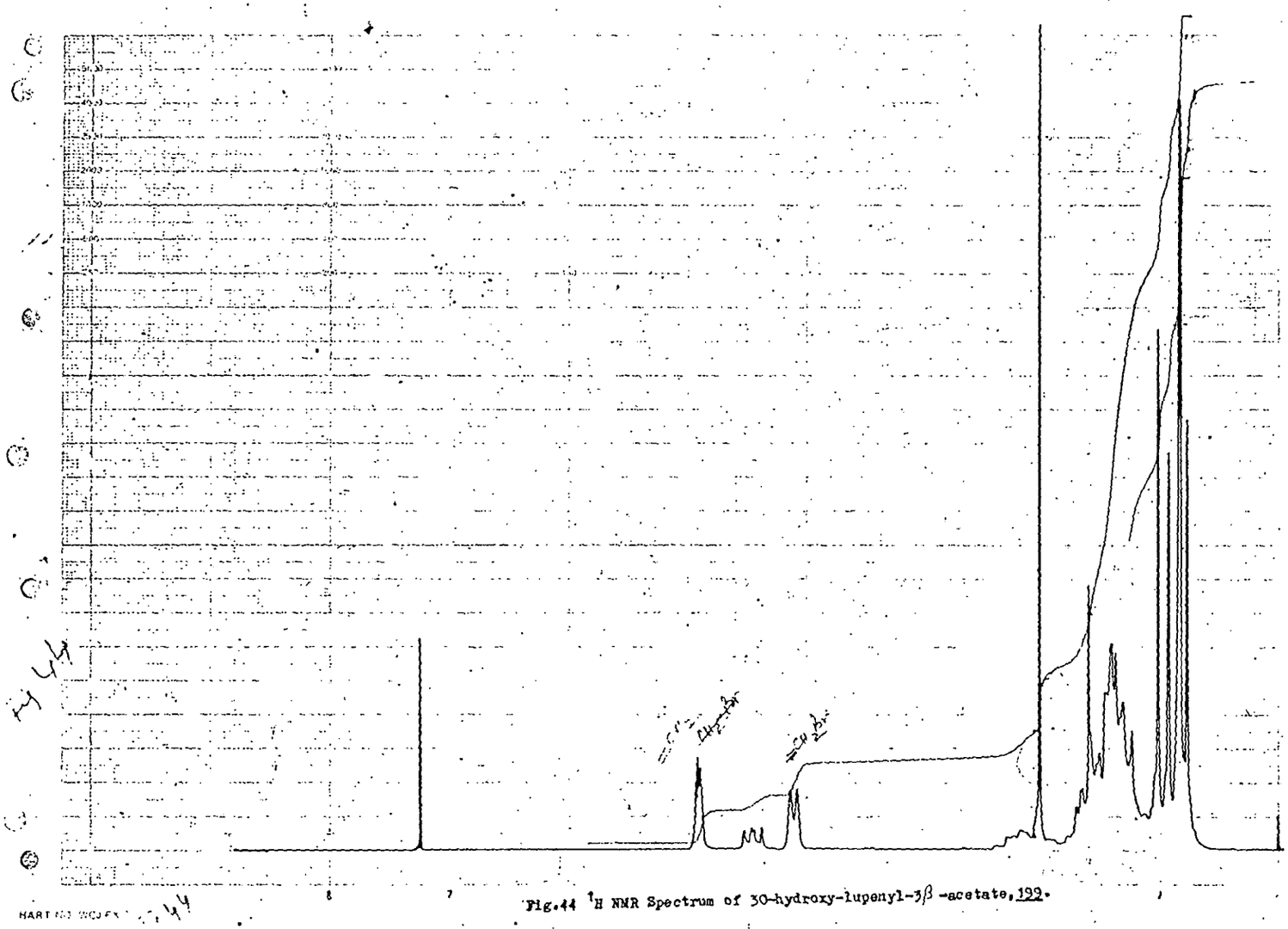
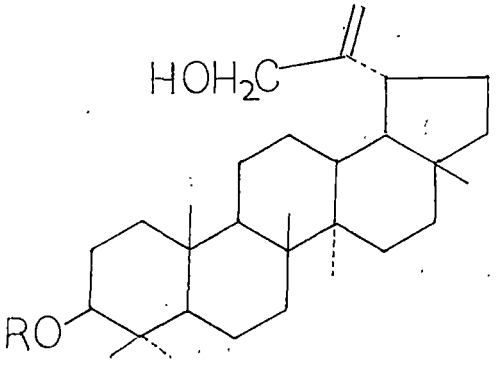


Fig.44 ^{1}H NMR Spectrum of 30-hydroxy-lupenyl-3β -acetate, 122.

to eighteen protons i.e. for six tertiary methyl groups; the multiplet at δ 4.94 ppm for two protons is assigned to an end methylene group; the quartet at δ 4.15 (J_{AB} = 6 Hz) is due to two non-equivalent protons of H_2C-OH group. The singlet at δ 2.04 and the multiplet at δ 4.5 are due to acetoxy methyl and a proton geminal to the acetoxy group respectively. The half-width value of the multiplet indicates the axial orientation of the proton, hence, the acetoxy group is equatorial. Thus, the IR and PMR spectra give sound support for compound N_4 to be a monohydroxy monoacetate, the hydroxy group being at C-30 position. Structure 199 is, therefore, depicted for compound N_4.



199, R = Ac
200, R = H

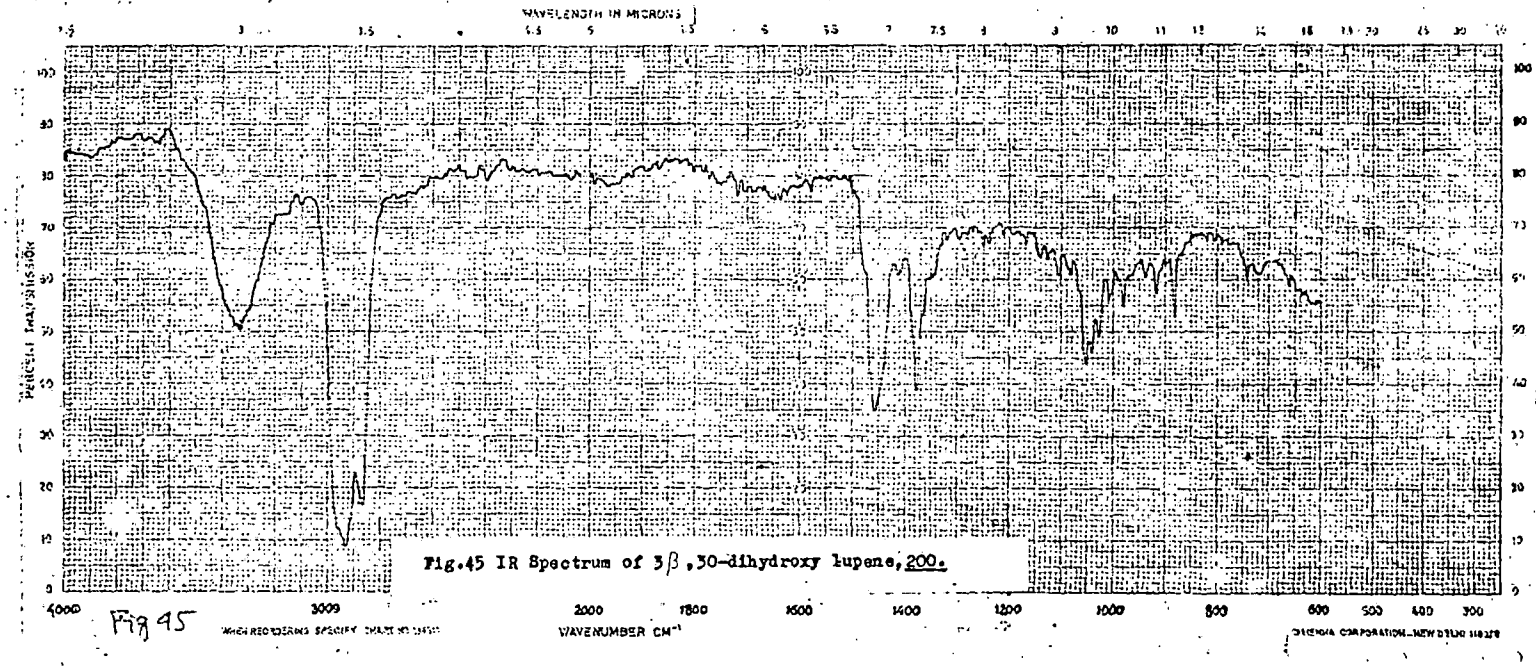


Fig.45 IR Spectrum of 3β,30-dihydroxy lupene, 200.

Fig 45

The compound on hydrolysis with 10% methanolic KOH furnished a solid 200 which on crystallisation from chloroform-methanol yielded fine crystals, m.p. 226-28°. Elemental analysis showed the molecular formula to be $C_{30}H_{50}O_2$ (M^+ 442). IR spectrum (Fig. 45) of the compound exhibits a broad peak between 3300 to 3400 cm^{-1} for the hydroxyl group, at 3100, 1640 and 880 cm^{-1} for exocyclic methylene double bond indicating that the compound has been hydrolysed.

Mass spectrum (Fig. 46) of 199 shows peaks at m/e (rel. int.) 483 (M^+-1, 6.9), 465 (4.3), 425 (5.6), 424 (5.6), 423 (14.3), 408 (8.3), 380 (6.3), 356 (7.5), 248 (18), 233 (7), 220 (14), 203 (28), 189 (100), 175 (30); the mass spectrum (Fig. 47) of 200 shows peaks at 442 (M^+, 5.3), 441 (14.6), 423 (14.5), 408 (9.9), 383 (6.1), 380 (5.6), 314 (15.1), 233 (24), 220 (28), 207 (75), 203 (45), 189 (100), 175 (30). From the two spectra (Fig. 46 and Fig. 47), it is evident that the molecular ions at m/e 483 and m/e 441 are formed by the loss of a hydrogen atom from the hydroxyl group of 199 and 200 respectively. Loss of a molecule of water from the ions m/e 483 and m/e 441 results in the formation of fragments at m/e 465 and m/e 423 in the two compounds 199 and 200 respectively. The peak at m/e 423 in the case of 199 is due to loss of acetic acid from the molecular ion. The common fragment at m/e 408 indicates the loss of a methyl group from the fragment m/e 423 for both the compounds. The existence of peaks at m/e 424 and m/e 383 in compound 199

MASS SPECTRUM : (5 TO 6)
SAMPLE:LB-1/111,DR.B.P.PRADHAN,W.BENGAL
NOTE :4.12.1981.
BASE PEAK : M/E 189.0 INT. 19.3

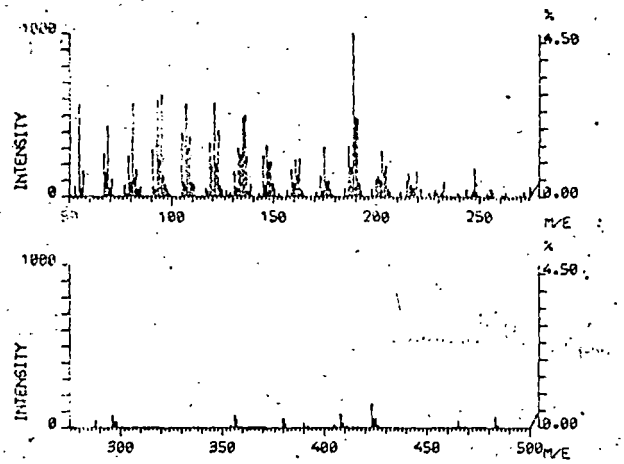


Fig.46 Mass Spectrum of 30-hydroxy-lupenyl-3β-acetate,199.

MASS SPECTRUM : (6 TO 7)
SAMPLE:LB-2/111,DR.B.P.PRADHAN,W.BENGAL
NOTE :4.12.1981.
BASE PEAK : M/E 189.0 INT. 22.5

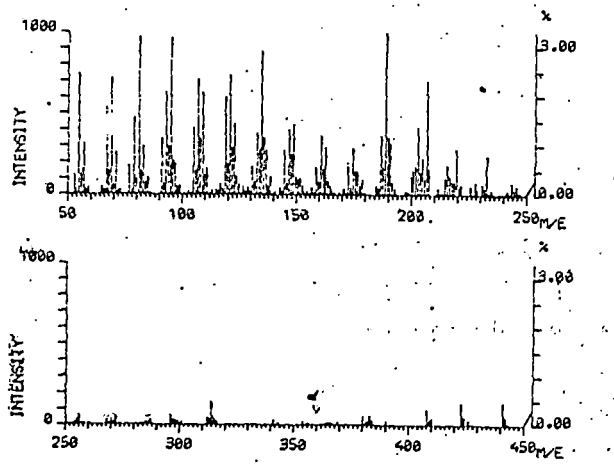
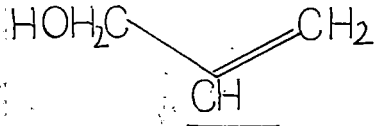
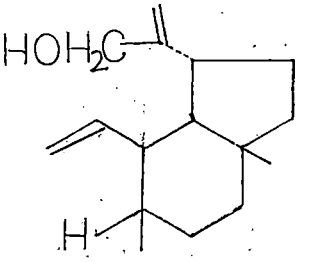


Fig.47 Mass Spectrum of 30-hydroxy-lupene-3β-ol,200.

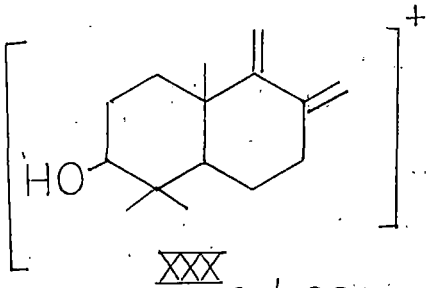
and 200 respectively can be explained by assuming the loss of 58 mass units for the fragment XXVIII from the molecular ions. The existence of common fragments at m/e 233 can be explained by assuming the formation of fragment XXIX in accordance with



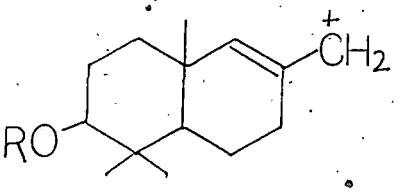
XXVIII



XXIX m/e 233



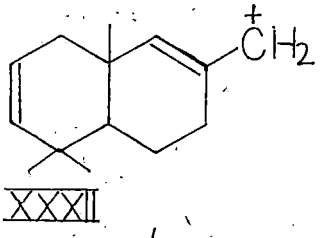
XXX m/e 220



XXXI

R=Ac m/e 249

R=H m/e 207



XXXII m/e 189

observation made by Djerassi et al[152]. The other fragment at m/e 220 can be attributed to the species XXX which is prominent in the case of dihydroxy compound 200. The existence of peak at m/e 249 and 207 in 199 and 200 respectively is probably due to the formation of fragment XXXI which ultimately loses acetic acid or a water molecule to furnish the fragment XXXII responsible for the peak at m/e 189. The existence of peak at m/e 175 may be attributed to loss of 58 (XXVIII) mass units from the fragment XXIX.

Thus, IR, ^{1}H NMR and mass spectral data of compound N_4 and its hydrolysed product 200 establish the compound N_4 to be 30-hydroxy-lupenyl-3 β-acetate 199.

The compound 199 on acetylation with acetic anhydride-pyridine yielded a crystalline solid 201, m.p. 163-64°, $[\alpha]_D$ +8°. Its IR spectrum (Fig. 48) shows bands at 1750, 1730 cm^{-1} due to diacetate functionality which is also supported by the appearance of bands at 1250 and 1265 cm^{-1}. The bands at 3080, 1640 and 840 cm^{-1} indicates the presence of $>C=CH_2$ group in the compound. Comparison of physical data of 3 β, 30-dihydroxy lupenyl diacetate[150] with those of diacetate 201 prepared from 199 were identical confirming the structure 199 as proposed for the monohydroxy monoacetate compound N_4.

Compound isolated on further elution of the column with benzene - ether (4:1) was crystallised from chloroform -methanol

Fig 48 IR Spectrum of 3β,30-dihydroxy lupenyl acetate,201c

and analysed for $C_{30}H_{50}O_2$, m.p. 226-28°, $[\alpha]_D$ +4°. The compound was found identical with 3 β, 30-dihydroxy lupenyl acetate 200 prepared by hydrolysis of 30-hydroxy-3 β -lupenyl acetate 199 from m.m.p and IR data.

Mechanism:

The triterpenes of lupeol series contain an isolated double bond very reactive towards several oxidising reagents[154-156] and facile oxidation occurs at the allylic C-30 methyl group. The alternate C-19 hydrogen is perhaps greatly hindered.

It is well known that NBS is a good reagent for allylic bromination and 30-bromo compound 195 is produced by free radical bromine. The 29-bromo compound 196 may be formed by isomerisation of the double bond from C-20 (29) position to C-20 (30) position in the presence of polar solvent like DMSO.

The 30-bromo-lup-20(29)-en-3 β-acetate 195 may be attacked by the bromonium ion present in the polar solvent (DMSO) on C-20-29 π bond causing the formation of a carbonium ion that probably compels carbon skeleton transformation from lupane system to

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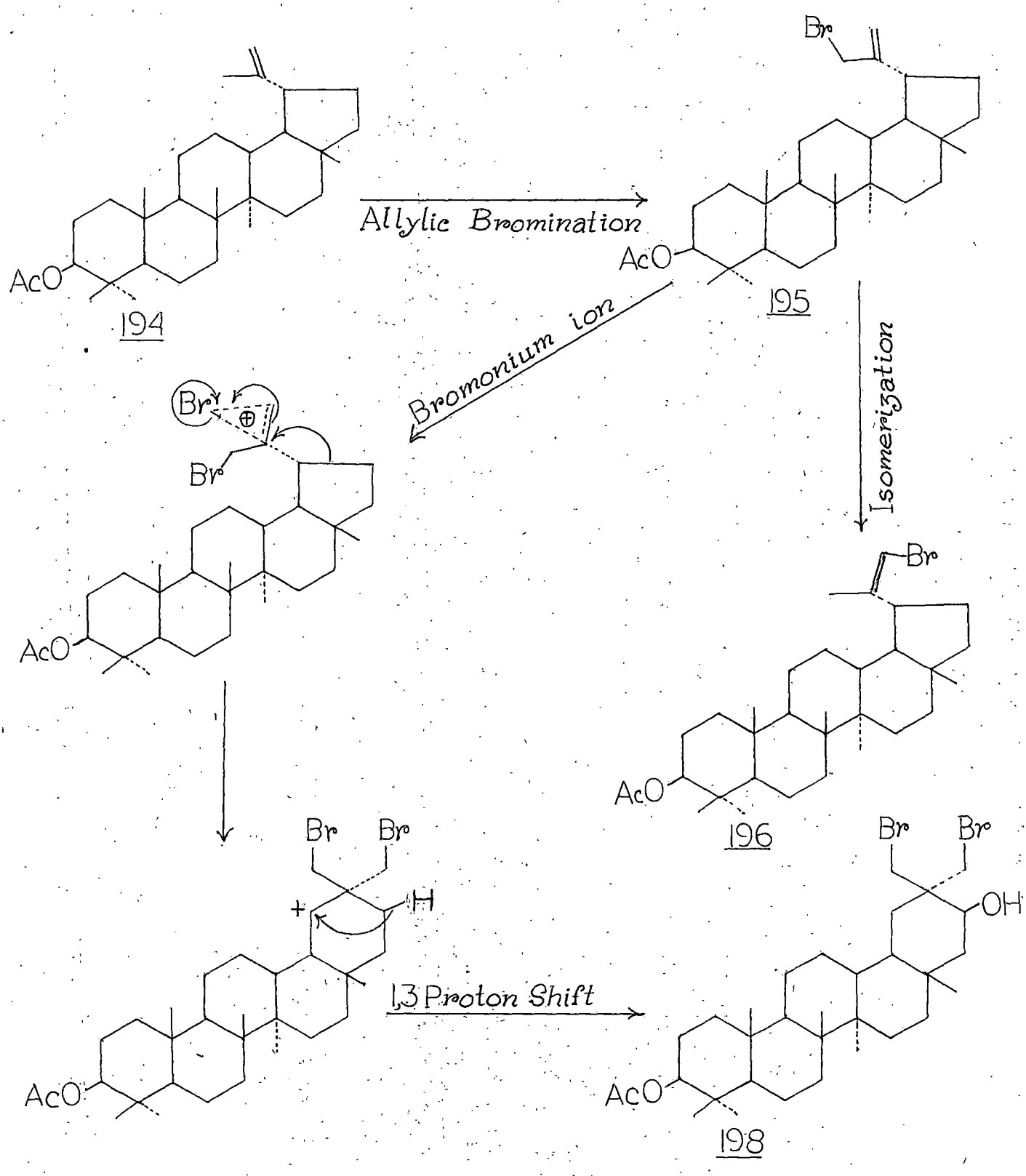
154. L. Ruzicka, M. Brenner and Ed. Rey, Helv. Chim.Acta, 25 (1942), 161.

155. L. Ruzicka and Ed. Rey, Helv. Chim. Acta, 25 (1942), 171.

156. L. Ruzicka and G. Rosenkranz, Helv. Chim. Acta., 22 (1939), 778.

oleanane system. The environment may be such that the carbonium ion generated at C-19 position is rather a crowded site for attack by the hydroxyl ion so that a proton is pushed from the nearby C-21 position by 1-3 hydride shift to make a site for the attacking anion to furnish C-21-hydroxy-29, 30-dibromo oleanan-3β-acetate 198. Though the 1, 3 shift of a proton from C-21 to C-19 position is proposed to explain the formation of 20-hydroxy compound 198, there is no such example of migration of carbonium ion from C-19 to C-21 position. In most of the earlier cases, the carbonium ion at C-19 is stabilized either by removal of a proton from C-18 position to give germanicol derivative (double bond at C-18, C-19 position) or by migration of the carbonium ion from C-19 position to C-18 position that is stabilized by loss of a proton from C-13 position to give a stable double bond at 13-18 position. In either of the two cases, the geometry may be such that the two bromine atoms present at C-29 and C-30 carbons prevent the formation of double bonds at C-18 (19) or C-13 (18) position. Under the forceful condition, the carbonium ion at C-19 perhaps migrates to the C-21 position by 1, 3 hydrogen shift. The mechanism has been represented in Scheme XXXI.

Scheme - XXXI


AcO
194
Allylic Bromination
Br
AcO
195
Isomerization
Bromonium ion
Br
Br
AcO
Br
AcO
196
Br
Br
H
+
AcO
1,3 Proton Shift
Br
Br
OH
AcO
198

It is reported[150] that 30-bromo-lup-20(29)-en-3 β -acetate 195 is stable to silver and sodium acetate, but the hydrolysis of 195 to 30-hydroxy-lup-20(29)-en-3 β -acetate 199 may be due to surface activity of 195 when in contact with active alumina. Lupenyl acetate 194 under similar condition resisted hydrolysis of the 3 β -acetate group, whereas the 3 β -acetyl group in 199 underwent hydrolysis to produce 200 showing that the catalytic amount of HBr produced causes the hydrolysis. It would be pertinent to point out here that while Thomson and Finucane[128] carried out the NBS reaction on β -amyrin acetate and chromatographed the reaction product on alumina, they isolated 11-α -OH- β -amyrin acetate and 3 β, 11α -diol. The methoxy acetate was the major product when a methanolic solution of 11α -ol was stirred with alumina.

SECTION - C

EXPERIMENTAL

Melting points are uncorrected. Petroleum-ether used throughout the experiment had b.p. 60-80°. All optical rotations were determined in chloroform solution. ^{1}H NMR spectra were determined using deuterated chloroform solution containing tetramethyl silane as reference. TLC was done on chromatoplate of silica gel (E. Merck) and the spots were developed with benzene: ethylacetate (9:1) mixture.

Oxidation of lupenyl acetate with N-Bromo-Succinimide:

To a solution of lupenyl acetate 194 (1g) in chloroform (50 ml) was added NBS (1g) in portions followed by addition of DMSO (25 ml) and the reaction mixture was kept overnight in dark. On the following day, the reaction mixture was poured on ice cold water when a white solid separated out which was extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous Na_2SO_4. Removal of chloroform gave a solid (850 mg). TLC of the later showed distinct spots indicating the presence of at least two compounds in it. The residue was dissolved in benzene (10 ml) and poured on a column of silica gel developed with petroleum ether. The following solvents were used for elution.

Table - 35

Eluent	Fractions 100 ml each	Residue on evaporation	Melting point
Petroleum ether	1-6	Solid (220 mg)	205-12°
Petroleum-ether: benzene (4:1)	7-11	Solid (460 mg)	226-30°
Petroleum-ether: benzene (3:2)	12-14	Nil	-
Petroleum-ether: benzene (2:3)	14-18	Solid (80 mg)	244-48°

Further elution with more polar solvents did not afford any solid material.

Examination of fraction 1-6:

The fraction 1-6 (220 mg) (Table -35) were combined. TLC experiment of the compound showed two distinct but close spots; hence, this was set aside for further purification. Beilstein test response was positive.

Examination of fraction 7-11: Isolation of 30-bromo-lup-20(29)-en-3β -acetate 195:

The fraction 7-11 (Table - 35) were combined (460 mg) and crystallised from a mixture of chloroform and methanol for three times which afforded needle-shaped crystals (375 mg), m.p. 236-38°,

$[\alpha]_D$ +12°. TLC of the compound showed a single round spot.

TNM test response was positive. So was Beilstein test.

Analysis:	% C	% H
Found:	70.12	9.29
Calculated for $C_{32}H_{51}O_2Br$:	70.23	9.31

IR : ν_{max}^{nujol} 1725, 1255 ($-O-CO-CH_3$), 3015, 1640 and 880 ($>C=CH_2$) cm^{-1}. [Fig. 35]

^1H NMR (δ, $CDCl_3$) 2.04 (s, 3H, $-O-CO-CH_3$), 4.48 (m, 1H, H-C(=O)-C-O-), 3.99 (s, 2H, H_2C-Br), peaks at 5.04 and 5.12 (2s, 2H, $C=CH_2$), peaks at 0.79, 0.84, 0.85, 0.95, 1.04 (5s, 18H, 6-$C-CH_3$) [Fig. 36]

Examination of fraction 14-18: Isolation of 29, 30 dibromo 21 β-hydroxy-3 β-acetate :

The fraction 14-18 (Table - 35) were combined (≃ 80 mg) and crystallised from chloroform-methanol to afford amorphous solid (60 mg), m.p. 258-60°. It showed positive Beilstein test for halogen.

TLC of the compound showed a single round spot.

Analysis :	C %	H %
Calculated for $C_{32}H_{52}O_3Br_2$	59.66	8.07
Found	59.59	8.09

IR : $\overset{\text{nujol}}{\text{max}}$ 3330 (-OH), 1732, 1250 (O-CO-CH_3), 1270-80 (CH_2Br) cm^{-1}

(Fig. 37)

^1H NMR (, $CDCl_3$) : Signals from 353 to 389 (two AB quartet, 4H, $2H_2C$-Br), 4.01 (q, 1H, J_{aa} = 12 Hz, J_{ae} = 6 Hz, H_2C - CHOH), 2.04 (s, 3H, -O-CO-CH_3), 4.48 (m, 1H, -H - C-CO-O-), 0.84, 0.85, 0.87, 0.89, 0.95, 1.06 (6s, 18H, 6-C-CH_3).

(Fig. 38)

^{13}C NMR : 171.025 (s, -O-CO-CH_3), 36.33, 36.87, 37.74, 41.17, 42.80, 44.44 (6s, 6 C -), 37.78, 45.54, 49.12, 55.18 (4s, 4 CH) , 18.16, 21.14, 23.61, 25.00, 26.36, 28.29, 34.12, 36.54, 37.68, 38.07, 38.29, 43.02 (12s, 12 CH_2), 14.40, 15.95, 16116, 16.50, 18.29, 21.32, 27.91 (7s, 7 - CH_3), 80.92 (d, HC-O-CO-CH_3), 73.06 (d, CHOH) ppm.

(Fig. 39)

Mass: Molecular ion peak (M^+) 646, m/e 628, 626, 624, 586, 584, 565, 547, 504, 483, 466, 453, 423, 297, 283, 269, 189 (base peak).

[Fig. 41]

Re-examination of fraction 1-6 (Table - 35) : Chromatographic separation on alumina column:

The fraction 1-6 (Table -35) were mixed together (200 mg), dissolved in minimum volume of benzene and poured on an active alumina column (15 gm) developed with petroleum-ether. It was allowed to stand for 24 hr. and then eluted with the following solvents:

Table - 36

Eluent	Fractions 50 ml each	Residue on evaporation	Melting point
Petroleum-ether	1-3	Solid (≃ 15 mg)	180-84°
Petroleum-ether: benzene (4:1)	4-6	Solid (≃55 mg)	228-30°
Petroleum-ether: benzene (3:2)	7-8	Nil	-
Petroleum-ether: benzene (2:3)	9-11	Nil	-
Benzene	12-17	Solid (≃120 mg)	240-42°
Benzene-ether (4:1)	18-20	Solid (≃20 mg)	220-22°

Elution with more polar solvent yielded no solid material.

Examination of fraction 1-3: Isolation of 29-bromo-lup-20(29)-en-3 β-acetate:

The solid in fraction 1-3 (Table -36) were combined (≃ 15 mg) and crystallised from chloroform-methanol to afford white amorphous solid, m.p. 186-88°, $[\alpha]_D$ +32°. It responded to TNM test and showed positive Beilstein test for bromine.

	C %	H %
Calculated for $C_{32}H_{51}O_2Br$:	70.23	9.31
Found :	70.19	9.28
IR : ν_{max}^{nujol}	1735, 1240 ($-O-CO-CH_3$), 1265 (= CHBr) cm^{-1}	

[Fig. 42]

Examination of fraction 4-6: Isolation of 30-bromo-lup-20(29)-en-3 β-acetate:

The solid in fraction 4-6 (Table - 36) were combined (≃ 55 mg) and crystallised from chloroform-methanol to afford shining crystals, m.p. 236-37°.

Beilstein test response was positive.

TNM test response was negative.

It was identified as 30-bromo-lup-20(29)-en-acetate 195 by comparison of m.p. and IR with an authentic sample.

Examination of fraction 12-17: Isolation of 30-hydroxy-lup-20(29)-en-3 β -acetate:

The solid in fraction 12-17 (Table -36) were mixed together ($\simeq$120 mg) and crystallised from a mixture of chloroform-methanol to afford needle-shaped crystals, m.p. 248-49°. TLC of the compound on elution with a mixture of benzene: ethylacetate (9:1) showed a single round spot. However, it did not respond to Beilstein test for halogen, but responded to TNM test. $[\alpha]_D$ 0°

Analysis	C %	H %
Calculated for $C_{32}H_{52}O_3$	79.29	10.81
Found :	79.31	10.75

IR : ν_{max}^{nujol} 3500 (-OH), 1715, 1250 (-O-CO-CH_3), 3100, 1640, 890 (>C = CH_2) cm^{-1}

[Fig. 43]

^{1}H NMR : (δ, $CDCl_3$) 4.15 (q, J_{AB} = 6 Hz, 2H, -CH_2OH), 2.04 (s, 3H, -O-CO-CH_3), 4.48 (m, 1H, HC-C(=O)-O-CH_3), 4.94 (m, 2H, -C = CH_2), 0.78, 0.83, 0.84, 0.85, 0.94, 1.03 (6s, 18H, 6-C-CH_3).

[Fig. 44]

Mass: 483 (M^+ -1), m/e 465, 425, 424, 423, 408, 380, 356, 248, 233, 220, 203, 189 (base peak), 175.

[Fig. 46]

Hydrolysis of 30-hydroxy-lup-20(29)-en-3 β -acetate: Isolation of 3 β, 30-lupenyl diol

30-hydroxy-lup-20(29)-en-3 β -acetate 199 (50 mg) was refluxed with 10% methanolic potassium hydroxide solution (5 ml) for four hours. The solution was cooled, acidified with cold 10% hydrochloric acid (10 ml) and extracted with ether. The etheral layer was washed with water till neutral and then dried (Na_2SO_4). The ether was distilled off and the solid residue obtained was crystallised from methanol. After three crystallisations from methanol, it gave a crystalline solid m.p. 226-28°.

TMM test response was positive

	C %	H %
Found :	81.21	11.36
Calculated for $C_{30}H_{50}O_2$	81.39	11.38

IR : ν_{max}^{nujol} : Broad peak between 3300-3400 (OH), 3100, 1640, 880 ($>C=CH_2$)cm^{-1}

[Fig. 45]

Mass: m/e 442 (M^+), 441, 423, 408, 383, 380, 314, 233, 220, 207, 203, 189 (base peak), 175.

[Fig. 47]

Acetylation of 30-hydroxy-lup-20(29)-en-3 β-acetate: Isolation of 3 β, 30-lupenyl diacetate:

To a solution of 30-hydroxy-lup-20(29)-en-3 β-acetate (50 mg) in pyridine (5 ml) was added acetic anhydride (5 ml) and kept over night at room temperature. After usual work up, the solid residue obtained was crystallised from chloroform-methanol for three times which resulted in a needle shaped crystals, m.p. 163-64°, $[\alpha]_D$ 8°. TLC of the compound showed a single round spot in the solvent system benzene : petroleum-ether (2:1).

Analysis:	C %	H %
Calculated for $C_{34}H_{54}O_4$:	77.52	10.33
Found:	77.59	10.31
IR : ν_{max}^{nujol}	1750, 1730, 1265, 1250 (-O-CO-CH_3), 1640, 840 ($>C=CH_2$) cm^{-1}	

[Fig. 48]

Examination of fraction 18-20 : Isolation of 3 β, 30 lupenyl diol:

The fraction 18-20 (Table -36) were combined together (≃ 20 mg) and crystallised from a mixture of chloroform-methanol to afford crystals of 3 β, 30 lupenyl diol 200, m.p. 226-28°, $[\alpha]_D$ 4° . It showed single round spot on t.l.c. plate developed with a solvent mixture of benzene-ethylacetate (9:1).

TNM test response was positive

Beilstein test response was negative.

The compound was found identical with 3 β, 30 lupenyl diol prepared by hydrolysis of 30-hydroxy 3 β-lupenyl acetate 199 from m.m.p and IR data comparison.

CHAPTER - IV

SECTION - A

A short review on autoxidation and isomerisation in ring A in triterpenoids.

Autoxidation, a slow oxidation process affected by oxygen (e.g. by air) at moderate temperature are prompted by light and small quantities of catalyst, notably the oxides and oil soluble salts of heavy metals as well as by various peroxidic substances. Again, they can be markedly retarded by mere traces of oxidizable organic substances, such as phenols and amines.

The autoxidation of quinone to quininic acid in a boiling solution of potassium enolate in benzene was studied by Woodward[157] and in presence of t-butoxide by Doering[158]. The latter worker also studied the autoxidation of ketones and isolated α, β diketones, dicarboxylic acids and lactols[159]. The formation of various products was explained on the basis of addition of oxygen molecule on the enolate double bond to

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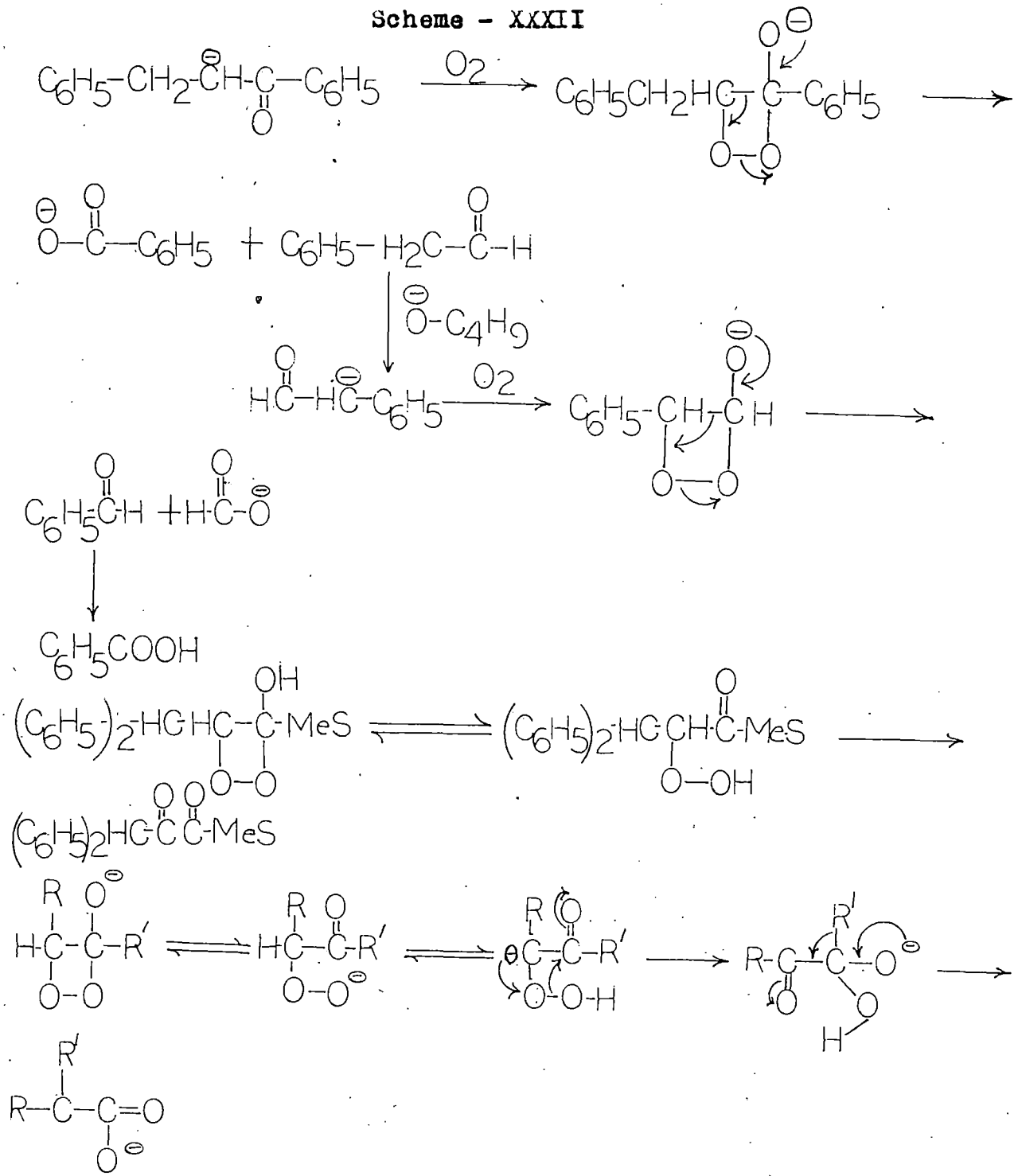
157. Woodard, Wendler and Brutschy, J.Am.Chem.Soc. 67, 1425 (1945)

158. W.E. Doering and J.D. Chanley, J.Am.Chem.Soc. 68, 586 (1946)

159. W.E. Doering and R.M. Haines, J.Am.Chem.Soc., 76, 483 (1954)

form the four membered cyclic hydroxy peroxide as shown in Scheme - XXXII.

Scheme - XXXII



The action of potassium tert-butoxide as a catalyst for the autoxidation of ketones and esters to α-hydroperoxides was studied by Gersmann et al[160] in early sixties. Hanna and Ourisson[161] reported the autoxidation of several cyclic ketones in hexa methyl phosphotriamide in the presence of potassium tert-butoxide. The reaction was found to proceed in accordance with the previously proposed mechanism in which the initial formation of an α-hydroperoxy ketone is followed by transformation into an α-ketol and then to an α-diketone, attack of the α-diketone followed by decarboxylating fragmentation, cleavage into a keto acid or an aldehyde acid or rapid oxidation of the aldehyde acid.

It was found by Hendry et al[162] that the initial oxidation of cyclohexane gave mostly cyclohexyl hydroperoxide and gave cyclohexanol and cyclohexanone as chain termination products. The hydroperoxide was converted directly to ketone on further reaction.

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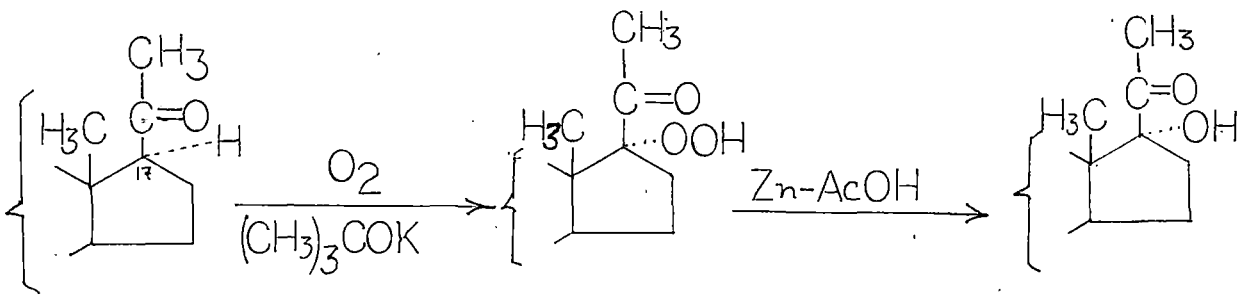
160. H.R. Gersmann, H.J.W. Nieuwenhuis and A.F. Bicket, Proc. Chem. Soc., 279 (1962)

161. R. Hanna and G. Ourisson, Bull. Soc. Chim. Fr. 10, 3742 (1967)

162. D.G. Hendry, C.W. Gould, D. Schnetzle, I.R. Mayo, J. Org. Chem., 41(1), 1 (1976)

Barton et al[163] found that when a 20-keto steroid was shaken with oxygen in the presence of potassium tert-butoxide in tert-butanol it was oxidised to the 17α-hydroperoxide, which could be reduced to the 17α alcohols with zinc and acetic acid. Under the same conditions[164], 3-keto-5 β-steroids were oxidised to 4-hydroxy - Δ^4 -3-ketones, the 5-α-isomers were oxidised to the 2-ketones (enolic forms) and cholestenones was oxidised to diosterol-1 in low yields. Since in each case attack was at the site of enolisation, oxygen evidently attacked the enolate ion.



163. E.J. Bailey, D.H.R. Barton, J. Elks and J.F. Templeton, J. Chem. Soc., 1578 (1962)

164. B. Camerino, B. Patelli and R. Sciaky, Tet. Lett. 554 (1961)

In view of the fact that Section - B of this chapter deals with autoxidation of triterpenoid, it will be of interest to make a short review of autoxidation of some triterpenoids.

Oxidation of ring A in Euphol.

Lavie and co-workers[165] studied the autoxidation of euphadiene-3-one, 202. The introduction of an oxygen function α to the C-3 carbonyl group was performed by shaking in oxygen a solution of euphadiene-3-one in tert-butanol saturated with K-tert-butoxide[163]. The first mole of oxygen which was rapidly absorbed produced the α -diketone derivative, which was found on chromatoglate to consist of a mixture of two tautomeric forms, the diosphenol 203a and the -diketone 203. Upon acetylation, a diosphenol acetate, 203b, was obtained.

During the process of autoxidation, a second mole of oxygen was absorbed and the product isolated was identified as the lactol 204a. The formation of the lactol was interpreted through the formation of ring A seco-2-nor aldehydo carboxylic acid, which cyclized on acidification. The loss of a carbon atom (C-2) in the process and the formation of the heterocyclic six membered ring were shown unequivocally by the ^{1}H NMR spectrum of the substance. Indeed, a characteristic singlet related

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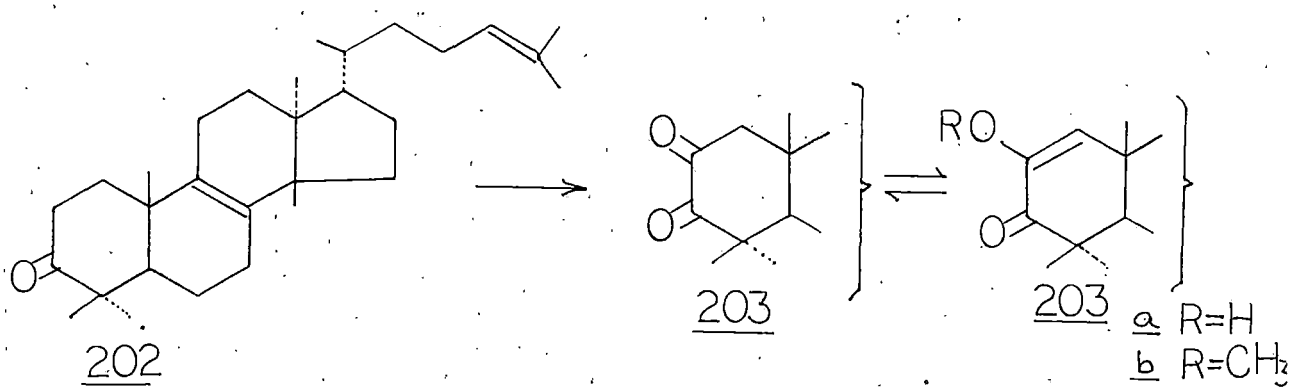
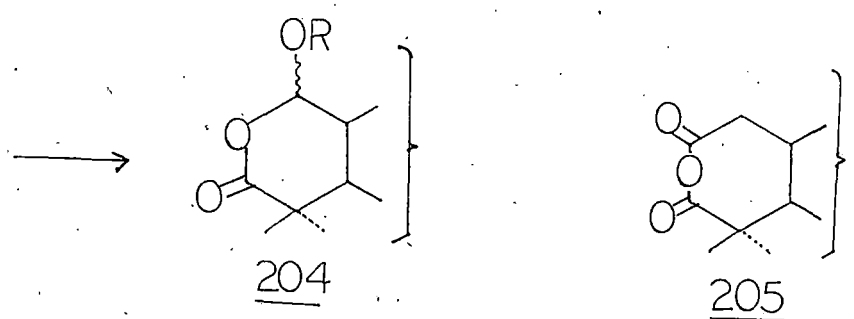
165. D. Lavie, E. Glotter and Y. Shvo, Tetrahedron, 19, 1377 (1963)

to the C-1 proton was found at δ 5.60; this peak was not sharp due to coupling with the proton of the adjacent hydroxyl group. However, upon acetylation, the signal in the lactol acetate 204b was found to be shifted down field to δ 6.42 as sharp peak. It was, therefore, decided that no proton was present neighbouring the C-1 hydrogen as would be expected from a lactol derived from a 2,3-seco-aldehydo acid.



202 203 203



204 205

It is note worthy that a substance, identified as the anhydride, 205, was also formed during the autoxidation of 202 to diosphenol 203a . The formation of the anhydride was explained by the initial formation of an α -hydroperoxy ketone and its cleavage to seco-2-aldehyde-3-carboxylic acid either by a four membered ring intermediate mechanism[159] or by an alternative peroxide mechanism[166]. The aldehyde under the basic reaction condition, is subsequently oxidised to a carboxylic group thus forming the 2,3-seco dicarboxylic acid, which upon cyclization formed the anhydride, 205.

Oxidation of ring A in oleanolic acid

In connection with their work to confirm the structure of bredemolic acid, 206, and crategolic acid 207, Tschesche and co-workers[167] performed the autoxidation of ring A in methyl oleanonate, 208. Methyl oleanonate was stirred in tert-butanol containing potassium metal at 25 - 50^{o} with simultaneous introduction of oxygen.

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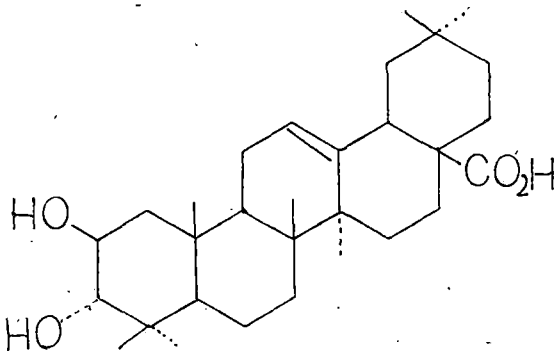
166. E. Elkik, Bull. Soc. Chim. Fr. 933 (1959)

167. R. Tschesche, E. Henckel and G. Snatzke, Ann, 676, 179 (1964)



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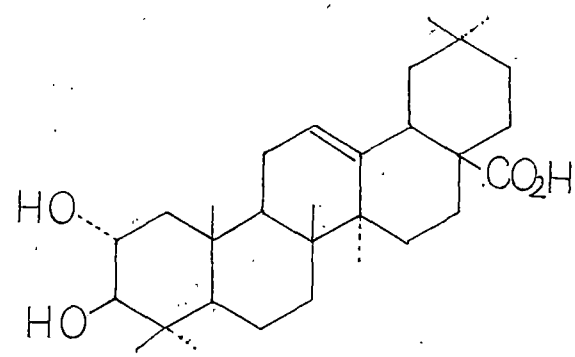

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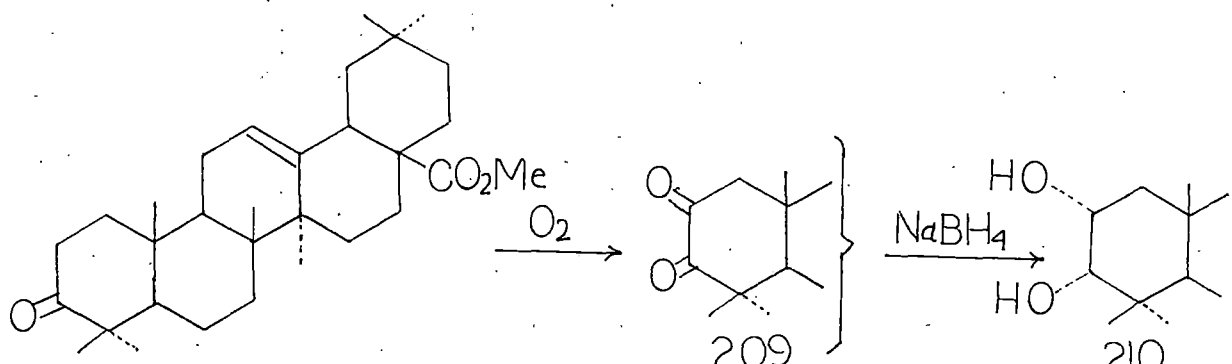
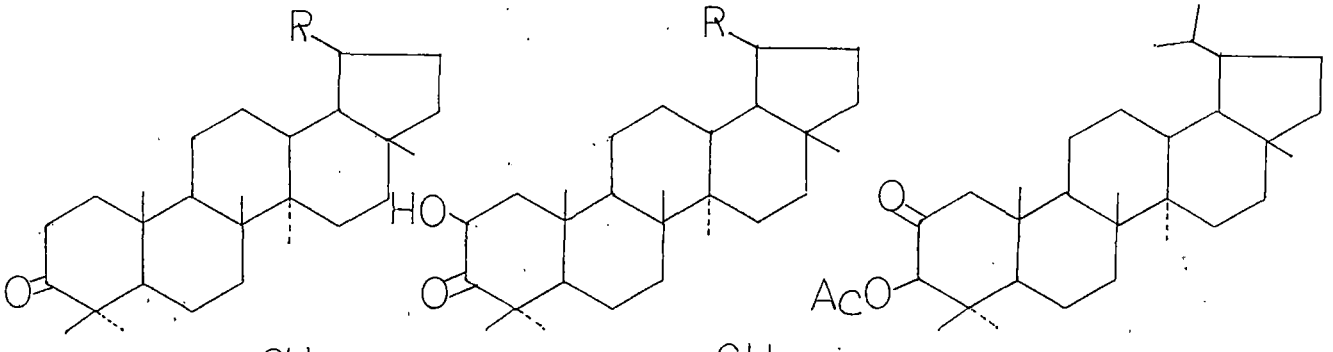


208 209 210

The reaction mixture on acidification and usual working up gave an amorphous solid for which they proposed the structure 209, methyl-2, 3-dioxo-olean-12-en-28-oate, m.p. 130-35°, $[\alpha]_D$ 104° ± 4° . Sodium borohydride reduction of 209 gave methyl 2α , 3α -dihydroxy-12-en-olean-28-oate, 210, which on oxidation with Kiliani solution gave a mixture of several compounds in which 10% of 209, was found.

Oxidation in ring A in Lupeol

Ganguly and co-workers[168] carried out the oxidation of lupenone 211 and lupanone 212 to the corresponding diosphenol 213 and 214 respectively by passing oxygen in dry tert-butanol containing K-tert-butoxide. Diosphenol 214 on hydrogenation afforded a non-crystalline alcohol, which on acetylation yielded the keto-acetate, 215.

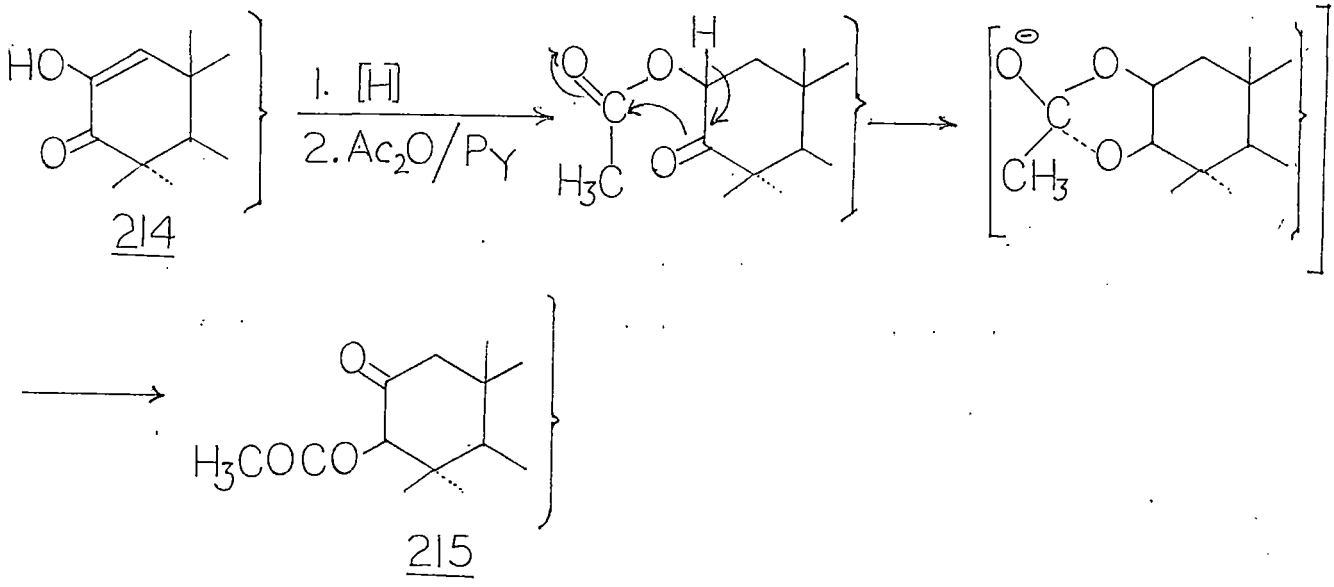


211, R= $-C(=CH_2)-CH_3$ 213, R= $-C(=CH_2)-CH_3$ 215

212, R= $-CH(CH_3)-CH_3$ 214, R= $-CH(CH_3)-CH_3$

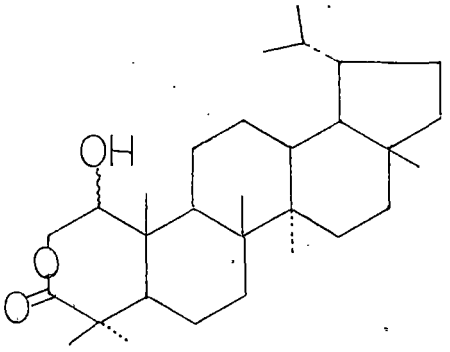
168. A.K. Ganguly, T.R. Govindachari and P.A. Mohammed, Tetrahedron, 22, 3597 (1966)

Formation of 215 from 214 was explained by the mechanism shown below:



214 215

Diosphenol, 214, on ozonolysis gave a neutral compound $C_{29}H_{48}O_3$, whose structure was assigned as 216 on the basis of mode of formation, spectral characterisation and elemental analysis. Diosphenol 213 was cleaved by alkaline hydrogen peroxide to the dicarboxylic acid $C_{30}H_{48}O_4$. The acid was converted into the dimethyl ester 217, which on refluxing with alcoholic alkali yielded a neutral crystalline compound 218.



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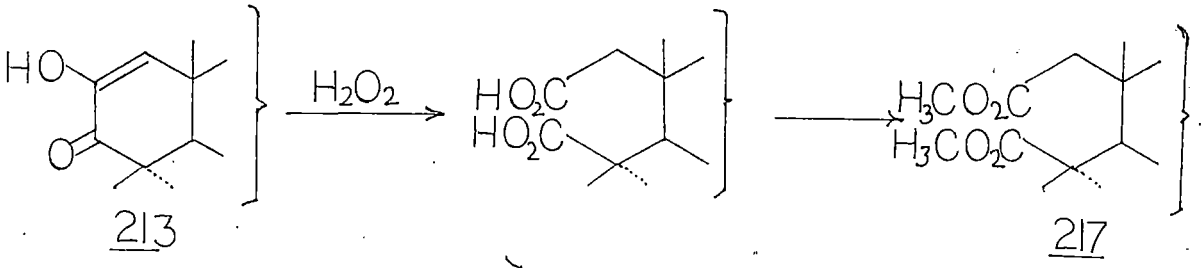
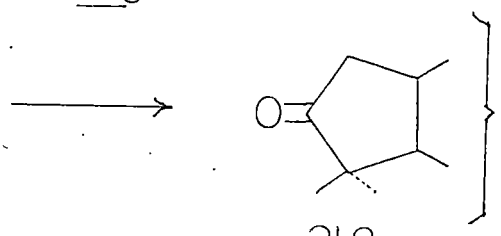


213 217



218

Autoxidation of Lanostenyl acetate

Horn and Ilse[169] reported that lanostenyl acetate in ethyl acetate was extensively converted into a mixture of 7-hydroperoxy and 7, 11-dihydroperoxy lanostenyl acetate by

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169. D.H.S. Horn and D. Ilse, J. Chem. Soc. 2280 (1957)

treatment with gaseous oxygen at 50° for 48 hours. Scotney and Truter[170] later found that the autoxidation of lanostenyl acetate in ethyl acetate at 50° after 14 days was a mixture of at least eight peroxides. The two most plentiful peroxides were recovered and shown to be 7β and 11β-hydroperoxy lanostenyl acetates. The structure of 11β-hydroperoxide was proved by converting it to 11-oxo-lanostenyl acetate with ferrous ion. Furthermore, lithium aluminium hydride reduction of the 11-hydroperoxide afforded one product, which was identical with 11β-hydroxylanostenol.

Autoxidation of 7, 11-dioxolanost-8-enyl-3β-acetate in cyclohexane at 40° proceeded via 1β-hydroperoxy-7, 11-dioxolanostenyl acetate to 1, 7, 11-trioxo-lanost-8-enyl acetate[171]. The location of ketone at 1-position was deduced from the behaviour of the trione acetate with alkali. With alkali 1,7,11-tri oxo lanost-8-enyl-acetate yielded 1,7, 11-trioxo lanosta-2, 8-diene and it had been derived from the trione acetate by elimination of the 3β-acetate group and the formation of a conjugated unsaturated grouping (219, 220, 221). That the precursor for the trione is a monohydroxy -

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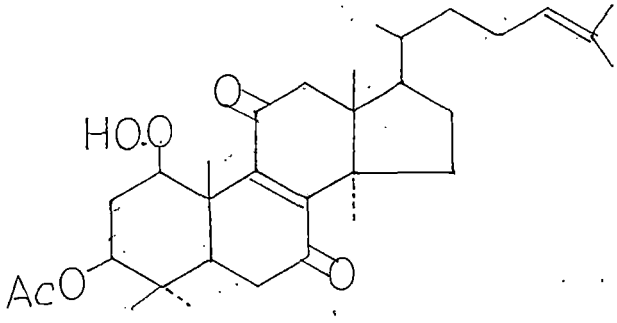
170. J. Scotney and E.V. Truter, J. Chem. Soc. (C), 1911(1968)

171. J. Scotney and E.V. Truter, J. Chem. Soc (C), 2184(1968)

171a. Idem, J. Chem. Soc., 9516 (1968)

peroxide of 7, 11-dioxo lanostenyl acetate was established by the fact that it was decomposed by ferrous ion to 1,7,11-trioxo lanostenyl acetate.



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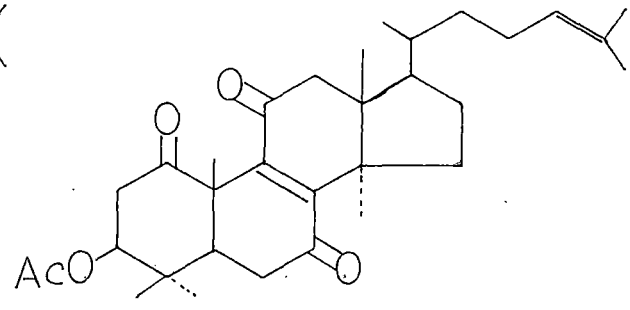

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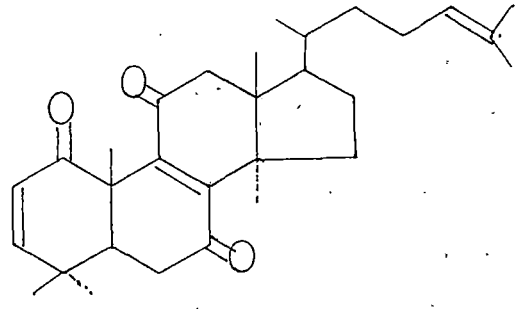

221

In an experiment a solution of lanost-8-en-3β-yl-acetate in cyclohexane at 40^{o} was oxidised by passing oxygen through it[171a]. After twelve months of treatment, the neutral fraction was examined and was found to contain at least sixteen components. From Rf values several components have been identified e.g. 1,7,11-trioxolanostenyl acetate, 1,7,11-trioxolanosta-2,8-diene. Besides those compounds, 15β-hydroxy-7-oxo, 5α-

hydroxy-7-oxo, 7, 15-dioxo- and 11, 15-dioxo-lanostan-3 β -yl-acetate were also identified.

Autoxidation of β -amyrone

Khastgir et al[172] studied autoxidation of β -amyrone in an attempt to introduce more oxygen function in a triterpenoid molecule. -amyrone was stirred in tert-butanol containing potassium metal with simultaneous introduction of oxygen. One mole of oxygen was rapidly absorbed by the compound producing ∝ -diketone derivative, m.p. 200-2°. The material showed positive ferric chloride test and two spots on a chromatoplate indicating that two compounds were present in the mixture, diketone 223 and diosphenol 224. Acetylation of 224 with acetic anhydride and pyridine gave the acetate 225.

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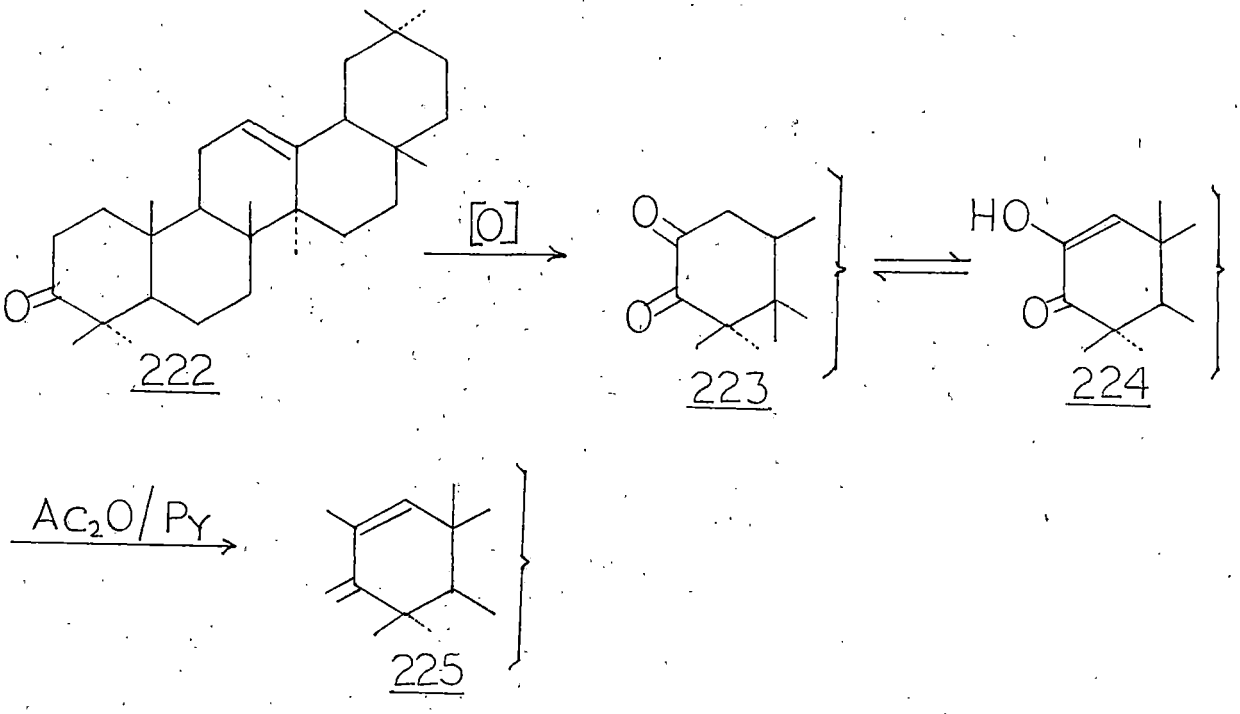
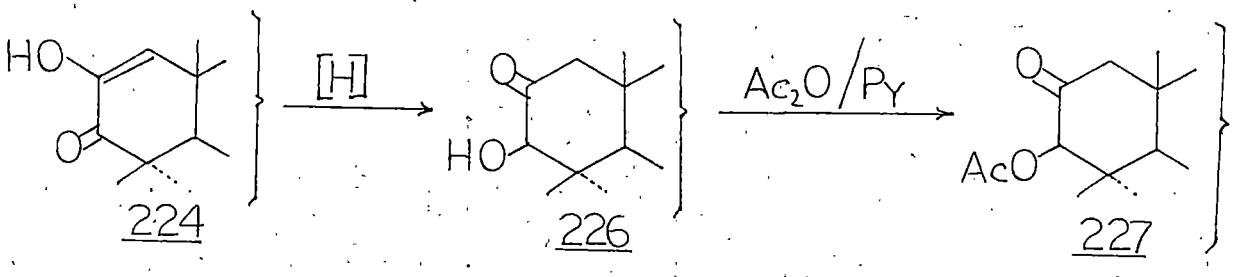
172. D.R. Misra, H.N. Khastgir, M. Sung and L.J. Durham, Ind. J. Chem. 14B, 407 (1976)



In order to prepare the α -hydroxy ketone derivative in ring A, catalytic hydrogenation of the diosphenol 224 was investigated in presence of 10% palladium charcoal catalyst. It yielded 2-keto-3-hydroxy compound 226 which on acetylation afforded the corresponding acetate 227.



The formation of 3-hydroxy-2-keto derivative 226 in the process of hydrogenation was explained by Khastgir et al as in the following. During the process of hydrogenation a rear attack of the hydrogen from the less hindered side of the molecule might take place resulting in the formation of the 2-hydroxyl group in the β-axial orientation. It is known that the conformation of ring A in triterpenoids as well as in 4, 4- dimethyl steroids are dependent on the 1,3 homoannular interactions of the methyl groups at C-4 and C-10[173-175]. Therefore, the C-2 β-axial hydroxyl group, which could be formed by rear attack of hydrogen would produce further 1,3 diaxial interactions resulting in a great strain in the molecule. The strain could be released by ready conversion to 3-hydroxy-2-keto derivative, 226, through enolisation of the 2 β-hydroxy-3-keto derivatives.

During the process of autoxidation, a second mole of oxygen was absorbed by the diosphenol, 224, which resulted in the formation of a lactol, 228 (1-hydroxy-2-oxo-β-amyrone), m.p. 262-65°. The formation of such a lactol had already been

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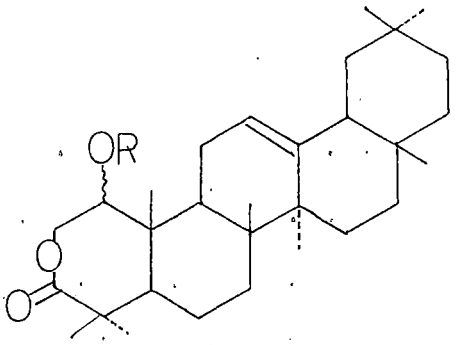
173. J.S.E. Holker, Proc. Chem. Soc. 464 (1961)

174. N. Allinger and M.A. DaRooge, Tet. Lett. 19, 676 (1961)

175. N. Allinger and M.A. DaRooge, J. Am. Chem. Soc. 84, 4561 (1961)

described and was interpreted through the formation of a ring A-seco-2-nor-aldehydo carboxylic acid, which cyclizes upon acidification[176]. Acetylation of 228 with acetic anhydride-pyridine gave an acetate 229, m.p. 186-87°.



228, R=H
229, R=Ac

Autoxidation of Moretanone

Moretanone, 230 obtained by hydrogenation of moretenone[177] was autoxidised by passing oxygen through a suspension of 230

176. R. Hanna and G. Ourisson, Bull. Soc. Chim. Fr. 1945 (1961)

177. H.N. Khastgir, B.P. Pradha n, L.J. Durham and A.M. Duffield, Chem. Commun, 1217 (1967)

in dry tert-butanol containing K-tert-butoxide[178], which resulted in the formation of corresponding diosphenol 231. Acetylation of diosphenol afforded the diosphenol acetate 232. Diosphenol acetate, 232 on hydrogenation in presence of palladium charcoal catalyst in ethanol solution gave the reduced product 233, m.p. 179-81°. Diosphenol 231 on hydrogenation in presence of palladium on charcoal catalyst in ethanol solution afforded a solid 234, m.p. 181-83°, which on acetylation afforded the corresponding acetate 235, m.p. 264-67°. The acetate 233 on isomerisation by absorbing it on basic alumina column was converted to the stable 2-keto moretanyl acetate structure 235.

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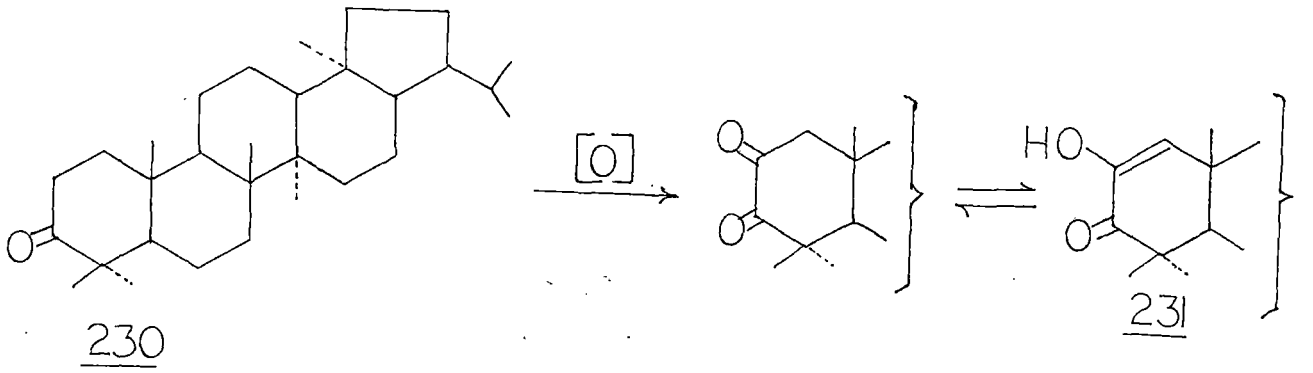
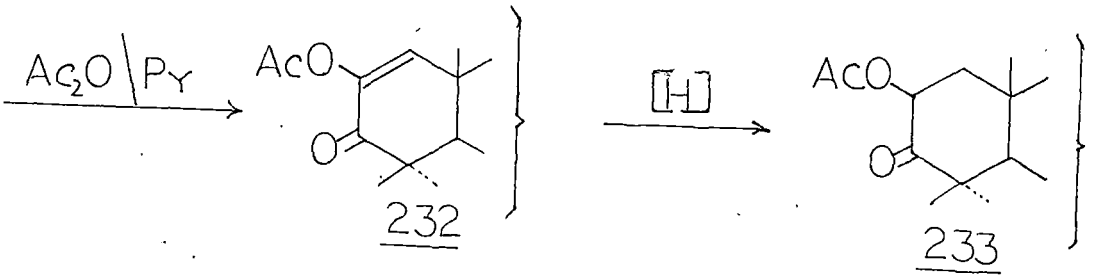
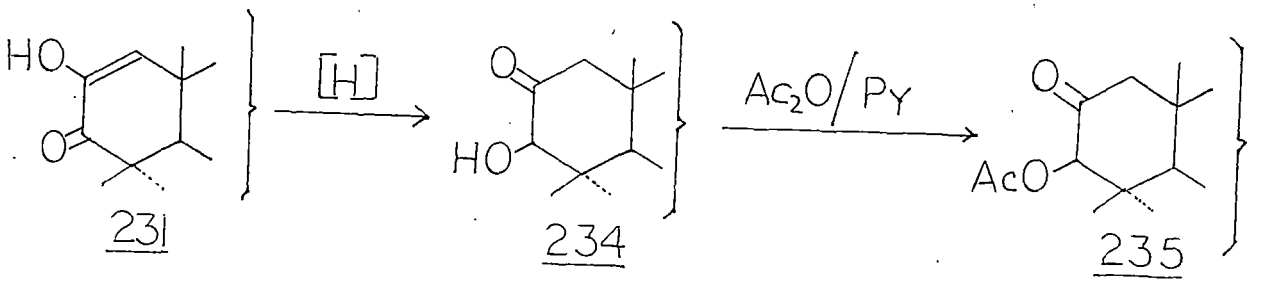
178. K. Chattopadhyaya, D.R. Misra, H.N. Khastgir, Ind. J. Chem. 15B, 21 (1977)


[O]
HO
230
231


Ac2O/Py
AcO
[H]
AcO
232
233


HO
[H]
HO
Ac2O/Py
AcO
231
234
235

SECTION - B

Autoxidation of Friedelin. Result and Discussion

The discussion in the preceding pages of this chapter show that autoxidation of several triterpenoids results in the formation of different compounds depending on the condition of the reaction. Such products possibly play a vital role in the physiological processes where triterpenoids are associated, such as selective action of triterpenoids on neoplastic cells and antitumor activity. Lavie and co-workers[165] extensively studied the autoxidation of ring A of certain species of Euphorbiaceae family and found that the occurrence of an α-hydroxy ketone or of a diosphenol grouping in ring A attributes to their activity.

In our attempt for introducing more oxygen functions in a triterpenoid molecule, we undertook the autoxidation of friedelin. The reaction resulted in the formation of different A-nor-compounds. No diosphenol was detected. This part of the desertation describes the characterisation of the products formed during the reaction and the possible mode of formation of the compounds.

The oxidation of friedelin 136 was carried out by stirring the compound in dry tertiary butyl alcohol containing potassium tertiary butoxide in an atmosphere of oxygen for

three hours. The product obtained, a mixture of compounds was subjected to chromatographic separation over an active alumina column. On elution with solvents like petroleum ether, petroleum ether-benzene and benzene yielded no solid material. The column was then eluted with a solvent mixture of methanol-acetic acid (19:1) which yielded a white amorphous solid substance. Infra-red spectrum of the crude product indicated the presence of a hydroxy functionality. The compound was then acetylated with acetic anhydride-pyridine. It was noted that it took several hours for the compound to dissolve in the solvent mixture at 80°. The acetylated product showed the presence of three compounds on chromatoplate developed with benzene-ethyl acetate (9:1) solvent mixture. The compounds were separated by chromatography over deactivated alumina column. Elution of the column with petroleum ether yielded a white compound A_1. Elution with benzene-petroleum ether solvent mixture (4:1) afforded solid A_2. Further elution with benzene-chloroform (3:2) yielded a gummy solid A_3.

Characterisation of A_1 :

The compound on repeated crystallisation from chloroform-methanol recorded m.p. 225-27°. Elemental analysis and mass spectrum confirmed its molecular formula as $C_{29}H_{48}$. It responded to TNM test for unsaturation.

The infrared spectrum (Fig. 49) shows peaks at 1650 and 790 cm^{-1} which indicates the presence of double bond in the compound. The 360 MHz ^1H NMR spectrum (Fig. 50) indicates the presence of eight tertiary methyl groups at δ 0.84, 0.94, 0.97, 1.00, 1.01, 1.17 and at δ 1.57. It also gives support for the presence of a vinyl proton by appearance of peak at δ 5.26 integrable for one proton. As one of the methyl groups

Table - 37

^1H NMR Signals of A1 in $CDCl_3$

Chemical shift δ	No. of protons	Multiplicity of signals	Probable assignment
0.84	3	Singlet	7t $-CH_3$
0.94	3	Singlet	
0.97	3	Singlet	
1.00	6	Singlet	
1.01	3	Singlet	
1.17	3	Singlet	
1.57	3	Singlet	Methyl group on double bond
5.26	1	Singlet	Trisubstituted double bond

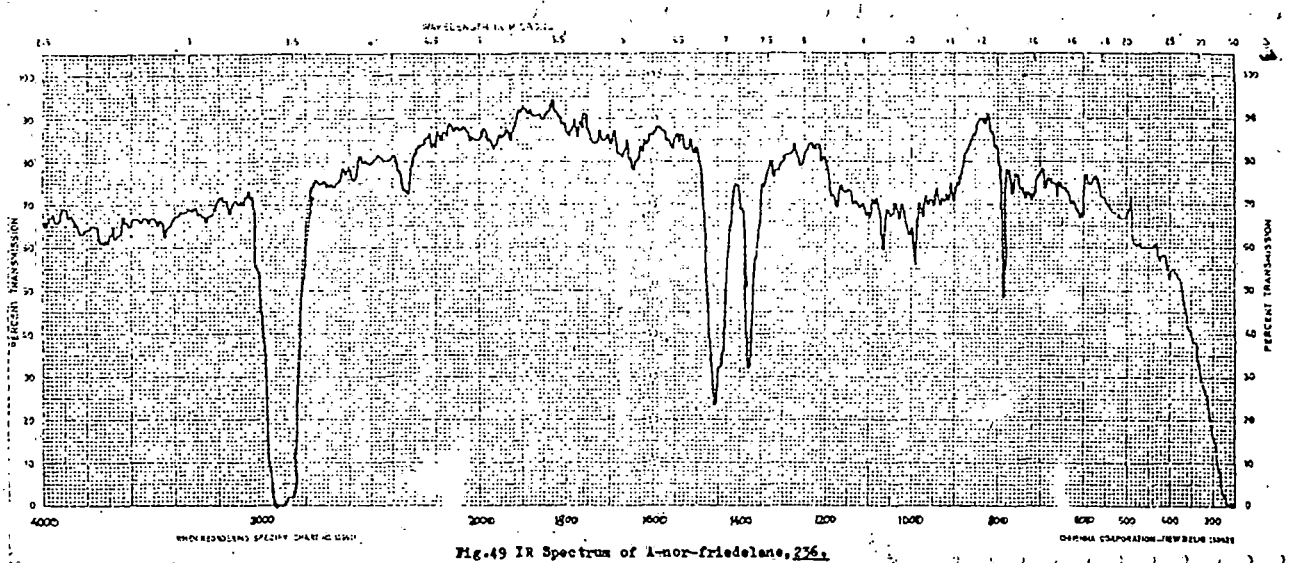


Fig.49 IR Spectrum of A-nor-friedelane, 236.

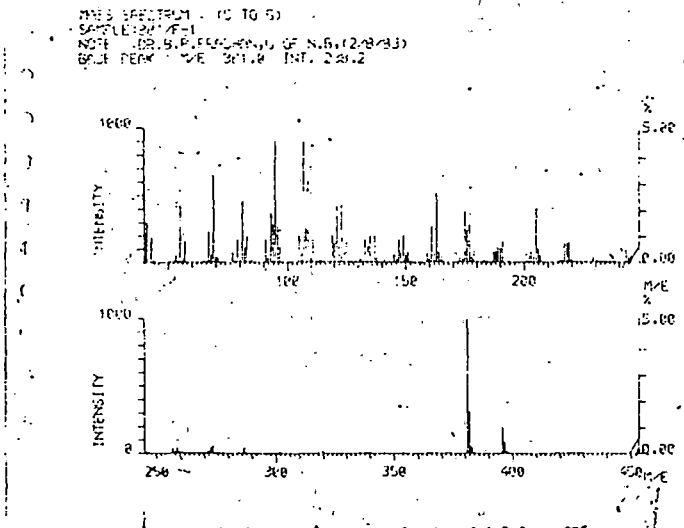


Fig.51 Mass Spectrum of A-nor-friedelane, 236.

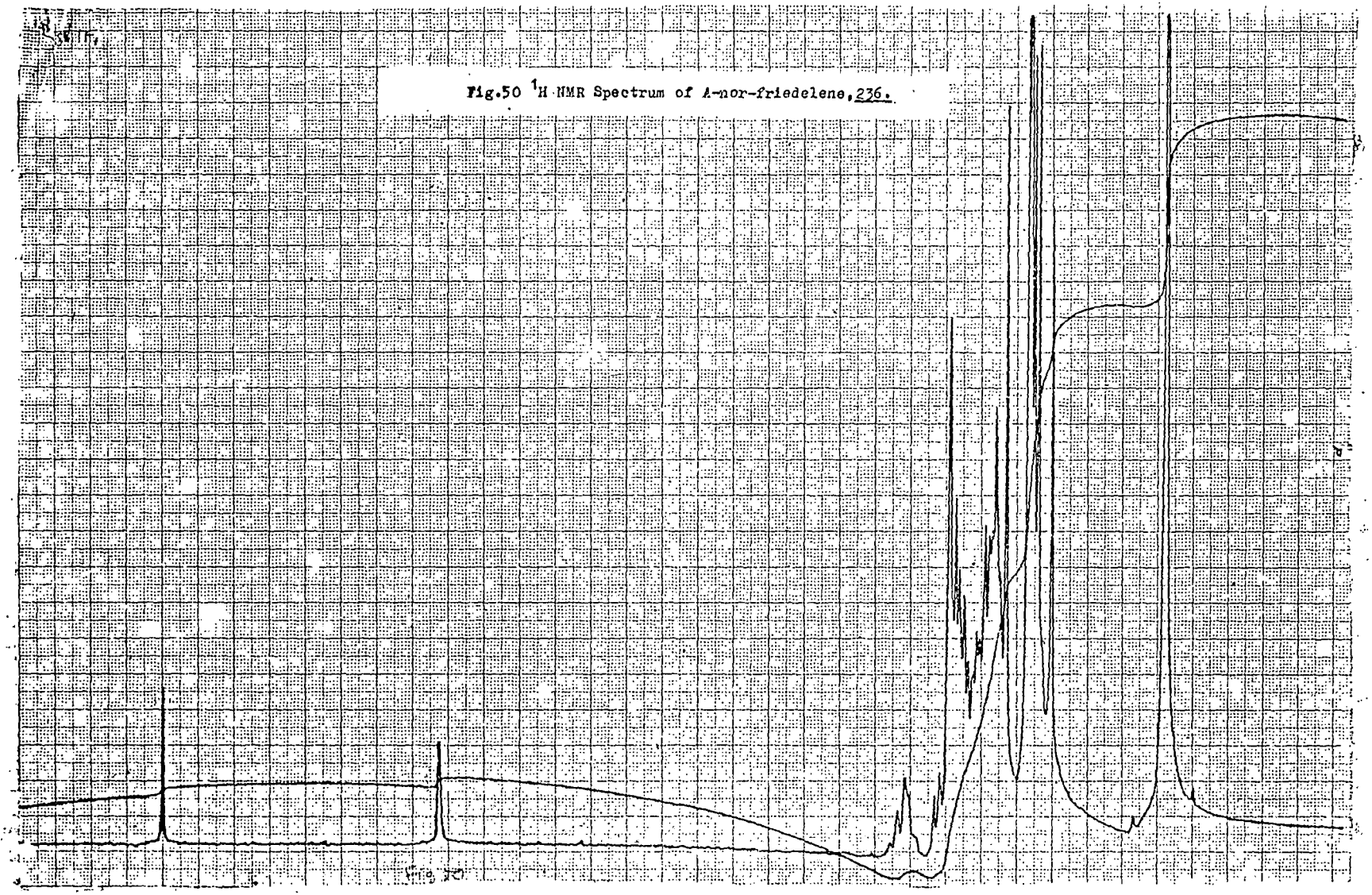
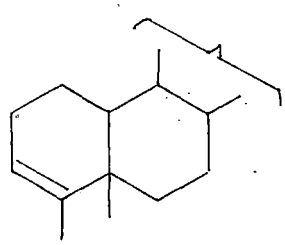


Fig.50 ^{1}H NMR Spectrum of *A-nor-friedelene*, 236.

resonates at considerably lower field i.e. at δ 1.57, it can be inferred that the methyl group is on a double bond. The absence of a doublet in the region δ 0.85 to 0.95 that is generally observed for the secondary methyl group at C-4 position of friedelin[179,180] indicates that the peak at δ 1.57 is due to the methyl group at C-4 position which is situated on a double bond. Hence, it may be said that the C-23 methyl group is on double bond in compound A_1. The appearance of vinyl proton as a broad singlet at δ 5.26 indicates that the signal would couple with the proton on adjacent carbon with a coupling constant $J \simeq 0.5$ Hz[180a] but the value is so small that the signal is only intensely broadened instead of being splitted.

Thus the presence of the grouping $H_3C-\overset{|}{C}=CH-\overset{|}{C}H$ in compound A_1 is established that can be best fitted in ring A of friedelin as



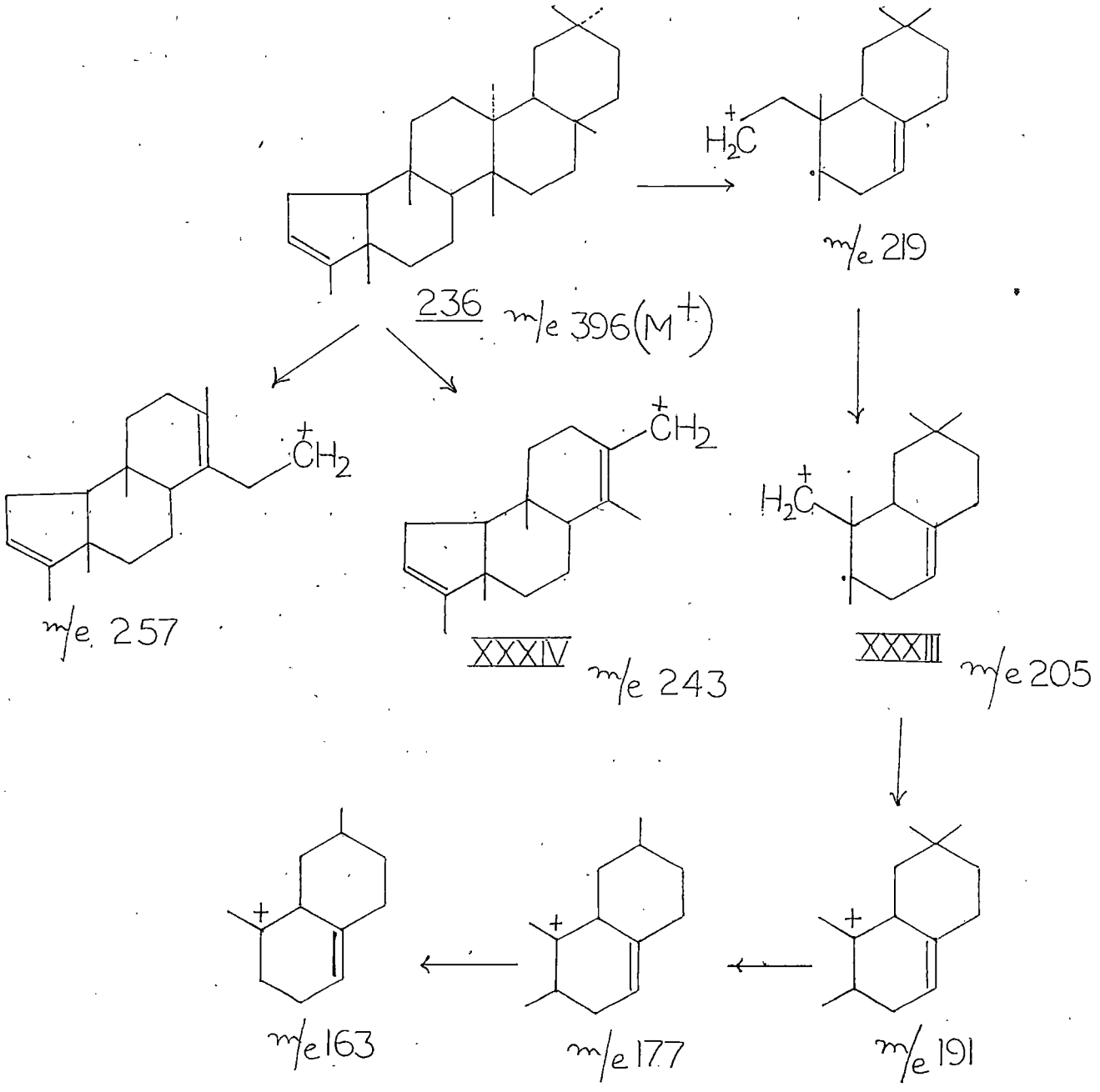
179. A.S.R. Anjaneyula and M. Narayan Rao, Phytochemistry, 19, 1163 (1980)

180. B. Talapatra, B. Lahiri, A. Basak, D.K. Pradhan and S.K. Talapatra, Ind. J. Chem., 22B, 741 (1983)

The molecular formula of A_1 indicates that the total number of carbon atoms in the compound to be 29 instead of 30 as in the starting compound friedelin. Absence of oxygen function in the form of carbonyl or hydroxyl group which is evident from IR and ^1H NMR spectra indicates that the oxygen atom present in the form of ketone in friedelin has been knocked off along with a carbon atom. Mass spectrum (Fig. 51) of the compound is of great help in ascertaining which of the carbon atoms has been lost during the course of the reaction. The mass spectrum exhibits peaks at m/e (rel. int.) 396 (M^+, 20.7), 381 ($M^+ - CH_3$, 100), 257, 243 (5.00), 205 (20) and 191 (15). The peak at m/e 205 is typical of friedelin skeleton comprising ring D and E and is due to the fragment XXXIII. It is, therefore, clear that the loss of carbon atom has occurred in the ring other than D and E. The genesis of the fragment XXXIV, m/e 243 can be rationalised by assuming structure 236 for compound A_1 which explains very well all the spectral observations. The fragmentation pattern is shown in Scheme - XXXIII.

180a. K.B. Wiberg and B.J. Nist, J. Am. Chem. Soc., 83, 1223 (1961)

Scheme - XXXIII



The structure of compound A_1 is thus established as A-nor-friedelene[181].

Characterisation of A_2 :

Elemental analysis and mass spectrum showed the molecular formula of A_2 to be $C_{31}H_{50}O_2$. On crystallisation from a mixture of chloroform-methanol, the compound had m.p. 235-37°. It responded to TNM test thus showing the presence of double bond. Its IR spectrum (Fig. 52) shows absorption at 1740, 1220 and 890 cm^{-1}. The bond at 1740 cm^{-1} is interpreted as due to the presence of an acetoxy group which is supported by the apperance of a band of strong intensity at 1220 cm^{-1}. It is known that the usual "acetate band" at 1240 cm^{-1} is shifted to lower frequency by 20 cm^{-1} in vinyl acetate[182]. Thus it appears that the acetate group is present on the double bond. The peak at 890 cm^{-1} supports the presence of double bond in compound A_2.

The 360 MHz ^1H NMR spectrum (Fig. 53) of the compound is presented here represent in tabular form with the chemical shift and their probable interpretations.

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181. Simonsen and Ross, The terpene, Volm. IV, p. 470, Cambridge (1957)

182. R.N. Jones and C. Sandorfy, "Chemical Application of Spectroscopy", 482 (1956).

Table - 38

^1H NMR Signals of compound A_2 in $CDCl_3$

Chemical shift δ	Number of protons	Multiplicity of signals	Probable assignment
0.94	6	Singlet	7t - CH_3
0.98	3	Singlet	
0.99	3	Singlet	
1.01	6	Singlet	
1.17	3	Singlet	
1.55	3	Singlet	-C - C - CH_3
2.13	3	Singlet	-O - C - CH_3

The spectrum shows the presence of seven tertiary methyl groups in the region between δ 0.94 to 1.17 and one acetoxy methyl at δ 2.13. The peak at δ 1.55 is due to methyl group on double bond, which is quite broad. Such broadening of vinyl methyl group is due to long range coupling propagated through π system of the double bond. The methyl proton of a n enol-acetate function resonates in the region between δ 2.0 to 2.2, although usually at slightly lower field than a saturated acetate because of the prominity of double bond[183]. Hence, the singlet

183. N.S. Bhacca and D.H. William, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc, 33 (1964)

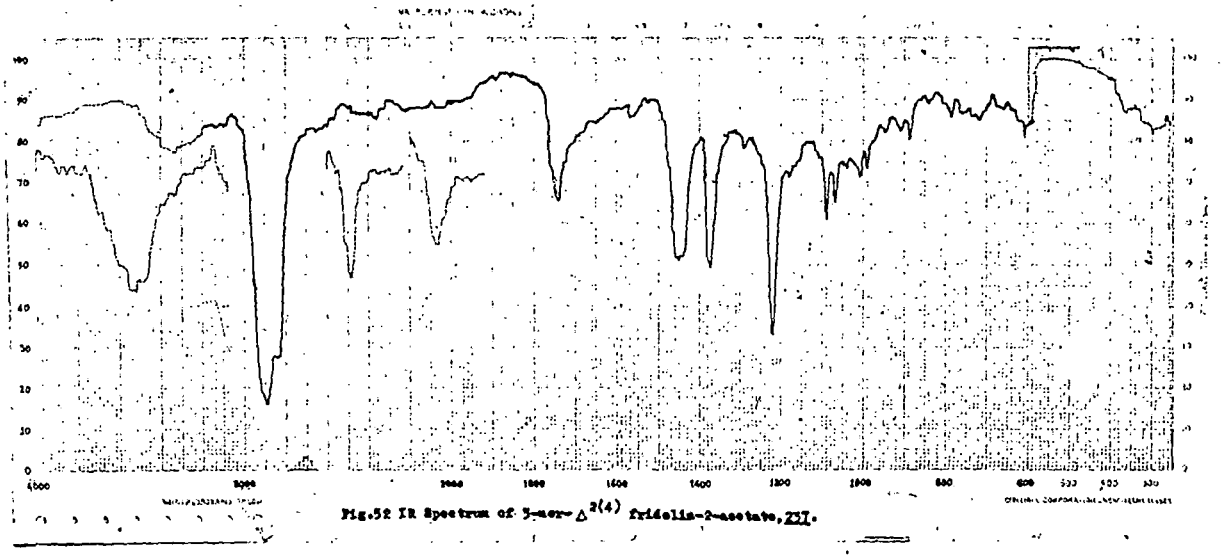


Fig.52 IR Spectrum of 3-oxo-$\Delta^{2(4)}$ friedelin-2-acetate,237.

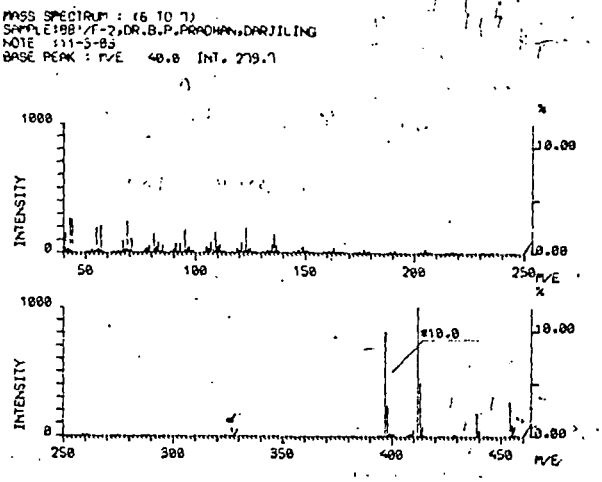


Fig.54 Mass Spectrum of 3-oxo- $\Delta^{2(4)}$ - friedelin-2-acetate,237a

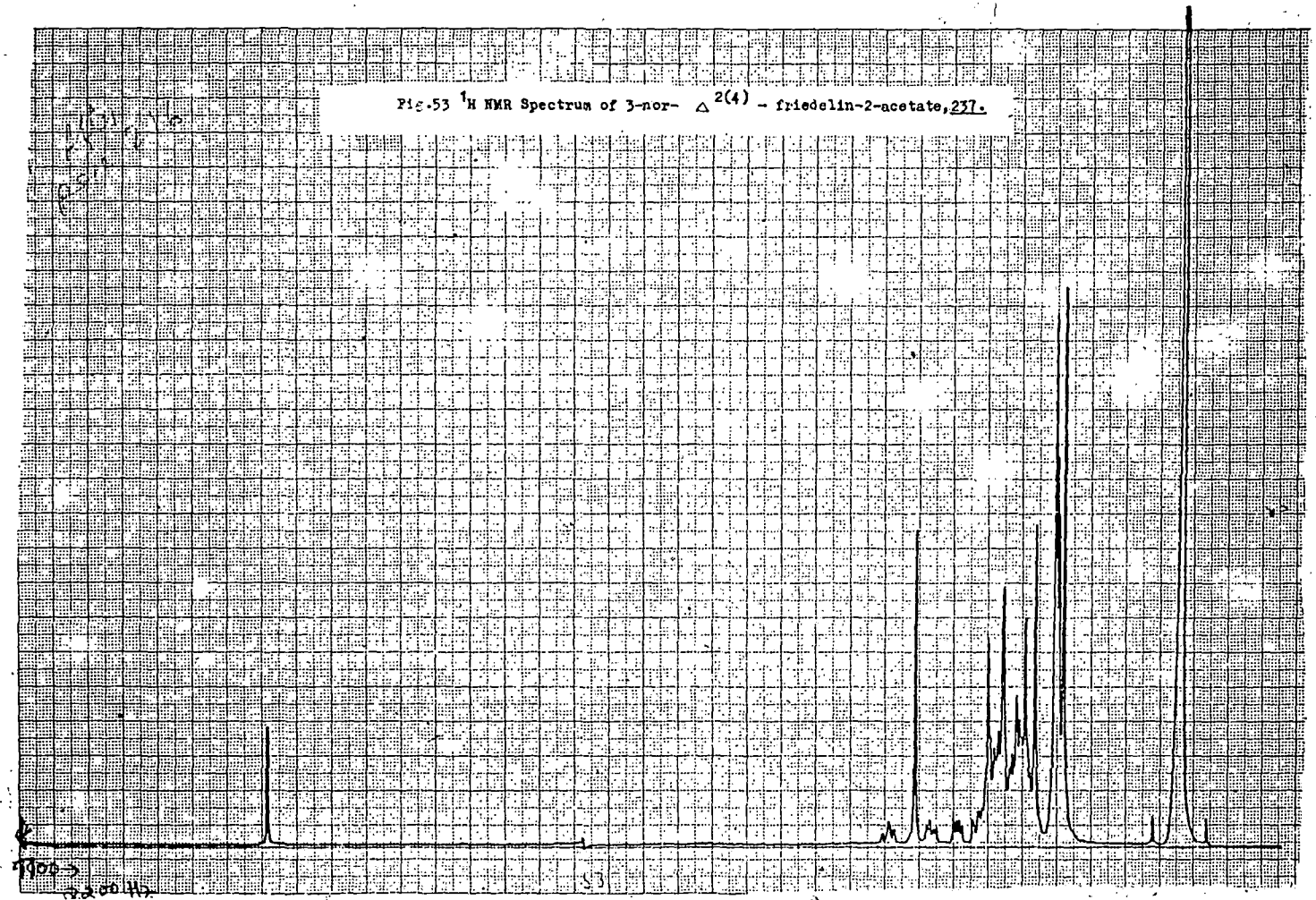
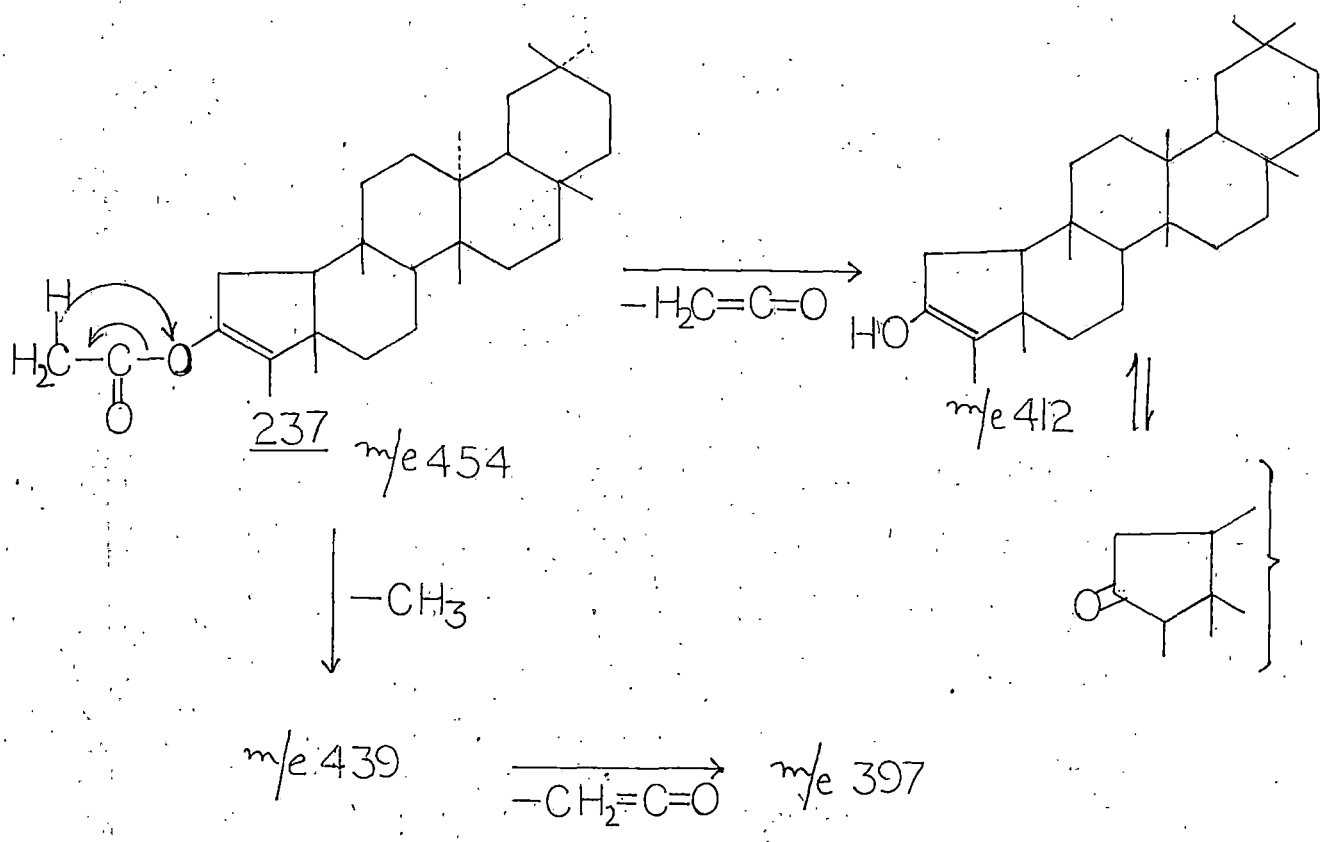


Fig.53 ^{1}H NMR Spectrum of 3-nor- $\Delta^{2(4)}$ - friedelin-2-acetate, 237.

at δ 2.13 is attributed to acetoxy methyl group on a double bond. Since, there is no doublet for a secondary methyl group in the δ 0.75 to 0.95 region, it may be inferred that the C-4 methyl group of friedelin is on the double bond in compound A_2. Again, the absence of olefinic resonance in the region δ 4.5 to 6.5 indicates that the double bond is tetrasubstituted which support the existence of acetate and C-23 methyl groups on the double bond. Further, the absence of peak due to proton geminal to carbon containing acetate group shows that the acetate group is certainly present on the double bond.

The molecular formula of A_2 ($C_{31}H_{50}O_2$) indicates that the compound has got a nor-triterpenoid skeleton. With the help of mass spectral data the complete structure of the compound was finally established. The mass spectrum (Fig. 54) exhibits peaks at m/e (rel. int.) 454 (M^+, 2%), 439, 412 (9.70), 397 (59.32), 381 (0.7), 205 (2) and 191 (2). Since there is no prominent peak due to loss of an acetoxy function from the total mass 454, it is to be inferred that the loss of acetoxy group is mechanistically prevented due to the attachment of the acetate group on a double bond. However, the loss of acetyl group from the total mass is evident from the peak at m/e 412 as shown in the Scheme XXXIV. The genesis of these fragments can be explained by assuming structure 237 for compound A_2 which explains the IR and ^1H NMR spectral observations too.

Scheme - XXXIV



Thus, the structure of compound A_2 is established as 3-nor-$\Delta^{2(4)}$ friedelin-2-acetate 237.

Characterisation of A_3 :

Elemental analysis and mass spectrum of A_3 indicated its molecular formula to be $C_{30}H_{48}O_2$. Crystallisation of the compound from chloroform-methanol afforded amorphous solid, m.p. 290-92°. It responded to TNM test showing the presence of unsaturation in the compound.

The IR spectrum of the compound (Fig. 55) shows bands at 3380 and 1675 cm^{-1} which are indicative of the presence of a carboxyl group. Appearance of bands at 1620 and 780 cm^{-1} are due to the presence of a double bond. The IR spectrum also gives some information regarding the position of the carboxyl group and the double bond. The $>C = O$ vibration occurs at lower frequency than a saturated acid which is due to the conjugation of the double bond with the carboxyl group. In α,β-unsaturated acids, the force constant of the $>C = O$ bond is affected on one hand by the -I effect of the double bond and on the other hand by the conjugative effect acting in the opposite direction. The -I effect tends to increase the $>C = O$ bond order whereas the conjugative effect tends to lower it. Generally, the mean frequency of the $>C = O$ stretching vibration in the α,β-unsaturated acids occur in the range 1690-1700 cm^{-1}. In compound A_3 further decrease in $>C = O$ frequency has been attributed to the presence of a methyl group

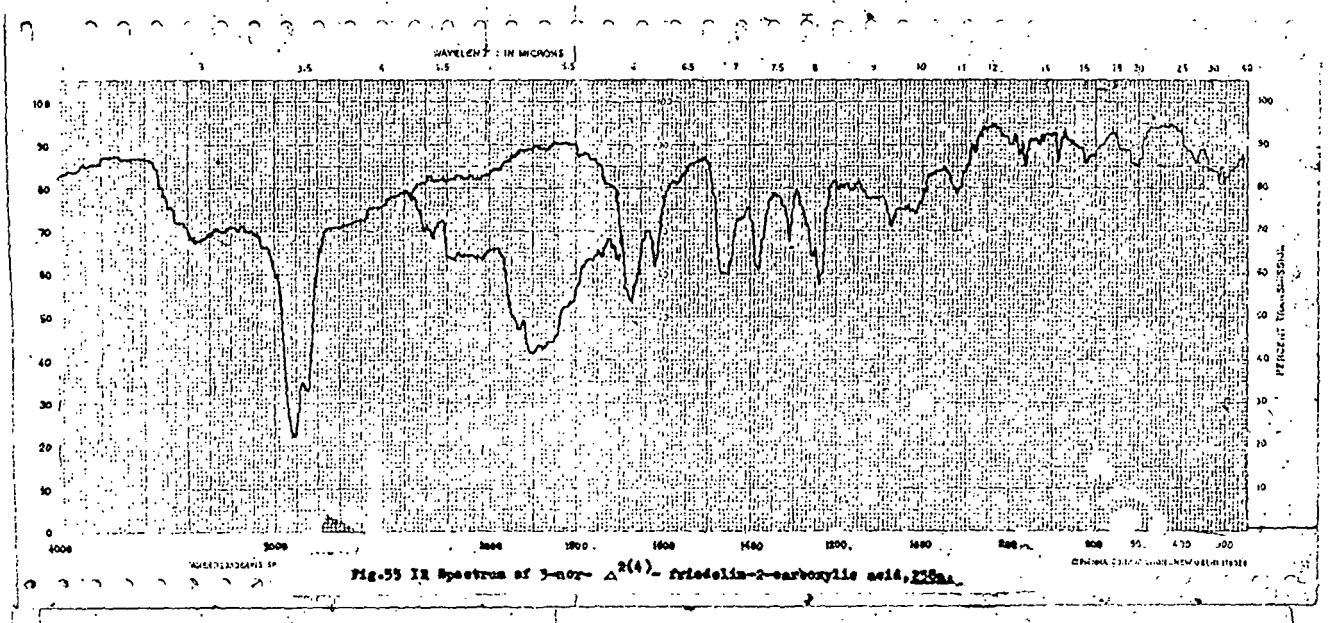


Fig.55 IR Spectrum of 3-nor- $\Delta^{2(4)}$- friedelin-2-carboxylic acid, FIIIa.

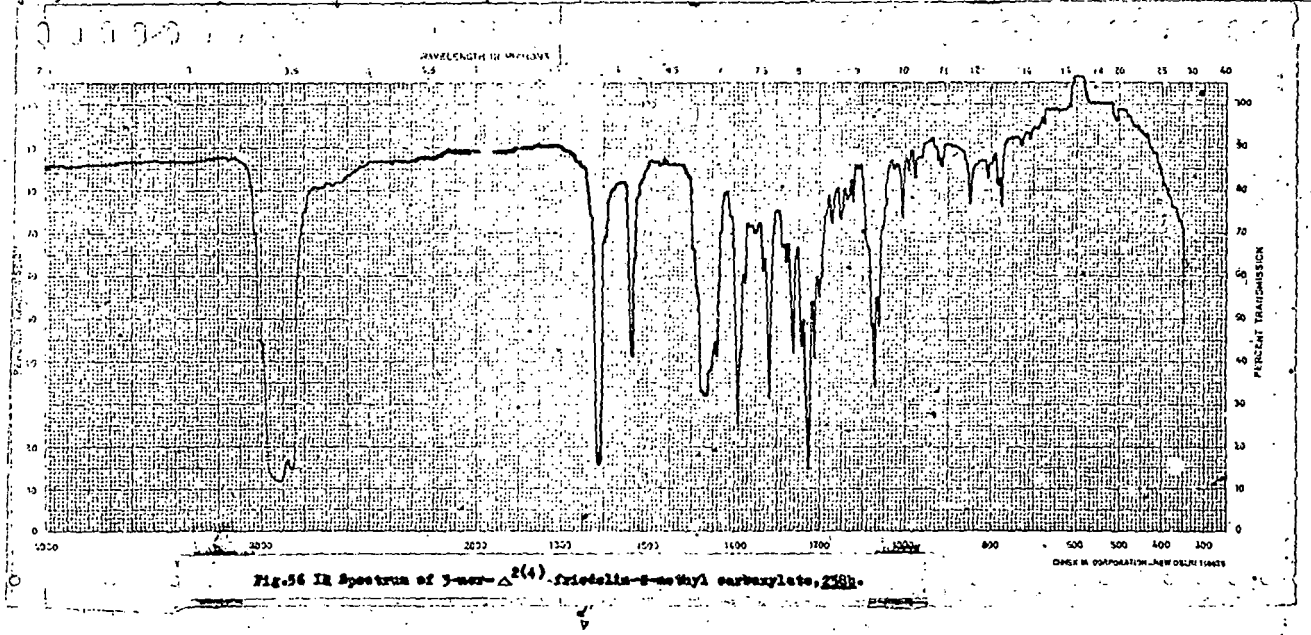


Fig.56 IR Spectrum of 3-nor- $\Delta^{2(4)}$-friedelin-2-methyl carboxylate, FIIIb.

which enhances the conjugative effect thus reducing still further the >C = O bond order[184].

Compound A_3 on esterification gave the methyl ester which on crystallisation from chloroform-methanol afforded m.p. 205-7°. Elemental analysis and mass spectrum showed its molecular formula to be $C_{31}H_{50}O_2$. Its IR spectrum (Fig. 56) exhibits bands at 1720, 1225 ($-COOCH_3$), 1640, 850 and 810 (tetrasubstituted double bond) cm^{-1}. The absorption band of $-COOCH_3$ group in lower frequency region indicates that it is an ester of α,β-unsaturated acid with the double bond adjacent to the $-COOCH_3$ group.

The 360 MHz ^1H NMR spectrum (Fig. 57) of the compound has been recorded in Table-39

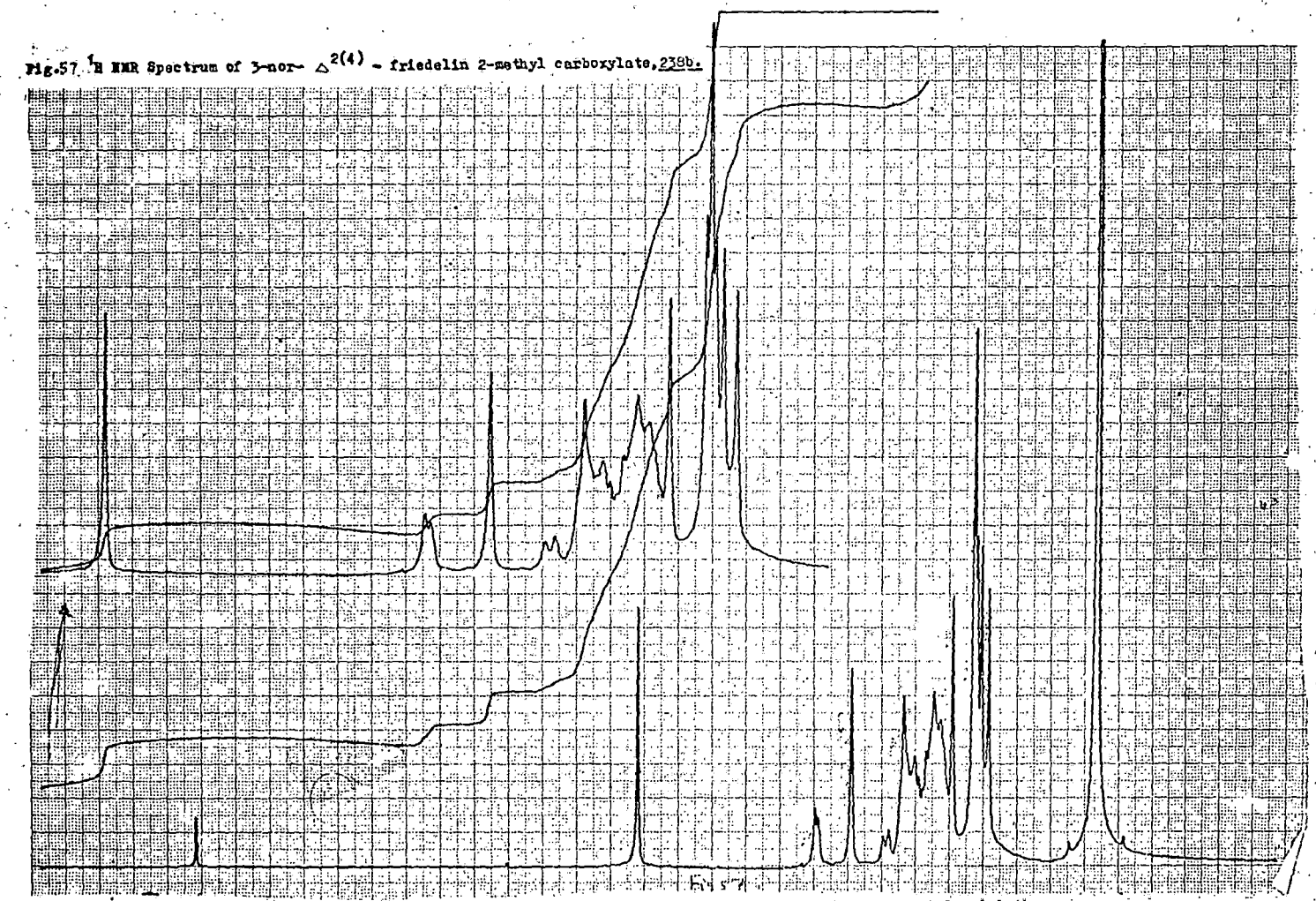
Table -39

^1H NMR Signals of Ester of A_3 in $CDCl_3$

Chemical shift δ	Number of protons	Multiplicity of signals	Probable assignment
0.88	3	Singlet	
0.94	3	Singlet	8t $-CH_3$
0.97	3	Singlet	
0.99	6	Singlet	
1.02	3	Singlet	
1.18	3	Singlet	
1.98	3	Singlet	
3.70	3	Singlet	$-COOCH_3$
2.25 2.28	2	Singlet	$H_2C-C-COOCH_3$

184. "Infrared Spectra of Organic Compounds", M. Avram, G.H. Mateescum, Willey-Interscience, 398 (1970)

Fig.57 ^{1}H NMR Spectrum of 3-nor- $\Delta^{2(4)}$ - friedelin 2-methyl carboxylate, 238b.



The appearance of singlets in the region δ 0.88 to 1.98 integrable for twenty four protons indicates the presence of eight tertiary methyl groups in the compound. The methyl carboxylate, however, appears as singlet at δ 3.70. The appearance of a methyl group at considerably lower field i.e. at δ 1.98 may be explained if the methyl group is on a double bond which in turn is in α,β position with the carbomethoxy group. The two peaks that appear at δ 2.25 and δ 2.28 and are integrated for two protons seem to be due to the methylene group vicinal to carbomethoxy group. These peaks are shifted downfield by the electromeric effect of the two π bonds of the double bonded carbon and the carbonyl group. The downfield shift of one of the methyl groups as singlet at δ 1.98 and the absence of C-23 methyl group that generally appears as doublet in the region δ 0.75 to 0.95 in case of friedelin shows that the double bond must be present at C-4 position. The absence of olefinic proton below δ 4.7 indicates that the double bond is tetrasubstituted. The absence of resonance due to proton geminal to carbomethoxy group that generally appears around δ 2.8 led to the assumption that the carbomethoxy group is situated on double bond. A tentative structure for the compound A_3 has been given as 3-nor-$\Delta^{2(4)}$-friedelenic acid 238. This structure has been confirmed by mass spectral analysis. The mass spectrum of A_3 (Fig. 58) exhibits molecular peak at m/e 440 which readily loses a methyl group to give fragment at m/e 425. The peak that appears at

MASS SPECTRUM : (4 TO 5)
SAMPLE:88/F-3,DR.B.P.PRADHAN,DARJILING
NOTE :11-3-89
BASE PEAK : M/E 40.0 INT. 285.6

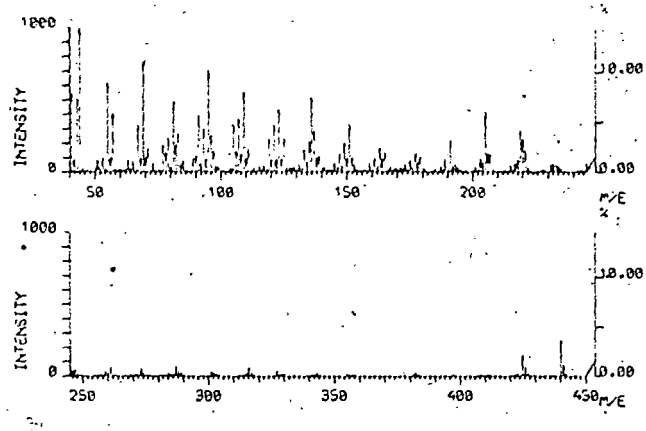


Fig.58 Mass Spectrum of 3-nor-$\Delta^{2(4)}$- friedelin 2-carboxylic acid, 238a.

MASS SPECTRUM : (3 TO 8)
SAMPLE:88/F2/E,DR.B.P.PRADHAN,DARJEELING
NOTE :17/2/89
BASE PEAK : M/E 95.0 INT. 224.4

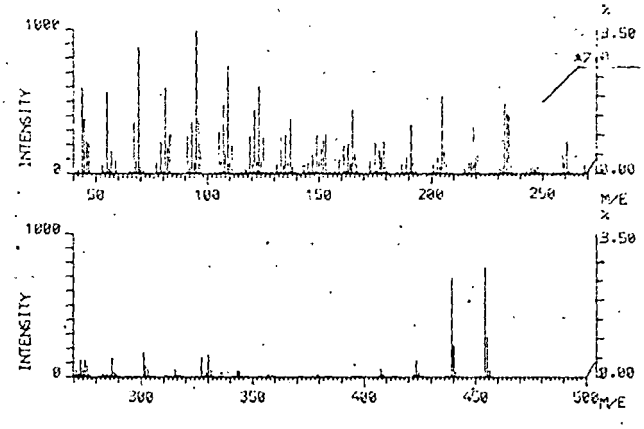
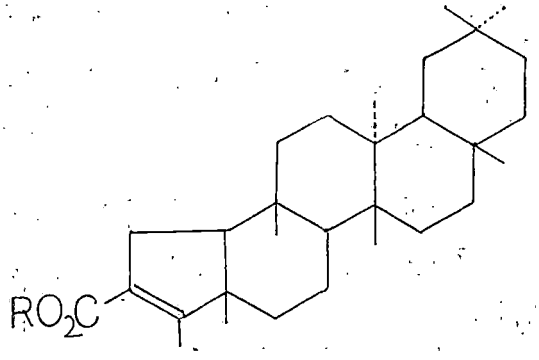
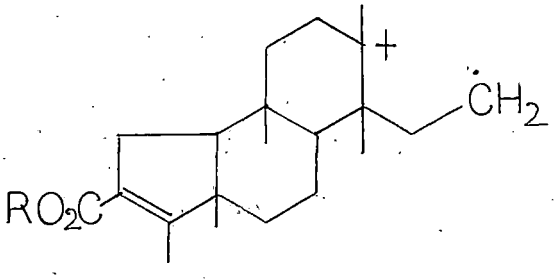


Fig.59 Mass Spectrum of 3-nor-$\Delta^{2(4)}$- friedelin 2-methyl carboxylate, 238b.

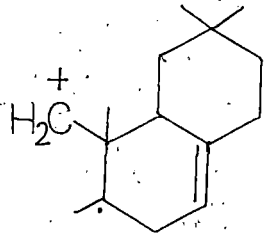
m/e 360 is probably due to fragment XXXVa. The existence of the ion peak at m/e 205 indicates the formation of fragment XXXIII. The fragment XXXV is formed by cleavage of ring D which is typical of friedelin skeleton. The mass spectrum of



238 a R=H m/e 440
b R=CH3 m/e 454



XXXV
a R=H m/e 316
b R=CH3 m/e 330



XXXIII m/e 205

methyl ester of A_3 238b (Fig. 59) shows molecular ion peak at m/e 454 and existence of ion peak at m/e 330, 205 due to formation of fragments XXXVb and XXXIII respectively. Thus from the genesis of the mass fragmentation pattern and combination with IR as well as ^1H NMR spectral data, the structure of the acid and its corresponding methyl ester has been conclusively established as 3-nor-$\Delta^{2(4)}$ friedelin 2-carboxylic acid and its methyl ester respectively. That the compound A_3 is 3-nor-$\Delta^{2(4)}$ friedelin-2-carboxylic acid is further confirmed by catalytic hydrogenation of its methyl ester 238b which affords 2α-carbomethoxy-A-nor-friedelin 138, m.p. 263-65°.

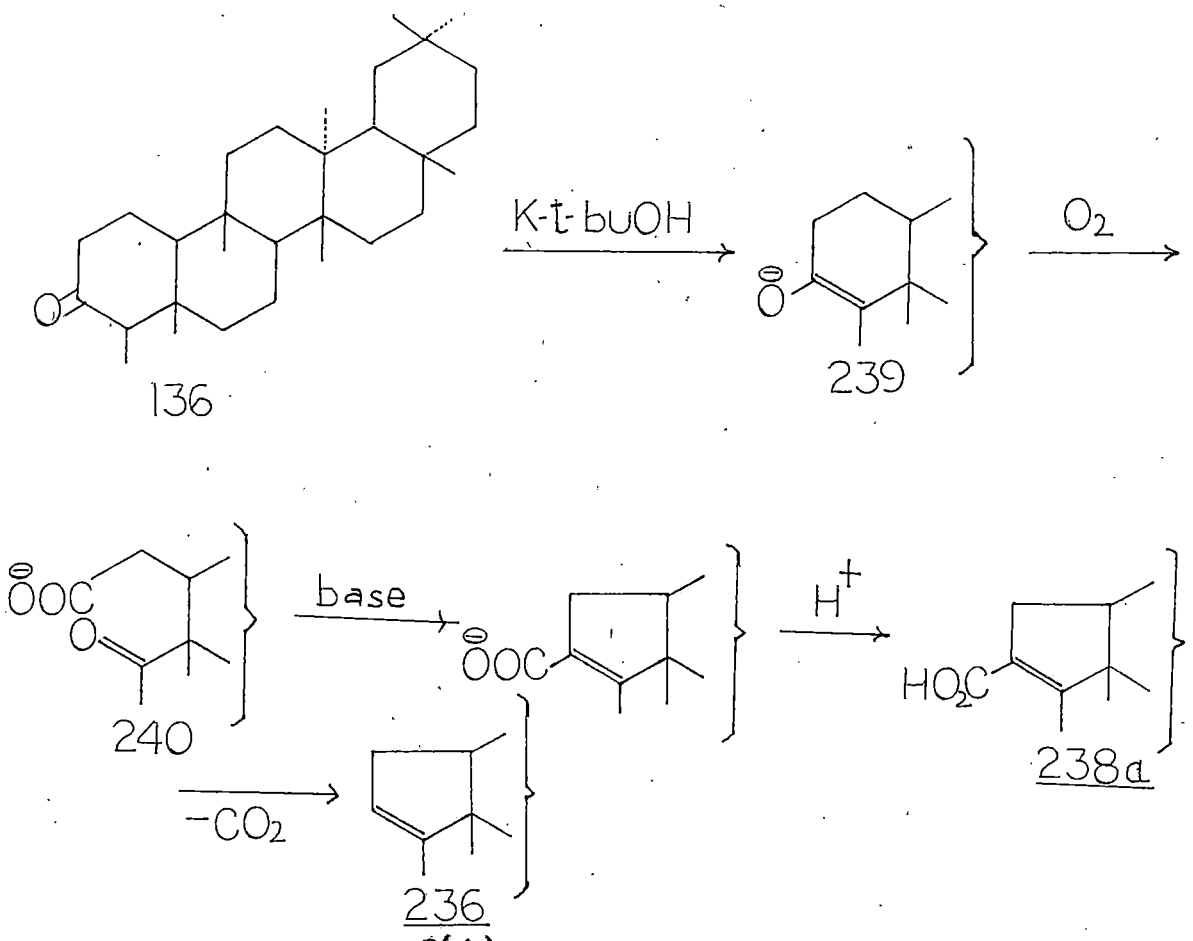
Proposed mechanism of the reaction: Formation of 3-nor-$\Delta^{2(4)}$ friedelin-2-carboxylic acid 238a and A-nor-friedelene 236:

The difference in the behaviour of friedelin with 4,4 dimethyl triterpenoids is attributed mainly to the conformational and sterical factors arising out of the presence of only one methyl group at C-4 position. The t-axialα-hydrogen atom at C-4 position is more reactive than the secondary hydrogen at C-2 position[185]. Thus, in the strongly alkaline medium of K-tert-butoxide, friedelin may undergo enolisation with the shift of C-4 proton to give friedel-3(4)-en-3-ol 239 which may

185. V.V. Kane and R. Stevenson, Tetrahedron, 15, 223 (1961)

undergo oxygenation to give 3-4-seco-4-keto-friedelin-3-carboxylic acid 240. This keto acid under the basic reaction condition may undergo cyclization with loss of a molecule of water to form the unsaturated acid 238a.

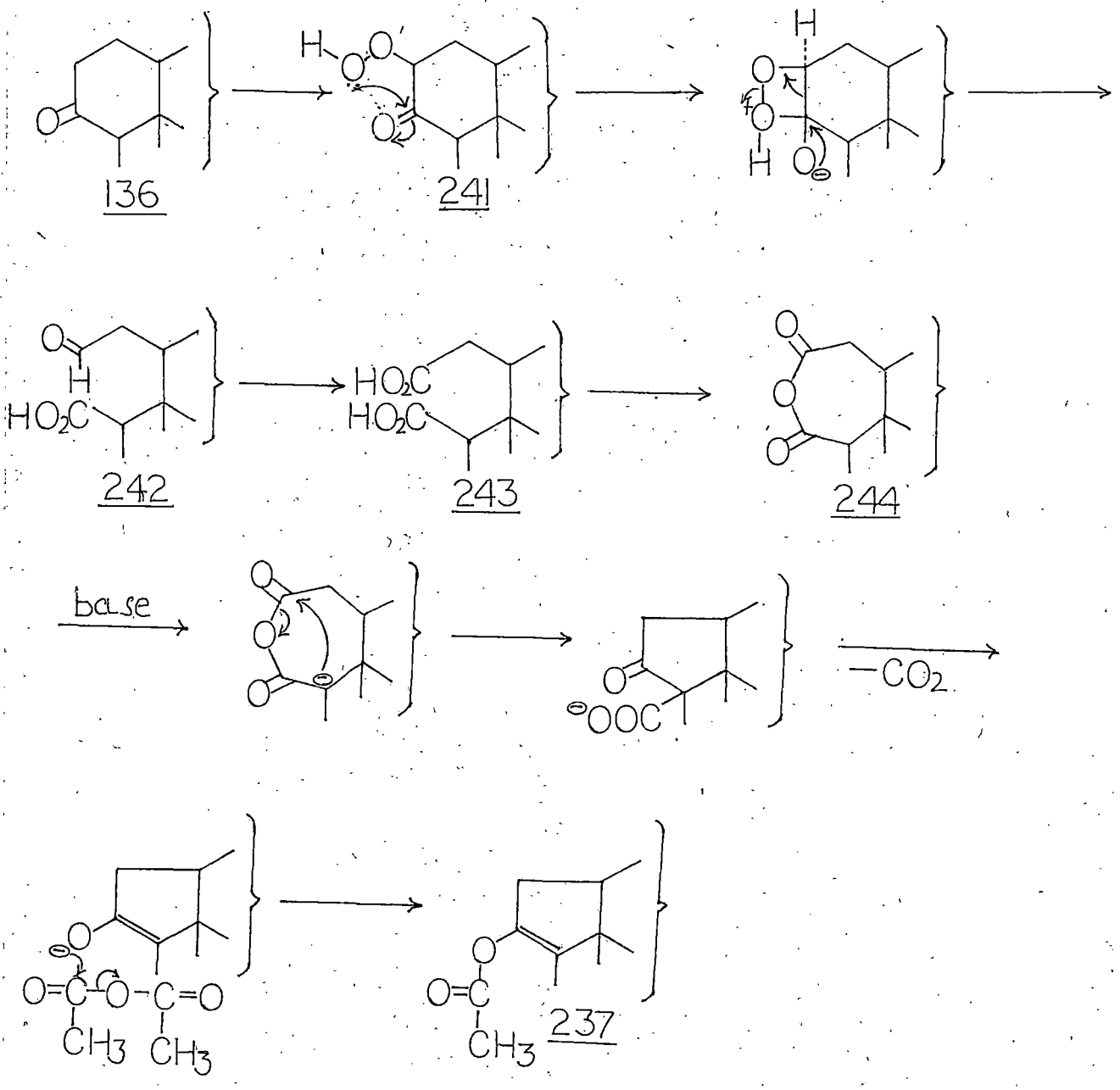
This acid 238a, which is α,β -unsaturated is expected to undergo easy decarboxylation. Since the reaction mixture was kept over water bath for 24 hours mixed with Py and Ac_2O, part of the acid 238a undergo decarboxylation to form the hydrocarbon C-3-nor friedel-2(4)-en 236. It may be mentioned that the hydrocarbon was obtained only after the compound eluted from the active alumina column was acetylated. So, it is evident that the hydrocarbon 236 is formed by the decarboxylation of acid 238a during the acetylation period. Such a mechanism has also been proposed earlier[181] for the formation of identical product, nor-friedelene, m.p. 228.5-30° by oxidation of friedelin with chromic acid followed by heating the acid thereby obtained in nitrogen atmosphere at 250°.



Formation of 3-nor- $\Delta^{2(4)}$-friedelin-2-acetate 237:

It is possible that friedelin is oxidised to form α-hydroperoxy ketone 241 which is cleaved subsequently to seco-2-aldehyde-3-carboxylic acid 242. This under basic reaction condition is oxidised further to 2, 3 seco-dicarboxylic acid 243 which upon cyclization forms the anhydride 244. The anhydride in basic medium may undergo rearrangement to form β-keto acid 245 which undergoes decarboxylation followed by acetylation

to give the compound 3-nor-friedelin-enol-acetate 237.



Though we have proposed the formation of the anhydride 244, as intermediate in the formation of enol-acetate 237, we could not isolate the anhydride as such. Such a mechanism is, however, supported by the work of Lavie et al[165] where they were able to isolate anhydride 205 on autoxidation of 203.

SECTION - C

EXPERIMENTAL

Melting points are uncorrected. The petroleum-ether used throughout the investigation had b.p. in the range of 60-80°. The infrared spectra were recorded in Beckman IR-20 Spectrophotometer. Mass spectra were recorded by electron impact method. Silica gel used for column chromatography was of 60-120 mesh (B.D.H) and alumina used for column chromatography was of active basic grade (B.D.H). TLC were performed in chromatoplates prepared on glass strips with silica gel G (B.D.H).

Autoxidation of friedelin, 136:

Friedelin was isolated from bark cork. The procedure has been described in Chapter II, page 126.

Friedelin (2 gm) suspended in potassium tertiary butoxide in tertiary butanol (prepared from 6 gm of potassium and 60 ml of tertiary butanol) was shaken in a stream of oxygen for three hours. The reaction mixture was then diluted with water and then 6N hydrochloric acid was added till the solution was acidic. It was then extracted with chloroform (150 ml) and the combined extract was dried (Na_2SO_4) and the solvent was removed under reduced pressure. A yellowish gummy foam was first obtained (1.8 gm). It gave a positive ferric

chloride test for phenol on standing for sometime. The product showed two spots on chromatoplate (using benzene as eluent) indicating the presence of mixture of compounds. The product could not be purified by crystallisation, hence was subjected to chromatographic separation on active alumina column. It was presumed that the compound was a tautomeric mixture of diosphenol and diketone and their polarity would be low to affect easy separation. But elution of the column with petroleum-ether, benzene, mixture of benzene-petroleum ether did not yield any material. The column was, therefore, eluted with a solvent mixture of methanol-acetic acid (19:1), which resulted in the yield of a white amorphous solid substance. It also showed presence of at least two compounds on chromatoplate.

Acetylation of the solid mass: Isolation of Δ-nor-friedelene, 236 3-nor-friedelin Δ$^{2(4)}$ 2-acetate 237 and 3-nor- Δ$^{2(4)}$-friedelin- 2-carboxylic acid 238a.

The solid mass (800 mg) was acetylated by treatment with acetic anhydride (10 ml) and pyridine (10 ml) for 48 hours at 80°. After working up in the usual manner, the crude acetate (700 mg) was obtained. It showed three spots on a chromatoplate (developed with benzene: ethyl acetate, 9:1). This was then chromatographed over a column of alumina (50 gm) deactivated with 2.00 ml of aqueous acetic acid.

Table - 40

Chromatography of the above solid (700mg)

Eluent	Fractions 100 ml each	Residue after evaporation	m.p.
Petroleum ether	1-3	Solid ($\simeq$ 100 mg)	215-20°
Pet. ether: Benzene (4:1)	4-8	Solid ($\simeq$ 200 mg)	228-32°
Pet. ether: Benzene (3:2)	9-10	Nil	-
Pet. ether: Benzene (2:3)	11-12	Nil	-
Benzene	13-19	Solid ($\simeq$ 350 mg)	281-85°

Further elution with more polar solvent did not afford any solid material.

Examination of fraction 1-3 : Isolation of A-nor-friedelene,236

The solid (100 mg) from fractions 1-3 (Table - 40) were collected, which after crystallisation from a mixture of chloroform and methanol afforded white crystals, m.p. 225-27°. It showed a single round spot on chromatoglate and responded to TNM test.

Analysis	% C	% H
Found	88.01	12.79
Calculated for $C_{29}H_{48}$	87.80	12.20

IR : ν_{max}^{nujol} 1650, 790 cm^{-1}

(Fig. 49)

^1H NMR (360 MHz) : Peaks at 0.94 to 1.17 (21H, seven tertiary $-CH_3$ group), 1.57 (s , 3H, methyl group on double bond), 5.26 (s, 1H, $>C = CH$)

(Fig. 50)

Mass (m/e) : 396 (M^+), 381 ($M^+ - CH_3$), 257, 243, 205, 191, 177, 163, 149.

(Fig. 51)

Examination of fraction 4-8: Isolation of 3-nor friedelin-Δ2(4)-2-acetate 237.

The solids (200 mg) from fractions 4-8 (Table -40) were collected and after crystallisation from a mixture of methanol and chloroform afforded needle shaped crystals, m.p. 235-37°. It showed a single round spot on chromatoplate and responded to TNM test.

Analysis	% C	% H
Found	81.69	11.32
$C_{31}H_{50}O_2$	81.88	11.08

IR : ν_{max}^{nujol} 1740, 1220 ($-OCOCH_3$), 890 ($>C=CH$) cm^{-1}

(Fig. 52)

^1H NMR (360 MHz) $\delta, CDCl_3$: Peaks at 0.94 to 1.17 (21H, 5s, seven tertiary methyl group), 1.55 (s, 3H, methyl group on double bond), 2.13 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-CH_3$)

(Fig. 53)

Mass (m/e) : 454 (M^+), 439 ($M^+ - 15$), 412, 397, 205, 149.

(Fig. 54)

Examination of fraction 13-19: Isolation of 3-nor-$\Delta^{2(4)}$ friedelin-2-carboxylic acid, 238a

The solid from fractions 13-19 (Table -40) were collected (350 mg) and after crystallisation from chloroform-methanol mixture afforded amorphous solid, m.p. 290-92°.

Analysis	% C	% H
Found	81.93	11.02
Calculated for $C_{30}H_{48}O_2$	81.76	10.98

IR : ν_{max}^{nujol} 3380, 1675, 1620, 730 cm^{-1}

(Fig. 55)

Mass (m/e) : 440 (M^+), 425 ($M^+ - CH_3$), 316, 219, 205, 191, 177, 163.

(Fig. 58)

Esterification of 3-nor-$\Delta^{2(4)}$ friedelinic acid 238a to 3-nor-$\Delta^{2(4)}$-methyl friedelinate 238b.

3-nor-$\Delta^{2(4)}$-friedelinic acid 238a (250 mg) was dissolved in ether and cooled to 5°. To this was added well cooled solution of diazomethane prepared from 1 gm of nitrosomethyl urea and was kept overnight. On the following day excess of diazomethane was destroyed with acetic acid. The ether solution was washed with water, 10% sodium bicarbonate solution and again with water till neutral and then dried over anhydrous Na_2SO_4. Evaporation of ether yielded a solid residue (230 mg). This after several crystallisations from acetone-methanol

mixture gave needle shaped crystals (210 mg), m.p. 205-7°. On chromatoplate it gave a single round spot. It was characterised as 3-nor- $\Delta^{2(4)}$ methyl friedelinate 238b.

Analysis	% C	% H
Found	81.79	11.23
Calculated for $C_{31}H_{50}O_2$	81.88	11.08

IR : ν_{max}^{nujol} 1720, 1225, 1640, 850, 810 cm^{-1}

(Fig. 56)

^1H NMR (360 MHz), δ, $CDCl_3$: Peaks at 0.88, 0.94, 0.97, 0.99, 1.02, 1.18 (6s, 21H seven t-CH_3), 1.98 (s, 3H, tertiary methyl group on double bond), 3.70 (s, 3H, -$COOCH_3$), 2.25 and 2.28 (2s, 2H, H_2C - $COOCH_3$)

(Fig. 57)

Mass (m/e) : 454 (M^+), 439, 423, 407, 330, 205, 191, 177, 149.

(Fig. 59)

Hydrogenation of 3-nor- $\Delta^{2(4)}$ methyl friedelinate 238b to 2α-carbomethoxy A-nor friedelin 138.

100 mg of 3 nor- $\Delta^{2(4)}$ methyl friedelinate in glacial acetic acid (3 (ml) and ethyl acetate (3 ml) was reduced with hydrogen at atmospheric pressure in presence of Adam's catalyst (2 mg). The catalyst was filtered off, the solvent evaporated in vaccum and the residue on crystallisation from chloroform-methanol mixture afforded fine crystals (70 mg), m.p. 263-65^{0}, identical with sample of 2α-carbomethoxy-A-nor-friedelin 138 (Co-IR, m.m.p).

P A R T - II

CHAPTER - I

Section - A

Morphological features of the plants of Flacourtiaceae family.

Flacourtiaceae is a family of seventy Genera and more than five hundred species, which are chiefly found in tropical and sub-tropical regions.

Members of this family are usually shurbs or trees[186].

Leaves are simple, alternate, stipules often soon falling off.

Flowers are hermaphrodite or unisexual, often diocious or polygamous and variously arranged. Sepals are sometimes not distinguishable from the petals, imbricate or open in bud. Petals sometimes are not arranged regularly in relation to the sepals - large, small or absent, with or without an opposite scale inside the base imbricate. Stamens numerous, rarely few hypogynous, free; anthers 2 celled, often short, opening lengthwise by slits. Ovary 1 celled with one or more parietal placentals or rarely the placentals meeting in the middle; ovules two or more on each placenta; styles or stigmas as many as the placentas.

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186. "Indian Medicinal Plants", K.R. Kirtikar and B.D. Basu, Volm. I, page 218 (1975)

Fruit indehiscent, mostly a berry or drupe, very rarely a capsule, sometimes large. Seeds with fleshy endosperm and medium sized embroys; cotyledous often broad.

Flacourtiaceae Jangomas (Lour) Raeusch (also known as F. Cataphracta Roxb).

A small tree[187]; spines compound. Branches white-dotted glabrous young armed; leaves oblong or oblonglanceolate long acuminate quite glabrous crenate-serrate; 2-4 by 1 - 1¼ inches, membranous, lower on the branches often obtuse. Ovary flask-shaped, neck contracted. Flowers very small, $\frac{1}{10}$ - $\frac{1}{8}$ inch diameter. Fruit the size of a small plum, purple, very acid. Plant is called Paniyala in Bengali; Talispatri in Hindi and Marathi.

Caseria Kurzii

Branchlets[188] minutely pubscent. Leaves 5 by 2 inch; petiole nearly $\frac{1}{2}$ inch. Pedicels not very many together, ¼ - ⅓ in Calyx minutely pubsescent. Fruit not ripe but can not become very large. The pedicels are much longer in this species than in any of the others; and the pubescence of the leaves beneath differs from all.

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187. "The Flora of British India", J.D. Hooker, L. Reeve & Co., Ltd., Volm. 1, page 193 (1875)

188. "The Flora of British India", J.D. Hooker, Volm. 2, Page 595 (1875).

Caseria Graveolens Dalz

A shrub or tree 20 ft; branchlets glabrous to the final stipules[189]. Leaves 4 by 2½ in., broadly elliptic, little acuminate, rounded at the base; petiole ¼ in., but the leaves are often narrower, almost lanceolate, and acute at the base. Pedicels usually short, sometimes ¼ in., jointed at or above the base, aureopubescent below the articulation glabrous above to near the base of the calyx. Calyx always pubescent at the base, above sometimes densely aureo-pubescent, sometimes glabrous.

It is called chilli in Hindi and Bar Kaunle in Nepali[190].

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189. "The Flora of British India ", J.D. Hooker, L. Reeve & Co., Ltd., Volm. 2, page 592 (1875).

190. "The Trees of Northern Bengal", Govt. of Bengal Publication, A.M. Cowan and J.M. Cowan, page 16 (1929).

Section - B

Review of the plants investigated.

The Flacourtiaceae is well known for its characteristic medicinal oils obtained from their seed kernals. Some of the plants are reported to have medicinal applications in liver diseases, diarrohea, enlarged spleen and to relieve nausea. A short review of the plants of this family with particular reference to triterpenoids isolated out of them which have been investigated by different workers are given in the following.

Hydrocarpus Kurzii king Warb (formerly called Taraktozenous Kurzii King).

Oils obtained from their seed Kernals, Chaulmoogra oil[191] has been used for a very long time for the treatment of skin diseases and especially for leprosy[192] and as an ointment for tuberculosis[193] patients. Although many other fatty acids, monosaccharides and glycerides have been

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191. F.B. Power, Am. J. Pharm., 88, 493 (1915)

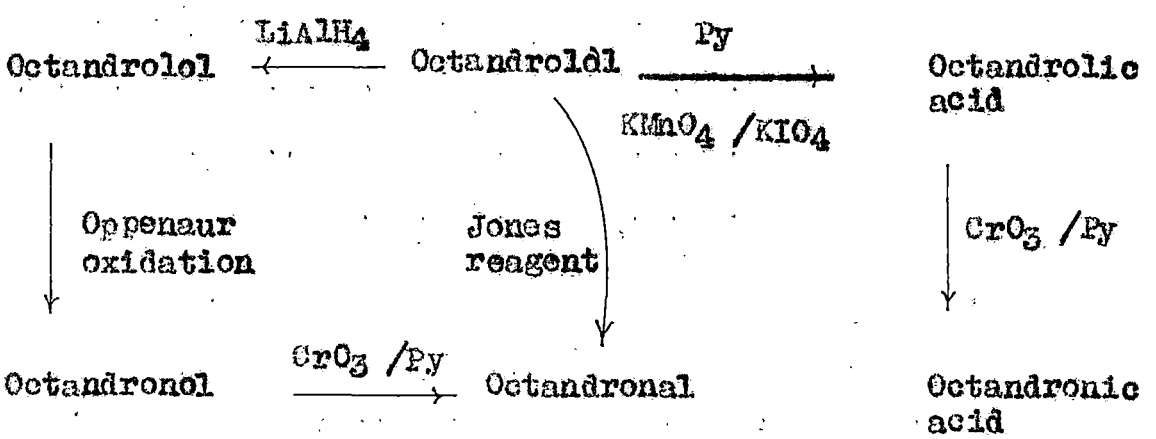
192. P.C. Kianz, China Med., 37, 142 (1923)

193. T.R. Govindachari, S.J. Jadhir, B.S. Joshi, V.N. Kamat, P.A. Mohammed, P.L. Patenkar, D. Prakash, D.F. Rane and N. Viswanath, Ind. J. Chem., 308 (1969)

reported from seed extracts and bark extracts of the plant, no triterpenoid has been reported.

Hydnocarpus Octandra

Mangostin[194] has been isolated from the bark of the plant. Six new triterpenoids, namely, octandrolal, octandrolol, octandrolic acid, octandronal, octondronol and octrandronic acid have also been reported[195] from the bark of the plant. All the compounds belong to friedelane skeleton. The isolation of these six related friedelane type compounds from a single plant is unique for triterpenoids.



194. S.P. Gunasekera, M.U.S.Sultanbawa and S. Balasubramaniam, Phytochemistry, 12(1), 232 (1973)

195. S.P. Gunasekera and M.U.S. Sultanbawa, Chemistry and Industry, 790 (1973).

Hydnocarpus Venenata Gaertn

Therapeutically effective oils have been obtained from Hydnocarpus Venenata[196]. The bark of the plant has been found also to contain small amounts ($\simeq$ 0.004%) of acetyl betulinic acid, acetyl ursolic acid, betulinic acid, ursolic acid sitosterol[197].

Hydnocarpus Anthelminthicus Pierre.

Therapeutically effective oils have also been obtained from seeds of Hydnocarpus Anthelminthicus Pierre[198]. The seeds have also been found to contain monosaccharides and glycosides[199].

Trichadenia Zeylanica Thw

From the bark and wood extracts of Trichadenia zeylanica Thw, six new triterpenoids have been reported[200] by Sultanbawa and co-workers. The triterpenoids are trichadenic acid A (3α-hydroxy friedelan-26-oic aid), O-acetyl

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196. S.Ghosh, Ind. J. Med. Res., 6, 211 (1920)

197. S.P. Gunasekera, M.U.S. Sultanbawa and S.Balasubramanium, Phytochemistry, 12, 232 (1973)

198. L. Adrians, Inst. Roy. Colonial Belze. Soc., Sci Nat. ed. Med. 15, 87 (1965)

199. Y. Hajime and U. Ariyoshi, Nippon Daigaku Yakugaku Kenkyu Kokoku, 14, 27 (1974)

200. S.P. Gunasekara and M.U.S. Sultanbawa, JCS Perkin I, 483 (1977)

trichadenic acid A, O-acetyl trichadenic acid B (3 β-acetoxy-friedelan-26-oic acid), trichadenic acid (3-oxo friedelan-26-oic acid), trichadenal (3 β-hydroxy friedelan-26-al) and O-acetyl trichadenal.

The hot light petroleum extract an a column of silica gel gave O-acetyl trichadenal, β-sitosterol and O-acetyl trichadenic acid B.

Xylosma Velutina

Xylosma velutina afforded three products. Two were flavonoids, namely, velutin (3'7 -dimethoxy-4', 5 dihydroxy flavone) and genkwanin (4', 5-dihydroxy-7-methoxy flavone) have been isolated and the third one was a new triterpene acid, velutinic acid of friedelane skeleton.

Caseria Thwaitesii

The timber and bark of the plant yielded β-amyrin and sitosterol[201].

Scolopia Schreberi

β-amyrin, epi-friedelinol, friedelin and sitosterol have been reported[201] to be present in the bark and timber of the plant.

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201. S.P. Gunasekera, S. Balasubramanium, and M.U.S. Sultanbawa, Phytochemistry, 16(6), 788-9 (1977)

CHAPTER - II

Section - A

Extraction of neutral and acid parts of Flacourtiaceae Jangomas.

Dried and powdered trunk, bark and stem (5 kgs) of Flacourtiaceae Jangomas was extracted with benzene in Soxhlet apparatus for 36 hours. The extract was cooled to room temperature and benzene was distilled off. The gummy residue (50 gm) obtained was dissolved in ether ($\simeq$ 1.5 litre). The ether solution was washed with 10% aqueous NaOH solution (3 x 700 ml) and then with water till neutral. The neutral ether was dried over anhydrous sodium sulphate and it was evaporated to yield a gummy residue ($\simeq$ 30 gm), which constituted the neutral part (Part A) of the extract.

The alkali washed portion on acidification with dilute hydrochloric acid (10%) yielded a solid, which was extracted with ether. The ethereal solution containing the acid part was washed with water till neutral and dried. The ether solution was then esterified with diazomethane. The crude methyl ester obtained after evaporation of ether constituted the acid part (Part B) of the extract (5.2 gm).

Section - B

The neutral part (Part A) of the extract was dissolved in minimum volume of benzene and placed on a column of alumina (1200 gm, deactivated with 48 ml of 10% aqueous acetic acid). The chromatogram was developed with solvents as shown in Table - 41.

Examination of fraction 1 (Table - 41) : Isolation of 1-hexacosanol.

Fraction 1 under column B (Table - 41) was purified by chromatography over active alumina and crystallised from methanol into waxy solid $C_{26}H_{54}O$, m.p. 78-79°, $[\alpha]_D \pm 0°$, IR, ν_{max}^{nujol} 3350 cm^{-1} and was identified as 1-hexacosanol by direct comparison with an authentic sample and preparing its acetate, m.p. 68-69°.

Examination of fraction 3 (Table - 41): Isolation and identification of β-sitosterol.

Fraction 3 column B (Table - 41) on repeated crystallisation from chloroform-methanol gave flakes, m.p. 136-37°, $[\alpha]_D$ -34° and was analysed for $C_{29}H_{50}O$. The compound gave positive Libermann-Buchardt colour test for sterol and was identified as β-sitosterol by direct comparison with an authentic sample and preparing its acetate, m.p. 130-32°, $[\alpha]_D$ - 40°.

Table - 41

Chromatography of neutral part

Fraction number	Solvent	Details about eluates with different amounts of eluent A	B	C	Melting of residue
1	Petroleum ether	5 x 500 ml oil (5 gm)	2 x 500 ml waxy solid with oil	500 ml Nil	Low m.p.
2	Pet. ether Benzene (4:1)	4 x 500 ml oil (3 gm)	-	500 ml Nil	-
3	Pet. ether Benzene (3:2)	2 x 500 ml oil with little solid (1 gm)	6 x 500 ml solid with oil (5 gm)	500 ml Nil	126 - 33°
4	Pet. ether Benzene (2:3)	2 x 500 ml oil (1 gm)	-	500 ml Nil	-
5	Pet. ether Benzene (1:4)	2 x 500 ml oil (0.3 gm)	500 ml solid with trace oil (0.1 gm)	500 ml Nil	209 - 11°
6	Benzene	2 x 500 ml oil with trace of solid (0.5 gm)	500 ml, solid with trace oil (0.4 gm)	Nil	240 - 41°

Further elution with more polar solvents did not afford any solid material.

Examination of fraction 5 : Isolation and identification of 20-hydroxy lupan-3-one:

Fraction 5 column B (Table - 41) on repeated crystallisation from chloroform-methanol afforded a crystalline solid, m.p. 213-14°. It gave positive Libermann Burchardt test but gave no colouration with TNM. Elemental analysis and mass spectrum analysis indicated its molecular formula as $C_{30}H_{50}O_2$. IR spectrum of the compound (Fig. 60) shows bands at 3450 and 1690 cm^{-1} indicating the presence of hydroxy group and a carbonyl group thus accounting for the two oxygen atoms of the molecule, $C_{30}H_{50}O_2$. The compound does not show any absorption above 220 nm in the UV spectrum. The ^1H NMR spectrum (Fig. 61) shows peaks at δ 0.80 (s), 0.92(d), 0.94(d), 1.01(s), 1.06 (s), 1.08, 1.1, 1.21, integratable for 24 protons indicating the presence of eight methyl groups situated on saturated carbon atoms. The presence of a multiplet at δ 2.47 is for integratable for two protons. The coupling pattern as A_2M_2 type system suggests that the keto group is at C-3 of a triterpenoid skeleton.

Perbenzoic acid titration of the keto alcohol showed the absence of unsaturation in the molecule in conformity with the negative TNM test and NMR spectrum. Thus the compound is a saturated one. The presence of eight tertiary methyl and absence of any peak due to the

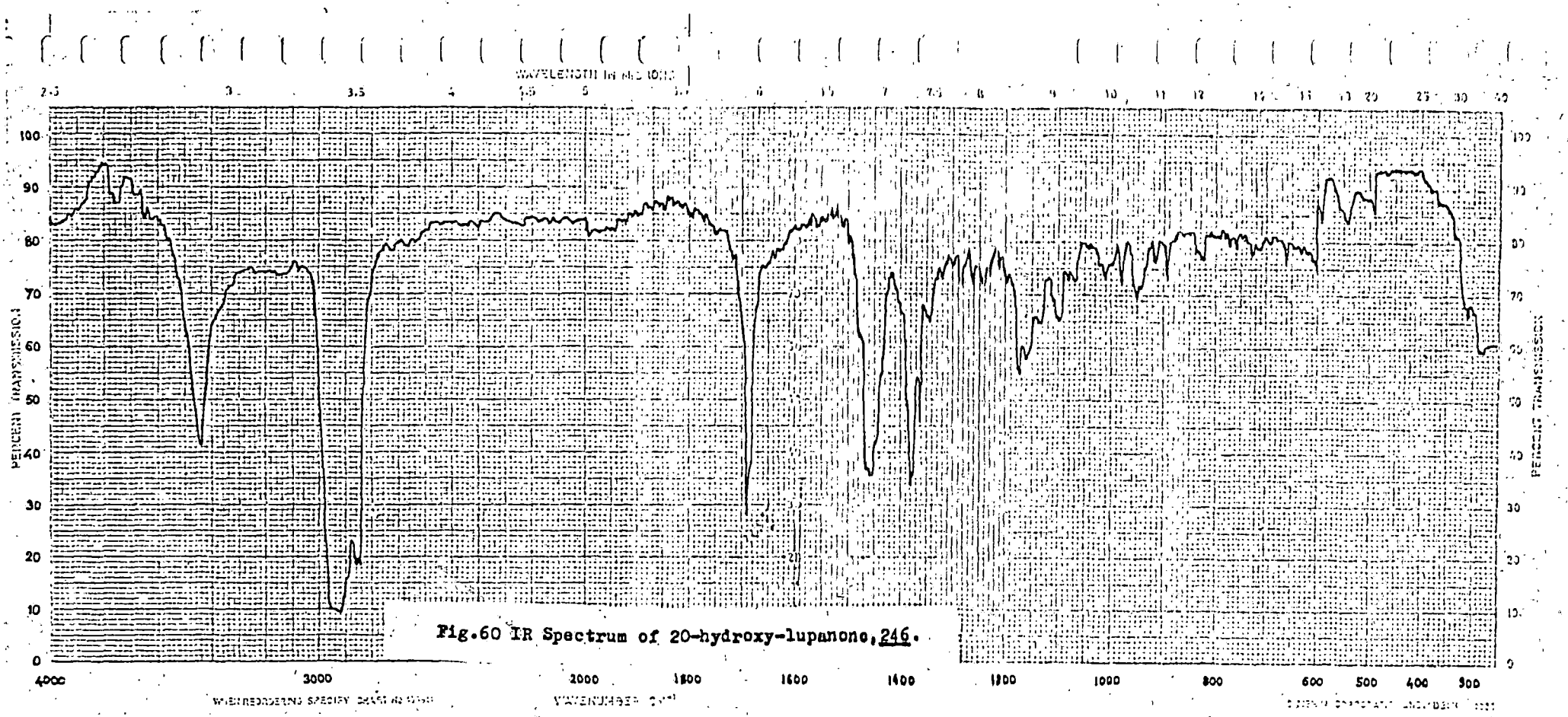
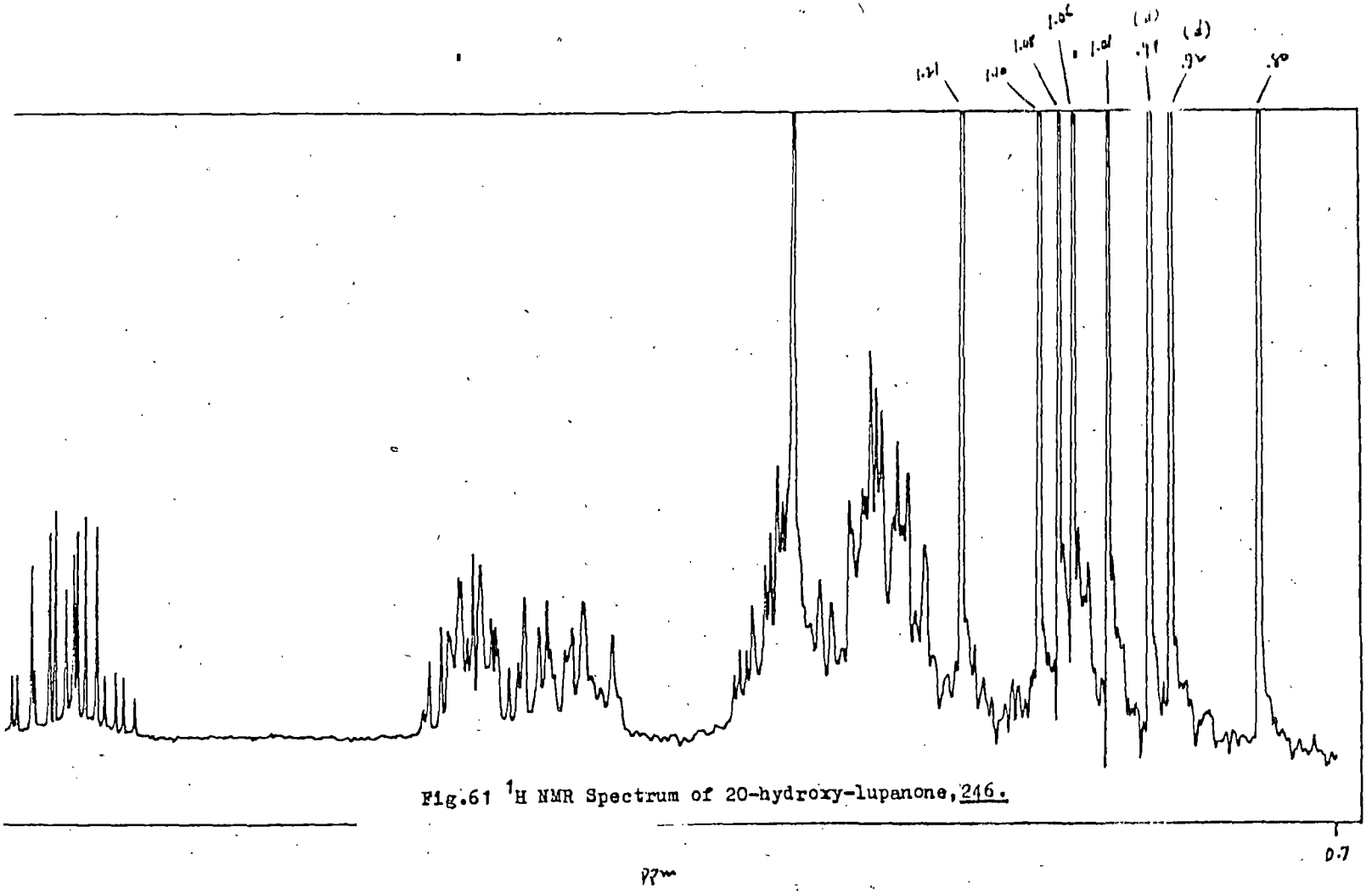


Fig.60 IR Spectrum of 20-hydroxy-lupanone, 246.



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SOLVENT TEMP.
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OBSERVE
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SPECT. WIDTH Hz NO. PTS
ACQ. TIME sec DELAY
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FN RE sec CD
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Fig.61 ^{1}H NMR Spectrum of 20-hydroxy-lupanone, 246.

proton geminal to the hydroxy group indicates that the hydroxy group is situated at the tertiary position of the molecule. This observation is supported by the fact that the hydroxy group is resistant to acetylation at room temperature.

The ^{13}C NMR spectrum (Fig. 62) of the compound displays 29 resolved lines, the one at 15.82 ppm being twice the amplitude of the other confirms a total of 30 carbon atoms. The singlet at 213.84 ppm indicates the presence of carbonyl group in a cyclohexane ring and the singlet at 73.22 ppm indicates that the hydroxy group is on a tertiary carbon atom.

The APT spectrum[202] (Fig. 63) indicates the nature of the carbons in the compound which are represented in the table (Table -42) below.

202.(a) C. Le Coeq and J.Y. Lalleman, Chem. Comm., 150 (1980).

(b) J.M. Shoolery and S. Patt, J. Mangn. Reson., 46, 353 (1982)

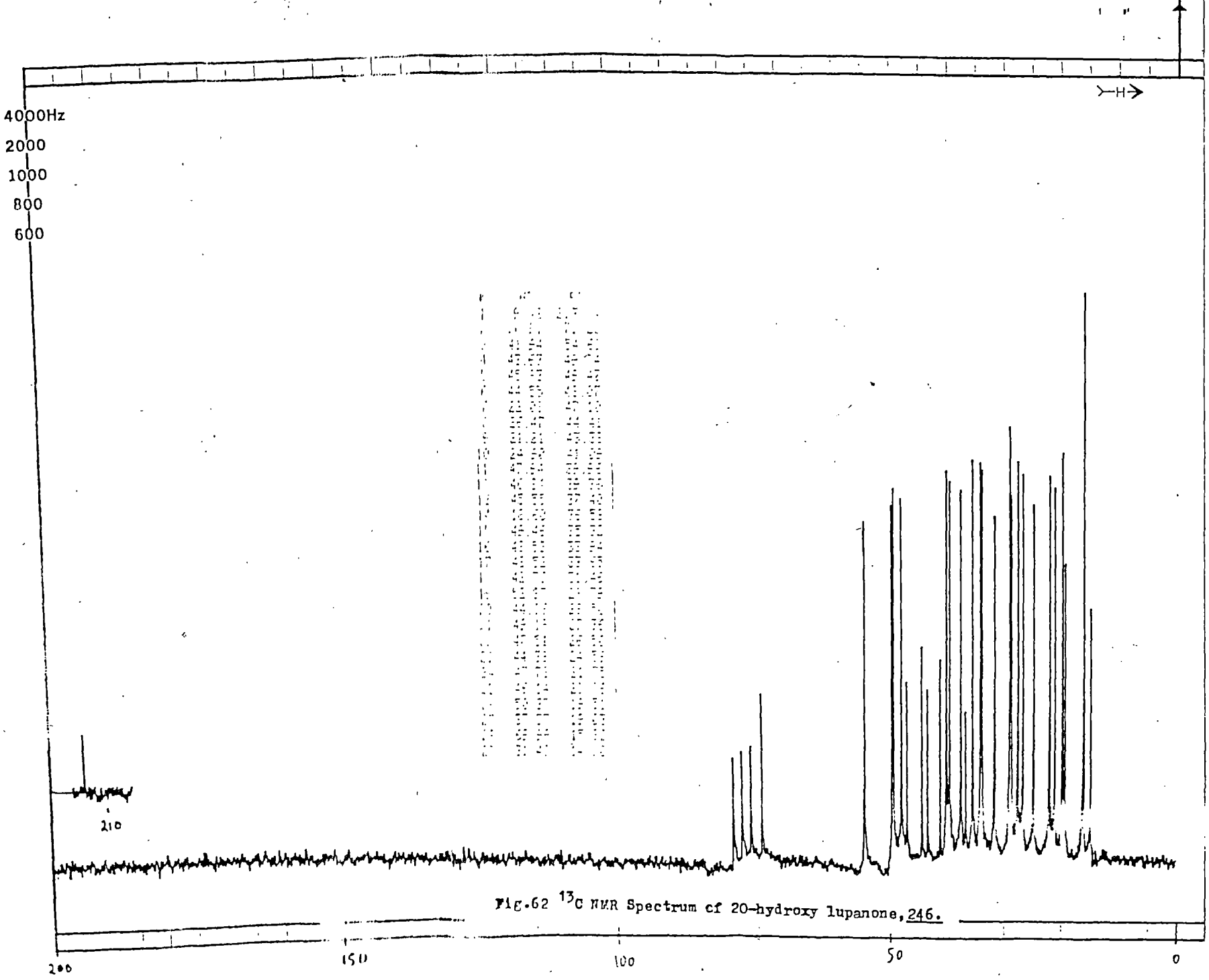


Fig.62 ^{13}C NMR Spectrum of 20-hydroxy lupanone, 246.

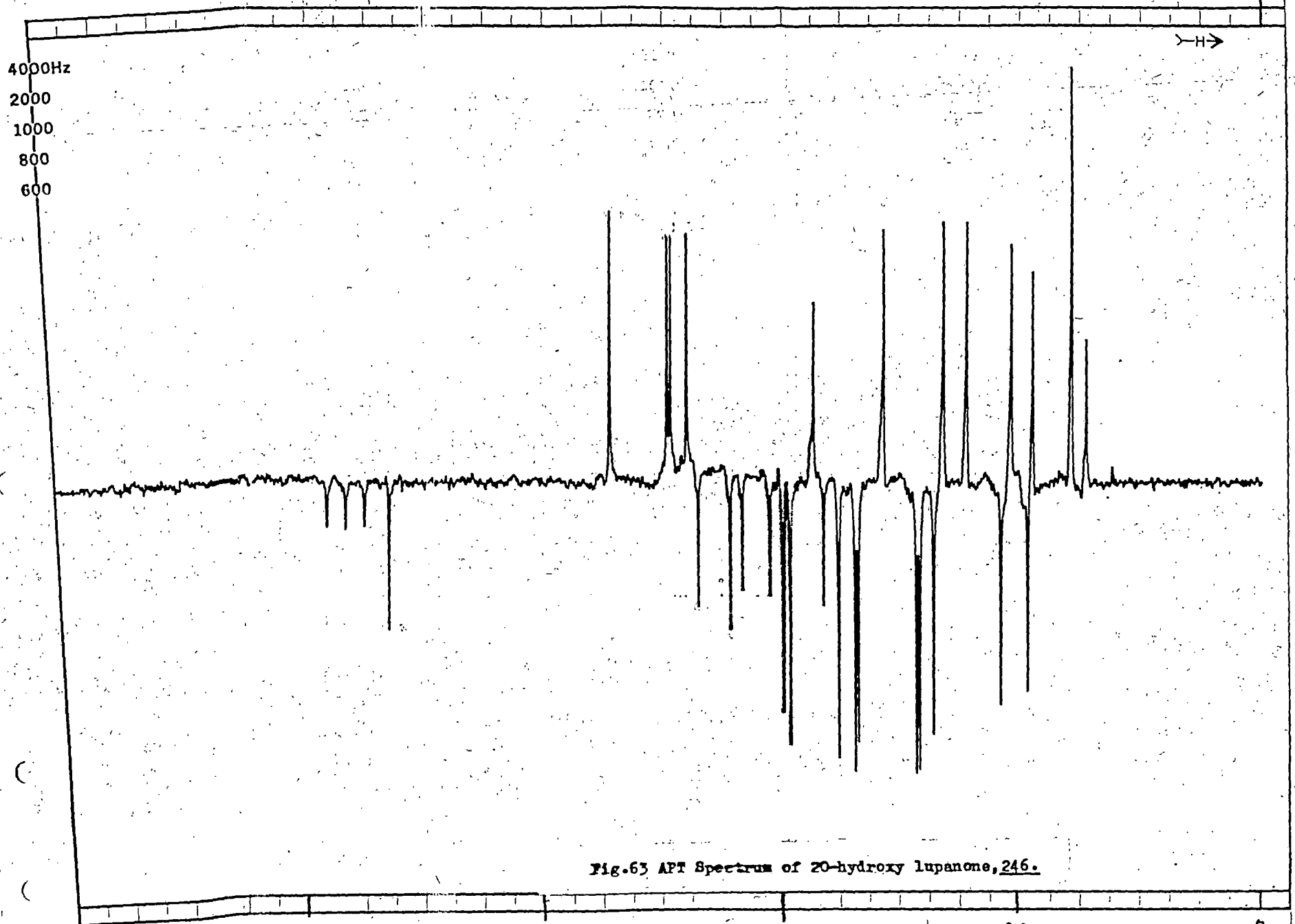


Fig.63 APT Spectrum of 20-hydroxy lupanone, 246.

Fig 63

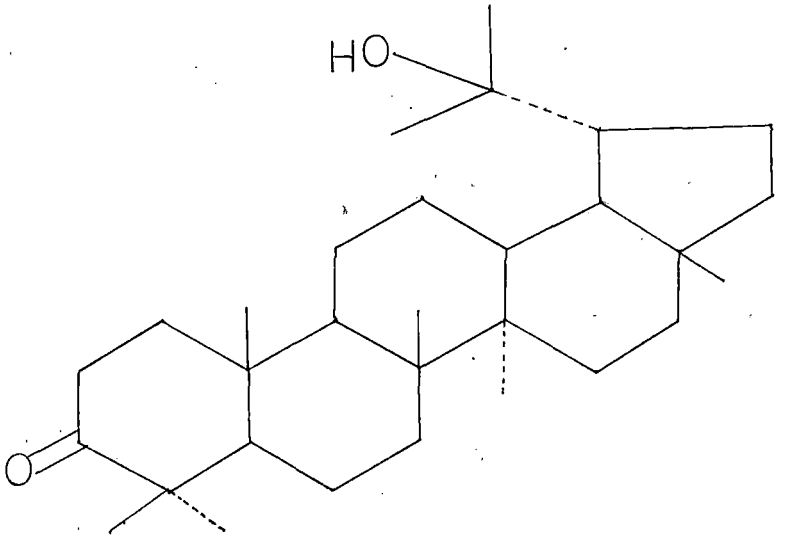
Table - 42

Number of different groups and their ^{13}C shift values.

Different groups	Number	^{13}C shift
$-CH_3$	8	14.60, 15.82, 15.82, 19.03, 20.86, 24.56, 26.50, 31.46
$>CH_2$	10	19.51, 21.75, 27.36, 28.50, 28.79, 33.65, 33.94, 35.32, 39.36, 39.96.
$\rightarrow CH$	5	37.40, 48.07, 49.43, 49.74, 54.60
$\rightarrow C-$	5	36.58, 41.09, 43,38, 44.41, 47.10
$\rightarrow C-OH$	1	73.22
$>C=O$	1	213.84

These data can be well accommodated if the hydroxy group is placed at the C_{20} of lupane or C_{23} of hopane (or iso hopane) skeleton, the keto group being placed at C-3 position.

A comparison of the ^{13}C NMR data of the compound with those previously reported triterpenoid hydroxy compounds reveals that it has strikingly similar values with that of 20-hydroxy lupanone with a few exceptions, which are indicated in 245.



245

The data in the parentheses are for 20-hydroxy lupanone reported by Wazeer et al[203]. A similar comparison of methyl resonance of the compound with those of 20-hydroxy lupanone[204] (Table -43) also indicates the compound to be 20-hydroxy lupanone.

Table - 43

Methyl resonance (ppm in $CDCl_3$)

No. of methyl carbons	20-hydroxy lupanone	The compound of Fraction 5 (Table -41)
C - 23	1.10	1.08
C - 24	1.02	1.01
C - 25	0.93	0.92
C - 26	1.09	1.06
C - 27	0.97	0.94
C - 28	0.80	0.80
C - 29/30	1.12/1.22	1.10/1.21

The above observation is further supported by conversion of hydroxy ketone to lupenone by heating the compound with

203. A.P. Dantanarayane, N.S. Kumar, P.M. Muthukuda and M.I.M. Wazeer, Phytochemistry, 21, 2065 (1982)

204. W.H. Hui and M.M. Li, Phytochemistry, 16, 111 (1977)

Ac_2O - Py containing a few drops of boron trifluoride etherate over water bath for 10 hours. The product on usual work up and purification by chromatography and crystallisation furnished a compound of m.p. 169-71°, $[\alpha]_D$ +57°. Elemental analysis showed the molecular formula to be $C_{30}H_{48}O$. Infrared spectrum (Fig. 64) shows the presence of peaks at 3060, 1695, 1640 and 880 cm^{-1} indicating the introduction of a methylenic double bond with the loss of hydroxy group. The peak at 1700 cm^{-1} shows that the carbonyl group is isolated from the newly introduced double bond. This is further supported by the UV spectrum that is transparent above 220 nm. The compound thus prepared is identified as lupenone by comparison with an authentic sample by m.m.p., Co-tlc and Co-IR.

Examination of fraction 6 : Isolation and identification of 20-hydroxy lupan 3 β-ol :

The fraction 6 (Table - 41) was rechromatographed over alumina and the residue obtained by evaporating the eluents (9:1, benzene : ether) on crystallisation from chloroform-methanol furnished solid m.p. 243-44°, $[\alpha]_D$ +26.7°. It responded to Liebermann-Burchard test but developed no colouration with TNM indicating absence of unsaturation. Elemental analysis and mass spectral data showed the molecular formula to be $C_{30}H_{52}O_2$. The infrared spectrum (Fig. 65) shows absorption at 3480 and 3580 cm^{-1} which

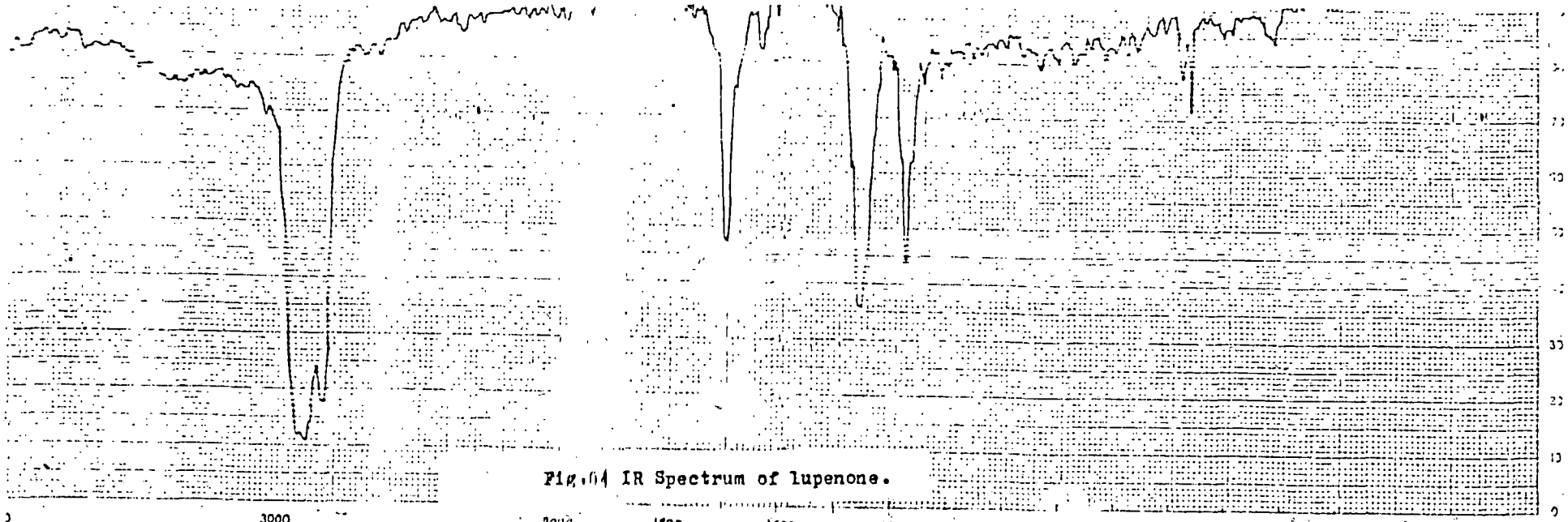


Fig.04 IR Spectrum of lupenone.

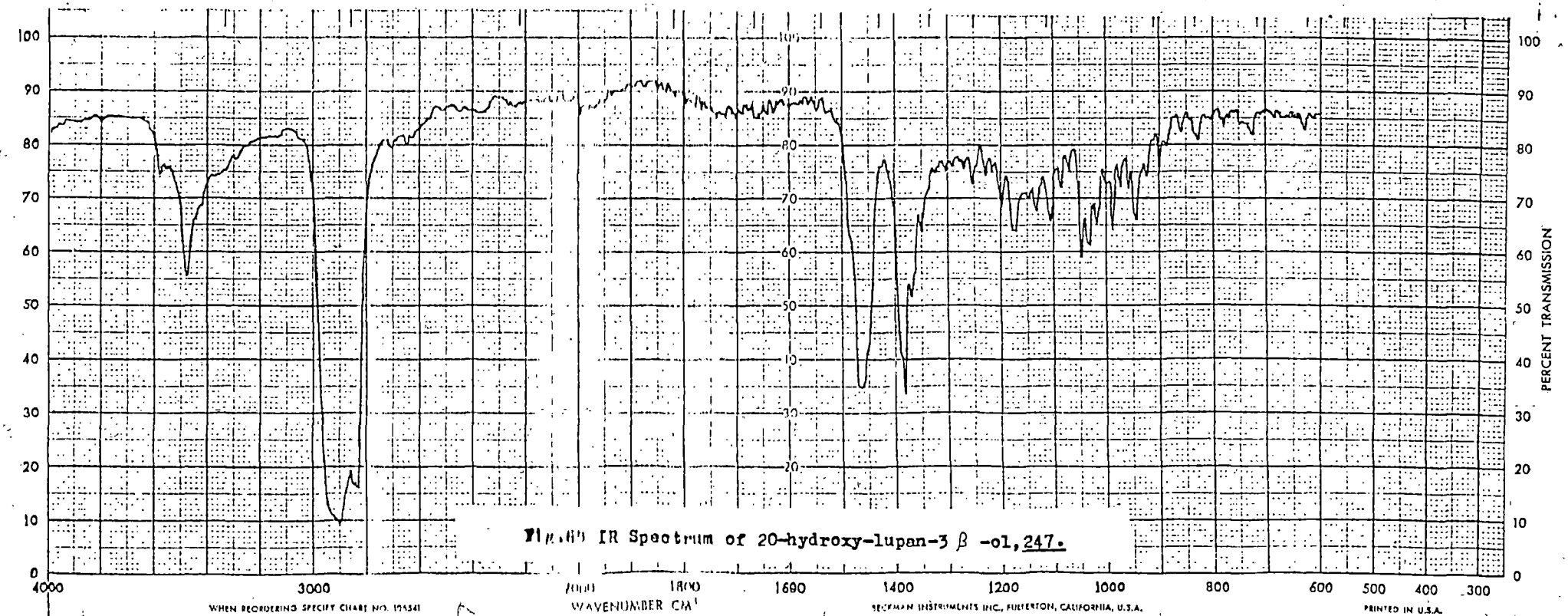


Fig.05 IR Spectrum of 20-hydroxy-lupan-3 β -ol, 247.

indicates the compound to be a dihydroxy one. On treatment with Py - Ac_2O at room temperature, it gave a mono acetate m.p. 253-54°, $[\alpha]_D$ +20.6. The IR spectrum (Fig. 66) of the acetate shows the presence of a hydroxy group at 3490 cm^{-1} and an acetate group at 1710 and 1260 cm^{-1}. Acetylation of the second hydroxy group at higher temperature furnished a solid m.p. 216-18°, $[\alpha]_D$+47.5 which was analysed for $C_{32}H_{52}O_2$. The IR (Fig. 67) absorption band of the product at 3040, 1640, 1730, 1260 and 888 cm^{-1} indicates the introduction of a disubstituted methylene double bond with the loss of hydroxy group.

The ^1H NMR spectrum (Fig. 68) of the dehydrated product of mono hydroxy mono acetate shows the presence of seven methyl groups. The peak at δ 2.02 represents the methyl group of the acetate. The multiplets at δ 4.6 and δ 4.7 are due to the two terminal methylene protons coupled to the methyl at δ 1.25 which confirms the presence of isopropylidine moiety. The multiplet at δ 4.5 has arisen from the proton at C-3 with the acetoxy substituent in β-orientation.

The physical data of the dehydrated product are in consistent with the lupenyl acetate and are found to be identical with authentic sample in all respects. The monohydroxy mono acetate was also found to be identical

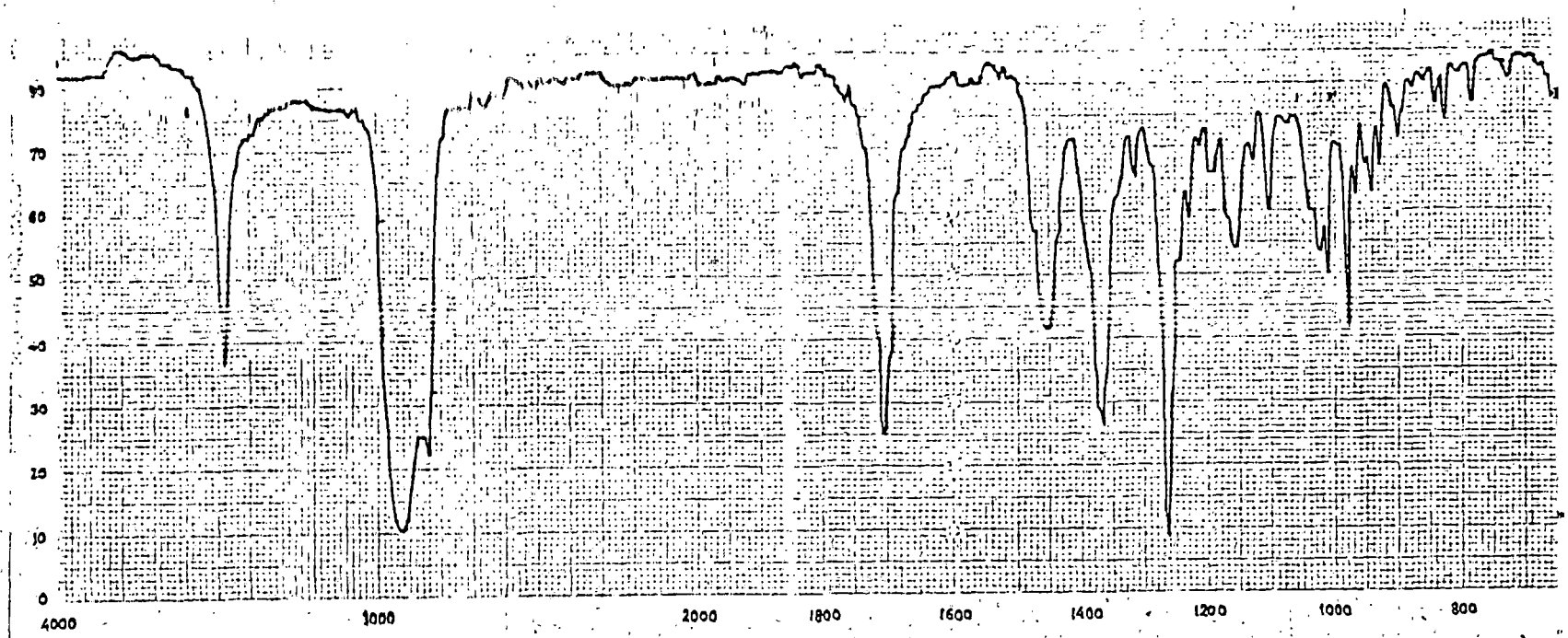


Fig.66 IR Spectrum of 20-hydroxy-lupan-3β -acetate, 248.

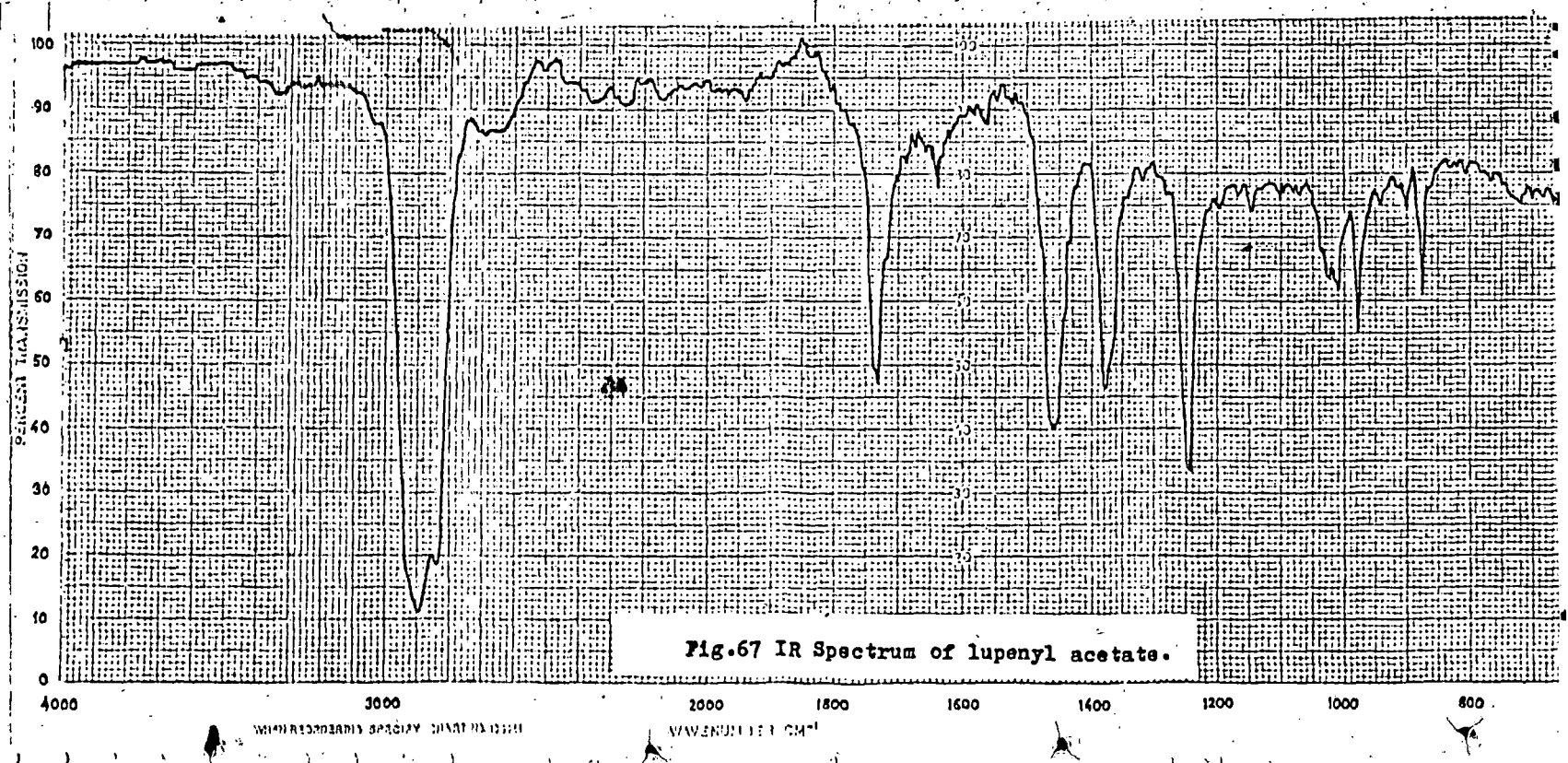
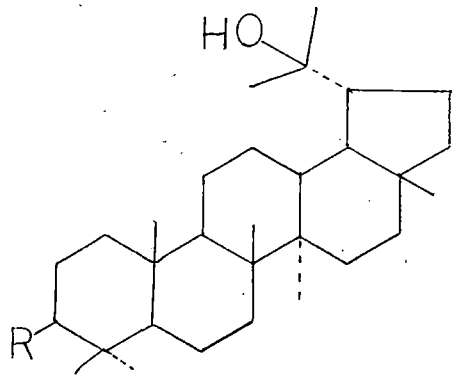


Fig.67 IR Spectrum of lupenyl acetate.

Fig.68 ^{1}H NMR Spectrum of lupenyl acetate

with an authentic lupane.

Further, CrO_3 - Py oxidation of the diol 247 afforded the keto-ol 246. Thus, the structure of diol is confirmed as that of 3 β-20-dihydroxy lupane 247



246 R=O
247 R=OH
248 R=OAc

Isolation and identification the compounds from acid part (Part B)

The acid part after esterification was dissolved in minimum volume of benzene and was chromatographed over neutral alumina column (850 gm).

Table - 44

Chromatography of the esterified product

Serial No	Eluent	Fraction in 100 ml	Residue	Melting point
1.	Petroleum ether	1-4	Oil	-
2.	Pet. ether-benzene (4:1)	5-9	Nil	-
3.	Pet. ether-benzene (3:2)	10-15	Oil	-
4.	Pet. ether-benzene (2:3)	16-22	Oil	-
5.	Pet. ether-benzene (1:4)	23-30	Solid (≃ 300 mg)	237-38°

Further elution with more polar solvent did not afford any solid material.

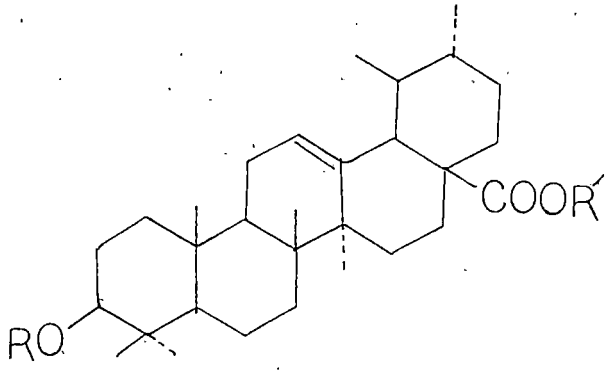
Examination of the portions 23-30 (Table - 44): Isolation of methyl ursolate.

Fractions 23-30 (Table - 4) were first compared in a tlc plate and combined to a single lot. On repeated crystallisation from chloroform-methanol mixture, needle-shaped crystals were obtained which had m.p. 243-44°. Elemental analysis showed the molecular formula to be $C_{31}H_{50}O_3$. IR spectrum exhibited peaks at 3530 (-OH), 1710, 1245 ($-OCOCH_3$) and 885 (trisubstituted double bond) cm^{-1}.

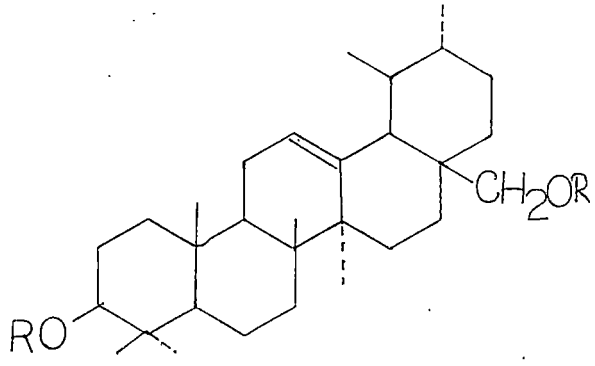
The hydroxy - ester on acetylation furnished an ester - acetate m.p. 240-41°, $[\alpha]_D$+40° which was found to be identical with an authentic sample of methyl ursolate acetate (m.m.p. and co-tlc).

The ester-acetate was then reduced with LAH in THF. The product on chromatography followed by crystallisation from methanol afforded crystals of 250a, $C_{30}H_{50}O_2$, m.p. 230-31°, $[\alpha]_D$+70°.

This compound on acetylation afforded a diacetate $C_{34}H_{54}O_4$, m.p. 157-58°, $[\alpha]_D$+60° which was characterised as uvaol-diacetate[205] 250. The compound thus present in the plant is ursolic acid 249c.



249 a R=H R'=Me
b R=Ac R'=Me
c R=H R'=H



250 a R=H, R'=H
b R=Ac, R'=Ac

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205. J.L. Simonsen and W.C.J Ross, "The Terpene", Volm. IV, 169, Cambridge (1957).

Section - C

Experimental:

Melting points are uncorrected. Petroleum ether used had b.p. 60-80°. All optical rotations were determined in chloroform. IR spectra were recorded in Beckman IR-20 Spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ with Tetramethylsilane as an internal standard.

Extraction of the plant material has been described (page 243 of this chapter).

Isolation and identification of 1-hexacosanol:

The material under column B (Table - 41) of fraction 1 was dissolved in minimum volume of benzene and poured over active alumina (50 gm) column. The chromatogram was eluted with the following solvents (Table - 45).

Table - 45

Chromatography of the above material

Eluent	Fractions	Residue on evaporation	Melting point
Petroleum ether	1-4	Oil	-
Pet. ether-benzene (9:1)	5-7	Oil	-
Pet. ether-benzene (4:1)	8-10	Solid (0.5 gm)	76-77°

Further elution with more polar solvent did not afford any solid material.

Fractions (8-10) were combined and on crystallisation from methanol it afforded flaky crystals, m.p. 78-79°, $[\alpha]_D$ 0°. Elemental analysis, found: C 81.32, H 13.86%; calculated for $C_{26}H_{54}O$ C 81.69, H 14.13%. IR : ν_{max}^{nujol} 3350 cm^{-1}. UV : No absorption above 220 nm.

The compound (0.2 gm) was acetylated with pyridine (2 ml) and acetic anhydride (2 ml) and kept overnight at room temperature. After usual work-up, the solid obtained on crystallisation from methanol had m.p. 68-69°, $[\alpha]_D$ 0°. It was identical in tlc, m.p. and i.r. with an authentic sample of 1-hexacosanol acetate. Elemental analysis; found : C 78.84, H 13.62%, calculated for $C_{28}H_{56}O_2$ C 79.24, H 13.26%.

Isolation and identification of β-sitosterol:

The material under column B (Table - 41) on repeated crystallisation from chloroform-methanol mixture yielded silky solid, m.p. 135-36°, $[\alpha]_D$ -36°. Elemental analysis, found C 83.34, H 11.62%, calculated for $C_{29}H_{50}O$, C 83.98, H 12.15%. Mixed m.p. with authentic sample showed no depression.

β-sitosterol (0.3 gm) was acetylated with Py - Ac_2O in the usual method. The acetate on crystallisation had m.p. 124-26°, $[\alpha]_D$ - 34°. Mixed m.p. with authentic sample showed no depression. Elemental analysis, found C 81.15, H 11.35%, calculated for $C_{31}H_{52}O_2$: C 81.52, H 11.48%.

Isolation and identification of 20-hydroxy lupanone 246

Compound from fraction 5 under column B (Table - 41) was crystallised several times from chloroform-methanol to afford needle shaped crystals of 20-hydroxy lupanone, 246, m.p. 213-14°. Elemental analysis, found C 81.21, H 11.40%, calculated for $C_{30}H_{50}O_2$: C 81.39, H 11.38%.
IR : ν_{max}^{nujol} 3450 (-OH) and 1690 (>C = O) cm^{-1} (Fig. 60).
^1H NMR (δ, $CDCl_3$) : 0.80 (s, 3H), 0.92 (d, 3H), 0.94 (d, 3H), 1.01 (s, 3H), 1.06 (s, 3H), 1.08 (s, 3H), 1.1 (s, 3H), 1.21 (s, 3H), 2.47 (m, 2H).

(Fig. 61)

^{13}C NMR (ppm, $CDCl_3$) : 213.84 (s, >C = O), 73.22 (s, →C -OH), 36.58, 41.09, 43.38, 44.41, 47.10 (5s , 5→C-), 37.40, 48.07, 49.43, 49.74, 54.60 (5s, 5 →CH), 19.51, 21, 75, 27.36, 28.50, 28.79, 33.65, 33.94, 35.32, 39.36, 39.96 (10s, 10 >CH_2), 14.6, 15.82, 15.82, 19.03, 20.86, 24.56, 26.50, 31.46 (7s, 8-CH_3).

(Fig. 62)

Conversion of 20-hydroxylupan-3-one, 1, to lupenone:

100 mg of 1 was dissolved in pyridine (1 ml) and acetic anhydride (1 ml) and boron trifluoride etherate (few drops) were added to it. The reaction mixture was kept over water bath for 10 hours. The product on usual work up afforded an oily substance, which was dissolved

in minimum volume of benzene and poured on a column of alumina (5 gm) deactivated with 0.2 ml of 10% aqueous acetic acid. The chromatogram was developed with petroleum ether. Elution of the column with petroleum ether afforded a solid substance (Further elution with more polar solvents did not afford any material). The solid on crystallisation from chloroform and methanol furnished crystals of lupenone, m.p. 169-71°, $[\alpha]_D$ 57°. Elemental analysis, found C 88.12, H 11.93%. Calculated for $C_{30}H_{48}O_2$ C 88.16, H 11.84%. IR : ν_{max}^{nujol} 3060, 1695, 1640, 880 cm^{-1}.

(Fig. 64)

Rechromatography of fraction 6 (Table - 41): Isolation of 20-hydroxy-3 β-lupanol 247.

The oily mass from fraction 6 under column B (≃ 0.9 gm) (Table - 41) was dissolved in benzene (10 ml) and poured on a column of alumina (550 gm) deactivated with 22 ml of 10% aqueous acetic acid. The chromatogram was developed with petroleum ether and eluted with the following solvents (Table - 46).

Table - 46

Eluent	Fractions 100 ml each	Residue on evaporation
Petroleum ether	1-3	Nil
Pet. ether-benzene (4:1)	4-7	Nil
Pet. ether - benzene (3:2)	8-11	Nil
Pet. ether - benzene (2:3)	12-14	Nil
Benzene	15-17	Oil
Benzene : ether (9:1)	18-20	Solid (0.5 gm) m.p. 228-30°

Further elution with more polar solvents did not afford any solid material.

Fractions 18-20 (Table - 46) were combined and crystallised from chloroform-methanol mixture to give crystals of 20-hydroxy lupanol 247, m.p. 243-44°, $[\alpha]_D$ +26.7°. Elemental analysis, found C 80.92; H 11.84%, calculated for $C_{30}H_{52}O_2$: C 81.02, H 11.79%. IR : ν_{max}^{nujol} 3470, 3580 (2-OH) cm^{-1} (Fig. 65).

Acetylation of 20-hydroxy lupanol, 247: Isolation of 20-hydroxy-lupane-3β-acetate 248.

To a solution of 247 (300 mg) in pyridine (3 ml) was added acetic anhydride (3 ml) and left over night at

room temperature. After usual work up the compound obtained was purified by crystallisation from a solvent mixture of chloroform-methanol to afford needle shaped crystals of 20-hydroxy-lupane-3 β -acetate, 248, m.p. 253-54°, $[\alpha]_D$ +20.7. Elemental analysis, C 79.09, H 11.28%. Calculated for $C_{32}H_{54}O_3$: C 78.96, H 11.18%. IR : ν_{max}^{nujol} 3490 (-OH), 1710 and 1260 (-OOOCH$_3$) cm^{-1} (Fig. 66)

Acetylation of mono hydroxy mono-acetate, 248: Isolation of lupenyl acetate.

100 mg of 4 was acetylated by dissolving the compound in pyridine (1 ml) followed by addition of acetic anhydride (1 ml). The reaction mixture was kept at 80°C for 24 hours. After usual work up, a solid was obtained which on crystallisation from chlororm-methanol afforded crystalline solid, m.p. 217.18°, $[\alpha]_D$ 47.5°. Elemental analysis, found C 81.65, H 11.39%. Calculated for $C_{32}H_{52}O_2$ C 81.99, H 11.18%. IR : ν_{max}^{nujol} 3040, 1640, 888 (>C = CH$_2$), 1730, 1250 (-OOOCH$_3$) cm^{-1} .

(Fig. 67).

^{1}H NMR (δ, CDCl$_3$) : Peaks at 0.78 to 1.25 (21H, 7t-CH$_3$), 2.02 (s, 3H, -OCOCH$_3$), 4.6 and 4.7 (m, 2H, H$_3$C - C = CH$_2$), 4.5 (m, 1H, HC-OOOCH$_3$).

(Fig. 68)

Oxidation of 3β, 20-dihydroxy lupane, 247 to 20-hydroxy-lupan-3-one, 246.

To a solution of the alcohol (200 gm) dissolved in pyridine (5 ml) was added chromium trioxide-pyridine complex prepared from pyridine (2 ml) and chromium trioxide (200 mg) and the mixture was kept at room temperature for fifteen minutes. The crude product obtained after working up in the usual manner was crystallised from chloroform-methanol mixture. The melting point of the crystals was found to be 210-12° and the compound was found identical with 20-hydroxy-lupan-3-one 246 (m.m.p., co-tlc, co-IR).

Isolation and identification of methyl ursolate 249a

Fractions 23-30 (Table - 44) were combined and recrystallised several times from chloroform-methanol mixture. Needle shaped crystals had m.p. 240-42°. Elemental analysis, found C 79.25, H 10.39%; calculated for $C_{31}H_{50}O_3$ C 79.10, H 10.71%. IR : ν_{max}^{nujol} 3530, 1710, 1245, 835 cm^{-1}.

Acetylation of ester 249a: Isolation of acetyl-methyl ursolate 249b:

The ester (200 mg) was acetylated with Ac_2O - Py in the usual way. The acetylated product on purification by column chromatography yielded ester acetate 249b, m.p. 240-41°. Elemental analysis, found C 76.89, H 10.63%; calculated for $C_{33}H_{52}O_4$, C 77.30, H 10.22%.

$LiAlH_4$ reduction of the ester-acetate $C_{33}H_{52}O_4$:

To the ester-acetate $C_{33}H_{52}O_4$ (150 mg) dissolved in dry THF (25 ml) was added LAH (100 mg) and the reaction mixture was heated on a water bath for four hours. After completion of the reaction, excess of LAH was decomposed carefully with moist ether and then a saturated solution of sodium sulphate was added. The etheral solution was washed with water and was dried over anhy. Na_2SO_4 . After removal of the solvent a solid residue (140 mg) was obtained, which was chromatographed over alumina (10 gm), deactivated with 0.4 ml of 10% aqueous acetic acid.

Table - 47

Serial No	Eluent	Fraction in 50 ml	Residue on evaporation	M.P.
1.	Pet-ether	1-2	Nil	-
2.	Pet-ether-benzene(4:1)	3-4	Nil	-
3.	Pet-ether benzene(1:1)	5-6	Nil	-
4.	Pet-ether benzene (1:4)	7-8	Nil	-
5.	Benzene	9-15	Solid	220-5°

Further elution with more polar solvent did not afford any solid material.

Fraction 9-15 (Table - 47) were combined and the residue was crystallised from methanol when crystals of $C_{30}H_{50}O_2$ m.p. 230-31°, $[\alpha]_D$+70° were obtained. Found C 81.20, H 11.22%; calculated for $C_{30}H_{50}O_2$ C 81.39, H 11.38% .

The compound was found to be identical with Uvaol 250a.

Acetylation of Uvaol, 250a: Isolation of Uvaol diacetate 250b:

80 mg of the compound 250a was acetylated with Ac_2O - Py in usual way. Working up in usual manner followed by crystallisation from a mixture of chloroform-methanol yielded crystals of diacetate 250b m.p. 157-58°, $[\alpha]_D$+60°. Found C 77.45, H 10.21%; calculated for $C_{34}H_{54}O_4$ C 77.52, H 10.33% .

CHAPTER - III

Section - A

Extraction of neutral and acid parts of Caseria Kurzii Clark

Dried and powdered trunk, bark and stem (4 kgs) of Caseria Kurzii was extracted with benzene in soxhlet apparatus for 26 hours. The extract was cooled to room temperature and benzene was distilled off. The gummy residue (50 gm) obtained was dissolved in ether ($\simeq$1.00 litre). The ether solution was washed with 10% aqueous NaOH solution (3 x 700 ml) and then with water till neutral. The neutral ether was dried over anhydrous sodium sulphate and it was evaporated to yield a gummy residue ($\simeq$18 gm), which constituted the neutral part (Part A) of the extract.

The alkali washed portion on acidification with dilute hydrochloric acid ($\simeq$1N) yielded a solid, which was extracted with ether. The ethereal solution containing the acid part was washed with water till neutral and dried. The ether solution was then esterified with diazomethane. The crude methyl ester (7 gm) obtained after evaporation of ether constituted the acid part (Part B) of the extract.

Section - B

Isolation and identification of the compounds from the neutral part (Part A).

The neutral part (Part A) of the extract was dissolved in minimum volume of benzene and placed on a column of alumina (1000 gm, deactivated with 45 ml of 10% aqueous acetic acid). The chromatogram was developed with solvents as shown in Table - 48.

Table - 48

Chromatography of neutral part

Serial No.	Solvent	Fractions 250 ml each	Residue	M.P.
1.	Petroleum ether	1-6	Oil	-
2.	Pet. ether-benzene (4:1)	7-12	Waxy solid	65-67°
3.	Pet. ether-benzene (3:2)	13-17	Oil	-
4.	Pet. ether-benzene (2:3)	18-23	Solid	120-25°

Further elution with more polar solvent did not yield any solid material.

Examination of fraction 7-12 (Table - 48): Isolation of 1-hexacosanol.

Fractions 7-12 (Table - 48) were individually compared in a single t.l.c. plate, which showed a prominent

spot with the same Rf value (0.78 in benzene). These fractions were combined and crystallised several times from acetone which afforded flaky crystals of constant m.p. 78-79°, $[\alpha]_D \pm 0°$. Elemental analysis showed the molecular formula to be $C_{26}H_{54}O$. IR spectrum showed the presence of a hydroxy group at 3350 cm^{-1} (broad). It was transparent in the UV region and did not respond to TMM test. Acetylation of the above alcohol with acetic anhydride-pyridine furnished an acetate, $C_{28}H_{56}O_2$, m.p. 68-69°, $[\alpha]_D$ 0°; IR : 1720, 1240 cm^{-1}. This was found to be indistinguishable with an authentic sample of 1-hexacosanol acetate (IR and m.m.p. comparison). From the above facts it was evident that the original alcohol was 1-hexacosanol.

Examination of fractions 18-23 (Table - 48): Isolation and identification of β -sitosterol.

Each of the fractions No. 18-23 (Table - 48) was compared in a t.l.c. plate when all the fractions were found to contain a prominent spot with the same Rf value (0.4 in benzene as solvent). These fractions were combined and crystallised several times with chloroform-methanol mixture when fine needle-shaped crystals of molecular formula $C_{29}H_{50}O$, m.p. 135-37°, $[\alpha]_D$ - 34° was obtained. Acetylation of the alcohol with Ac_2O - Py furnished an acetate of molecular formula $C_{31}H_{52}O_2$, m.p. 127-28°,

$[\alpha]_D$ - 39. The acetate was compared with an authentic sample of β-sitosterol acetate and was found to be identical with it (m.m.p. co-IR, t.l.c.).

Isolation and identification of the compounds from the acid part (Part B).

The acid part after esterification was dissolved in minimum volume of benzene and was chromatographed over neutral alumina (7 gm).

Table - 49

Chromatography of the esterified product

Serial No.	Eluent	Fractions 100 ml each	Residue	Melting Point
1.	Petroleum ether	1-4	Oil	-
2.	Pet. ether-benzene (4:1)	5-8	Oil	-
3.	Pet. ether-benzene (3:2)	9-15	Solid (≃ 300 mg)	205-10°
4.	Pet. ether-benzene (2:3)	16-22	Solid (≃ 280 mg)	209-12°

Further elution with more polar solvent did not yield any solid material.

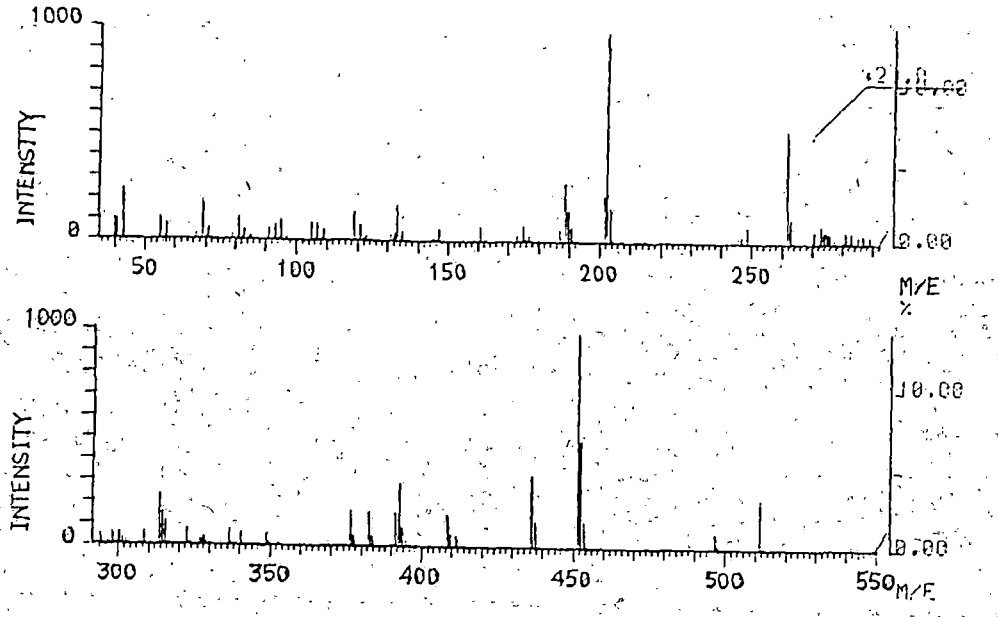


Fig.70 Mass Spectrum of acetyl methyl oleanolate, 251a.

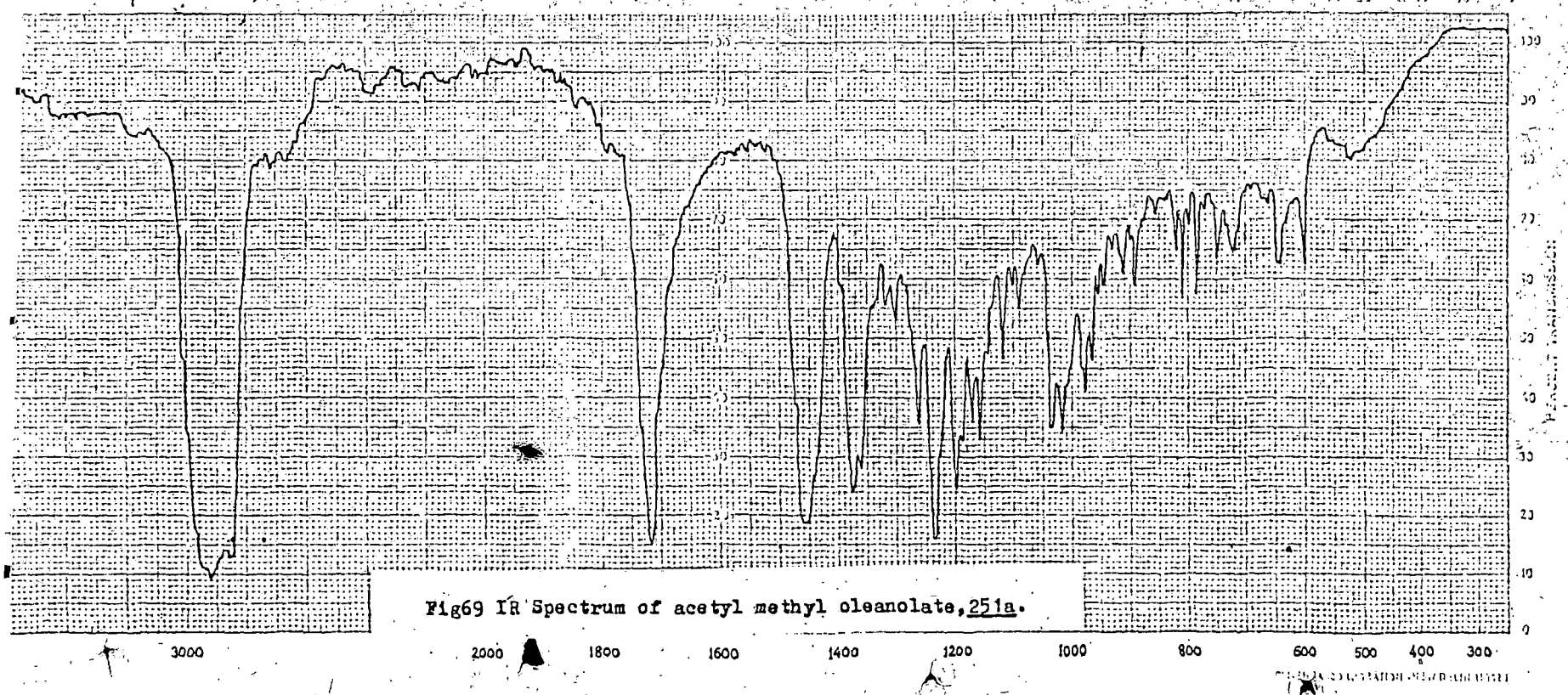
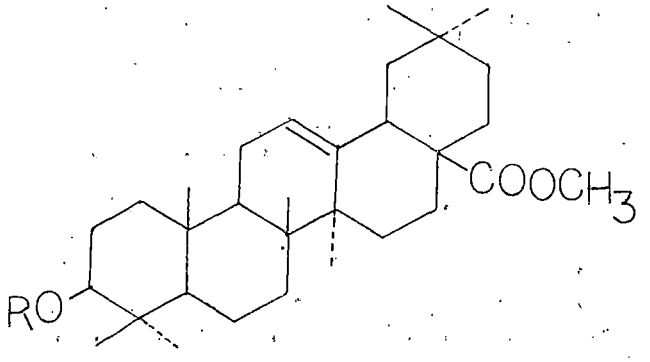


Fig69 IR Spectrum of acetyl methyl oleanolate, 251a.

Examination of fractions 9-15 (Table - 49): Isolation of acetyl methyl oleanolate 251a:

Fractions 9-15 were first compared in a t.l.c. plate and combined to a single lot. It was repeatedly crystallised from chloroform and methanol. Needle shaped crystals had m.p. 213-14°, $[\alpha]_D$ 56°; IR spectrum (Fig. 69) showed bands at 1720, 1240, 810 cm^{-1}. Elemental analysis of the compound showed the molecular formula to be $C_{33}H_{52}O_4$. Mass spectrum (Fig. 70) of the compound showed peaks at m/e 512 (M^+), 497, 452, 437, 393, 340, 282, 203 (base peak) 189. The fragmentation pattern of this compound showed the presence of a double bond at 12-13 position, typical of oleanane skeleton. The above compound was hydrolysed with 5% methanolic KOH by refluxing for four hours. The product after usual work up had the m.p. 192-94°, IR spectrum showed the presence of a hydroxy group at 3530 and ester group at 1735 and a trisubstituted double bond at 820 cm^{-1}. Elemental analysis showed the molecular formula to be $C_{31}H_{50}O_3$. The compound was characterised as methyl oleanolate by comparison (t.l.c., Co-IR and m.m.p) with an authentic sample. Thus the acid present in the plant was acetyl oleanolic acid 251b.



251. a R=Ac
b R=H

Examination of fraction 16-22 (Table - 49): Isolation of methyl betulinate 252a.

Fractions 16-22 (Table -49) were found to contain the same compound from t.l.c. experiment, hence, were combined. The solid was crystallised from chloroform-methanol, which afforded crystalline solid m.p. 219-20°, $[\alpha]_D$ +5°. IR spectrum (Fig. 71) showed the presence of a free hydroxy group at 3520 cm^{-1} and an ester group at 1710 cm^{-1}. The presence of an exocyclic methylene group was evident from the presence of peaks at 3030, 1640 and 880 cm^{-1}. Elemental analysis showed the molecular formula to be $C_{31}H_{50}O_3$. On acetylation of the above compound with acetic anhydride -pyridine an acetate of m.p. 200-2° was formed. The acetate was found to be identical with an authentic sample of acetyl methyl betulinate by

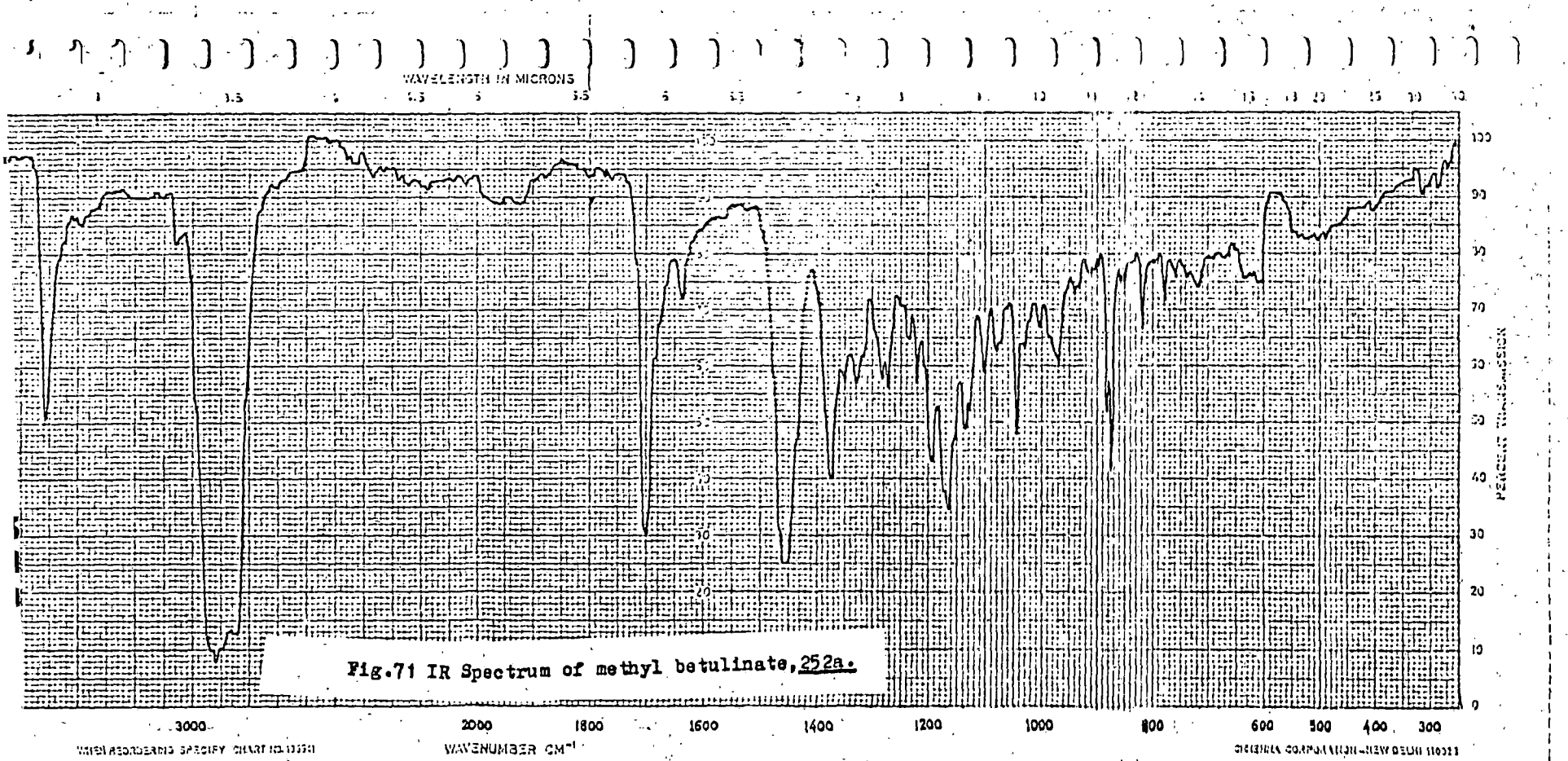
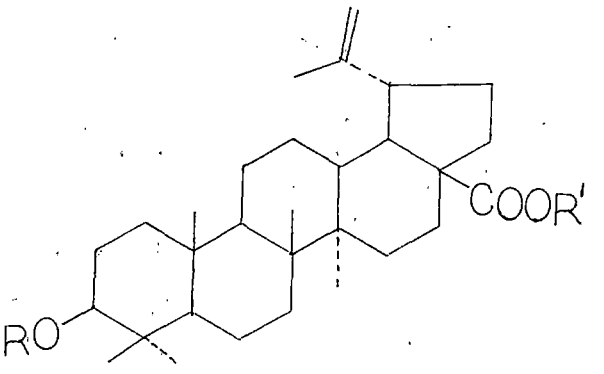


Fig.71 IR Spectrum of methyl betulinate, 252a.

comparison (t.l.c., m.m.p.). Thus it was found that the plant contained betulinic acid 252c.



252 a R=H, R'=CH_3
b R=Ac, R'=CH_3
c R=H, R'=H

Section - C

Experimental:

Melting points were uncorrected. Petroleum ether used had b.p. 60-80°. Optical rotations were determined in chloroform. IR spectra were recorded in Beckman IR-20 Spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ with tetramethyl silane as an internal standard.

Extraction of the plant has been described on page 265 of this chapter.

Isolation and identification of 1-hexacosanol.

Fractions 7-12 (Table -48) were mixed up and crystallised several times from acetone, which yielded flaky crystals, m.p. 78-79°, $[\alpha]_D \pm 0°$. Elemental analysis found C 81.44, H 13.13%; calculated for $C_{26}H_{54}O$ C 81.69, H 14.13%. IR : ν_{max}^{nujol} 3350.

UV : No absorption above 220 nm.

Acetylation of 1-hexacosanol.

Acetylation of the compound in the usual manner and after purification by crystallisation from methanol afforded crystals of m.p. 68-69°, $[\alpha]_D \pm 0°$. It was found to be identical in t.l.c., m.p. and i.r. with an authentic sample of 1-hexacosanol acetate. Elemental analysis, found, C 78.83, H 13.52, calculated for $C_{28}H_{56}O_2$, C 79.24, H 13.26% .

Isolation and identification of β-sitosterol:

Fractions 18-23 (Table-48) were combined and on repeated crystallisation from chloroform-methanol mixture yielded silky solid, m.p. 135-36°, $[\alpha]_D$ -36°. Elemental analysis, found C 83.56, H 11.76%; calculated for $C_{29}H_{50}O$, C 83.98, H 12.15%. Mixed m.p. with authentic sample showed no depression.

The compound (0.5 gm) was acetylated with Py-Ac_2O in the usual method. The acetate on crystallisation had m.p. 124-26°, $[\alpha]_D$ -34°. Mixed m.p. with authentic sample showed no depression. Co-IR with authentic sample was in complete agreement. Elemental analysis, found C 81.26, H 11.32%; calculated for $C_{31}H_{52}O_2$, C 81.52, H 11.48%.

Isolation and identification of acetyl methyl oleanolate 251a.

Fractions 9-15 (Table - 49) were combined and on repeated crystallisation from chloroform-methanol mixture afforded needle shaped crystals of m.p. 213-14°, $[\alpha]_D$ +56°. Elemental analysis, found C 77.92, H 11.08%; calculated for $C_{33}H_{52}O_4$ C 77.30, H 10.22%. IR: ν_{max}^{nujol} 1730, 1720, 1240, 810 cm^{-1} (Fig. 69). Mass spectrum of the compound showed peaks at m/e 512 (M^+), 497, 452, 437, 393, 340, 262, 203 (base peak) 189. (Fig. 70).

Hydrolysis of acetyl methyl oleanolate : Isolation of methyl oleanolate 251b:

Acetyl methyl oleanolate (100 mg) dissolved in benzene (2 ml) was refluxed in 10% methanolic KOH (15 ml) for 4 hours. The mixture was cooled, acidified with dil. HCl (20 ml) and extracted with ether. Removal of the solvent afforded a solid, which on repeated crystallisation from chloroform-methanol mixture furnished methyl oleanolate 251b, m.p. 192-94°. Found C 79.63, H 10.21%; calculated for $C_{31}H_{50}O_3$ C 79.10, H 10.71%. IR : ν_{max}^{nujol} 3530, 1735, 820 cm^{-1}.

Isolation and identification of methyl betulinate 252a:

Solids obtained from fraction 16-22 (Table - 49) were combined and on repeated crystallisation from a mixture of chloroform and methanol afforded shining colourless needle-shaped crystals of methyl-betulinate 252a, m.p. 219-20°, $[\alpha]_D$ +5°. Elemental analysis found C 73.91, H 10.80%; calculated for $C_{31}H_{50}O_3$, C 79.10, H 10.71%.

UV : no absorption in the region 220-300 nm.

IR ν_{max}^{nujol} : 3520, 3030, 1710, 1640, 880 cm^{-1}

(Fig. 71)

Acetylation of methyl betulinate : Isolation of acetyl methyl betulinate 252b:

Methyl betulinate 251a (100 mg) was acetylated with pyridine (1 ml) and acetic anhydride (1 ml) in the usual way. The solid obtained was purified by crystallisation from chloroform-methanol which afforded crystals of acetyl methyl betulinate 252b, m.p. 200-2°. Elemental analysis, found C 77.37, H 10.13%; calculated for $C_{33}H_{52}O_4$ C 77.24, H 10.02%.

CHAPTER - IV

Section - A

Extraction of neutral and acid parts of Caseria graveolens.

Dried and powdered bark (5 kgs) of caseria graveolens was extracted with benzene in Soxhlet apparatus for 36 hours. The filtrate was cooled to room temperature and then benzene was distilled off. The gummy residue (35 gms) obtained was dissolved in ether (≃1.00 litre). The ether solution was washed with 10% aqueous NaOH solution (3 x 700 ml) and then with water till neutral. The neutral ether was dried over anhydrous sodium sulphate and it was evaporated to yield a gummy residue (11 gm) which constituted the neutral part of the extract (Part A).

The alkali washed portion on acidification with dilute hydrochloric acid (≃ 1 N) yielded a solid, which was extracted with ether. The ethereal solution containing the acid part was washed with water till neutral and dried. The ether solution was then esterified with diazomethane. The crude methyl ester (7.5 gm) obtained after evaporation of ether constituted the acid part (Part B) of the extract.

Section - B

Isolation and identification of the compounds from the neutral part.

The neutral part (Part A) of the extract was dissolved in minimum volume of benzene and placed on a column of alumina (700 gm deactivated with 30 ml of 10% aqueous acetic acid). The chromatogram was developed with solvents as shown in Table -50.

Table - 50

Chromatography of neutral part

Serial No.	Solvent	Fractions 100 ml each	Residue	Melting point
1.	Petroleum ether	1-5	Oil	-
2.	Pet. ether-benzene (4:1)	6-12	Waxy solid	63-67°
3.	Pet. ether-benzene (3:2)	13-17	Oil	-
4.	Pet. ether-benzene (2:3)	18-23	Solid	120-24°
5.	Pet. ether-benzene (1:4)	23-27	Nil	-

Further elution with more polar solvent did not yield any solid material.

Examination of fraction 6-12 (Table - 50) : Isolation of 1 hexacosanol.

Fractions 6-12 (Table - 50) were individually compared in a single t.l.c. plate, which showed a prominent spot with the same Rf value. These fractions were combined and crystallised several times from acetone which afforded flaky crystals of constant m.p. 78-79°, $[\alpha]_D \pm 0^\circ$. On the basis of spectral data and elemental analysis the compund was identified as 1-hexacosanol.

Examination of fractions 18-23 (Table - 50) : Isolation of β-sitosterol.

Each of the fractions No. 18-23 (Table - 50) was compared in a t.l.c. plate when all the fractions were found to contain a prominent spot with the same Rf value (0.40 in benzene as solvent). These fractions were combined and crystallised several times with chloroform-methanol mixture when fine needle shaped crystals of molecular formula $C_{29}H_{50}O$, m.p. 135-37°, $[\alpha]_D$ - 34° was obtained. The acetyl derivative of the alcohol was found to be identical with an authentic sample of β-sitosterol acetate (m.m.p., Co-IR, t.l.c.).

Isolation and identification of the compounds from acid part (Part B)

The acid part after esterification was dissolved in minimum volume of benzene and was chromatographed over neutral alumina (450gm).

Table - 51

Chromatography of the esterified product

Serial No.	Eluent	Fraction 100 ml each	Residue	Melting Point
1.	Petroleum ether	1-4	Oil	-
2.	Pet. ether-benze (4:1)	5-8	Oil	-
3.	Pet. ether-benzene (3:2)	9-15	Oil	-
4.	Pet. ether benzene (2:3)	16-25	Solid (450 mg)	-
5.	Pet. ether-benzene (1:4)	26-30	Nil	-

Further elution with more solvent did not afford any solid material.

Examination of fraction 16-25 (Table - 51): Isolation of methyl betulinate 252a:

Fractions 16-25 (Table - 51) were found to contain the same compound from t.l.c. experiment. The fractions were, therefore, combined. The solid compound was crystallised from chloroform-methanol, which afforded crystalli- solid m.p. 219-20°, $[\alpha]_D^+ 5^0$; infrared spectrum showed the presence of free hydroxy group at 3520 cm^{-1} ester gro-

at 1710 cm^{-1}. The presence of an exocyclic methylene group was evident from the presence of peaks at 3030, 1640 and 880 cm^{-1}. Elemental analysis showed the molecular formula to be $C_{31}H_{50}O_3$. On acetylation of the above compound with acetic anhydride and pyridine an acetate of m.p. 200-1°, $[\alpha]_D$ 1.5° was formed. The acetate was found to be identical with an authentic sample of acetyl methyl betulinate 252b by comparison (t1.c., m.m.p. and Co-IR). Thus the acid fraction of the plant contained betulinic acid.

Section - C

Experimental:

Melting points are uncorrected. Petroleum ether used had b.p. 60-80°. Optical rotations were determined in chloroform. IR spectra were recorded in Beckman IR-20 Spectrophotometer.

Extraction of the plant has been described earlier (page 276 of this chapter).

Isolation and identification of 1-hexacosanol.

Fractions 6-12 (Table -30) were individually compared in a single t.l.c. plate, which showed a prominent spot with the same R_f value. These fractions were combined and crystallised several times from acetone, which afforded flaky crystals, m.p. 78-79°, $[\alpha]_D \pm 0°$. Elemental analysis, found C 81.48, H 13.96%; Calculated C 81.69, H 14.13%. IR : ν_{max}^{nujol} 3350 cm^{-1}, UV : no absorption above 220 nm.

Acetylation of 1-hexacosanol.

Acetylation of the compound (Ac_2O - Py, 1:1) in the usual manner and purification of the compound by crystallisation from methanol afforded crystals of m.p. 68-69°, $[\alpha]_D \pm 0°$. It was found to be identical in t.l.c., m.p. and i.r. with an authentic sample of 1-hexacosanol acetate. Elemental analysis, found C 78.96, H 13.56%, calculated for $C_{28}H_{56}O_2$ C 79.12, H 13.28%.

Isolation and identification of β -sitosterol.

Fractions (18-23) (Table - 50) were combined and on repeated crystallisation from chloroform-methanol mixture yielded silky solid, m.p. 135-36°, $[\alpha]_D$ -36°. Elemental analysis, found C 83.68, H 11.88%; calculated for $C_{29}H_{50}O$, C 83.98, H 12.15%. Mixed m.p. with authentic sample showed no depression.

The compound (0.40 gm) was acetylated with Py - Ac_2O (1:1) in the usual way. The acetate on crystallisation had m.p. 124-26°, $[\alpha]_D$ -34°. Mixed m.p. with authentic sample showed no depression. Co-IR with an authentic sample was in complete agreement. Elemental analysis, found C 81.18, H 11.22%; calculated for $C_{31}H_{52}O_2$, C 81.52, H 11.48% .

Isolation and identification of methyl betulinate 252a

Solids obtained from fractions 16-25 (Table - 51) were combined and on repeated crystallisation from a mixture of chloroform and methanol afforded shining, colourless, needle shaped crystals of methyl betulinate 252b, m.p. 220-22°, $[\alpha]_D$ +1.4° . Elemental analysis, found C 78.88, H 10.80%; calculated for $C_{31}H_{50}O_3$, C 79.40, H 11.71%. UV : no absorption in the region 220-300 nm. IR : ν_{max}^{nujol} 3520, 3030, 1710, 1640, 880 cm^{-1}. Co-IR with an authentic sample of methyl betulinate was in

complete agreement.

Acetylation of methyl betulinate 252a: Isolation of acetyl methyl betulinate 252b.

Methyl betulinate 252a (100 mg) was acetylated with pyridine (1 ml) and acetic anhydride (1 ml) in usual manner. The solid obtained was purified by crystallisation from chloroform-methanol to afford fine crystals of m.p. 200-2°. Found C 77.37, H 10.13%; calculated for $C_{33}H_{52}O_4$ C 77.34, H 10.15% .

Hydrogen Peroxide Oxidation of Lupanone in Presence of Selenium Dioxide

SIKHA RANI DUTTA (*née* DAS) & B. P. PRADHAN*
Chemistry Department, North Bengal University, Darjeeling

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The oxidation of lupanone (Ia) with molar proportion of hydrogen peroxide and catalytic amount of selenium dioxide in *t*-butanol affords lup-1-ene-3-one (Ib), lupane dicarboxylic acid (Ic) and 2α-carboxyl-A-nor-lupane (Id); with excess of hydrogen peroxide, Ia furnishes 4,23, 24-tri-nor-lupane-3 → 5-olide, a δ-lactone (Ie) together with lupane dicarboxylic acid (Ic).

THE selenium dioxide catalysed reaction of hydrogen peroxide on stereoidal 3-ketones was studied by Caspi and Balasubrahmanyam[1]. A similar reaction of pentacyclic triterpene-3-ketone is lacking and hence the title investigation was undertaken.

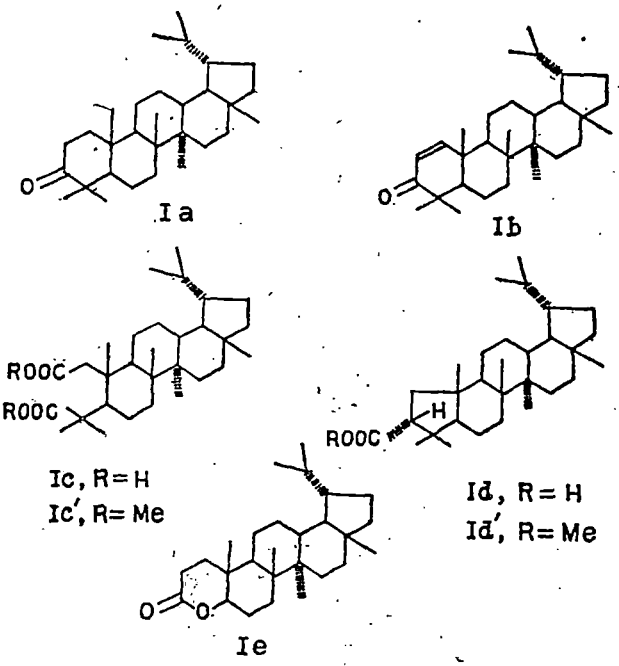
A solution of lupanone (Ia, 1.2 g) in *t*-butanol (60 ml) mixed with molar proportion of hydrogen peroxide (17%, 0.2 ml) and catalytic amount of selenium dioxide (0.008 g) was refluxed for 35 hr when black selenium metal precipitated out at the end of the reaction. The reaction mixture was then separated into acid and neutral fractions by usual method.

The neutral product on purification by chromatography and crystallisation from chloroform-methanol furnished a crystalline solid, $C_{30}H_{48}O$, m.p. 175-77°. That the product was an α, β-unsaturated ketone was indicated by characteristic UV absorption in methanol (λ_{max} 228 nm) and its IR spectrum in nujol (ν_{max} 1675 cm^{-1}). The PMR support for this product was forthcoming by the appearance of a pair of doublets each at δ 5.85 (J=10 Hz) and 7.19 (J = 10 Hz) assignable to the moiety —CO—CH=CH—C—. The compound was found to be identical (m.m.p and co-IR) with an authentic sample of lup-1-ene-3-one[2] (Ib).

The acidic part was esterified and then chromatographed. Elution with pet. ether (b.p. 60-80°) furnished a solid, which crystallised from chloroform-methanol and analysed for $C_{31}H_{52}O_2$ (M+ 456), m.p. 174-77°, IR (nujol) : 1740 cm^{-1} (carbomethoxy); PMR ($CDCl_3$, δ) : 0.8 (*s*, 3H, *t*-CH_3), 0.75 (*d*) + 0.85 (*d*) (J = 7 Hz, 6H, $HC(CH_3)_2$), 0.94-1.04 (5*s*, 15H, 5 × *t*-CH_3), 2.7 (*m*, J = 1 6Hz, 1H, *H*-C-$COOCH_3$) and 3.7 (*s*, 3*H*, —$COOCH_3$).

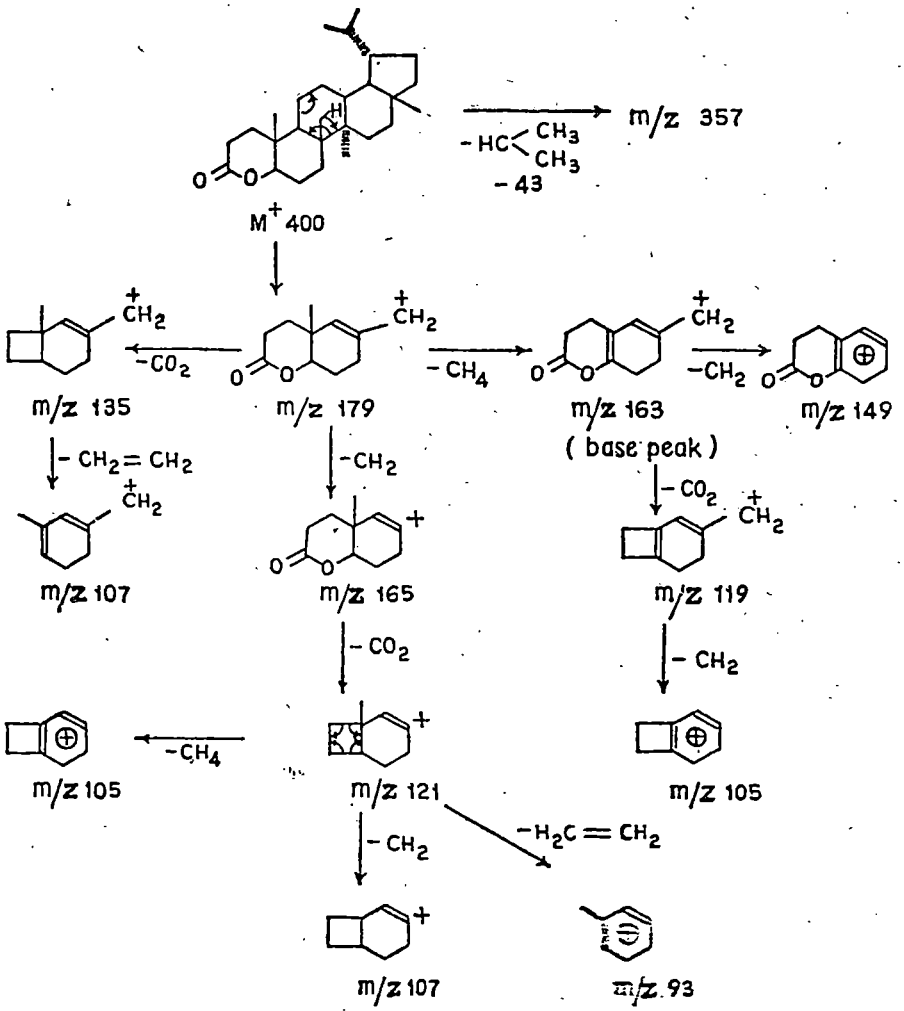
From the spectral data the ester has been identified as 2α-methoxycarbonyl-A-norlupane[3] (Id'), corresponding to the acid (Id).

Further elution of the column with pet. ether-benzene (4:1) gave a seco-diester, $C_{32}H_{54}O_4$, m.p. 116-18°; MS : *m/z* 502 (M^+), 443 (M^+—$COOCH_3$), 429 (M^+—CH_2COOCH_3), 400 [443-$CH(CH_3)_2$], 205, 189; IR (nujol) : 1740, 1730 cm^{-1} (2-carbomethoxyl groups); PMR ($CDCl_3$, δ) : 0.92 to 1.22 [24H, 6*t*-CH_3, 1 $HC(CH_2)_2$], 2.37 (*m*, 2H, CH_2-COOMe), 3.64 (*s*, 3H, $COOCH_3$), 3.68 (*s*, 3H; $COOCH_3$). Hydrolysis of the seco-diester (Ic') by methanalic KOH furnished a diacid, m.p. 270-71°, identical with lupane dicarboxylic acid[4] (Ic).

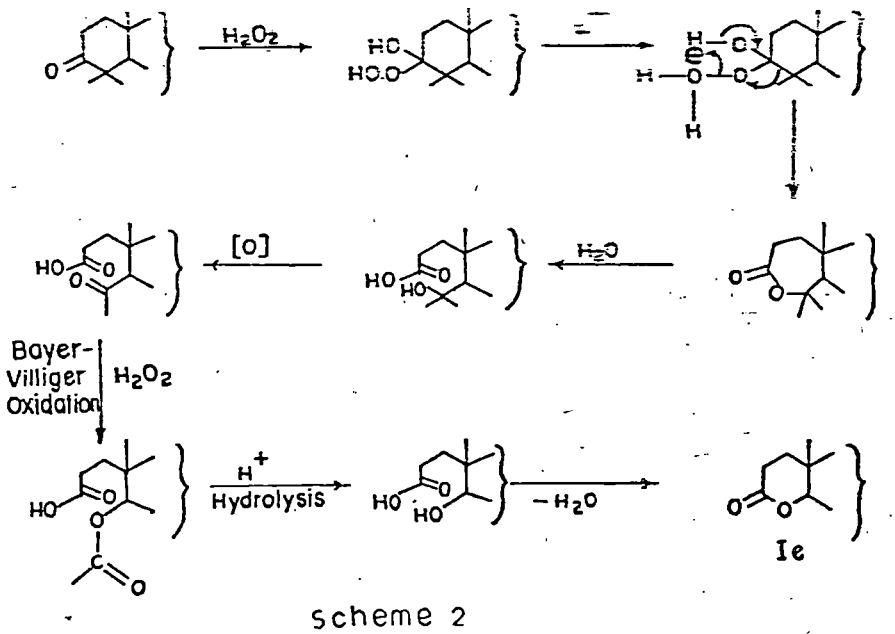


When lupanone (2g) was oxidised with excess amount of hydrogen peroxide (17%, 30 ml) by refluxing for 30 hr in the presence of selenium dioxide (0.5 g) in *t*-butanol (150 ml), it yielded in acidic fraction a compound characterised as Ic[4]. The neutral part on chromatography followed by elution with benzene afforded a solid, which recrystallised from chloroform-methanol and analysed for $C_{27}H_{44}O_2$ (M+ 400), m.p. 252°. The band at 1740 cm^{-1} in its IR spectrum indicated the presence of a δ-lactone, which was corroborated by the appearance of a lactonic proton (CO-O-C*H*-CH_2) at δ 3.9 as a triplet[5] (J=18Hz), in its PMR spectrum. The high J value showed the lactonic proton to be axially oriented with one axial and another equatorial neighbours. Besides, the compound gave a pair of peaks centred at δ 2.6 (2*H*) indicating the presence of methylene protons alpha to the carboxyl group (—CH_2—CH_2—COO). The structure of this compound as Ie was further supported by its mass spectral fragmentation pattern shown in Scheme 1. This is the first report of formation of a δ-lactone (Ie) by the loss of three carbon atoms of ring -A from a 3-keto-triterpene by the action of hydrogen peroxide in the presence of selenium dioxide.

The mechanism of formation of δ-lactone (Ie) is



Scheme 1



Scheme 2

suggested in Scheme 2, based on similar reaction by Pettit *et al.*[6] on steroidal systems.

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Oxidation of Friedelin with Hydrogen Peroxide in Presence of Selenium Dioxide

SIKHA RANI DUTTA (*née* DAS) &
BHIM PRASAD PRADHAN*
Department of Chemistry, North Bengal University,
Darjeeling 734 430

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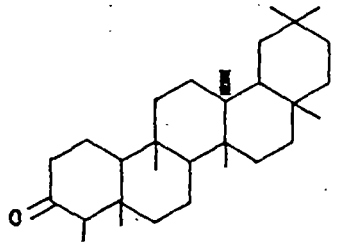
Friedelin (I) on oxidation with molar proportion of hydrogen peroxide and catalytic amount of selenium dioxide in *t*-butanol affords a δ-lactone (II), friedelin dicarboxylic acid (IIIa) and 2α-carboxyl-A-nor-friedelin (IVa). The compounds have been fully characterised by spectral data (IR, PMR).

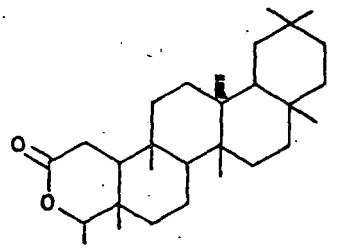
In our previous communication[1], hydrogen peroxide-selenium dioxide oxidation of lupanone was reported to afford 4, 23, 24-trinor-lupane-3→5-lide (A). Friedelin (I) on similar reaction gave a δ-lactone different from (B), obtained by Corey *et al.*[2] by the oxidation of I with peracetic acid. The preparation and characterisation of the different products obtained in the reaction of I with $H_2O_2-SeO_2$ are reported in this note.

A solution of friedelin (I, 0.9 g) in *t*-butanol (80 ml) mixed with hydrogen peroxide (15 ml, 22%) and selenium dioxide (0.225 g) was refluxed on a water-bath for 60 hr. Precipitation of black selenium metal in the reaction mixture indicated the completion of the reaction. The reaction mixture was then separated into neutral and acid parts by usual method.

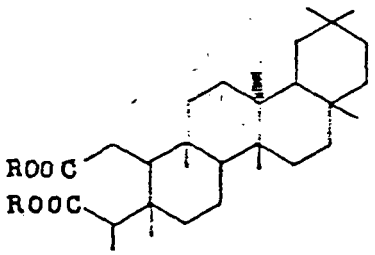
The acidic part on esterification with diazomethane followed by chromatography yielded two products. The less polar solid was crystallised from chloroform-methanol, m.p. 263-65°. It analysed for $C_{31}H_{52}O_2$;



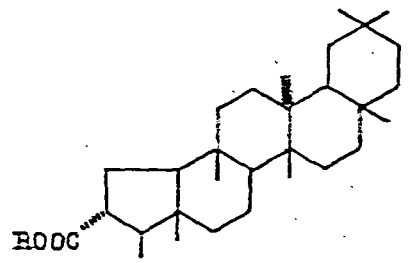
I



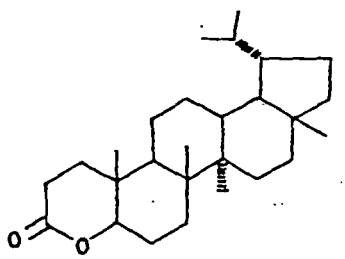
II



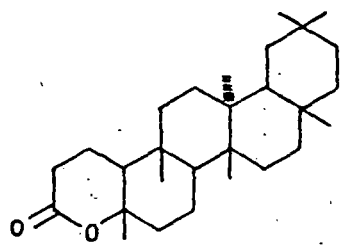
III a, R = H
III b, R = Me



IV a, R = H
IV b, R = Me



A

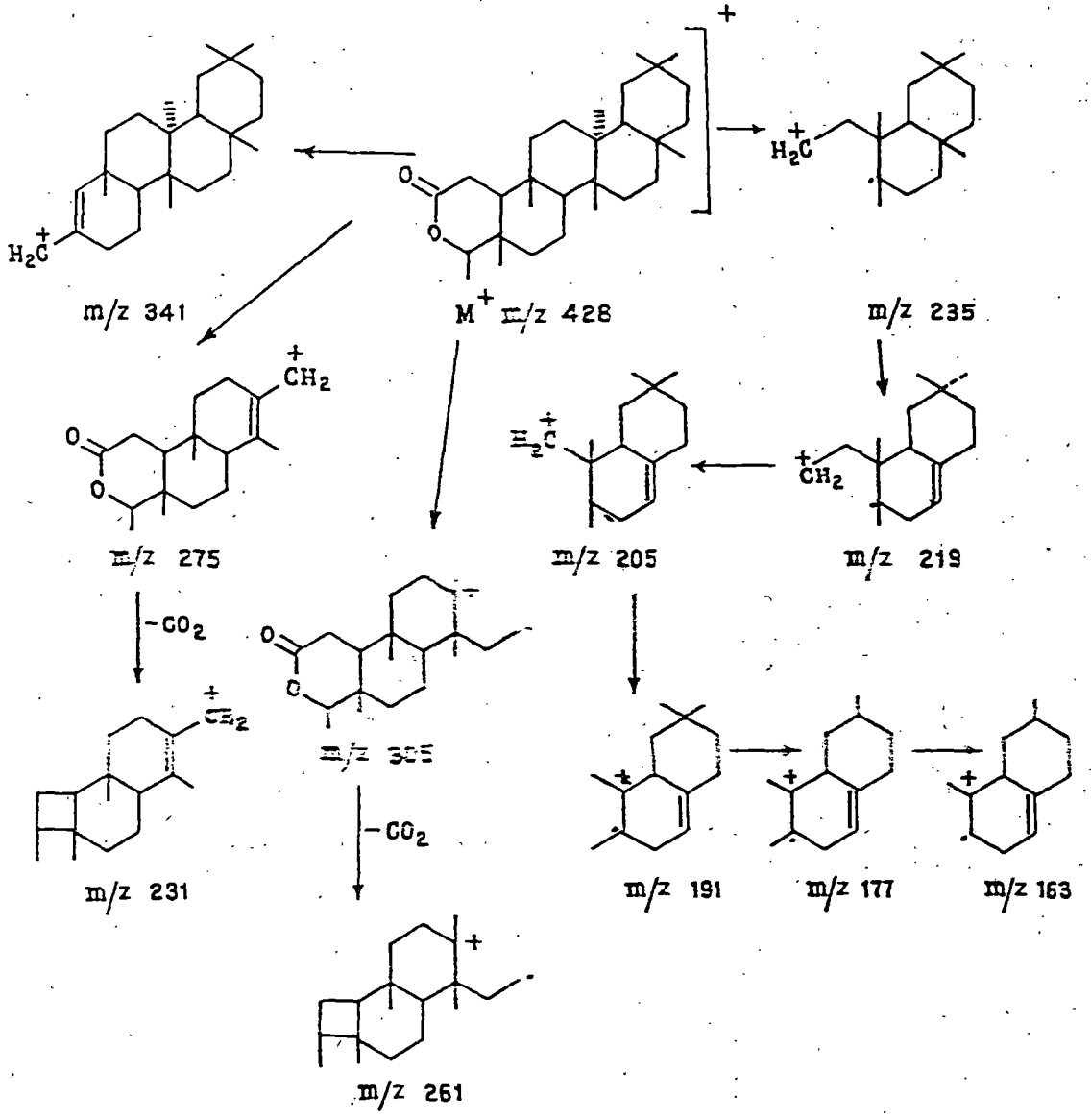


B

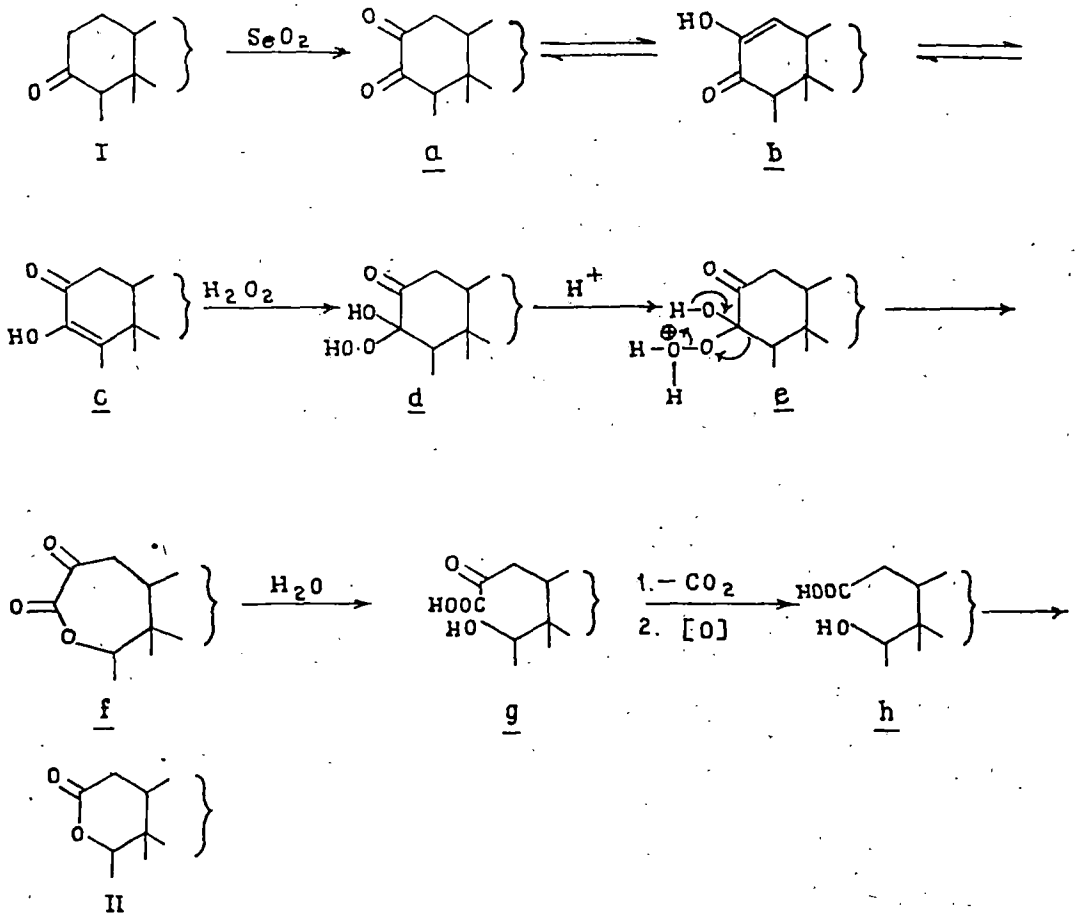
MS: m/z456(M^+), 332, 303, 276, 262, 248, 234, 223, 205(base), 191, 179, 121, 109 and 107; IR (nujol): 1720 cm^{-1} (one carbomethoxyl group); PMR ($CDCl_3$): δ 3.53 (*s*, 3H, $COOCH_3$), 2.8 (*m*, 1H, $H-\underset{|}{C}-COO$), 0.9 to 1.2 (7*s*, 21H, 7 × *t*-CH_3), 0.87 (*d*, 3H, $H-\underset{|}{C}-CH_3$, $J=7$ Hz) These spectral data led to the establishment of structure (IVb) for this compound and the corresponding acid presumably corresponded to structure (IVa).

The more polar product was purified by crystallisation from $CHCl_3$-MeOH. It analysed for $C_{32}H_{54}O_4$ (M^+ 502); m.p. 167-69°; IR (nujol): 1735 cm^{-1}; PMR ($CDCl_3$, δ): 3.53 (*s*, 3H, $COOCH_3$), 3.57 (*s*, 3H, $COOCH_3$), 0.9 to 1.2 (21H, 7 × *t*-CH_3), 1.32 (*d*, 3H, $H-\underset{|}{C}-CH_3$, $J=7$ Hz). Based on these data, this compound was assigned structure (IIIb). Hydrolysis of the seco-diester (IIIb) by methanolic KOH furnished the diacid (IIIa), m.p. 280° (d), identical with 3, 4-seco-friedelonic acid (IIIa)[2].

The neutral part was chromatographed over deactivated alumina column. Elution with petroleum-benzene (2 : 3) afforded a white solid (≈10 mg), which analysed for $C_{29}H_{48}O_2$ (M^+ 428), m.p. 262°; CD (hexane): 230 nm (ε − 0.56). In the IR spectrum, a band at 1740 cm^{-1} was characteristic of δ-lactone moiety, the presence of which was supported by its PMR spectrum (multiplet at δ 4.05 due to lactonic proton[3], $-CO-O-\underset{|}{C}H-CH_3$). The appearance of a pair of doublet at δ 2.48 (2H, $J_{aa}=7.5$ Hz, $J_{ae}=2.5$ Hz) indicated the presence of methylene protons adjacent



Scheme 1



Scheme – 2

to the carbonyl group ($-O-\underset{\underset{O}{\|}}{C}-\underset{\underset{OH}{|}}{CH}-CH_2-$). A three-proton doublet at δ 1.18 (J = 6.5 Hz) was assignable to methyl protons ($HC-CH_3$). The peaks between δ 0.88 and 1.10 represented seven tertiary methyl groups (21H). These observations led to the establishment of structure (II) for the lactone, further supported by its mass fragmentation pattern shown in Scheme 1. This is perhaps the first report of the formation of δ-lactone from friedelin.

The mechanism of formation of II is shown in Scheme 2. It is well known that SeO_2 oxidises α-methylene ketones to 1, 2-diketones[4,5]. The formation of II probably proceeds via the formation of the diketone (a) [$\rightleftharpoons$diosphenol b$\rightleftharpoons$c]. One mol of hydrogen peroxide may attack (c) to give the intermediate α-keto-ε-lactone (f), which may undergo hydrolysis to furnish the α-keto acid (g). The acid (g) on decarboxylation furnishes 3, 4-seco-C-3-nor-4-hydroxy-friedelin-2-carboxylic acid (h) which undergoes lactonization to form the δ-lactone (II). All the above intermediates are formed during the reaction conditions *in situ*. The formation of a similar lactone in the oxidation of lupanone by H_2O_2-SeO_2 is not possible due to the presence of *gem*-dimethyl group at C-4, which hinders the formation of a diosphenol, similar to c, from lupanone. Thus the oxidation of lupanone gave compound (A) only, different from II.

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Oxidation of Taraxerone with Hydrogen Peroxide in Presence of Selenium Dioxide

B P PRADHAN* & SIKHA RANI DUTTA (*neé* DAS)

Chemistry Department, University of North Bengal, P.O. North Bengal University, Darjeeling 734430

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Taraxerone (I) on oxidation with hydrogen peroxide in the presence of selenium dioxide in *t*-butanol affords 1α,2α-epoxide (II), 4,23,24-tri-nor-taraxerene-3→5-olide, a δ-lactone (III) and taraxerene-ε-lactone(IV) from neutral part and 2α-carboxy-A-nor-taraxerene(V) together with taraxerene-3,4-seco-dicarboxylic acid (VI) from the acid part.

We reported in our previous communications[1,2] the results of selenium dioxide oxidation of saturated triterpenoids. We have now extended the reaction to taraxerone, a 3-keto triterpenoid having a trisubstituted double bond, and the products obtained have been characterised.

To a solution of taraxerone (I) (0.9 g) in *t*-butanol (80 ml) was added hydrogen peroxide (15 ml, 17%) and selenium dioxide (0.225 g) and the mixture refluxed for 20 hr. The deposition of the precipitates of black selenium metal indicated the completion of the reaction. The reaction mixture was filtered and separated into neutral and acid parts.

Chromatography of the neutral part over deactivated alumina column and elution with benzene-pet. ether (1:4) gave a solid which crystallised from chloroform-methanol, m.p. 188°. It analysed for $C_{30}H_{46}O_2$; MS: *m/z* (re. int.) 438 (M^+, 39.9), 423 (23.2), 314 (70), 299 (28), 205 (75), 204 (100), 189 (10); IR(Nujol): 1705 (>C=O), 1255 (epoxide), and 820 cm^{-1} (trisubstituted double bond); no UV absorption above 220 nm; PMR($CDCl_3$, δ): 0.837 to 1.132 (s, 24H, $8\times t-CH_3$), 5.56 (*m*, 1H, >C=C*H*); a pair of doublets each at 3.52 (J=4 Hz) and 3.35 (J=4.5 Hz) assignable to two protons[3] of oxirane ring of each carbon. That this compound is a 1,2-epoxide of taraxerone is supported by presence of the fragments IIa, IIb, and IIc in its mass spectrum[4]. Thus from the above spectral data structure (II) has been assigned for the epoxide.

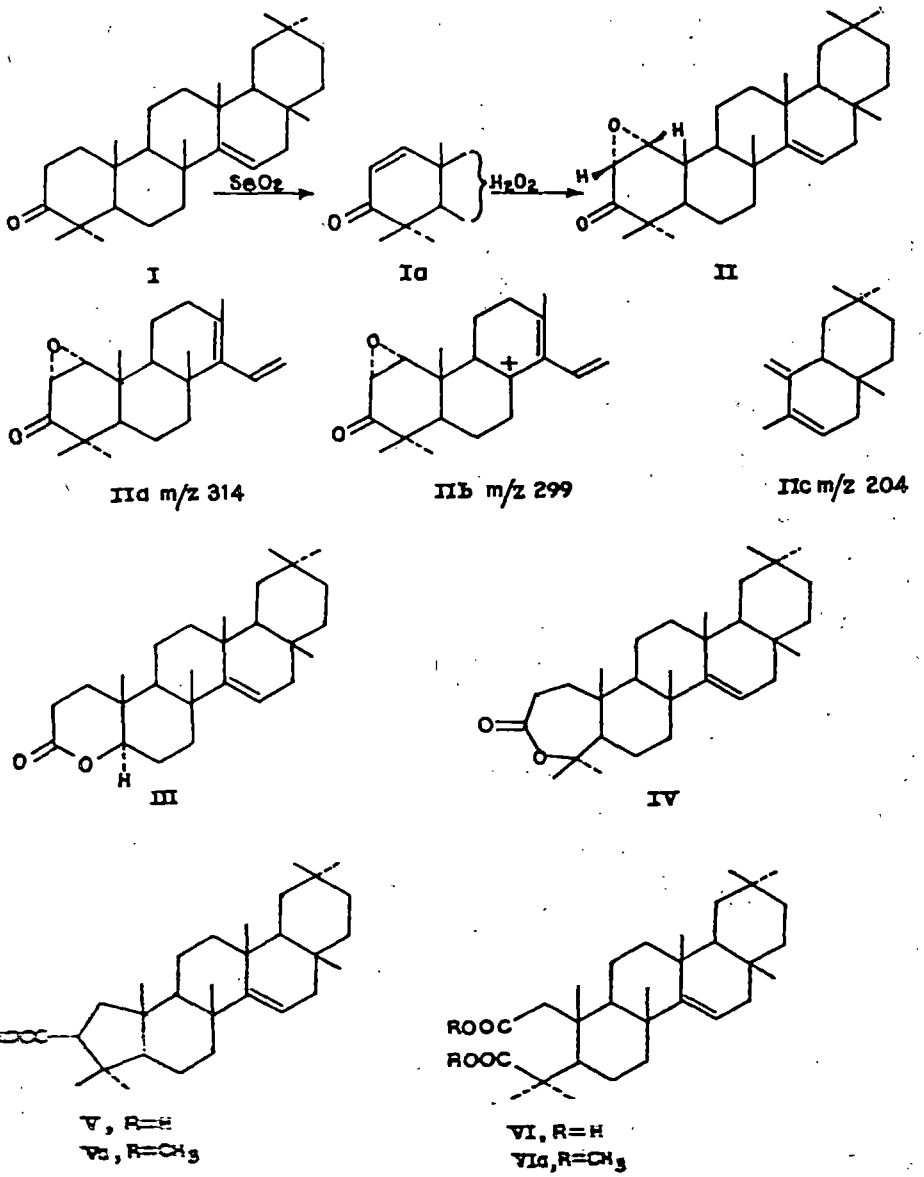
Further elution of the column with pet. ether-benzene (2:3) afforded a solid which on fractional crystallisations from chloroform-methanol afforded two solid compounds (A) and (B): A, m.p. 228-30°, $C_{27}H_{42}O_2$ (M^+ 398); and B, m.p. 218°, $C_{30}H_{48}O_2$ (M^+ 440). The IR spectrum of A exhibited bands at 1750 (δ-lactone) and 810 cm^{-1} (trisubstituted double bond); MS: *m/z* (rel. int.) 398 (M^+ 32.91), 383 (18.45), 274 (100), 259, 204 (75); PMR($CDCl_3$, δ): 0.83 to 1.12 (6*s*, 18H, $6\times t-CH_3$), 5.57 (*m*, 1H, >C=C*H*), 2.26 (*m*, 2H, $-CH_2-CH_2-CO-O-$), 3.92 (*q*, J_{ae}=5 Hz, J_{aa}=12 Hz, lactonic proton, $CO-O-CH-CH_2-$)[5]. The high J-value showed the lactonic proton to be axially oriented with one axial and another equatorial neighbours. On the basis of these data compound (A) is assigned structure (III). The IR spectrum of B exhibited bands at 1720 (ε-lactone) and 810 cm^{-1} (>C=C<H); MS: *m/z* 440 (M^+), 425, 316, 301, 204, 189. The mass spectrum of B confirmed its structure as IV.

The acidic part was esterified and subjected to chromatography over a deactivated alumina column. Elution with pet. ether (b.p. 60-80°) furnished compound (C) which crystallised from chloroform-methanol, analysed for $C_{31}H_{50}O_2$, m.p. 161-63°; MS: *m/z* (rel. int.) 454 (M^+, 32), 439 (13), 330 (14), 315 (10), 287 (20), 204 (75); IR(nujol): 1735 (carbomethoxy), 815 cm^{-1} (trisubstituted double bond); PMR($CDCl_3$, δ): 3.6 (*s*, 3H, $-COOCH_3$), 2.75 (*q*, 1H, J_{ae}=5 Hz, J_{aa}=11 Hz, $-CH_2-C-CO-O-$), 0.82 to 1.13 (24H, $8\times t-CH_3$), 5.54 (*m*, 1H, C=C*H*). The PMR data and the mass fragmentation pattern proved the ester as 2α-methoxycarbonyl-A-nor-taraxerone (Va).

Further elution of the column with pet. ether-benzene (1:1) gave a solid ester (D) which analysed for $C_{32}H_{52}O_4$, m.p. 151°; MS: *m/z* (rel. int.) 500 (M^+, 17), 485 (6), 470 (7), 468 (9), 440 (6), 395 (7), 376 (7), 361 (2), 344 (20), 316 (12), 287 (17), 204 (100); IR (Nujol): 1725 and 1730 (two carbomethoxy), 810 cm^{-1} (trisubstituted double bond); PMR($CDCl_3$, δ): 5.54 (*m*, 1H, >C=C*H*), 3.65 (*s*, 3H, $-COOCH_3$), 3.60 (*s*, 3H, $-COOCH_3$), 2.3 (*m*, 2H, $-CH_2-CH_2-COOCH_3$), 0.81 to 1.25 (24H, $8\times t-CH_3$). On the basis of the spectral data structure (VIa) has been assigned for D. This compound is reported in literature as taraxadioic acid[6].

The formation of the products II, III, IV, V and VI shows that in the SeO_2 oxidation of I no migration of 14-15 double bond has occurred. Compounds II, III, IV and V are probably being reported for the first time.

It may be concluded from the results of previous studies[1,2] and those obtained presently that the δ-lactones are formed irrespective of the presence of methyl groups at C-4 position. Further, isolation of ε-lactone (IV), though in a very small amount (2%), supports the mechanism of formation of the δ-lactone



via the δ-lactone. Efforts to confirm the reaction path for the formation of the δ-lactone as suggested previously[1] are in progress. The epoxide II is most probably formed via the unsaturated ketone (Ia).

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