CHAPTER - VII

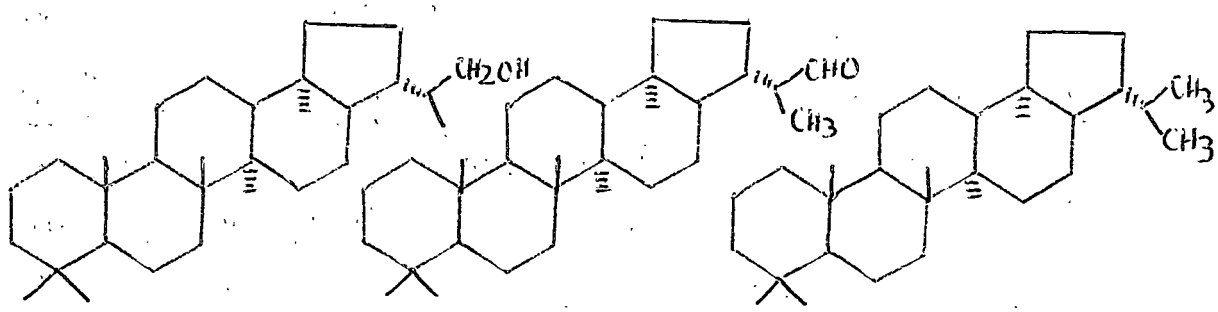
Some new observations in the (i) CrO_3-Pyridine oxidation of nerifoliol 19 , and (ii) in the attempted preparation of the tosyl derivative of nerifoliol :

Section A : CrO_3 - Pyridine oxidation of nerifoliol :

Mitra et al[26] converted nerifoliol 19 to the corresponding aldehyde nerifolial by sarret oxidation and recorded its m.p. as 76°, [redacted]. They reduced this aldehyde by Wolff-Kishner reduction and obtained a hydrocarbon, m.p. 190-92°, $(\alpha)_D$ +36° (m.m.p.) which they reported was same as hopane but did not establish its identity by comparison with an authentic sample. We, therefore, attempted to repeat their above reaction in order to obtain hopane and compare it with an authentic specimen of hopane.

Sarret oxidation of nerifoliol with hydrated CrO_3 - Pyridine complex was performed and the product obtained was found by TLC to consist of two compounds. Careful chromato - graphy of this mixture over alumina followed by crystallisation from a mixture of chloroform and methanol resulted in the isolation of a compound, m.p. 228-32°. TLC of the compound was carried out and the Rf value (0.46 ; Benzene - Petrol 9:11) was found to be identical with that of an authentic sample of

isoadiantone. Mixed melting point of the compound with an authentic sample supplied by Prof. Berti also showed no depression. The residue from the mother liquor of the above compound was again chromatographed over alumina. The solid eluted from different fractions on TLC examination showed the presence of adiantone and isoadiantone having same melting point and Rf values with their respective authentic specimen. In this reaction we failed to obtain any aldehyde nerifolial, having, m.p. 76° described by Mitra et al[26]. Moffatt[49] oxidation on nerifoliol was attempted several times but we failed to isolate the desired aldehyde, the original alcohol being recovered each time. We next tried CrO_3 - Pyridine oxidation with anhydrous CrO_3 - Pyridine complex according to the method described by Ratcliffe and Rodehorst[50]. The product from this oxidation was a single compound (TLC) which on chromatography followed by crystallisation afforded crystals m.p. 205-6°, ν_{max}^{nujol} 2720, 1730 cm^{-1} (Fig - 34), M^+ 426 (Fig - 35). NMR spectrum of the compound (Fig - 36) showed a peak chracteristic of the aldehydic proton at δ9.65. Elemental analysis corresponded to the formula $C_{30}H_{50}O$. It is significant to note here that all these data are consistent with the sturcture of nerifolial 43. Wolff-Kishner reduction of the aldehyde gave hopane 44 m.p. 218-19° identical with an authentic sample (IR Fig - 37).



42 43 44

The above observations concerning the products of the chromic acid reaction under different conditions suggest that the reaction proceeds by different mechanisms. In the Sarret oxidation with the hydrated complex obviously cleavage and oxidation takes place, but in the absence of kinetic and other data it is not possible to put forward any mechanism at this stage. This reaction is, however being studied in these laboratories in more detail. The product of oxidation by anhydrous CrO_3 - Pyridine - methylene chloride being an aldehyde only, it appears that, in this case normal oxidation[51] takes place.

Studies of the mechanisms of oxidations with chromium compounds[51] have been complicated by the fact that each stage in the oxidation of most organic compounds is accompanied by the net transfer of two electrons although the oxidising agents normally accept a total of three or five electrons. It is

therefore evident that intermediate valence states of chromium are important in the overall process. The problem is well illustrated by the oxidation of a secondary alcohol with a hexavalent chromium compound, one of the many possible reaction schemes for which is presented in the accompanying equations

$$Cr^{VI} + R_2 CHOH \longrightarrow R_2 C = O + 2H^+ + Cr^{IV}$$

$$Cr^{IV} + Cr^{VI} \longrightarrow 2\ Cr^{V}$$

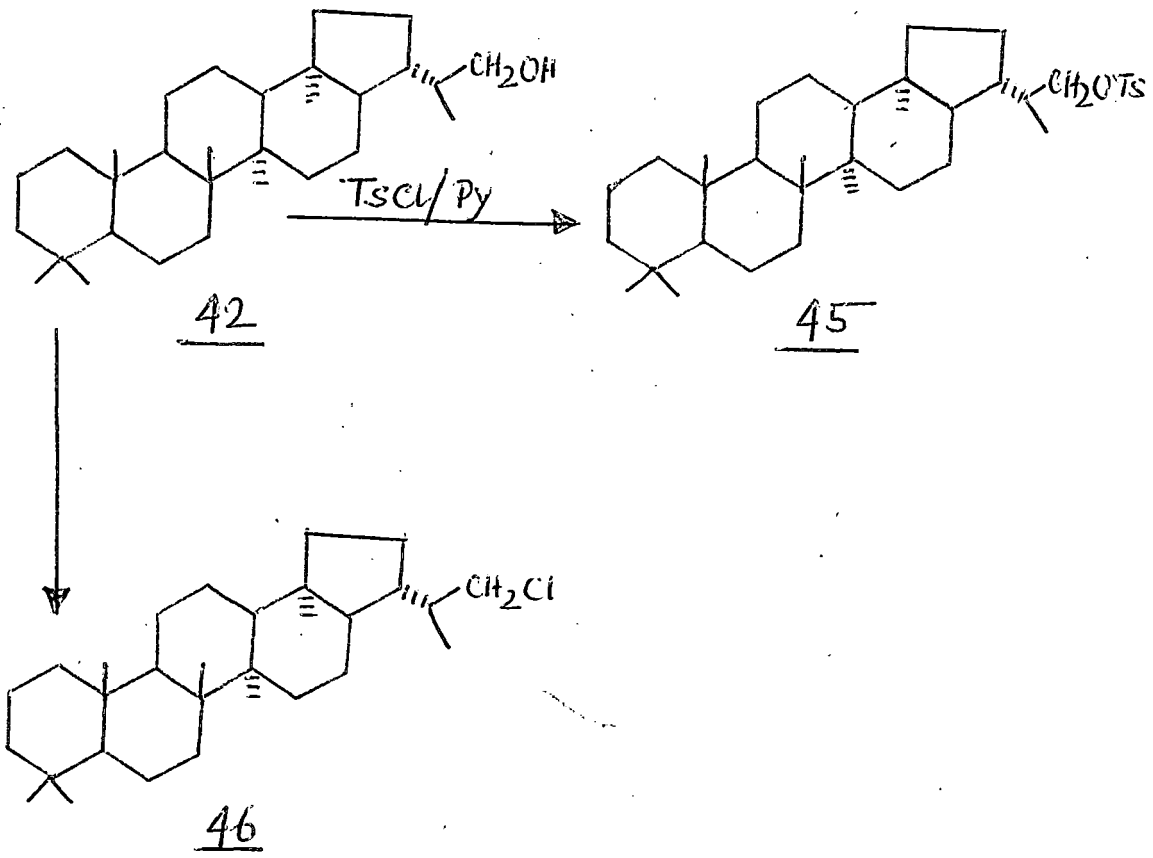
$$Cr^{V} + R_2 CHOH \longrightarrow R_2 C O + 2\ H^+ + Cr^{III}$$

Both the Cr^{V} and the Cr^{IV} species appear to be more powerful oxidising agents[51] than Cr^{VI}. It is evident from the equations that these intermediate valence states may be responsible for as much as two -thirds of the total oxidation and in some cases may lead to unwanted side reactions such as carbon-carbon bond cleavage[52].

Section B : Attempted preparation of Nerifoliol tosylate : Isolation of Nerifoliol chloride :

We had also planned to prepare nerifoliol tosylate 45 by the usual procedure with purified p-toluene sulfonyl chloride and pyridine at room temperature and then convert the tosylate to hopane by LAH reduction. But in our attempt to prepare the tosylate 45 by the usual procedure with highly purified

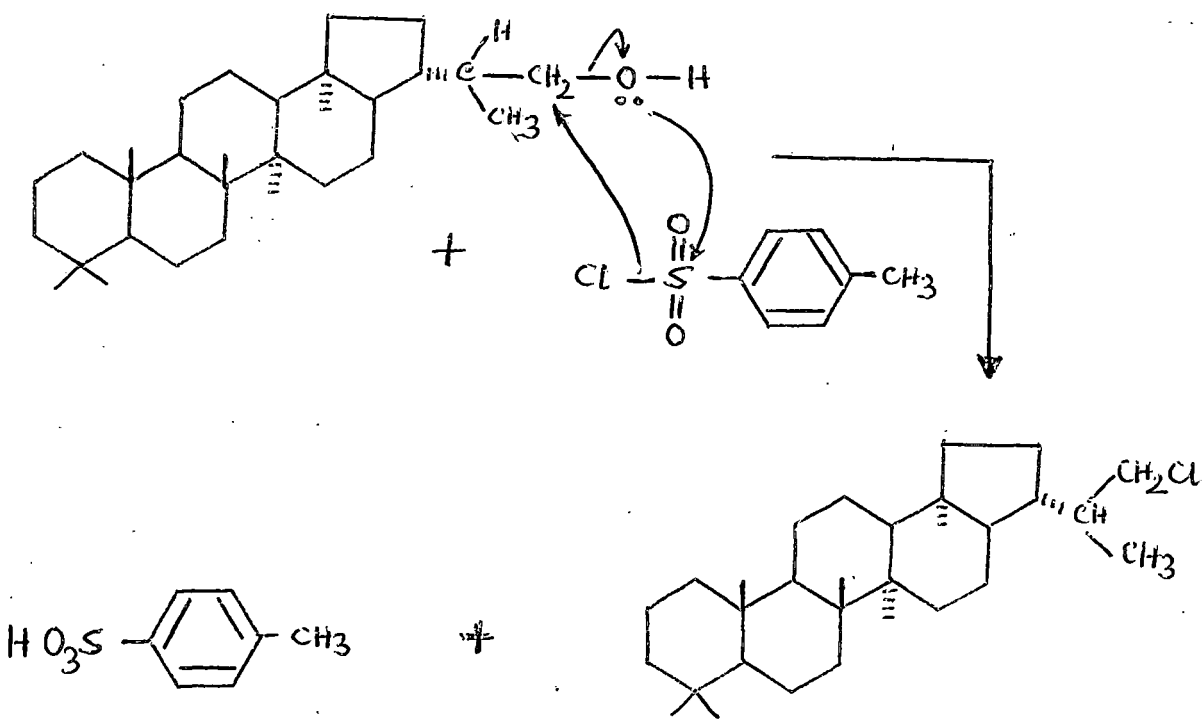
p - toluene sulfonyl chloride and pyridine we failed to isolate the desired tosylate but instead obtained a compound, m.p. 221-22° which gave a positive test for halogen. Elemental analysis



corresponded to the molecular formula giving correct analysis for the presence of one chlorine atom (see experimental). NMR spectrum (Fig-38) of the compound showed peak at δ 3.55.

which are closely in conformity with the structure 46. The The mass spectrum (Fig-39) of the compound showed peaks at m/e M^+ 446(M+), 431, 369, 227, 226, 225, 191, 149 which again confirms the assigned structure.

In the above reactions we see that the normal reaction is retarded and instead a different reaction takes place giving a product by substitution with a chloride ion. The most probable mechanism for the reaction may be depicted as shown below.



The reason for this retardation of the reaction may be due to steric factors. Construction of the model for Nerefoliol shows

that in the formation of the tosyl derivative severe steric interactions result - which in all probability diverts the reaction to a substitution reaction by frontal attack as shown in the mechanism above. We are, however studying the reaction with different substrates of similar nature and the results will be reported in a future communication. At the present moment, no definite conclusions can be drawn for this reaction behaviour. The mechanism, shown above, however, seems reasonable.

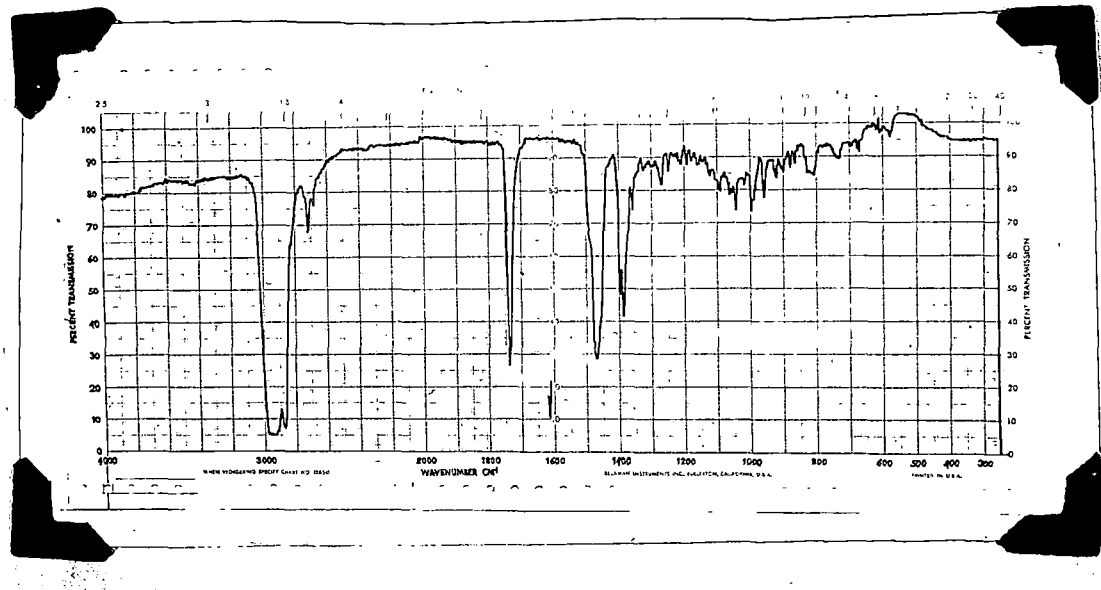


Fig. 34 : IR spectrum of nerifolial 43

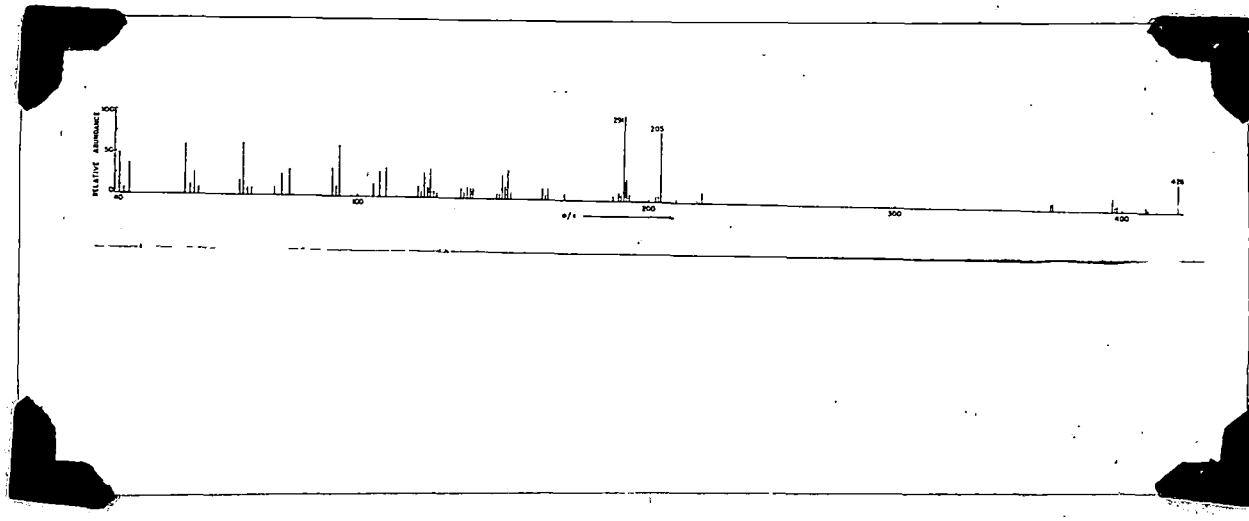


Fig. 35 : Mass spectrum of nerifolial 43

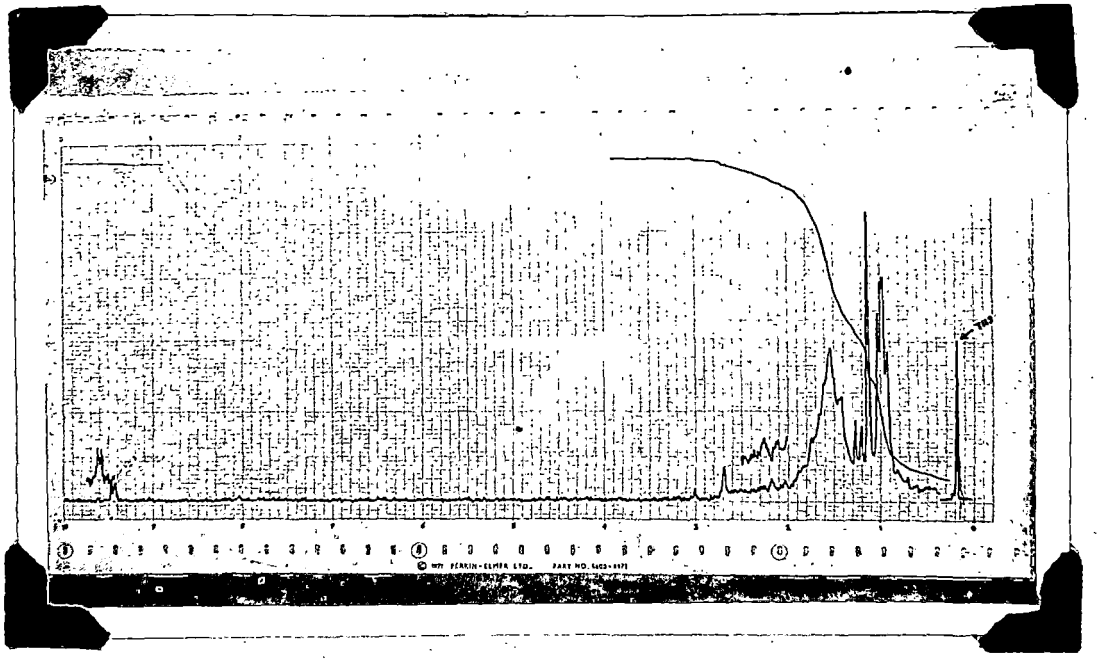


Fig. 36 : NMR spectrum of nerifolial 43

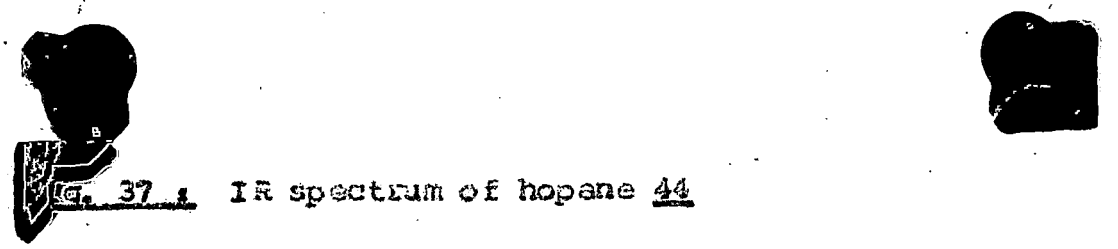
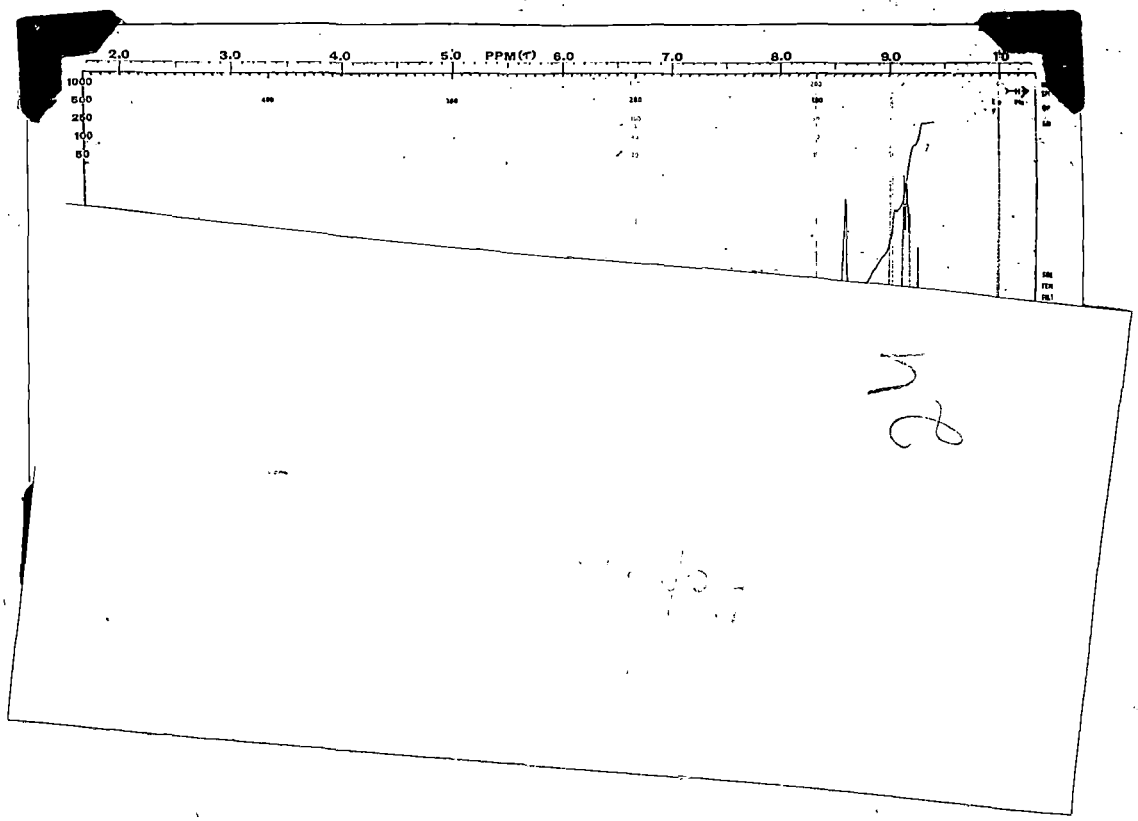


Fig. 37 : IR spectrum of hopane 44



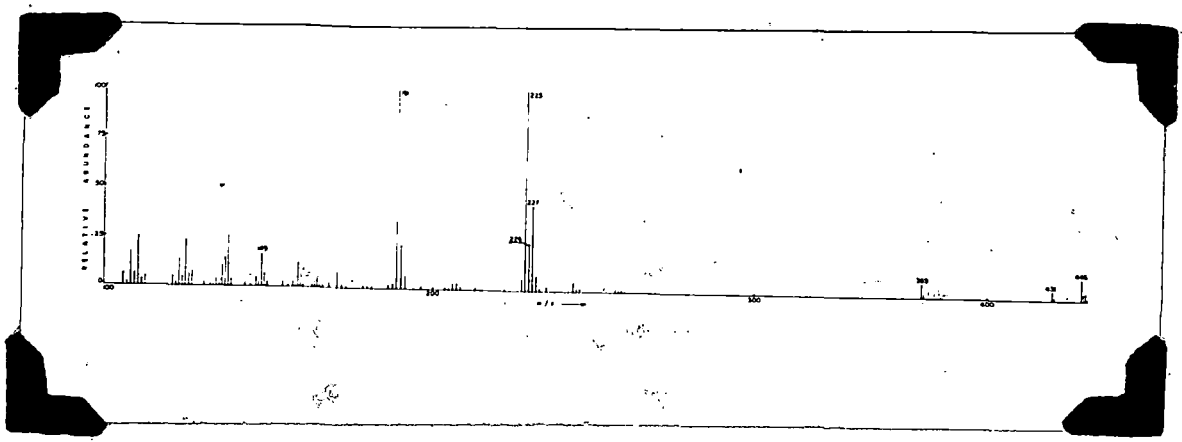


Fig 39 : Mass spectrum of the chloride 46

EXPERIMENTAL

Acetylation of nerifoliol 19 : Preparation of nerifoliol acetate 20 :

The alcohol 19 (200 mg) was treated with acetic anhydride (4ml) and pyridine (4ml) and kept overnight at room temperature. After working up in the usual manner the crude acetate (190 mg) was obtained. This product dissolved in benzene (3 ml) was placed over a column of alumina (15 gm, deactivated with 0.6 ml of 10% aqueous acetic acid) developed with petroleum and was eluted with the following solvents (Table - XX).

Table - XX

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum	1 - 5	Solid (180 mg) m.p. 192-4°.

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

Fractions 1 - 5 (180 mg) were combined and on crystallisation from a mixture of chloroform and methanol furnished nerifoliol acetate 20, m.p. 195-96°.

Found : C, 81.69; H, 11.50%

Calculated for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56%

IR : Fig - 2

Chromic acid - pyridine oxidation of nerifoliol 19 : Preparation of adiantone and iso-adiantone :

Nerifoliol 19 (200 mg) was oxidised with CrO_3 - Py complex prepared from pyridine (2 ml) and CrO_3 (200 mg) at 15°C. Excess CrO_3 was destroyed by adding 15 ml methanol, diluted with ethyl acetate and filtered. Ethyl acetate was removed, the concentrate was taken up in ether. The ether solution was washed with 5% hydrochloric acid solution, then with water until neutral and dried (Na_2SO_4). Removal of ether gave a gummy residue. It showed two spots in TLC examination. The residue (160 mg) dissolved in benzene (3 ml) was placed over a column of alumina (15 gm, deactivated with 0.6 ml of 10% aqueous acetic acid) developed with petroleum and was eluted with the following solvents. (Table XXI).

Table - XXI

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum	1 - 2	Solid, m.p. 192-94° (trace)
Petroleum :	3 - 4	Solid, m.p. 225-30°

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

Fractions 1-2 were combined and on crystallisation from a mixture of chloroform and methanol furnished [redacted] crystals of m.p. 193-95°. This could not be investigated further for want of sufficient material.

Fractions 3 - 4 were combined and on crystallisation gave crystals, m.p. 230-32°. This compound was identified as isoadiantone (IR and co - TLC). The mother liquor from isoadiantone on rechromatography and subsequent TLC examination showed the presence of adiantone.

Attempted oxidation of nerifoliol 19 according to the method of Moffatt et al[49]:

Nerifoliol 19 (300 mg) was added to DMSO (2.5 ml) and benzene (2.5 ml) containing DCC (0.5 gm), pyridine (0.6 ml) and the solution was kept overnight. Benzene (50 ml) was added and

filtered. The benzene solution was extracted with water, dried (Na_2SO_4) and evaporated. The residue (27 mg) on chromatography over silicagel (20 gm) and subsequent crystallisation of the solid (eluate - C_6H_6) from a mixture of chloroform and methanol furnished fine needle-shaped crystals, m.p. 244-46°. This compound was found to be identical with the starting material (m. m.p.)

Oxidation of nerifolil 19 in anhydrous condition ; Preparation of nerifolial 43 :

Dried chromium trioxide powder (0.6 gm) was added to a magnetically stirred solution of pyridine (0.95 gm) and anhydrous methylene chloride (15 ml). The flask was stoppered with a drying tube containing drierite, and the deep burgandy solution was stirred for 15 minute at room temperature. At the end of this period, a solution of the alcohol (0.426 gm, 1 m mol) in a small volume of methylene chloride was added in one portion. A tary, black deposit separated immediately. After stirring an additional 15 minute at room temperature, the solution was decanted from the residue, which was washed with 100 ml of ether. The combined organic solution was washed with three 50 ml portions of 5% aqueous sodium hydroxide solution, 50 ml of 5% aqueous HCl, 50 ml of 5% aq. sodium bicarbonate solution, 50ml of saturated aq. sodium chloride solution, and was dried over anhydrous sodium sulphate. Evaporation of the solvent at redueced pressure afforded a gummy residue (390 mg)

This product dissolved in benzene (5 ml) was placed over a column of alumina (25 gm, deactivated with 1 ml of a 10% aqueous acetic acid) and was eluted with the following solvents (Table - XXII)

Table - XXII

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum	1 - 3	Nil
Petroleum : benzene (4:1)	4 - 11	Solid, m.p. 202-4°.

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

Fractions 4-11 were combined and on crystallisation from a mixture of chloroform and methanol furnished colourless needles of aldehyde - nerifolial 43, m.p. 205-6°.

Found : C, 84.41; H, 11.85%

Calculated for $C_{30}H_{50}O$: C, 84.44; H, 11.81%

IR : 2720, 1730 cm^{-1} Fig - 34

NMR spectrum (90 MHz) : 9.65 (doublet, - C H O) Fig - 36

Mass spectrum : M^+ 426 Fig - 35

Wolff - Kishner reduction[37] of nerifolial 43 :

Preparation of hopane 44 :

Nerifolial 43 (200 mg) in diethylene glycol (30 ml) was refluxed with hydrazine hydrate (2.3 ml) for 30 minutes. After addition of KOH (200 mg) the mixture was further refluxed for one hour. The condenser was removed and the mixture was heated to 190°. After refluxing for another 2½ hours the reaction mixture was cooled, diluted with water when a solid separated out. The aqueous solution after usual working up gave a solid residue (180 mg). This product dissolved in petroleum was placed over a column of active alumina (15 gm) developed with petroleum and eluted with the following solvents (Table - XXIII).

Table - XXIII

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum	1 - 3	Solid, 216 - 18° 160 mg

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

Fractions 1 - 3 were combined and on crystallisation from a mixture of chloroform and methanol furnished fine needle - shaped crystals 44, m.p. 218-19°. This compound was found to be identical with an authentic sample of hopane (m.m.p. and identical IR).

Found : C, 87.43; H, 12.67%

Calculated for $C_{30}H_{52}$: C, 87.30; H, 12.70%

IR : Fig - 37

Attempted tosylation of nerifoliol 42 :

Formation of Nerifoliol chloride 46 :

To nerifoliol 19 (200 mg) dissolved in pyridine (10 ml) was added p-toluene sulfonyl chloride (200 mg; purified by crystallisation) and heated on a water bath for 3-hours. The reaction mixture after usual working up and subsequent crystallisation from a mixture of chloroform and methanol furnished fine crystals 46, m.p. 221-22°. Elemental analysis corresponds to the presence of one chlorine atom. This compound gave positive test for halogen.

Found : C, 80.70; H, 11.44%

Calculated for $C_{30}H_{51}Cl$: C, 80.62; H, 11.42%

NMR spectrum : δ 3.55 Fig - 38

Mass spectrum : M^+ 446 Fig - 39

Attempted dehydration of nerifoliol 19 :

To nerifoliol 19 (200 mg) dissolved in pyridine (10 ml) was added $POCl_3$ (5 ml). The reaction mixture was heated on water bath for 5 minutes and kept overnight at room temperature. This mixture after usual working up gave a solid residue (180 mg) which was subjected to chromatography over alumina (15 gm, deactivated with 0.6 ml of 10% aqueous acetic acid) developed with petroleum and eluted with the following solvents (Table-XXIV)

Table - XXIV

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum	1 - 3	Solid, m.p. 220-22° (175 mg)

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

Fractions 1 - 3 were combined and on crystallisation from a mixture of chloroform and methanol gave crystals, m.p. 221-22° which was found to be identical with the chloride 46 (m.m.p) IR, NMR and mass spectrum).

Attempted hydrogenolysis of the chloride 46 :

The chloride 46 (200 mg) dissolved in ethyl acetate (25ml) was shaken in an atmosphere of hydrogen in presence of Adam's catalyst. The reaction mixture after usual working up gave a solid residue (180 mg) which on subsequent crystallisation from a mixture of chloroform and methanol furnished colourless crystals, m.p. 221-22°, which was again found to be identical with the starting material (m.m.p.)

Attempted dehydrohalogenation of the chloride 46 with potassium hydroxide.

The chloride 46 (200 mg) was added to 10% methanolic KOH (10 ml) and refluxed for 7 hours. The reaction mixture after usual work up gave a solid residue (185 mg) which on crystallisation from a mixture of chloroform and methanol furnished crystals, m.p. 221-22°. This compound was found to be identical with the starting material (m.m.p.)

Attempted conversion of the chloride 46 to the corresponding iodide :

The chloride 46 (200 mg) dissolved in acetone (20 ml) was treated with NaI (200 mg) and refluxed on a water bath for 7 - hours. The reaction mixture after usual working up gave a solid residue (180 mg) which on crystallisation from a mixture of chloroform and methanol furnished crystals, m.p. 221-22°, identical with the starting material (m.m.p.).

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