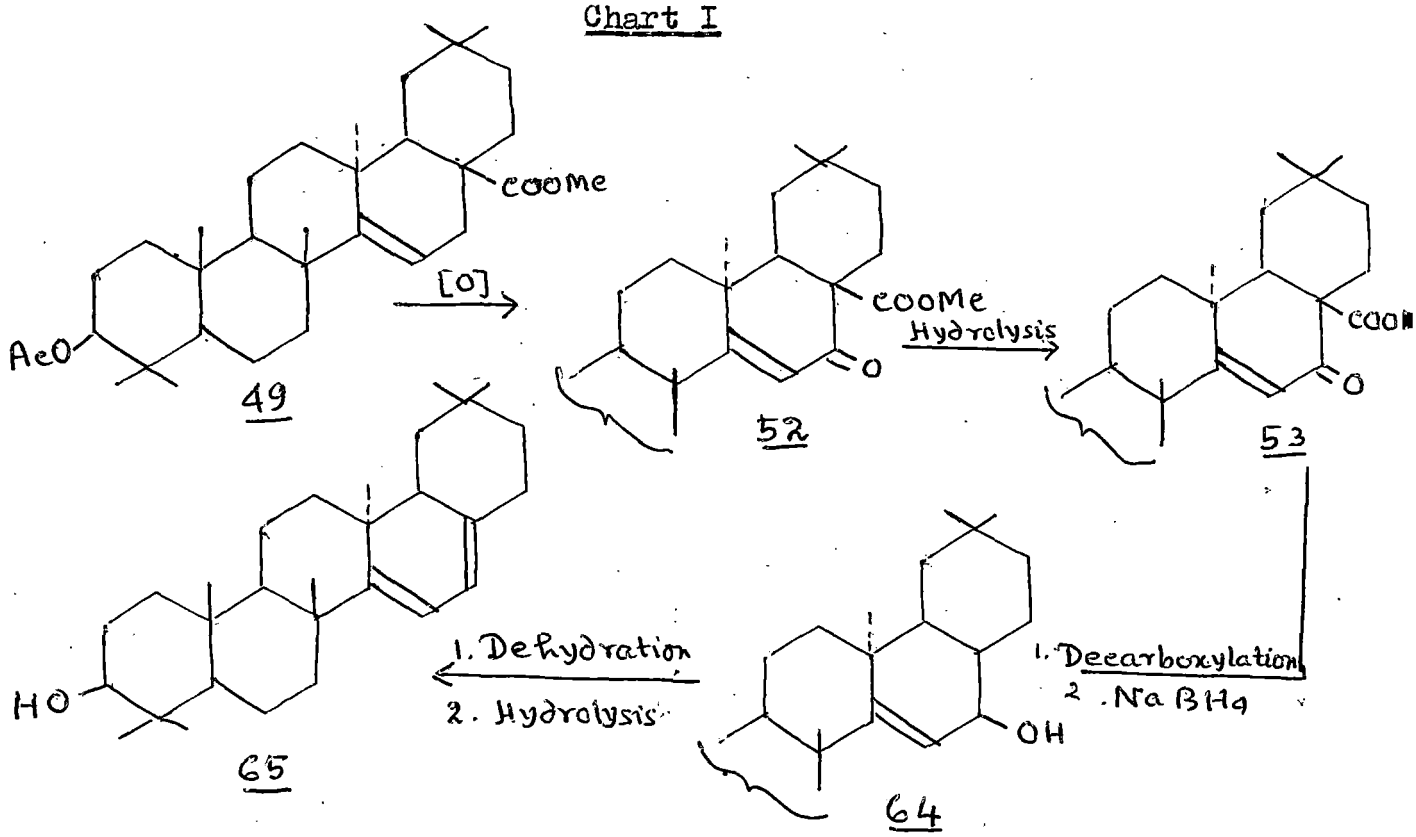
CHAPTER - II

Allylic Oxidation and bromination studies with NBS on taraxeryl acetate:

Section A: Introduction

In connection with the structure elucidation of another triterpenoid we required the compound 3β-hydroxy-28-nor-olean-14, 16-diene 65. We had planned to prepare the desired compound according to the sequence shown below. (Chart I), starting from acetyl methyl aleuritolate[41] 49. Allylic oxidation of 49 according to the method of Finucane and co-workers[34,42] would be expected to give the 16-oxo derivative 52, which on hydrolysis would furnish the β-keto acid 53. The latter on decarboxylation followed by sodium borohydride reduction would give 64, which on dehydration would afford the intended product 65.

Chart I



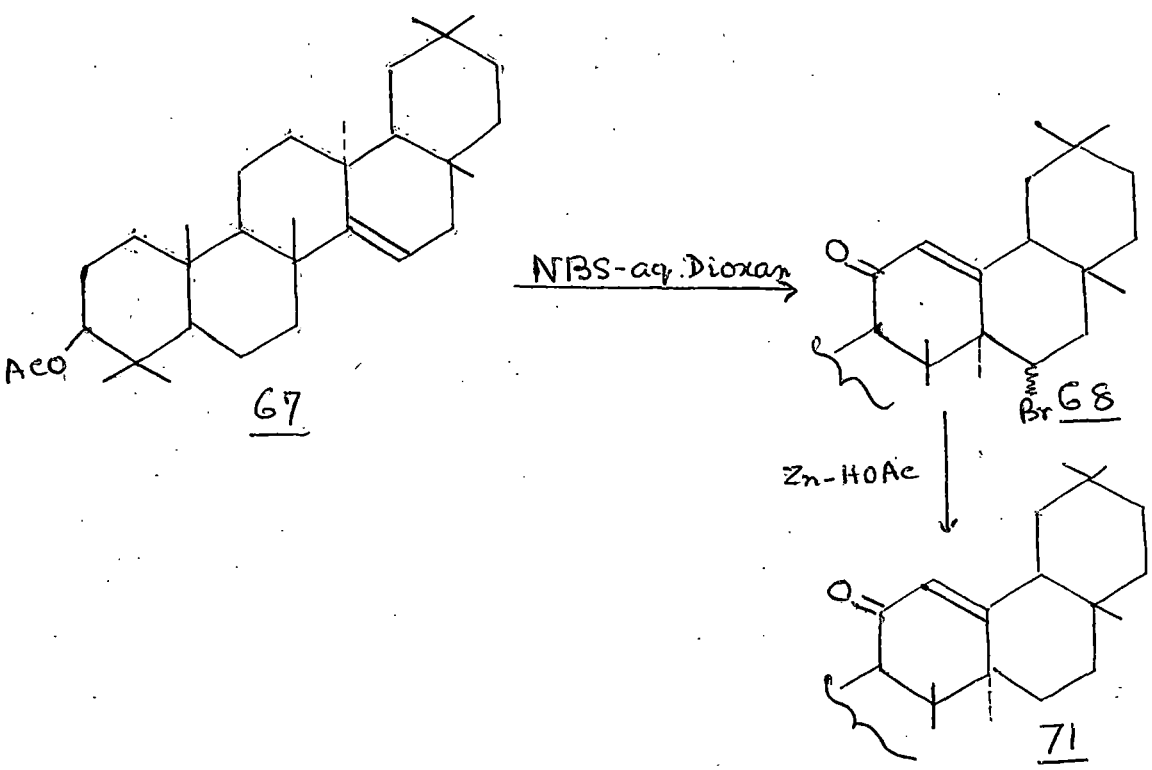
Finucane and Thomson[34,42] recently described a method for allylic oxidation of taraxeryl acetate, β-amyrin acetate etc. using NBS-$CaCO_3$ in aqueous dioxan in presence of visible light and claimed the isolation of the corresponding αβ-unsaturated ketones in high yield. Being encouraged by their results we also undertook a plan for the synthesis of 16-oxygenated β-amyrin derivatives starting from taraxeryl acetate. We planned to prepare 16-oxo taraxeryl acetate by following their procedure and then to reduce the 16-oxo compound to the 16-hydroxy derivative by a suitable method. Acid isomerisation of the latter was expected to give 16-hydroxy β-amyrin derivatives. In view of our intended plan discussed above, we first of all undertook the oxidation study on taraxeryl acetate. The results of our oxidation, was, however, widely different from those recorded by Finucane and Thomson[34,42] and are described in Section B.

Similarly with the expectation of obtaining a 16-bromo taraxeryl acetate we extended our studies on allylic bromination of taraxeryl acetate using NBS in dry carbon tetrachloride in presence of light and benzoyl peroxide as the initiator. The results obtained during these studies were interesting and is also described in Section B.

Section:B : Allylic oxidation and bromination studies with NBS on taraxeryl acetate:

Taraxeryl acetate 67 on oxidation[34] with NBS in aqueous dioxan for 5.5 hr in presence of $CaCO_3$ in visible light gave a mixture of compounds which on TLC examination showed the presence of at least

three compounds (3 distinct spots). Three compounds were separated by chromatography over alumina followed by crystallisation. The first solid 68, $C_{32}H_{49}O_3Br$, m.p. 238-40°, $(\alpha)_D$ 88.07°, λ_{max} 249.5 mμ (ε, 11,000), ν_{max}^{nujol} 1250, 1650 and 1750 cm^{-1}, indicating the presence of an αβ-unsaturated ketone. The compound also showed positive test for bromine and a single spot on a chromatoplate. In order to establish its structure, 68 was treated with Zn-dust in acetic acid and a halogen free compound 71, m.p. 265-70°, $(\alpha)_D$ 48.8°, λ_{max} 252.5 mμ (ε, 11,000) was isolated and was found to be identical with an authentic sample of β-amyrenonyl acetate[43] (m.m.p. and IR comparison) prepared

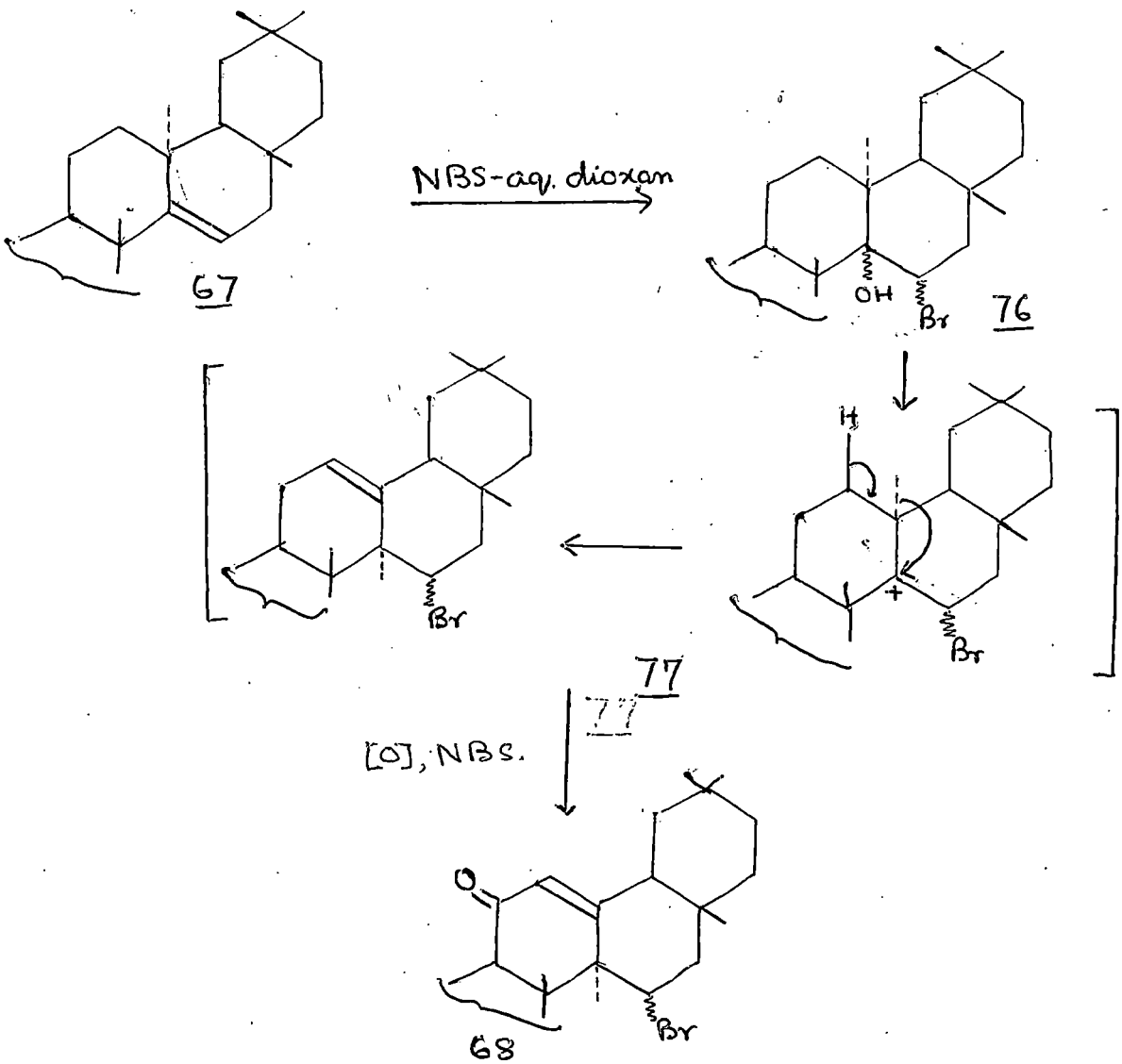


67 68 71

by oxidation of β-amyrin acetate with CrO_3 in acetic acid at 130°. This result indicated that the bromo compound was probably 11-keto-

15-bromo-β-amyrin which on treatment with Zn-acetic acid would give 71 by the removal of the bromine atom. The formation of 68 from taraxeryl acetate could be rationalised by the following mechanism (Chart II).

Chart II



The bromohydrin 76 is first formed which could easily isomerise to the β-amyrin derivative 77 through the carbonium ion intermediate

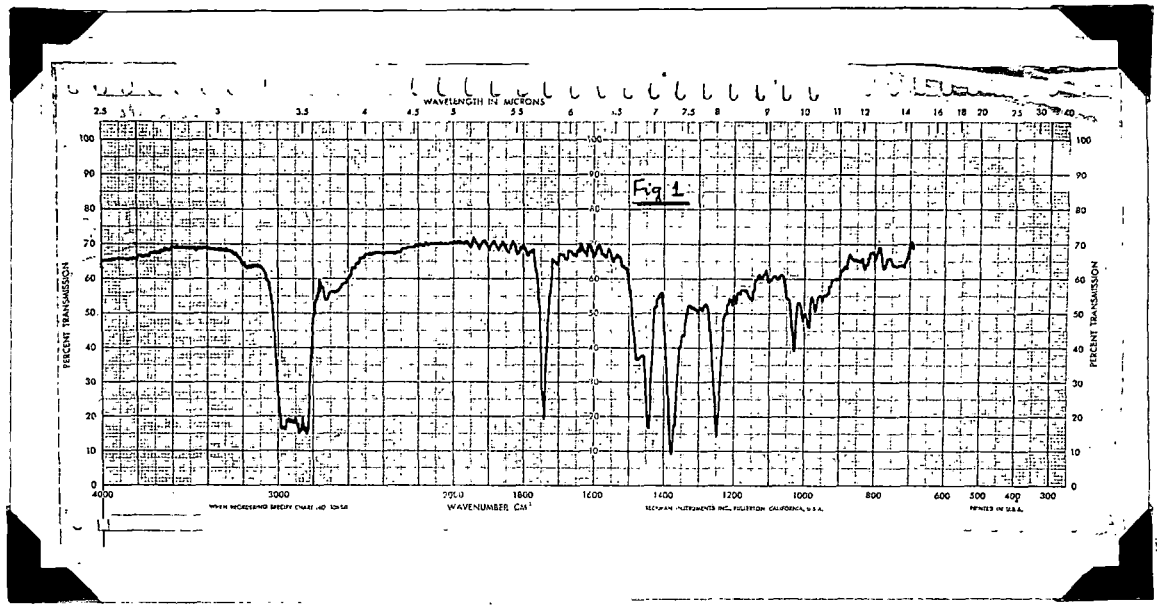


Fig. 1. IR spectrum of 15-bromo-β-amyrin acetate 72

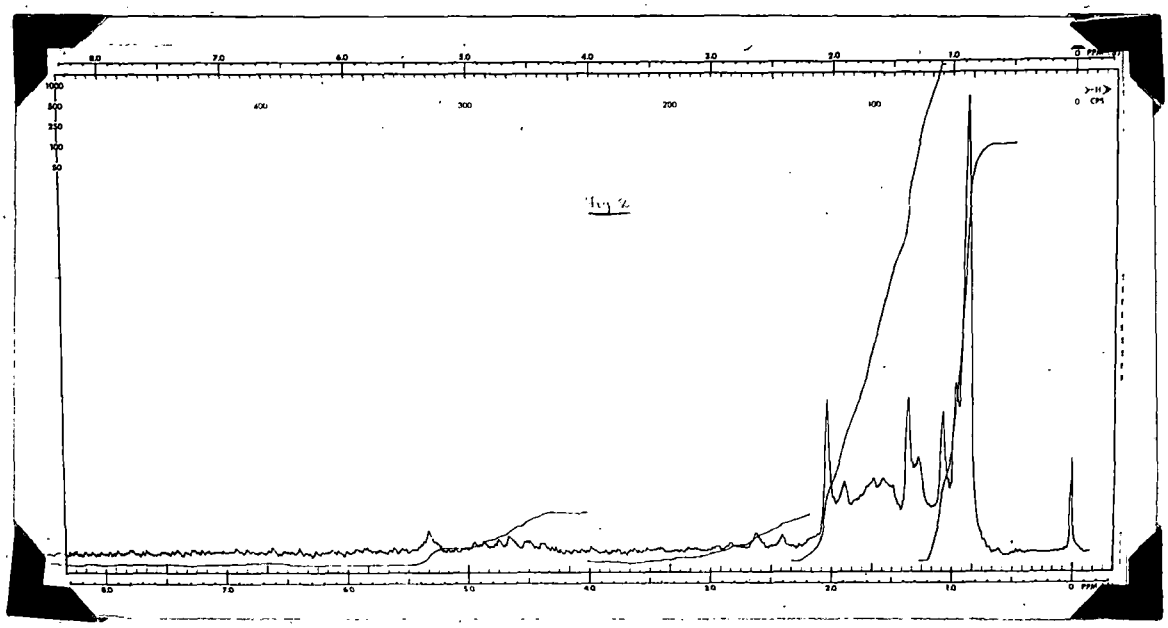
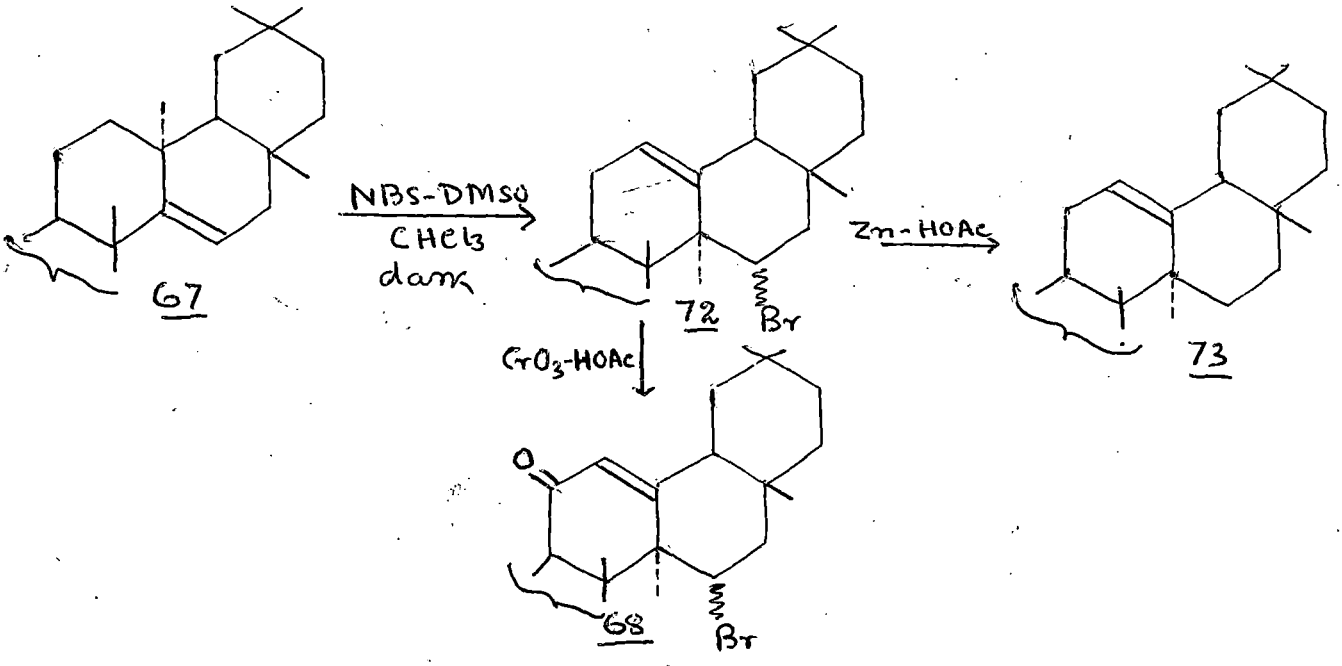


Fig.2. NMR spectrum of 15-bromo-β-amyrin acetate 72

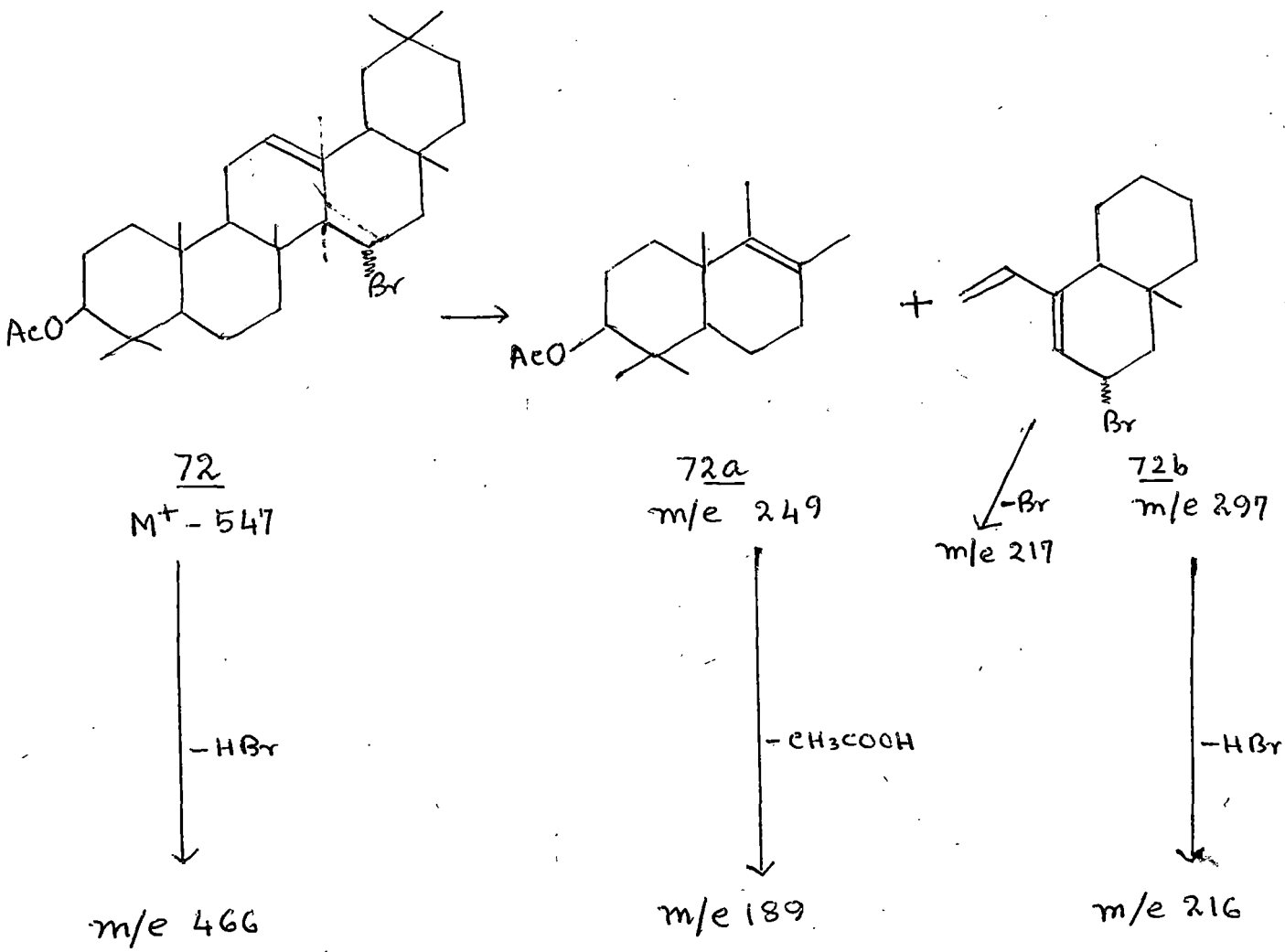
followed by methyl migration. The intermediate 77 then gets oxidised to the $\alpha\beta$-unsaturated ketone 68.

In order to prove our contention we looked for a method for the preparation of the 15-bromo compound 77 which on oxidation by established method would give 68. We tried to prepare the bromohydrin at the 14-15 double bond of taraxeryl acetate by the method of Dalton[44] using NBS in DMSO solvent[45]. Treatment of taraxeryl acetate with aqueous dimethyl sulfoxide in chloroform and NBS in dark afforded a solid 72, $C_{32}H_{51}O_2Br$, m.p. 180-2°, $(\alpha)_D$ 47.37°. The compound did not show any UV absorption between 220-330 mμ. IR spectrum of the compound (Fig.1) showed peaks at 1720 and 1250 ($-O.CO.CH_3$) cm^{-1}. NMR spectrum (Fig. 2) showed a multiplet centered at 5.3 ppm (vinyl proton) and a multiplet at 4.30 ppm for one proton attached to a carbon containing bromine and also peaks at 2.09 ppm ($-O.COCH_3$) and at 4.53 ppm for proton attached to the carbon bearing acetoxy group. All these physical evidences coupled with mass fragmentation pattern confirmed the structure depicted in 72 . The compound showed a mass



peak M^+548 (isotope) (Fig. 3) and peaks at 249 (72a) and 297 (72b) arising by retro-Diels-Alder Cleavage of β-amyrin skeleton[39]. The ion 72b gives a prominent peak at m/e 217 by the loss of bromine atom and at m/e 216 by the loss of HBr. There is also peak at m/e 189 arising by the elimination of the acetic acid from 72a. There was also a prominent peak at 466 (M^+ -HBr). The other fragmentation pattern is similar to those shown by β-amyrin acetate. These fragments are shown below (Chart III).

Chart III



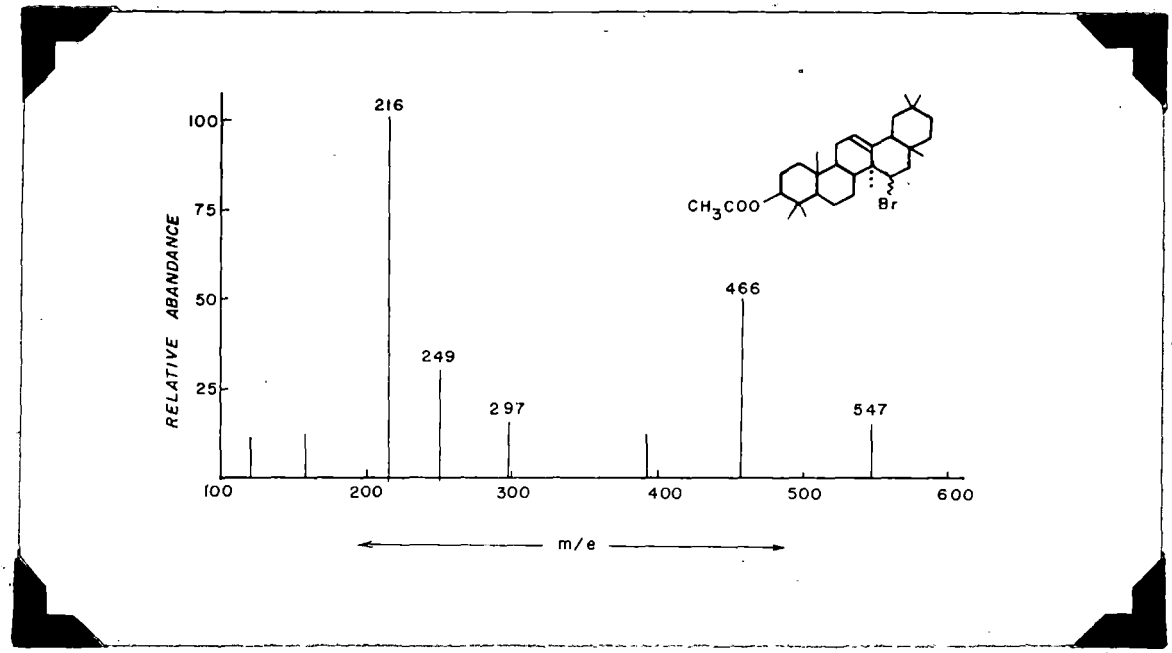


Fig. 3 Mass spectrum of 15 bromo-β-amyrin acetate 72

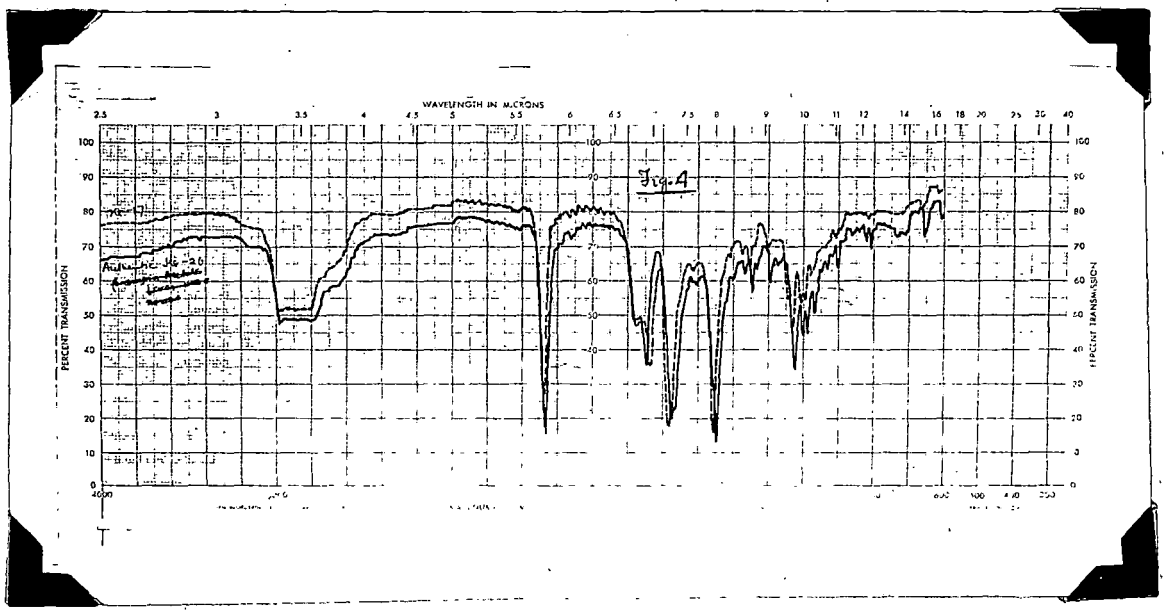
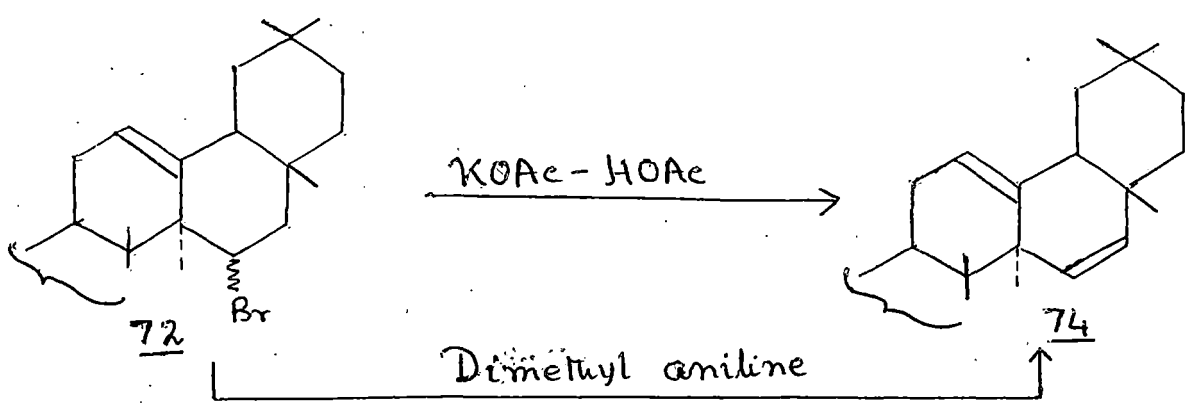


Fig. 4 IR comparison of
β-amyrin acetate 73 obtained from (broken line) 72
authentic β-amyrin acetate (solid line)

The compound 72 on treatment with zinc-acetic acid yielded a crystalline solid 73, m.p. 230-31°, $(\alpha)_D$ 85.1°, identical with an authentic sample of β-amyrin acetate (m.m.p. and IR comparison Fig. 4). The bromine atom at 15 position would be expected to have the same stereochemistry as in the product from NBS-aq. diaxan oxidation method. Compound 72 on oxidation with chromium trioxide-acetic acid[43] gave 68, m.p. 238-40° identical with the product obtained from NBS-aq. dioxan oxidation method (m.m.p and IR comparison Fig. 5). Thus the structure 72 predicted is established beyond doubt.

Solvolysis of compound 72 with K-acetate in acetic acid at 130° for four hours gave a product $C_{32}H_{50}O_2$, m.p. 199-200°, $(\alpha)_D$ 41.86°, no absorption in the UV region 220-300 mμ. NMR spectrum (Fig. 6). of this compound showed signals at 5.2 to 5.6 ppm for three vinyl protons accounting for one trisubstituted and one disubstituted double bond. From the foregoing evidences and the analytical data we assign structure 74 to this compound.



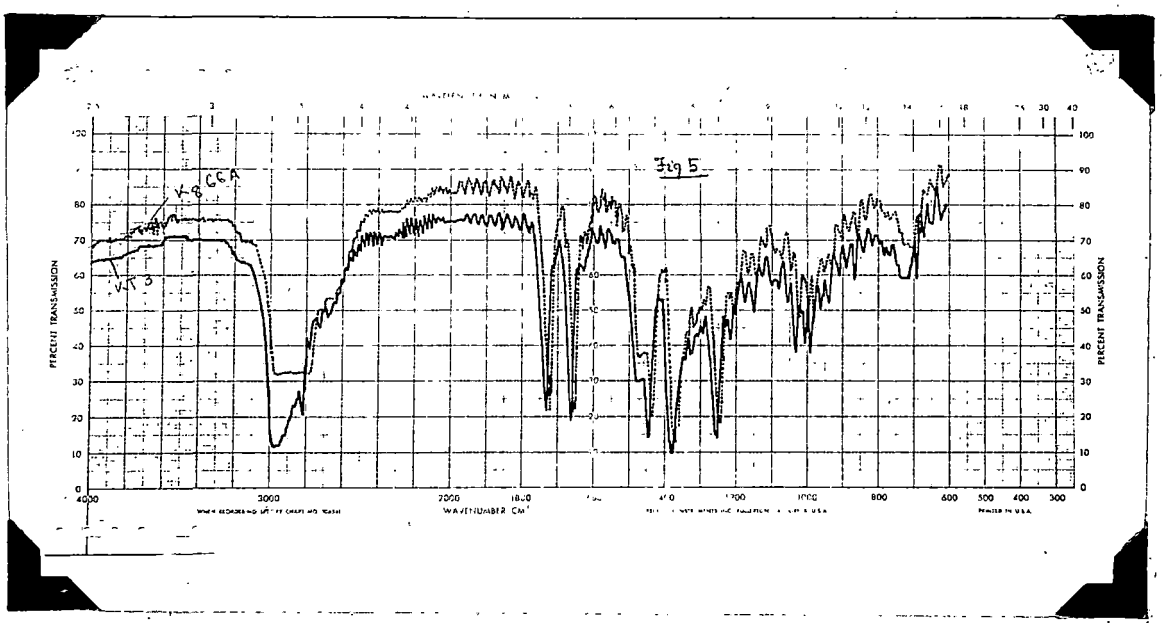


Fig. 5 IR comparison of

15 bromo β -amyrenonyl acetate 68 from taraxeryl acetate

15 bromo β -amyrenonyl acetate 68 from CrO_3-HOAc oxidation of 72

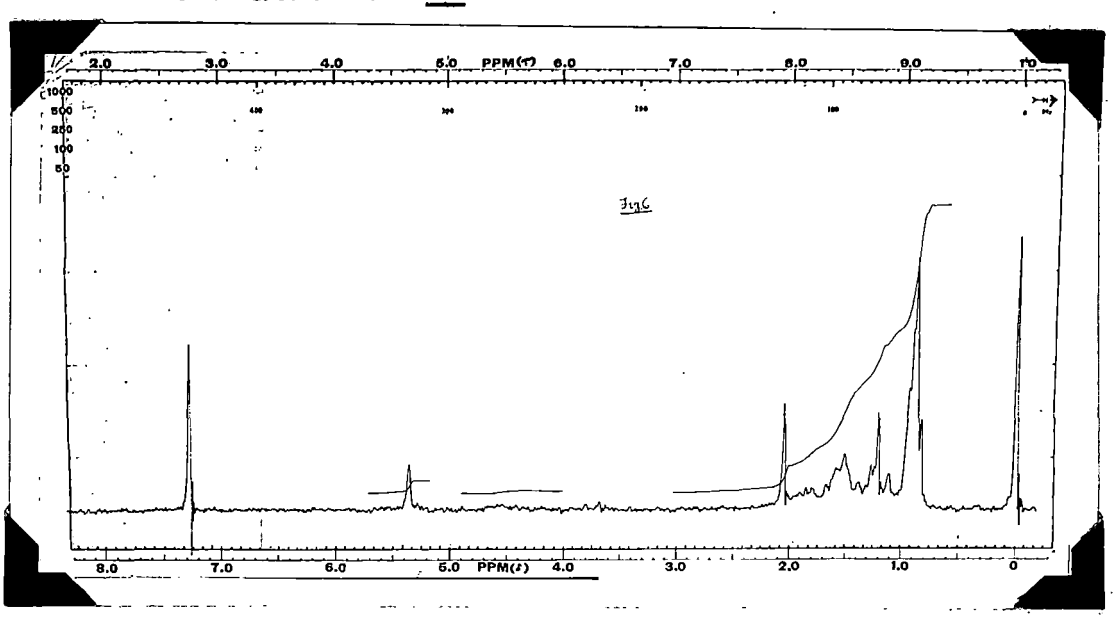
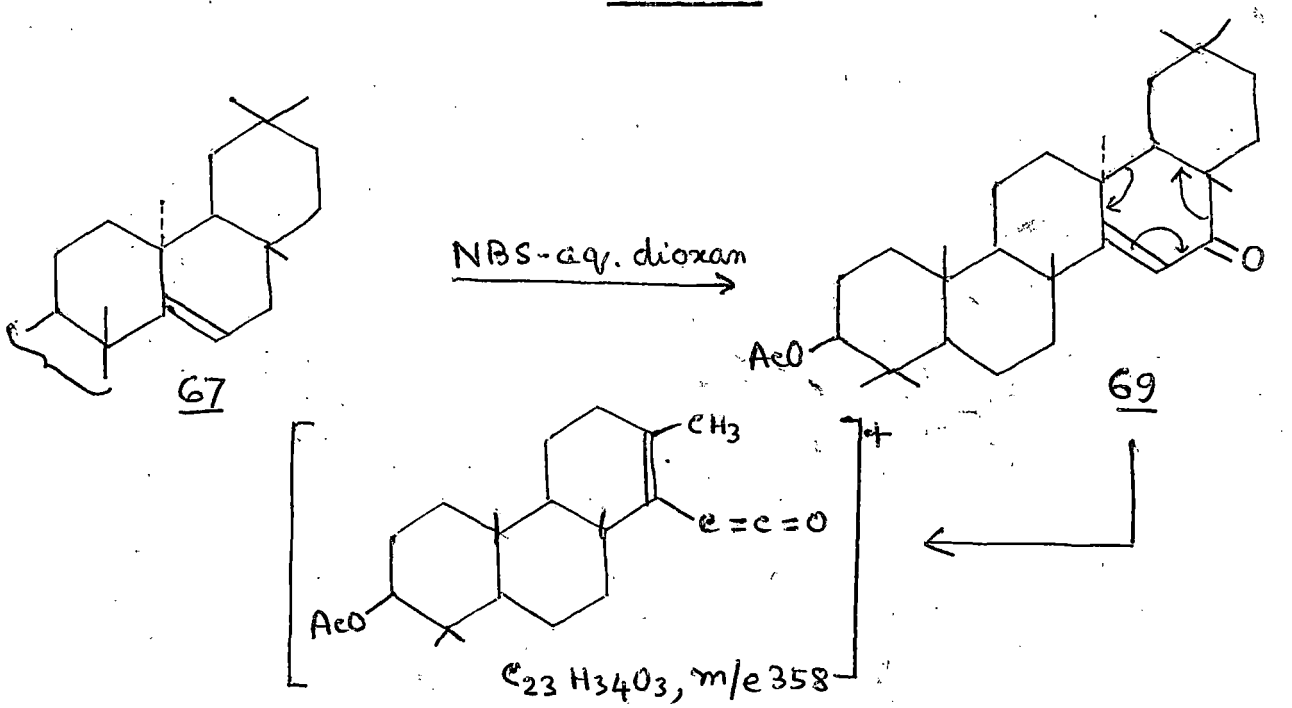


Fig. 6 NMR spectrum of olean-12, 15-dien 3β -yl acetate 74

Compound 72 on refluxing with dimethyl aniline for 4 hours also gave a compound, m.p. 199-200° which was found to be identical with 74 (m.m.p. and IR comparison Fig. 7).

The second solid 69, $C_{32}H_{50}O_3$, m.p. 280-82°, $(\alpha)_D$ - 38.71° isolated from the reaction was devoid of bromine. The compound showed UV maximum at 245 mμ (ε ,10,500), IR peaks at 1730, 1680, 1250 cm^{-1} (Fig. 8) indicating the presence of αβ-unsaturated ketone. NMR spectrum of 69 (Fig 9) showed a peak at 5.85 ppm for the vinyl proton. This low field singlet for the vinyl proton may be ascribed to the presence of the electronegative oxygen atom at C-16. In addition to this the compound also showed peaks at 2.10 (-O.CO.CH_3) and 4.5 (-C<u>H</u>-O-CO-CH_3) ppm. The mass spectrum of the compound (Fig. 10) showed mass peak at 482. Moreover, an abundant base peak at 358 was observed. The appearance of this peak may be explained by assuming that it arises from a 16-oxo taraxeryl acetate system by the following genesis. (Chart IV).

Chart IV



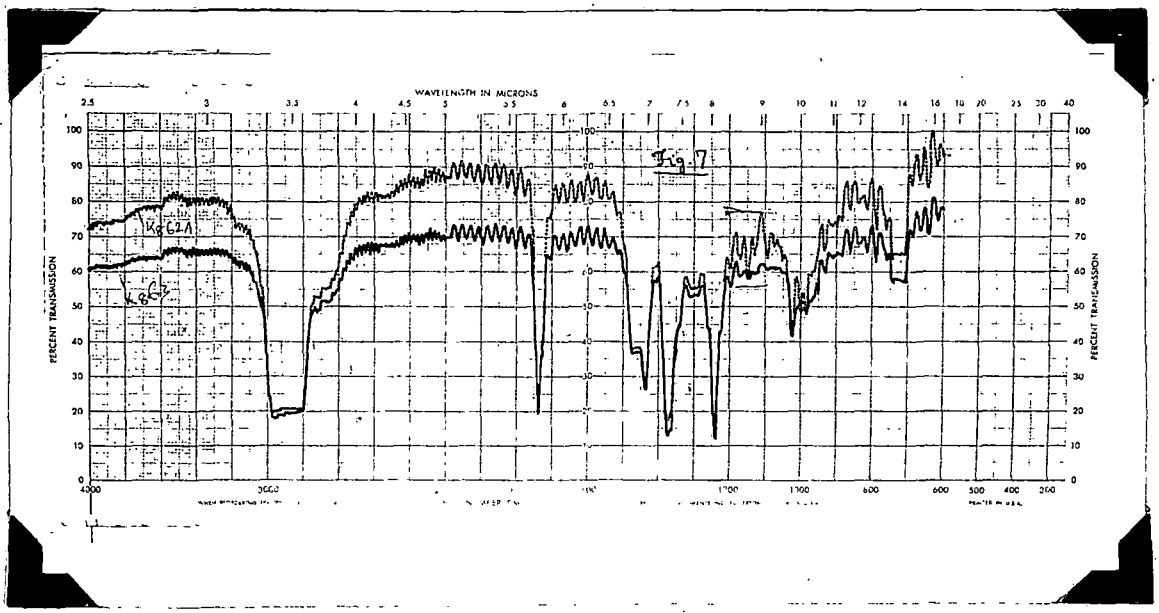


Fig. 7. IR comparison of

Olean-12,15-dien-3β-yl acetate obtained ✗ from solvolysis of 72 (dotted line)

Olean 12,15-dien-3β-yl acetate obtained from dimethyl aniline treatment of 72 (solid line)

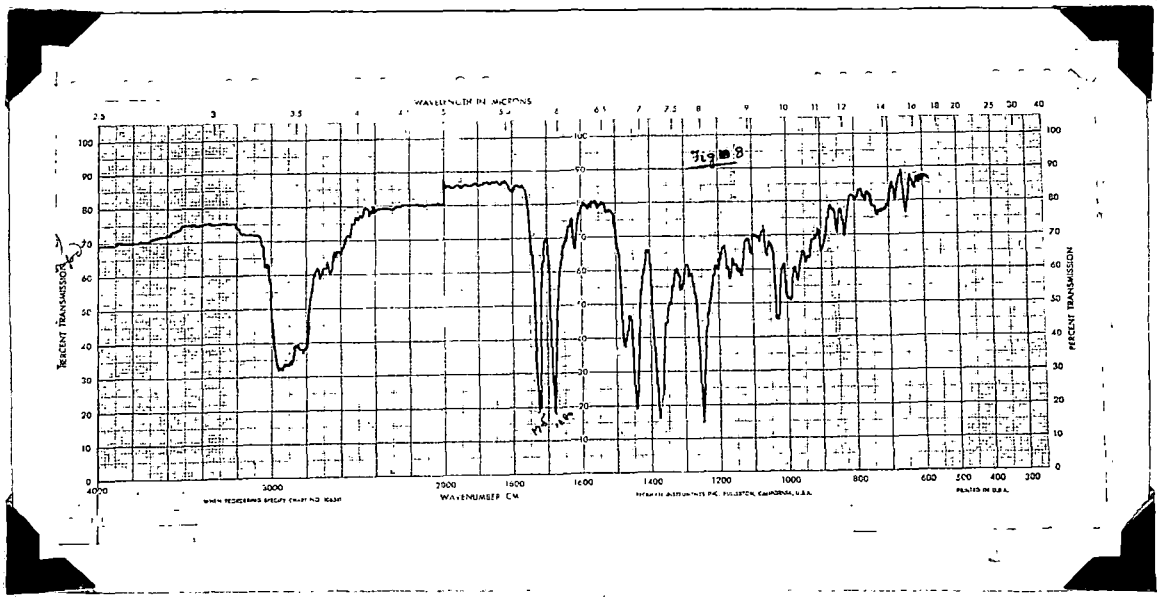


Fig.8.IR spectrum of 16-oxo taraxeryl acetate 69

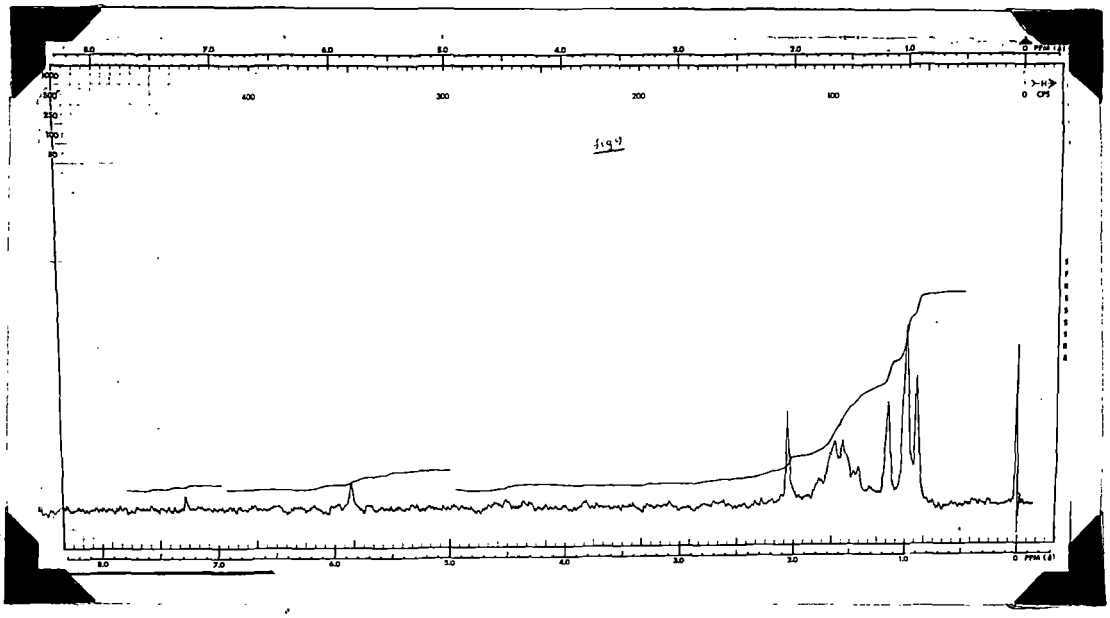


Fig. 9. NMR spectrum of 16-oxo taraxeryl acetate 69

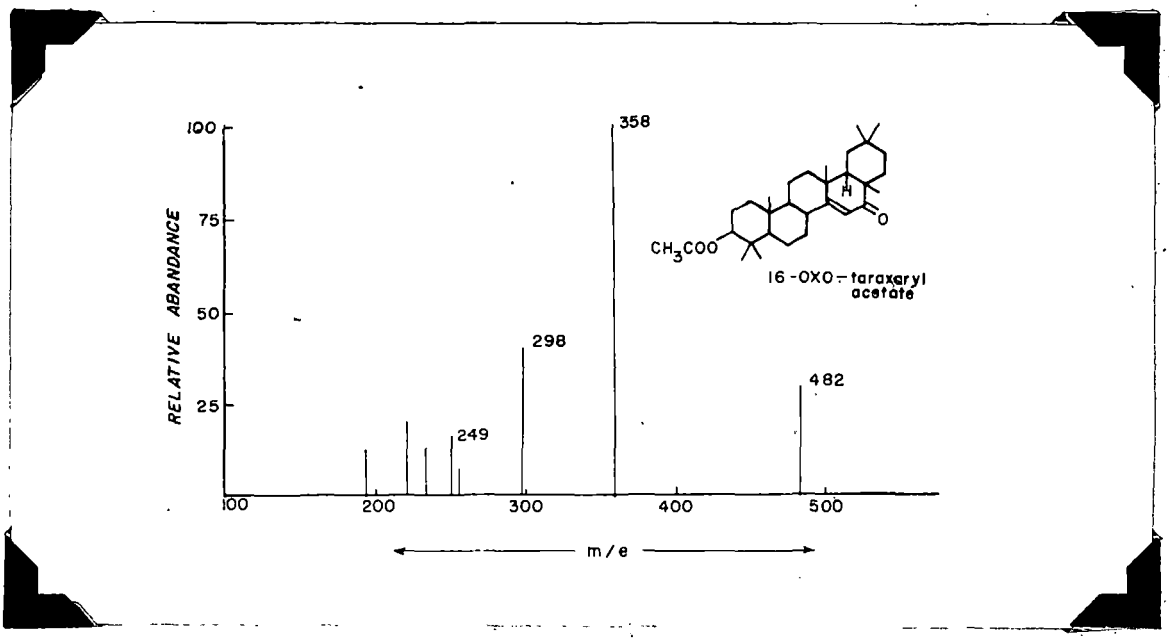


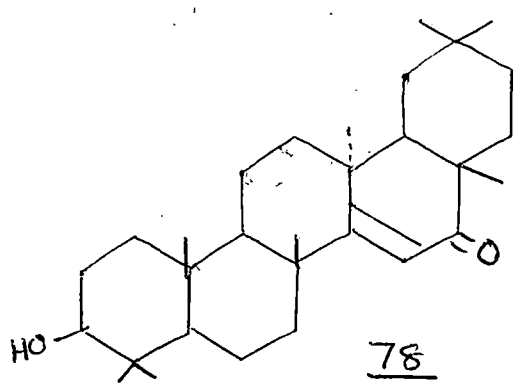
Fig. 10. Mass spectrum of 16-oxo taraxeryl acetate 69.

All the foregoing evidences led us to conclude that the product 69 was 16-oxo taraxeryl acetate although our melting point was widely different from that recorded by Finucane and Thomson[42] (m.p. 251-52° d^{42}, $(\alpha)_D$ 92°). We procured a sample of 16-oxo taraxeryl acetate, m.p. 259-60° d from Dr. Thomson which gave a positive bromine test and was different from our sample. In our hands the yield of the product never exceeded ten percent.

Further, we prepared 11-oxo-β-amyrin acetate[43] 71 from β-amyrin acetate 73 by treatment of the latter with chromium trioxide-acetic acid. The m.p., rotation and IR comparison clearly indicated that compound 69 was different from 11-oxo-β-amyrin acetate (IR comparison is shown in Fig. 11).

All these facts led us to conclude beyond doubt that our product 69, m.p. 280-2° was the correct 16-oxo taraxeryl acetate.

In order to prepare 16-hydroxy taraxeryl acetate, we attempted reduction of 69 with sodium borohydride in tetrahydrofuran and also in methanol. In both the cases, the starting material was recovered. Reduction of the carbonyl group at 16-position was also unsuccessful by Meerwein-Pondorff reduction procedure and produced 16-oxo taraxerol 78 m.p.292-3°, ν_{max}^{KBr} 3360, 1680 cm^{-1}. The same compound 78



78

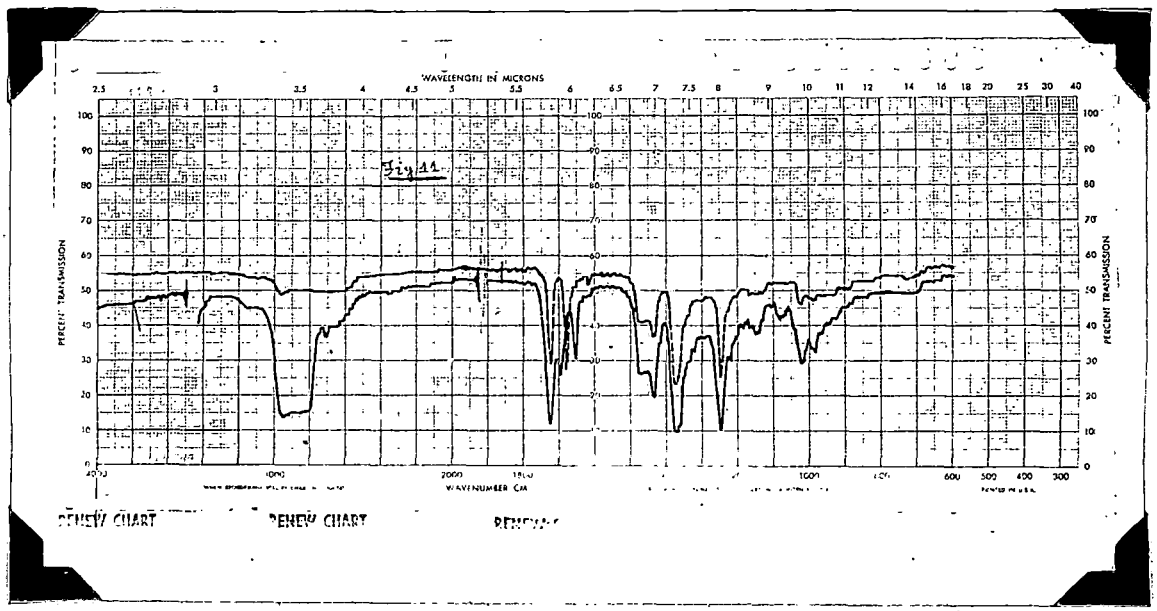


Fig. 11. IR spectra of

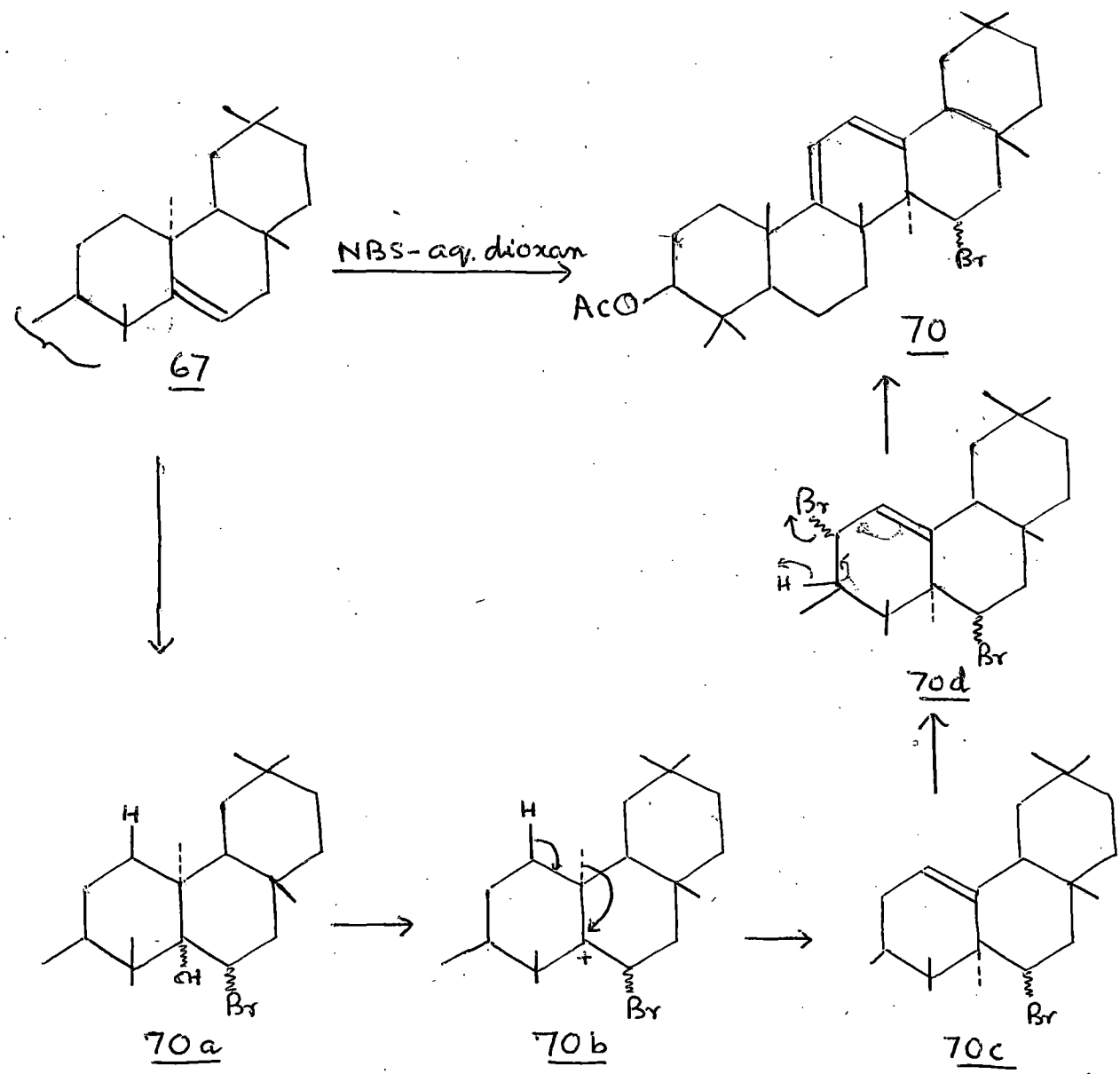
16-oxo taraxeryl acetate 69 (solid line)

11-oxo-β-amyrin acetate 71 (dotted line)

only could be isolated during reduction of 69 with lithium aluminium hydride in tetrahydrofuran solution. Acetylation of 78 with acetic anhydride pyridine gave back 16-oxo taraxeryl acetate (m.m.p. and IR comparison).

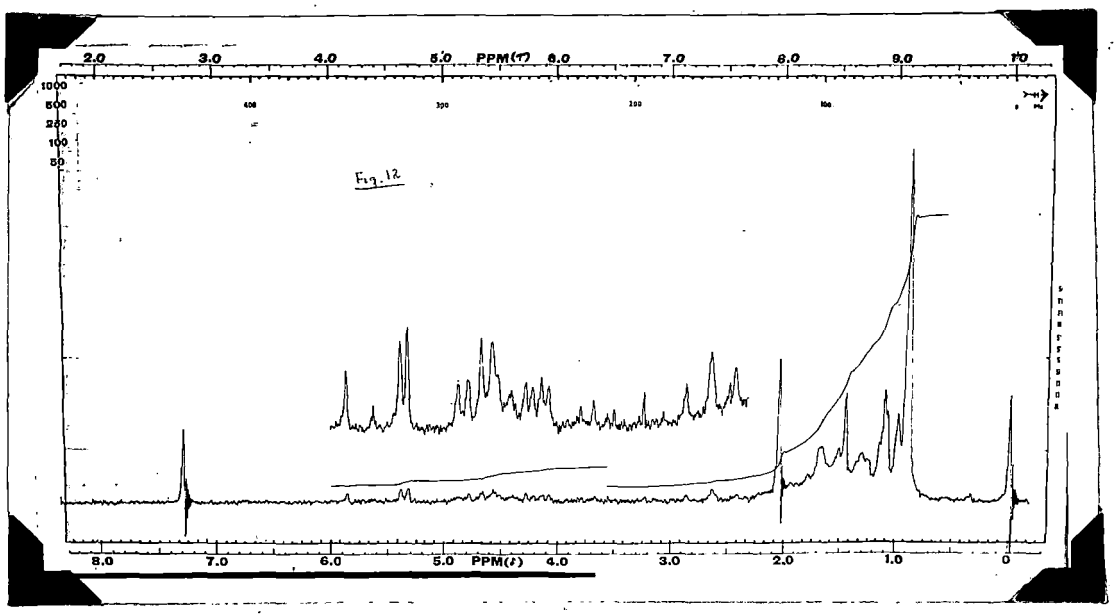
The third product, $C_{32}H_{49}O_2Br$, 70, obtained during chromatography of the mixture of products had m.p. 176-8°, $(\alpha)_D$ 249.12°, λ_{max} 276 mμ (ε, 6000) indicative of a homoannular diene. Examination of the NMR spectrum (Fig. 12) of the compound 70 showed signal at 5.34 ppm for one proton and a one proton signal at 5.85 ppm. These signals may be attributed to the protons in a homoannular diene system in which both the double bonds are trisubstituted. In addition to this the spectrum gave a sharp singlet at 2.08 ppm (-O-CO-CH_3) and a multiplet centered at 4.65 ppm for a proton attached to the carbon bearing the acetoxyl group and a multiplet centered at 4.18 ppm for the proton attached to the carbon bearing the bromine atom. On the basis of the above data the compound is assigned structure 70.

The mechanism for the formation of 70 from 67 can be explained in the following way. Most probably bromohydrin 70a is first formed which isomerises to the β-amyrin derivative 70c through the carbonium ion intermediate 70b followed by methyl migration. The intermediate 70c is further converted to the bromo compound 70d by allylic bromination which on further elimination gives 70.



67 70 70d 70a 70b 70c

The mass spectrum of the compound 70 showed a mass peak at M^+ 546 (weak), but a prominent peak was observed at 465 (m/e- HBr). Other fragments were similar to those of 15-ξ-bromo-9(11), 12-oleandiene. (Fig. 13)



Fir. 12 NMR spectrum of 15-bromo-9(11), 12 Olean-diene70

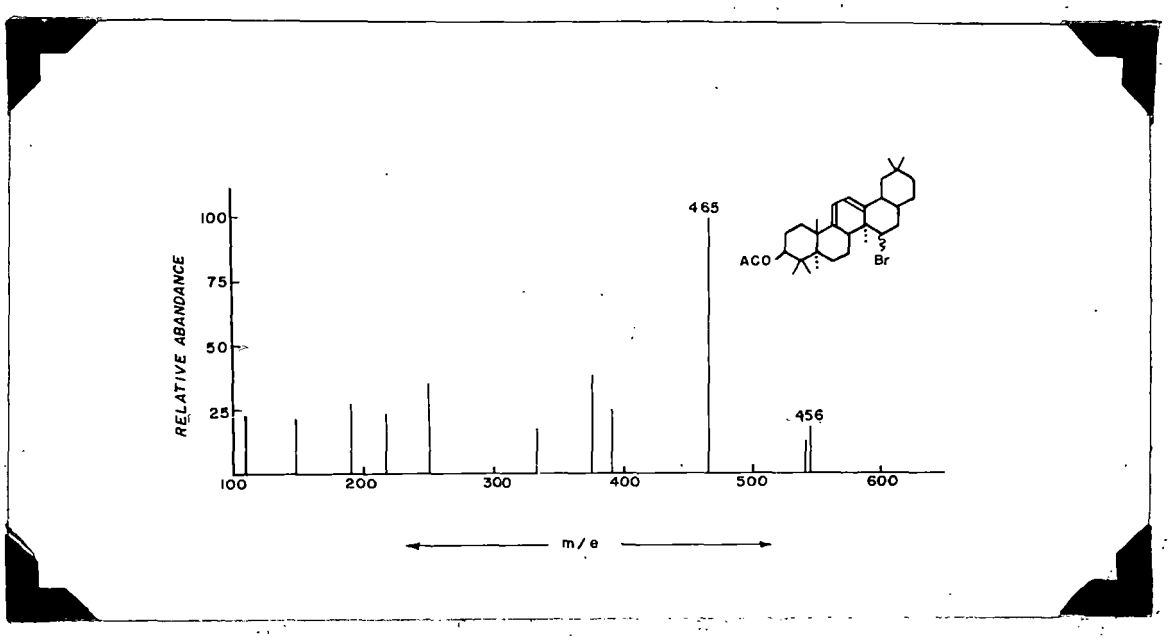


Fig. 13 Mass spectrum of 15-bromo-9(11), 12 olean-diene70

With a view to preparing 16-bromo taraxeryl acetate we studied the allylic bromination of taraxeryl acetate 67 with NBS in dry carbon tetrachloride in presence of light. The results obtained are discussed in the following lines.

When taraxeryl acetate 67 was refluxed with 2 mole equivalents of NBS in carbon tetrachloride using visible light for 3 hours, a product, $C_{32}H_{47}O_2Br$, m.p. 240°, $(\alpha)_D$ 267.53° was obtained. It showed a single spot in a chromatoplate and also gave positive test for bromine. UV spectrum showed a peak at λ_{max} 279 mμ (ϵ, 6000), indicating the presence of a homoannular diene system. IR spectrum (Fig. 14) of the compound showed peaks at 1725, 1250 (-O-CO-CH_3) and 840 (trisubstituted double bond) cm^{-1}. NMR spectrum (Fig. 15) showed the presence of three vinyl protons between 5.63 - 5.88 ppm. This can be explained by assuming that two of the vinyl protons arise due to the presence of a homoannular diene in ring C and the third vinyl proton is present in ring D. In addition to this it also showed a sharp singlet at 2.08 (-O-CO-CH_3), and a multiplet centered at 4.65 for a proton attached to the carbon bearing the acetoxyl group.

The bromine atom in ring D was resistant to reactions (i) Zn-HOAc (ii) H_2/Pd-C (iii) H_2/PtO_2 (iv) Li_2CO_3-LiBr (v) anhydrous KOAc-HOAc (vi) $C_6H_5N(CH_3)_2$. This inertness of the bromine atom in ring D can only be explained if it is assumed that the bromine atom is attached in ring D as a vinyl bromide. In conformity with the above facts we assign structure 75 to this compound. The mass spectrum of the

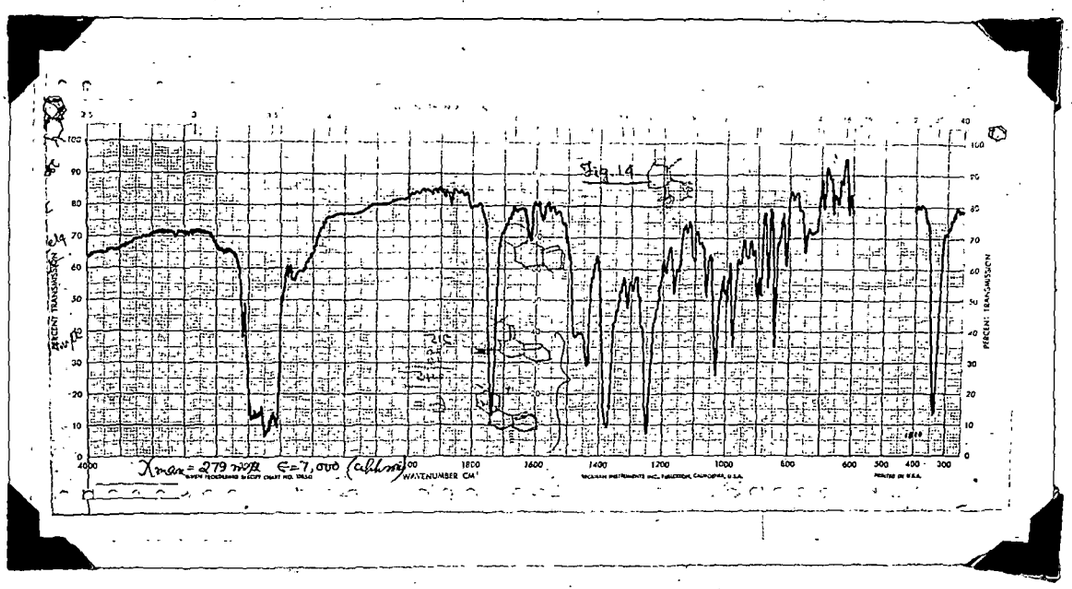


Fig. 14 IR spectrum of olean 9(11), 12,15 trien-3β -yl acetate 75

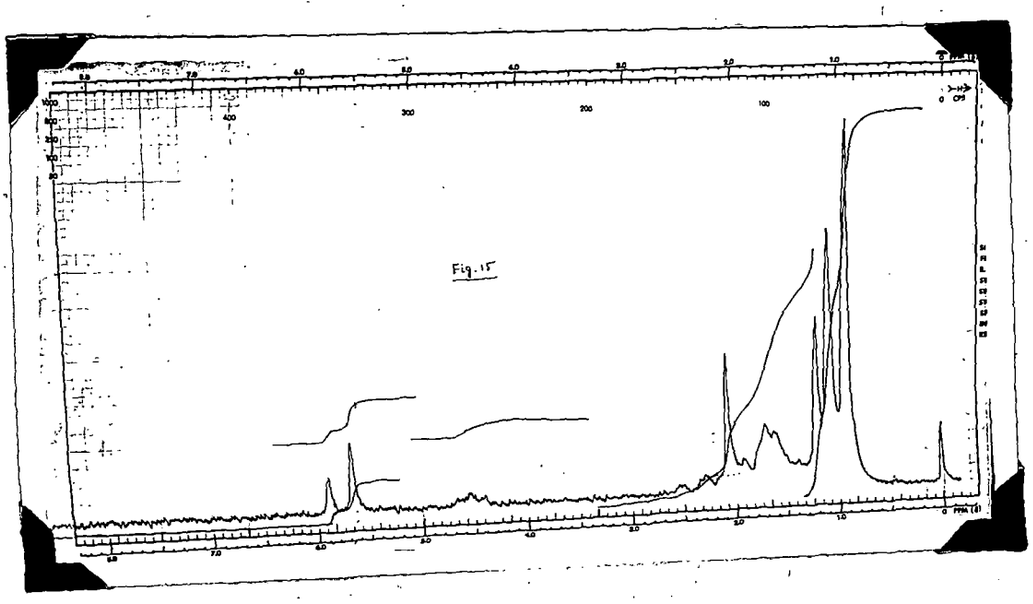
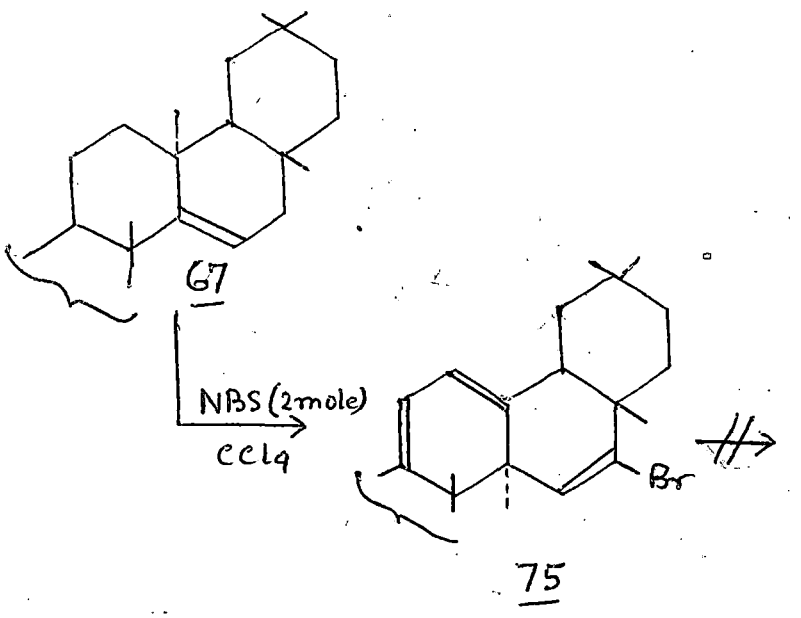


Fig. 15 NMR spectrum of olean, 9(11), 12,15 trien-3β-yl-acetate 75

compound 75 showed the mass peak (strong) at M^+ 542, (544 isotope). The intensity of the peak due to m/e 542 was greater compared to the molecular ion peak at m/e 543 showing that an allylic proton is probably lost initially from the molecular ion to give a peak at m/e 542. (Fig. 16) In another run of the same experiment we isolated the same compound 75 and its mass spectrum (Fig. 17) however, showed a weak peak around the region M 620 - 25 (it was not possible to count) in addition to peaks shown in Figure 16, which indicated that a small contaminant of a dibromo compound was present. This observation gave us a clue to the mechanism of the formation of allylic monobromo compound 75.



Most probably at first allylic 16-dibromo compound 75a is formed which immediately undergoes allylic rearrangement as shown in Chart V below

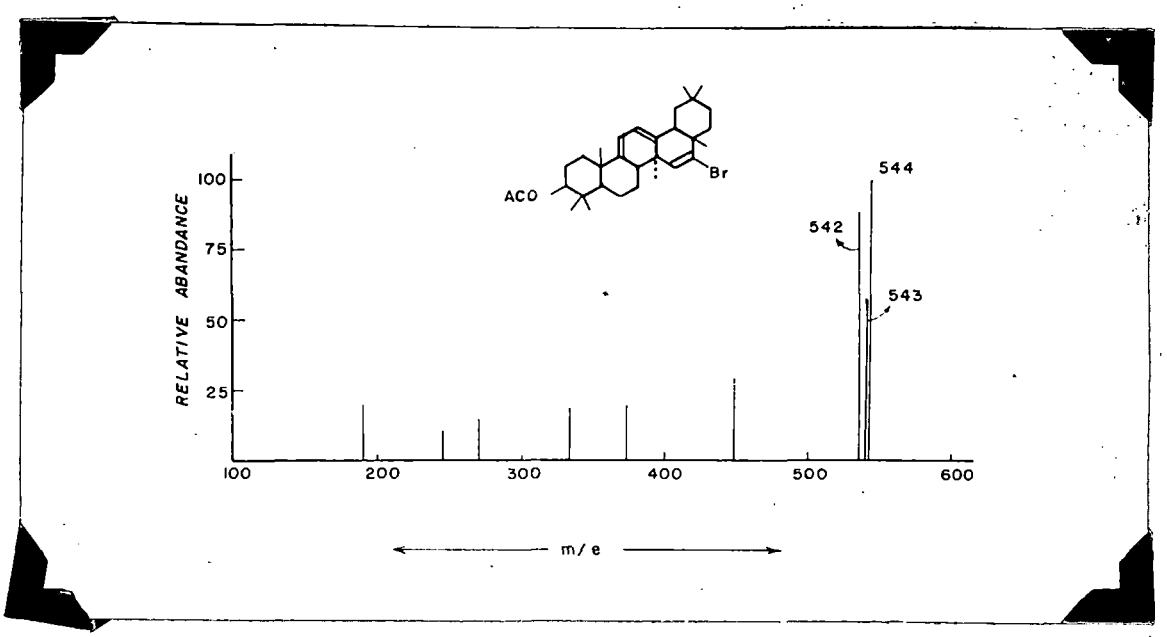


Fig. 16. Mass spectrum of olean-9(11), 12,15-trien 3 β-yl acetate 75

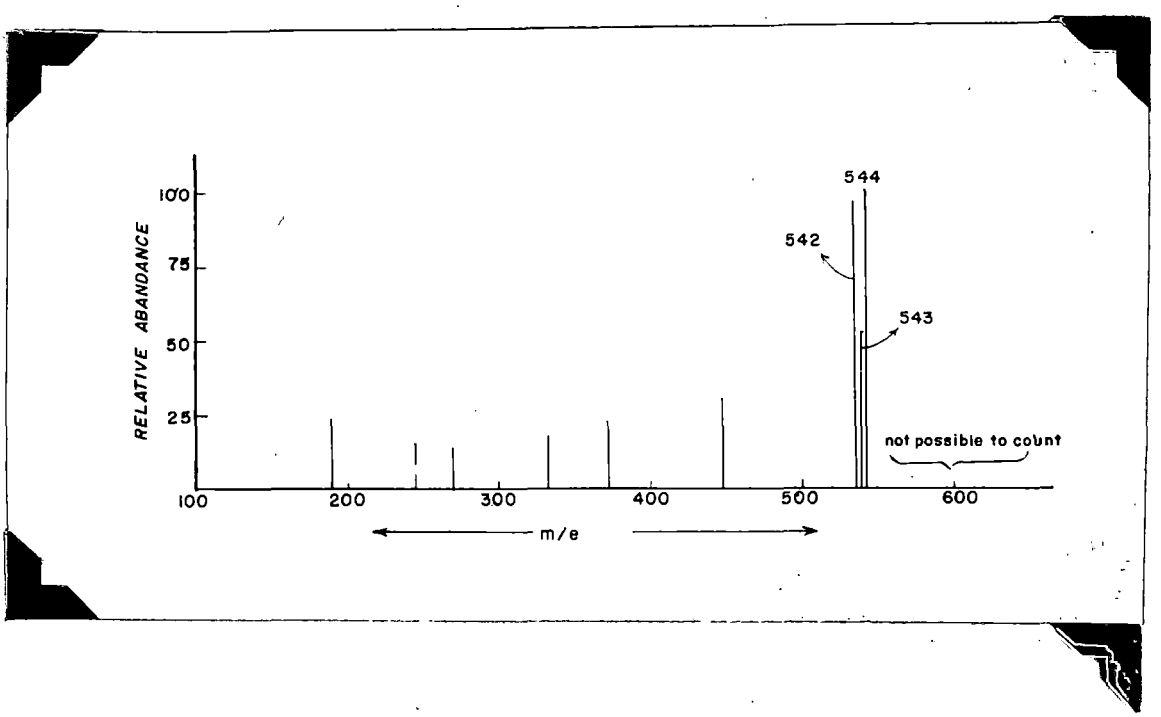
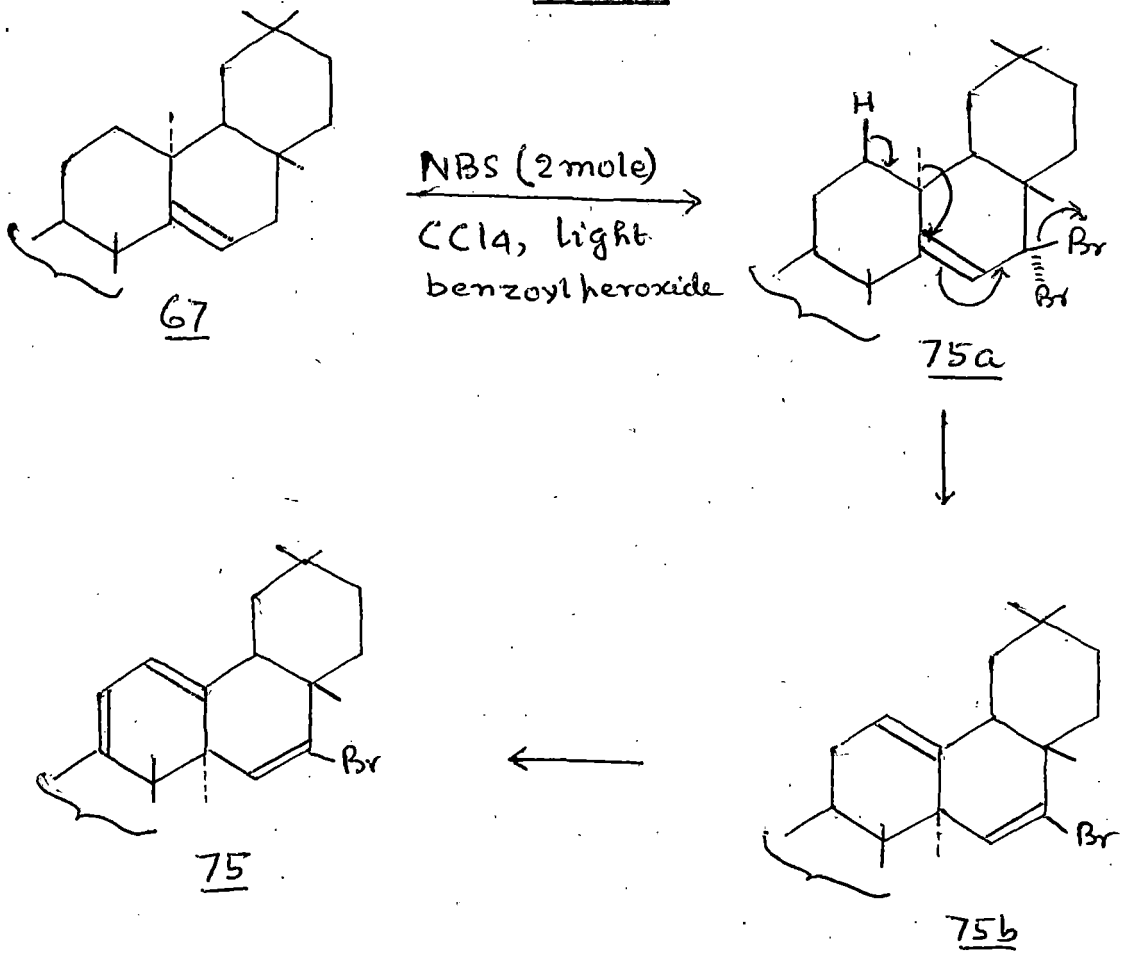


Fig. 17. Mass spectrum of 75 (second run)

to give predominantly the monobromo compound 75b which on allylic bromination at C-11 and subsequent elimination of HBr gives 75

Chart V

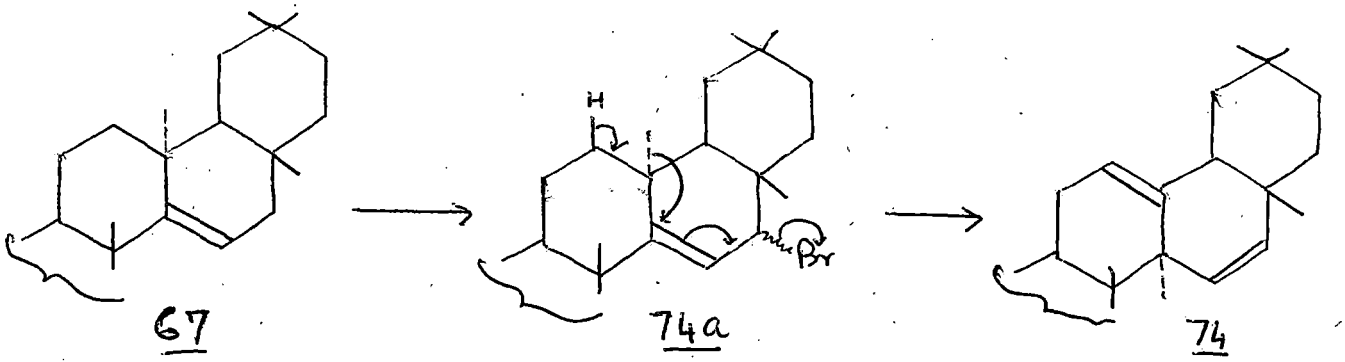


67 75a 75b 75

When the same reaction was carried out with 1 mole equivalent of NBS, it afforded a halogen free product, $C_{32}H_{50}O_2$, m.p. 196-9°, $(\alpha)_D$ 41.86° and was found to be identical with 74 by m.m.p. and IR comparison. The formation of this compound from taraxeryl acetate can also be explained by the same mechanism as depicted in Chart VI.

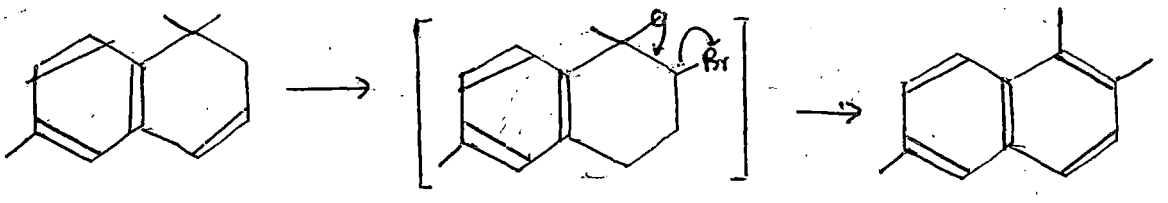
Most probably allylic monobromo compound 74a is first formed which undergoes allylic rearrangement followed by methyl migration as shown below:

Chart-VI



67 74a 74

Barnes and co-workers[46] have shown that treatment of 1,1,6-trimethyl-1-2-dihydronapthalene 75 with NBS gave an allylic bromide which aromatized to 1,2,6-trimethyl napthalene 76 by silver ion or heat (temperature of refluxing carbon tetrachloride).



75 76