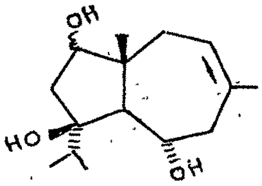
CHAPTER II

Structure and Stereochemistry of Jaeschkeanatriol

STRUCTURE AND STEREOCHEMISTRY OF JAESCHKEANATRIOL

Sukh Dev et al.[1] have reported the isolation of a sesquiterpene alcohol, jaeschkeanadiol from the roots of Ferula jaeschkeana Vatke. We have isolated three more sesquiterpene alcohols from the same plant. The isolation of these sesquiterpenes has been described in the experimental section of this chapter. The present chapter describes, in detail, the evidence leading to the stereostructure of jaeschkeanatriol, the second major component of Ferula jaeschkeana, as 1.



(1)

Jaeschkeanatriol: Structure

Jaeschkeanatriol, m.p. 164-65°, $[\alpha]_D$+20° analyses for $C_{15}H_{26}O_3$ (M^+-H_2O at m/e 236). Its IR spectrum (Fig. I) shows a strong OH absorption (3300, 1080, 975 cm^{-1}). Its PMR (Fig. II) reveals the following structural features: one -C-Me(3H, s, 0.95 ppm), $-CHMe_2$(6H, a pair of doublets centered at 0.91 and 0.95 ppm, J=7Hz each), -C=CMe(3H, s, 1.8 ppm), two CHOH(1H each, m, at 3.42 and 4.02 ppm) and -C=CH(1H, m, 5.46 ppm). By D-exchange (PMR), presence of three hydroxyls is inferred and, this information coupled with the earlier data clearly indicate that the compound must be a triol with two secondary and one tertiary hydroxyls.

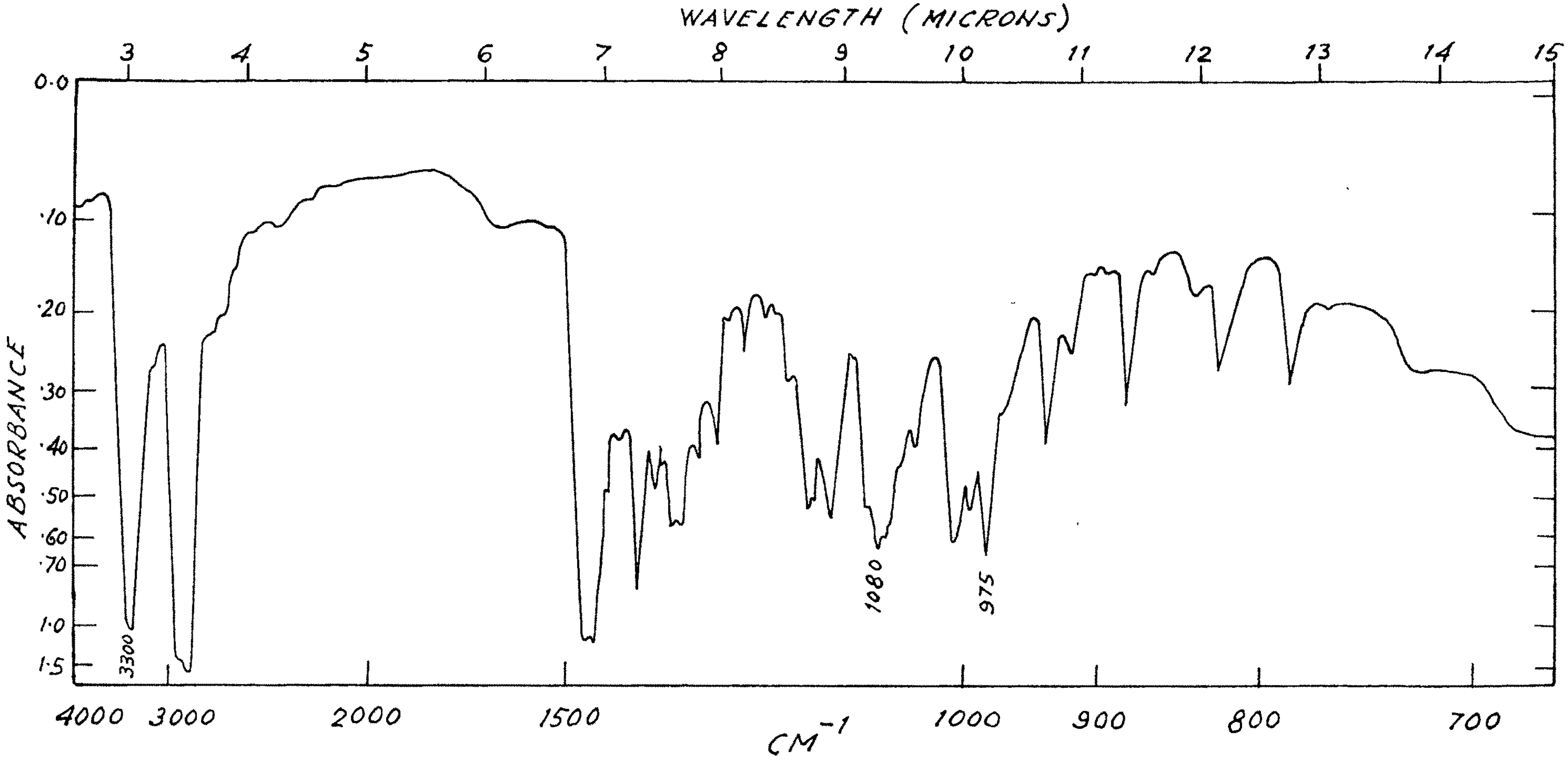


FIG. I. IR SPECTRUM OF JAESCHKEANATRIOL

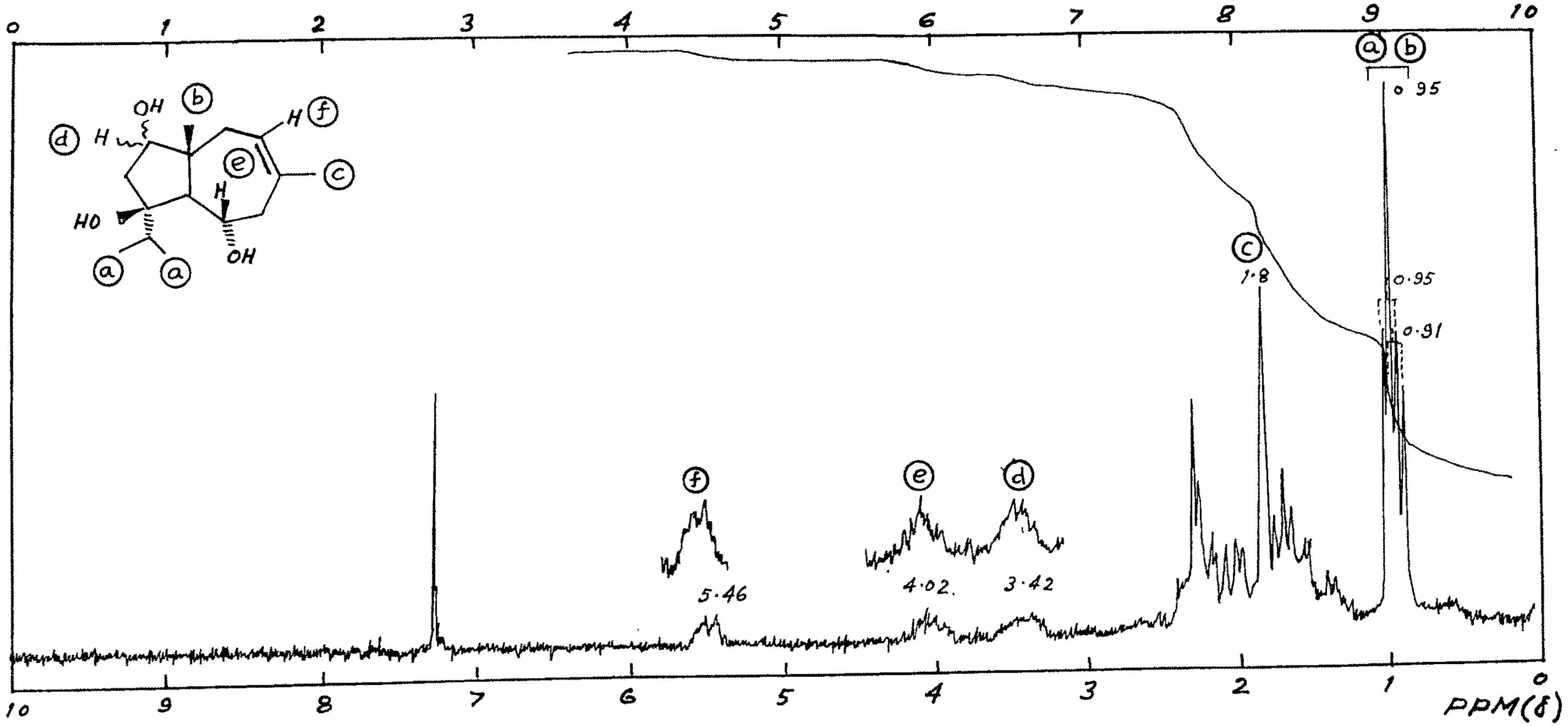


FIG. II. PMR SPECTRUM OF JAESCHKEANATRIOL

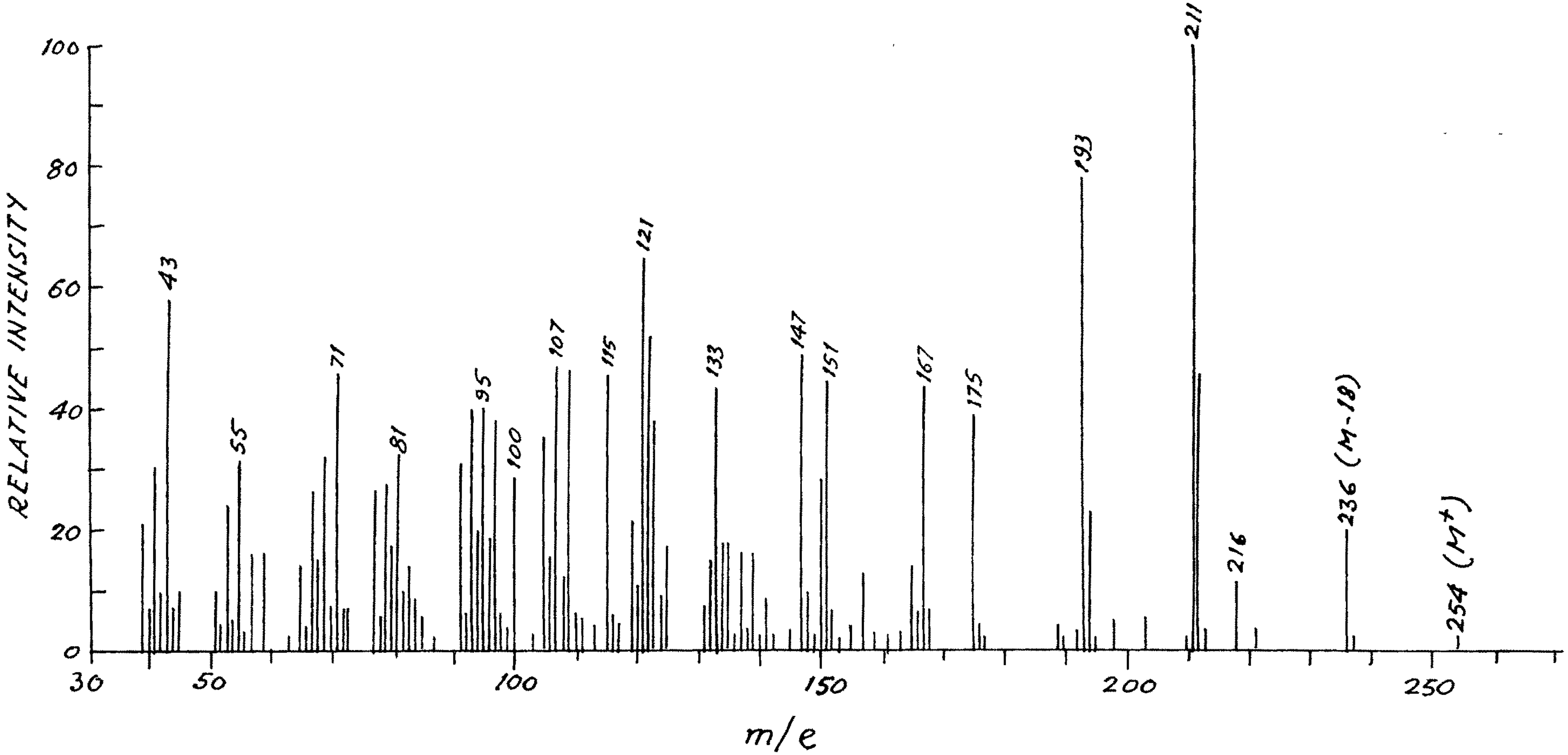


FIG. III. MASS SPECTRUM OF JAESCHKEANATRIOL

In confirmation of this, acetylation of the triol by the usual method (Ac_2O, pyridine) at room temp. (∽ 25°, 12 hr) afforded a hydroxy diacetate, m.p. 119-20° with the required spectral characteristics, IR:(Fig. IV) OH 3400 cm^{-1}; OAc 1735, 1245 cm^{-1}; PMR(Fig. V): two O$\underline{Ac}$(6H, two s, 2.05 and 2.1 ppm), two-C$\underline{H}$OAc(1H each, m 4.45 and 5.1 ppm).

Since the PMR spectral data of triol is very similar to that of jaeschkeanadiol, it is reasonable to assume the same carbon framework with the placing of tertiary hydroxyl as in jaeschkeanadiol. This is supported by a strong peak at m/e 211(M-43, 100%) in the mass spectrum of triol (Fig. III); this ion further fragments by loss of H_2O to m/e 193(M-61, 78%). The mass spectrum of the diacetate (Fig.VI) shows a small peak at m/e 295(M-43, 12%), which further fragments by loss of two AcOH to m/e 175(62%). Location of the remaining two secondary hydroxyls was carried out as follows (Fig. VII). Dihydrojaeschkeanatriol (2)(obtained by catalytic hydrogenation of triol) was oxidised with Jones reagent[2] to give a hydroxy diketone (3), whose IR spectrum shows

OH 3400 cm^{-1}; C=O 1740, and 1690 cm^{-1}. These data indicate that the C=O functions (and hence the original secondary hydroxyls) are located in five- and seven-membered rings respectively.

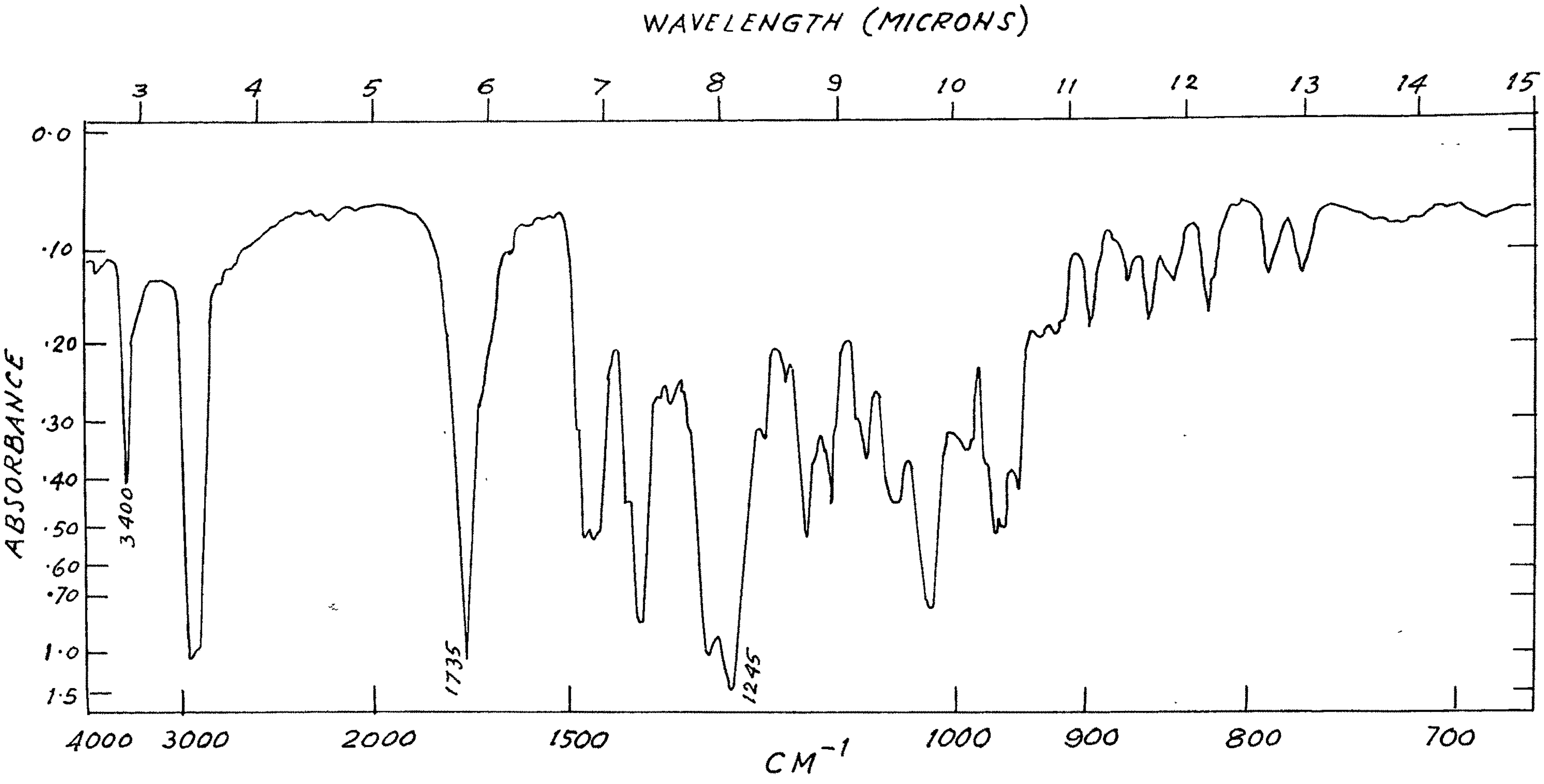


FIG. IV. IR SPECTRUM OF JAESCHKEANATRIOL DIACETATE

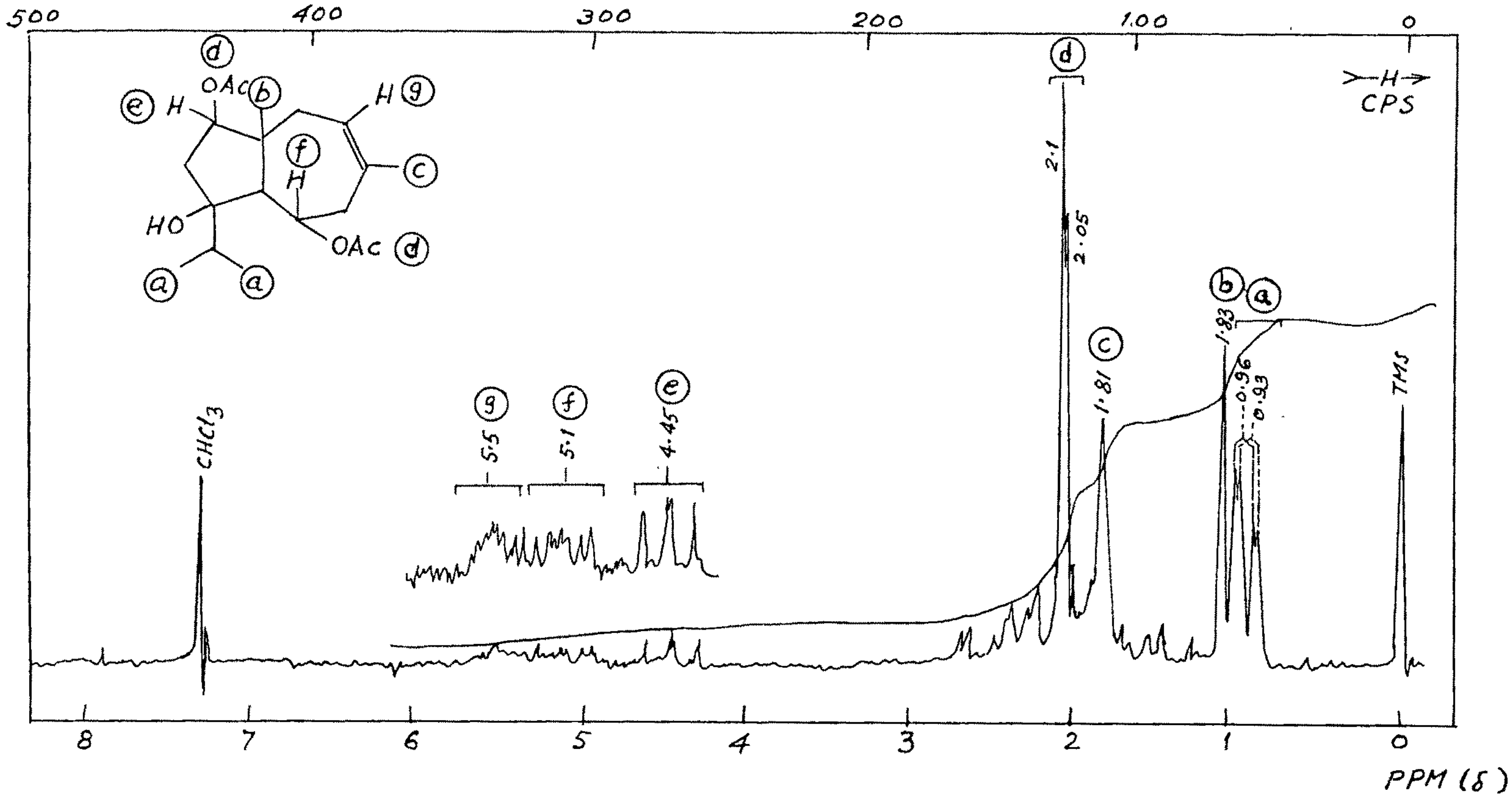


FIG. V. PMR SPECTRUM OF JAESCHKEANATRIOL DIACETATE

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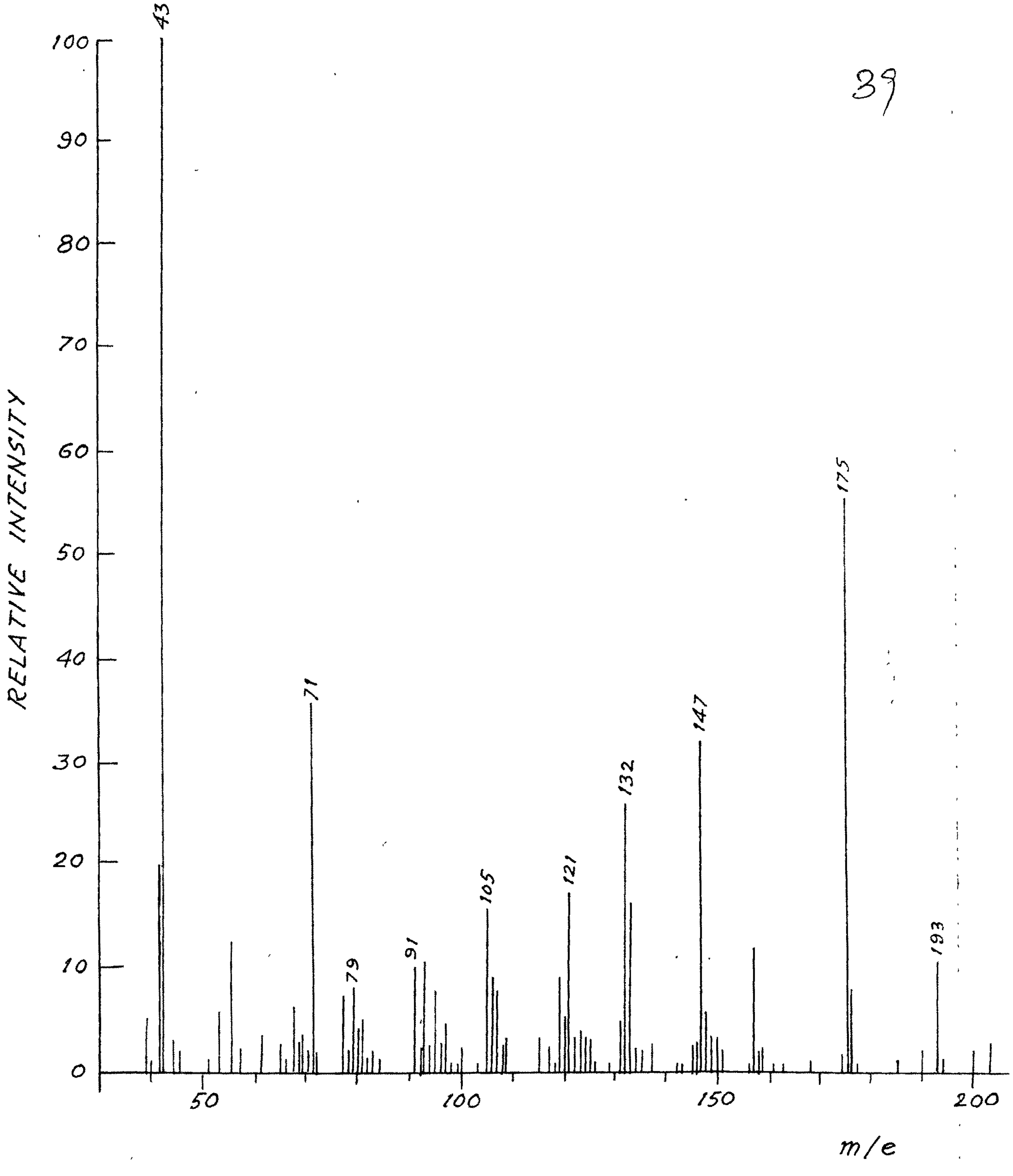
RELATIVE INTENSITY
100
90
80
70
60
50
40
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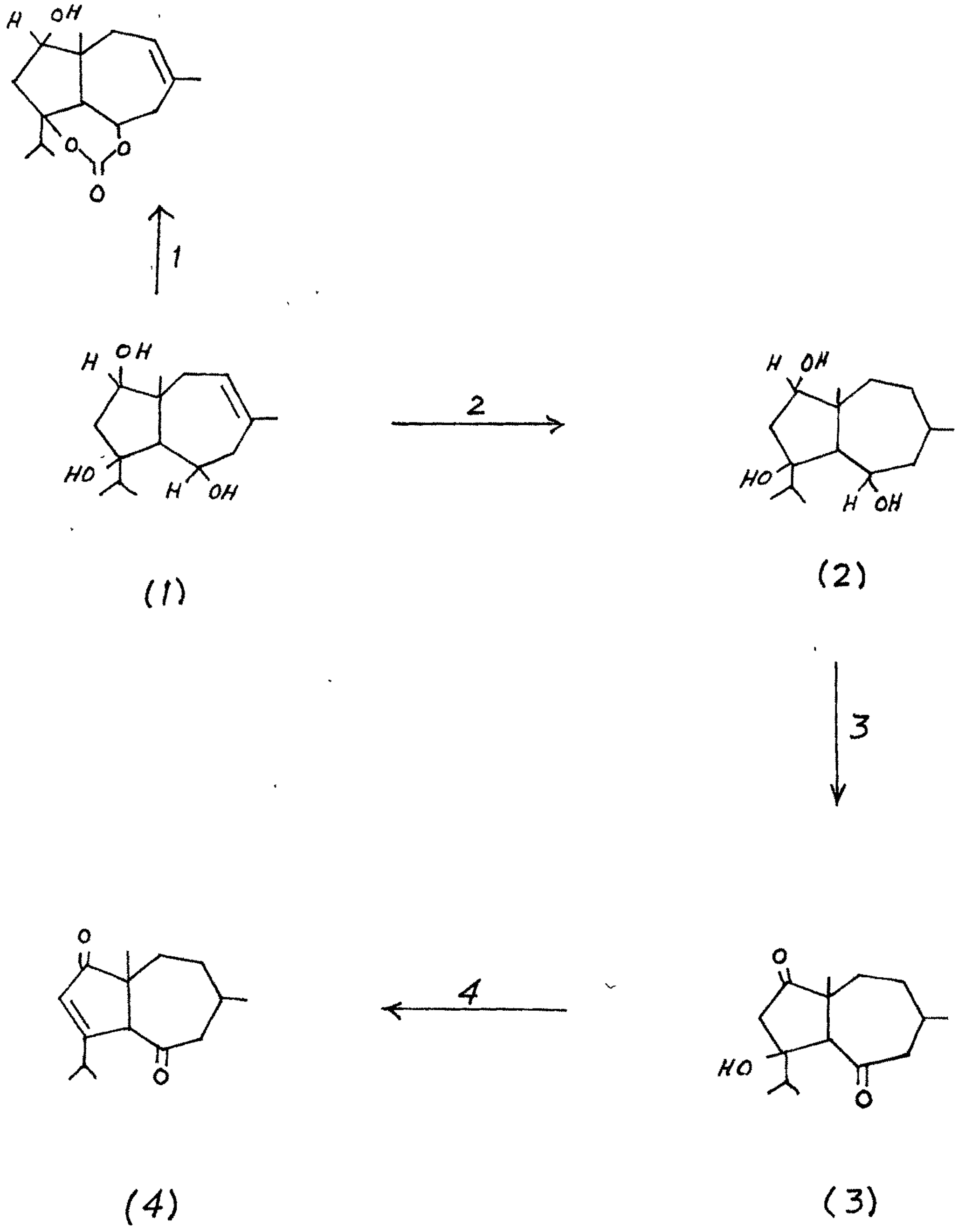
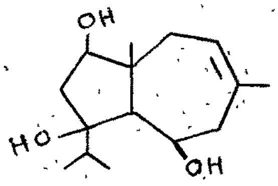


<u>REAGENTS</u> -

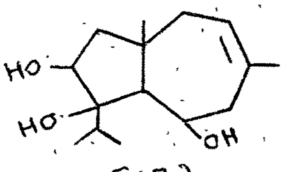
1. $COCl_2$ / PYRIDINE
2. PtO_2 / H_2
3. JONES REAGENT
4. 5% ETHANOLIC KOH

FIG. VII

Jaeschkeanatriol on exposure to phosgene in the presence of pyridine[3], furnished, in almost quantitative yield, a hydroxy carbonate (5), m.p. 124-25°, IR(Fig.VIII) OH 3480; O-CO-O[4] 1765 and 1255 cm^{-1}. Its PMR spectrum (Fig. IX) indicates a downfield shift of one of the -C$\underline{H}$OH signals (from 4.02 to 4.42 ppm), suggesting that in the carbonate formation one secondary and a tertiary hydroxyl groups are involved. To decide between which one of the two secondary hydroxyls is involved, hydroxy carbonate (5) was oxidised with Jones reagent to get keto carbonate (6). The IR spectrum (Fig.X) of this compound showed C=O frequency at 1740 cm^{-1}(5-membered ring), thus indicating that in the carbonate formation, secondary hydroxyl present in the seven membered ring is participating. The facile formation of the cyclic carbonate also suggests that the tertiary OH and the secondary OH(in the seven membered ring) are placed as in jaeschkeanadiol. These considerations lead to two possible gross structures (1A) and (1B), for jaeschkeanatriol.



(1A)



(1B)

It has been possible to adduce chemical evidence in favour of (1A) as follows. Keto carbonate (6), when treated with 5% ethanolic KOH gave a mixture of atleast three compounds, from which two major compounds were separated

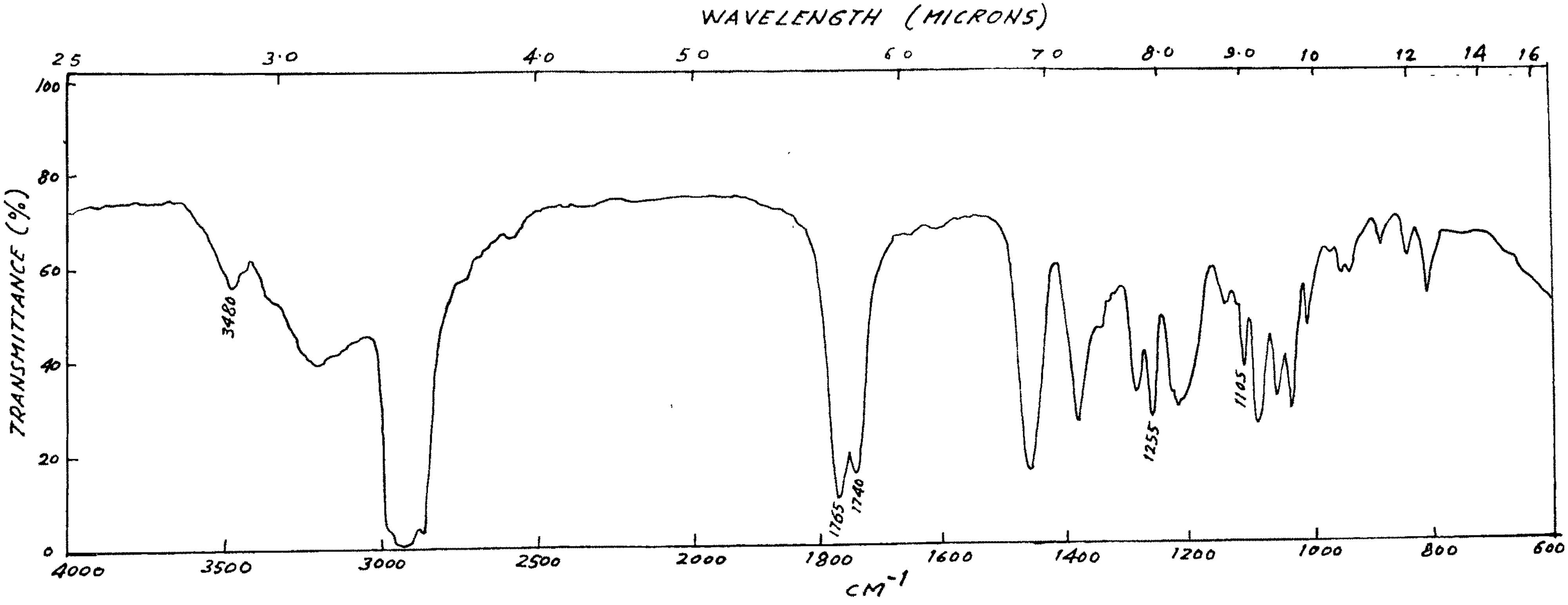


FIG. VIII. IR SPECTRUM OF HYDROXY CARBONATE (5)

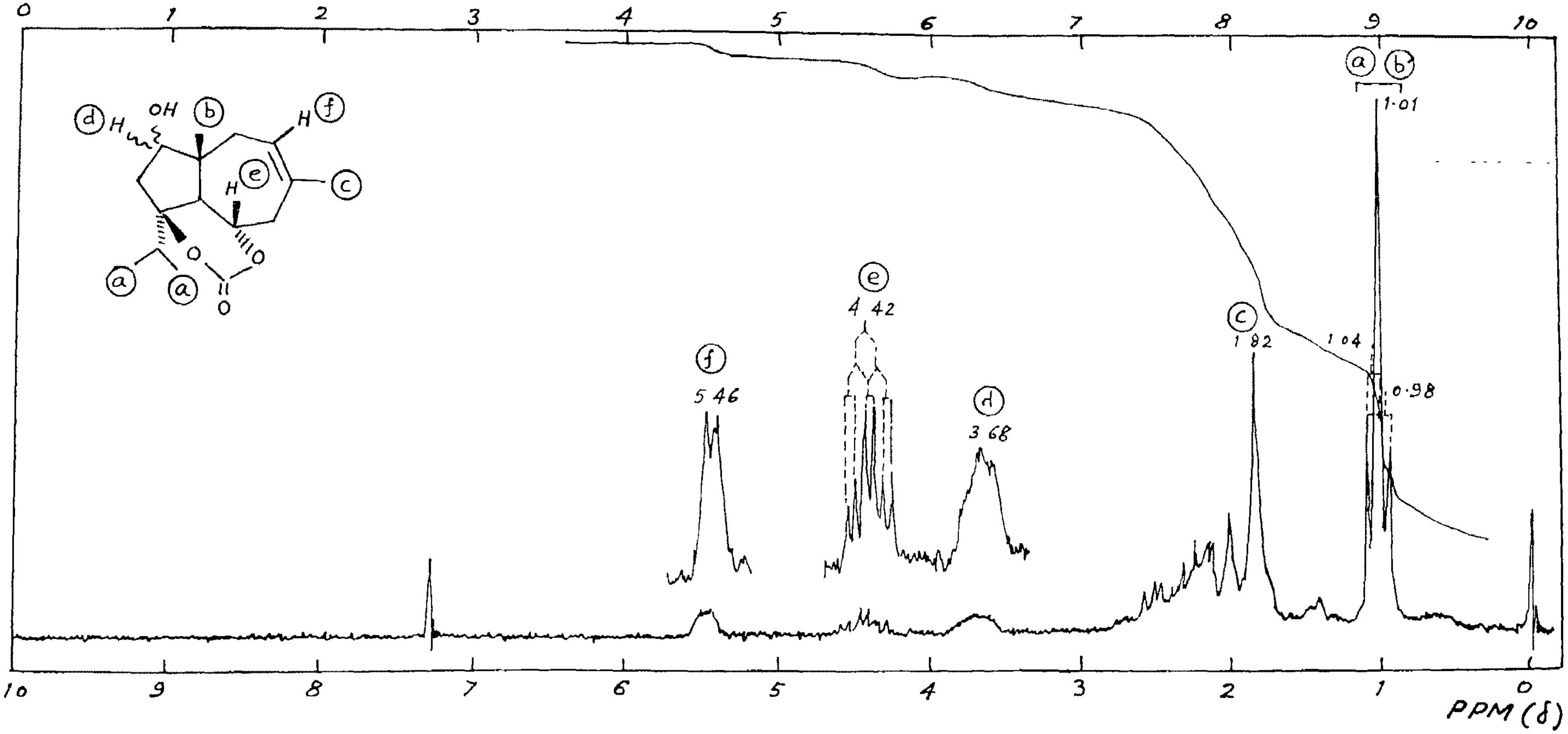


FIG. IX. PMR SPECTRUM OF HYDROXY CARBONATE (5)

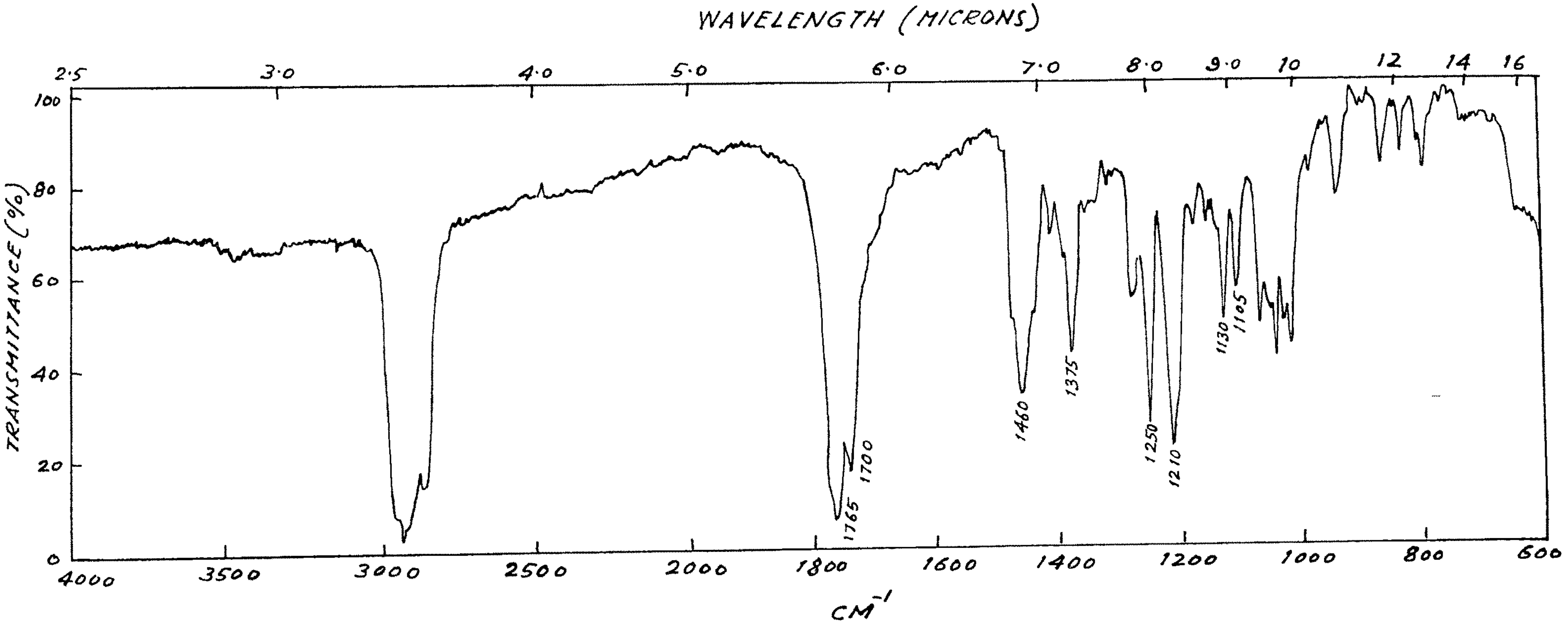


FIG. X. IR SPECTRUM OF KETO CARBONATE (6)

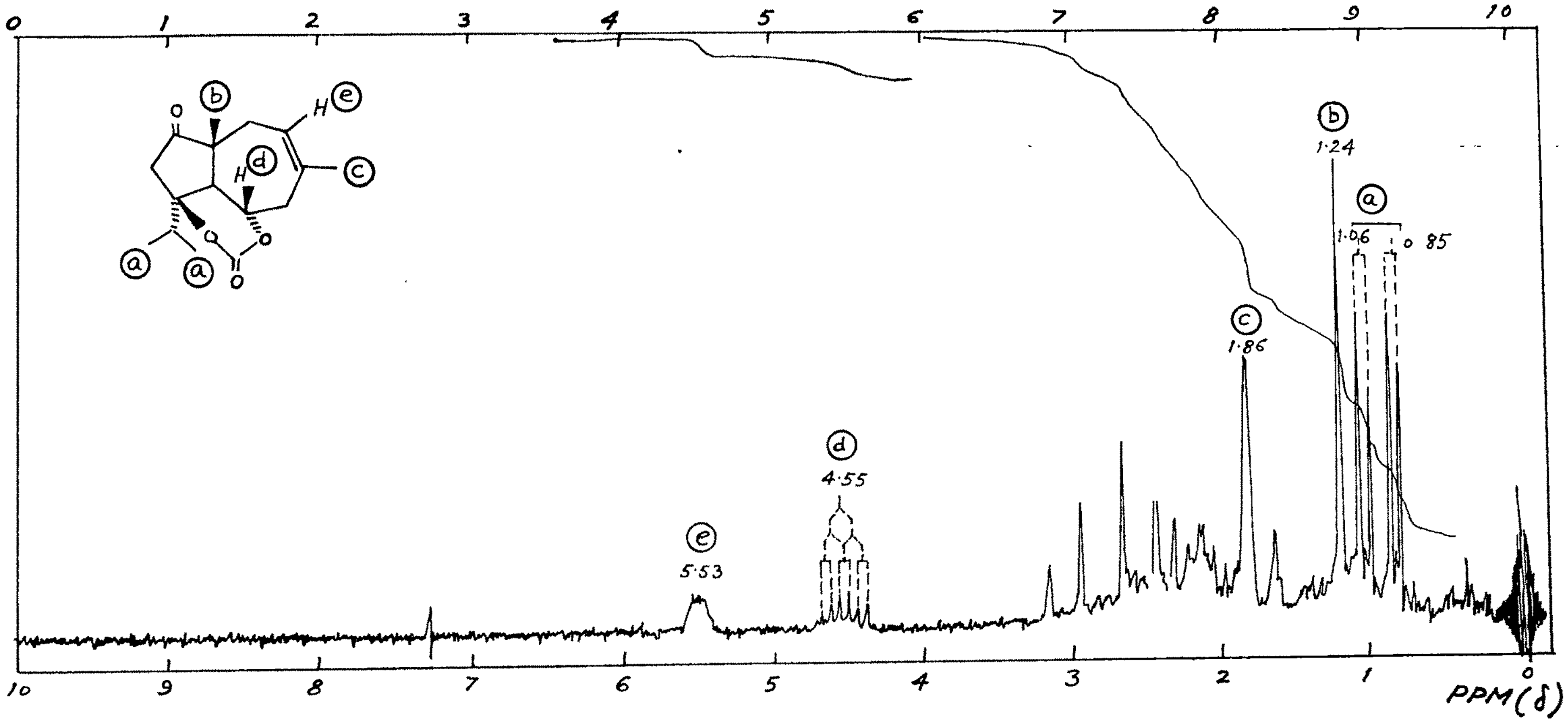


FIG. XI. PMR SPECTRUM OF KETO CARBONATE (6) pure by column chromatography. These two compounds are designated as (C) and (D).

Compound (C) in its IR (Fig.XII) showed no OH function, but indicated presence of C=O 1698 cm^{-1} and -C=C 1610 cm^{-1}. Its UV(Fig.XIII) showed maxima at 214 (ϵ ,2880), 241 (ϵ ,8930) and 342 nm(ϵ ,8498). The PMR (Fig. XIV) of compound (C) revealed the following characteristic features: $-C-\underline{M}e$(3H, s, 1.04 ppm), $-C=C-C\underline{HM}e_2$(6H, two doublets centered at 1.2 and 1.22 ppm, J=7Hz each),$-C=C\underline{M}e$(3H,s,1.9 ppm) $-C=C\underline{H}-C=O$ and $-C=C\underline{H}$ (3H, m, 5.97 ppm).

Compound (D) in its IR(Fig. XV) showed OH(3420 cm^{-1}); C=O (1685 cm^{-1}) and C=C (1600 cm^{-1}); Its UV has λ max at 233 nm(ϵ ,8853). The PMR (Fig.XVI) of compound (D) showed $-C-\underline{M}e$(3H, s, 1.11 ppm)$-C=C-CH\underline{M}e_2$(6H, a pair of doublets at 1.16 and 1.24 ppm, J=7Hz each)$-C=C-\underline{M}e$(3H, s, 1.62 ppm) $-C\underline{H}OH$(1H, m, 4.68 ppm),$-C=C\underline{H}$ (1H, m, 5.35 ppm) and $-C=C\underline{H}-C=O$ (1H, s, 6.04 ppm).

Based on the above data structures (7) and (8) are suggested for compound (C) and (D) respectively. (Fig.XVII) The formation of compounds (C) and (D) suggest that in jaeshkeanatriol, all the three hydroxyls are placed 1,3 to each other. Furthermore base treatment of the hydroxy diketone (3) furnished an α,β-unsaturated ketone (4), λ max 237 nm, ϵ,8231; IR:C=O 1690, 1625 cm^{-1}(cyclopentenone), 1680 cm^{-1}(seven membered ring ketone); PMR: $-C=C\underline{H}-C=O$ (1H, s, 5.95 ppm); M^+, m/e 234 . (see Fig. VII)

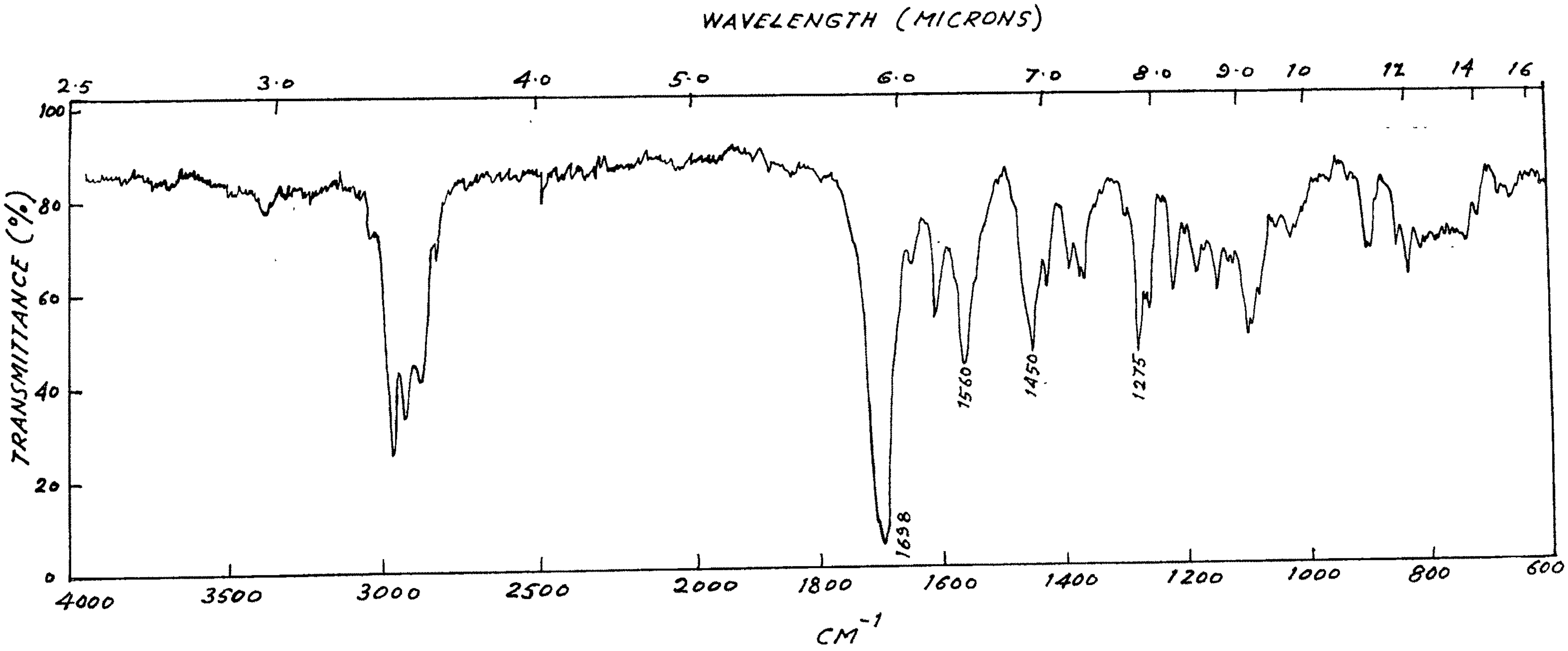


FIG. XII. IR SPECTRUM OF TRIENONE (7)

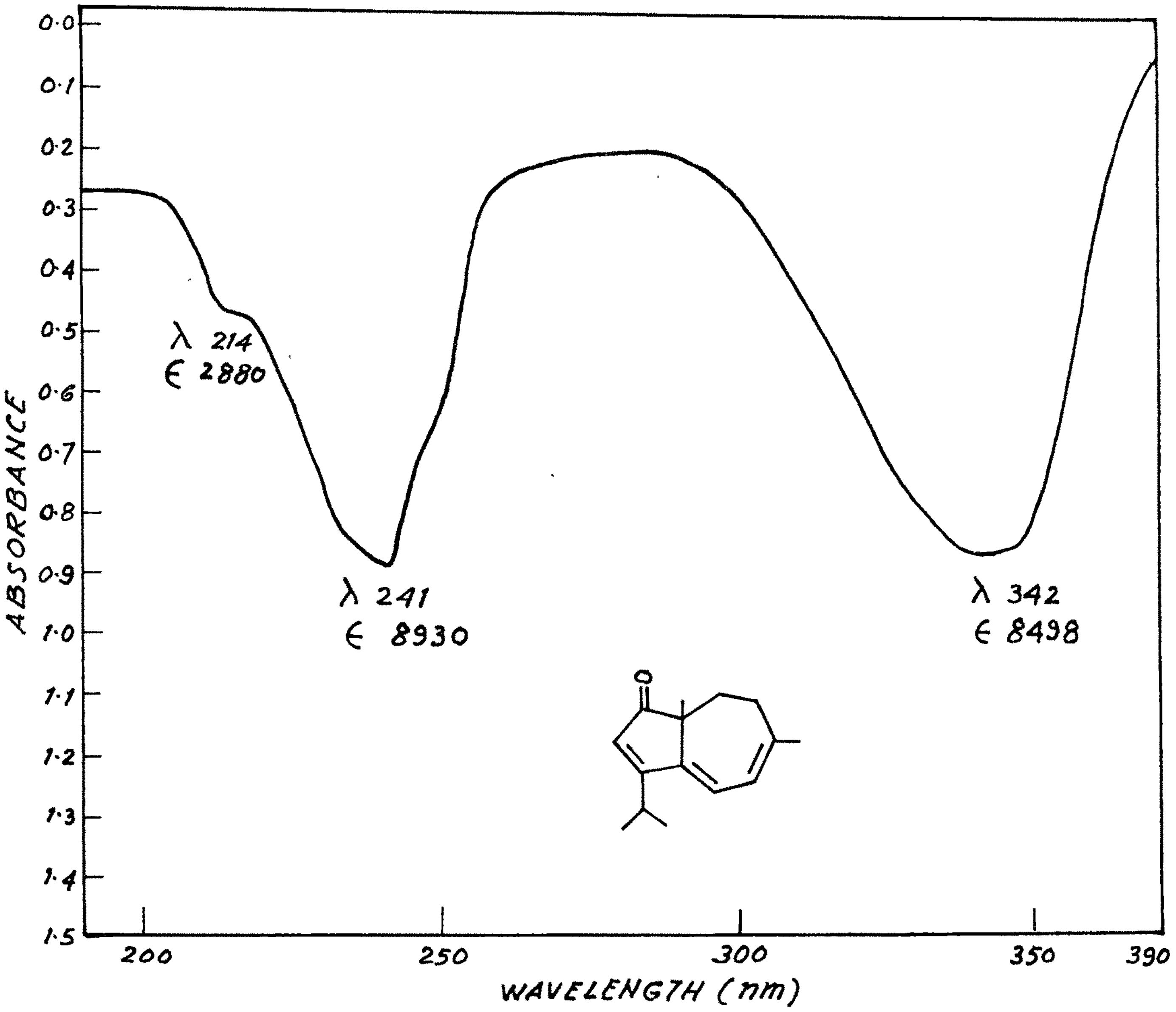


FIG. XIII. UV SPECTRUM OF TRIENONE (7)

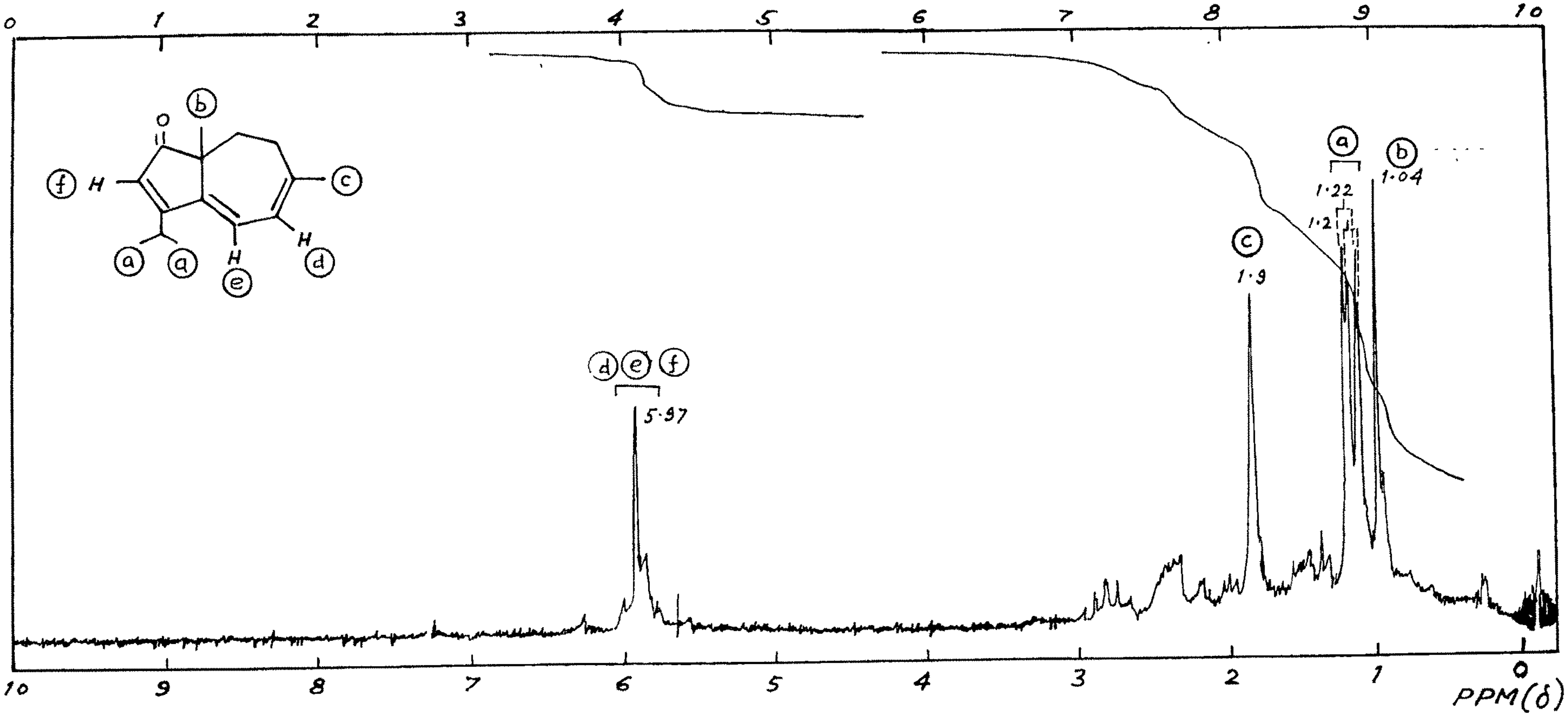


FIG. XIV. PMR SPECTRUM OF TRIENONE (7)

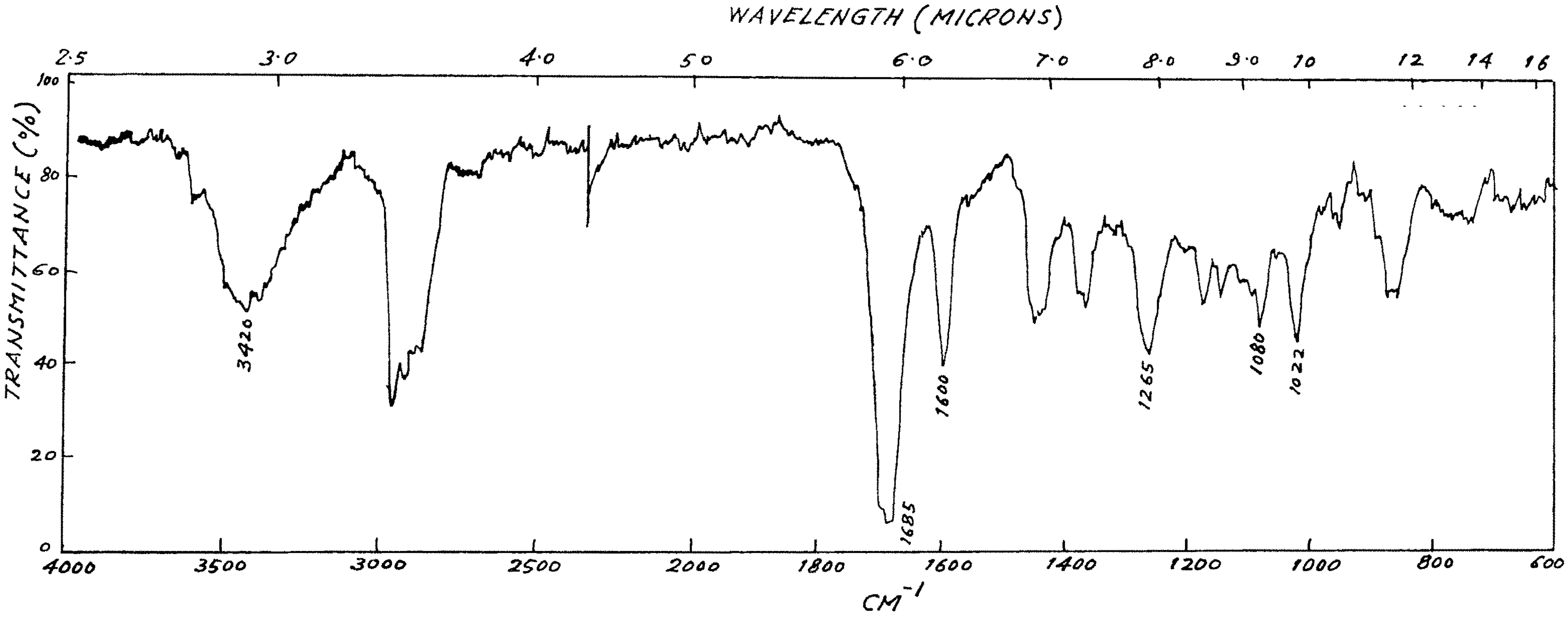


FIG. XV. IR SPECTRUM OF DIENONE (8)

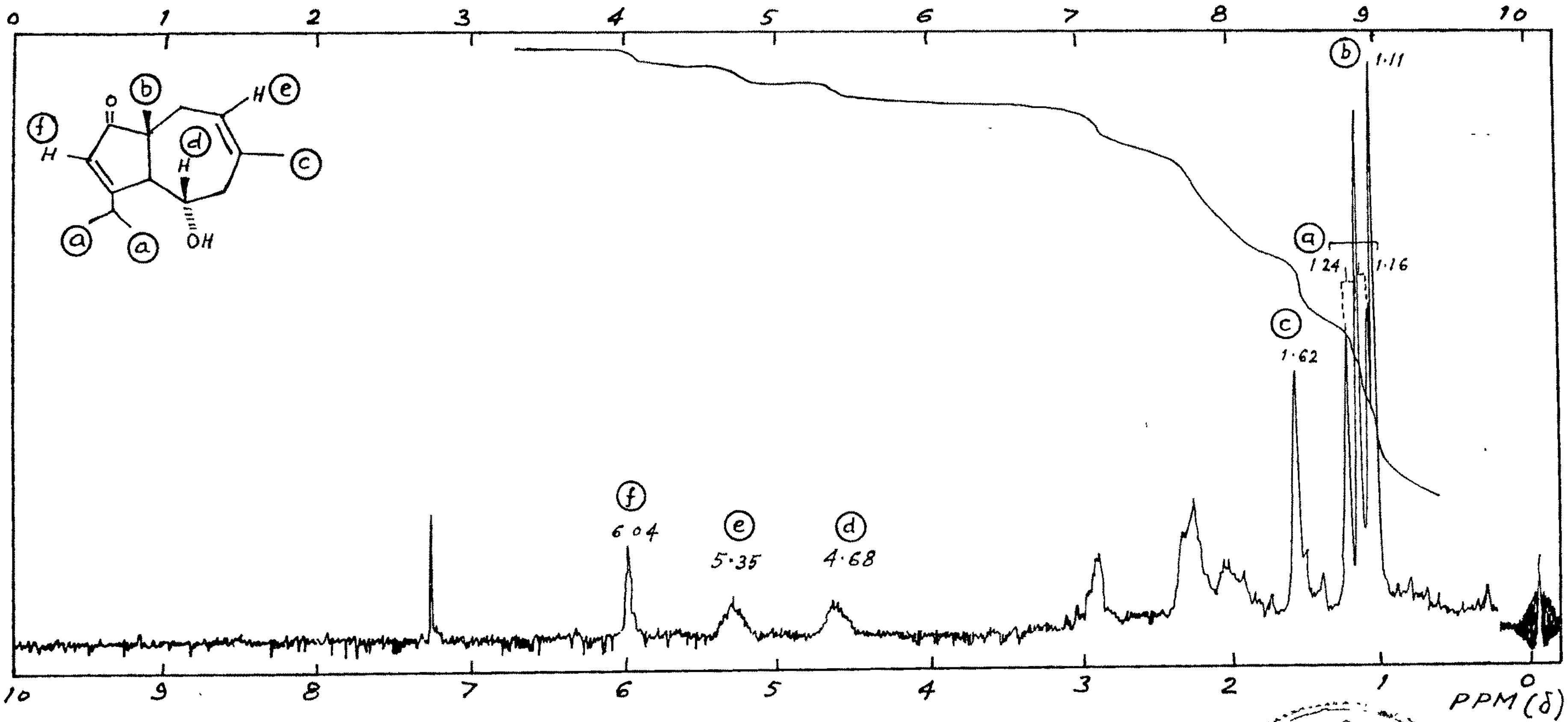
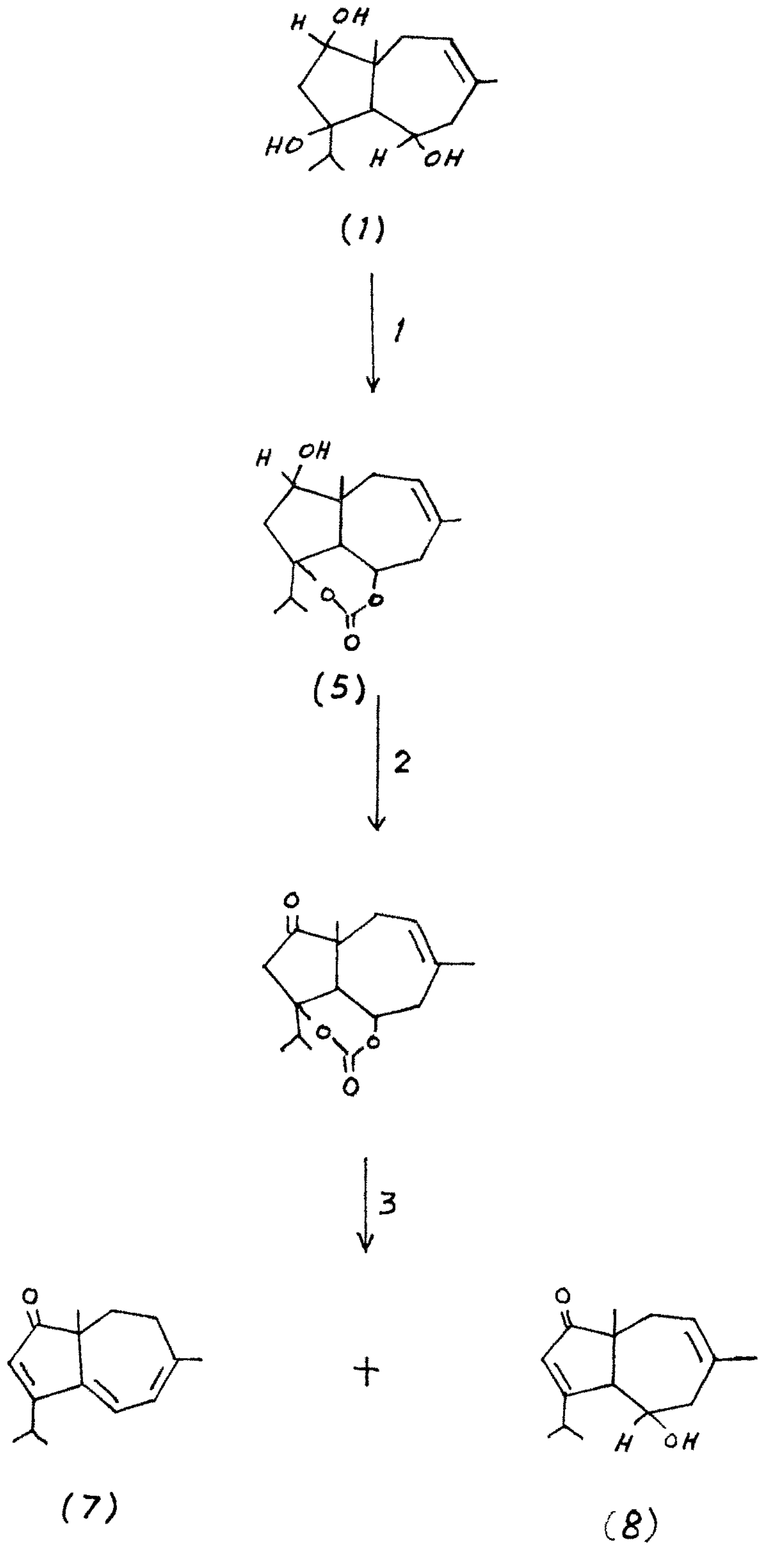


FIG. XVI. PMR SPECTRUM OF DIENONE (8)



REAGENTS -

1. $COCl_2$ / PYRIDINE 2. JONES REAGENT
3. 5% ETHANOLIC KOH

FIG. XVII

The above transformations are consistent with the formulation (1A) which, then must represent jaeschkeanatriol. The final proof of this came from the conversion of jaeschkeanatriol to jaeschkeanadiol.

An easy approach for achieving this transformation was by converting the hydroxycarbonate (5) to its sulfonate ester and the subsequent reduction of this ester with LAH. Accordingly, the hydroxycarbonate (5) was converted into corresponding tosyl derivative (p-toluenesulfonyl chloride-pyridine, 0°), IR:O-CO-O 1760 cm^{-1}; $O-SO_2-C$ 1380, 1185 cm^{-1}; PMR:-O-CO-O-C$\underline{H}$ and $-SO_2-O-C\underline{H}$ (2H, bm, 4.37 ppm); Ar$\underline{H}$(4H, a typical AA'BB' 'quartet'[5] of p,p'-disubstituted benzene centered at 7.63 ppm). When the tosylate was treated with LAH in either ether of THF, the product obtained after usual work up was found to be jaeschkeanatriol (m.p.,mixed m.p., PMR). Reduction of the tosylate was next attempted with $NaBH_4$[6]. In this reduction, it was observed that only the carbonate linkage had opened up leaving the sulfonate ester moiety intact; IR:OH 3520 cm^{-1}, $C-SO_2-O-1370$, 1180 cm^{-1}, C=CH(aromatic) 1600 cm^{-1}; PMR:-C$\underline{H}$OH(1H, m, 3.41 ppm),$-C\underline{H}-O-SO_2$ (1H, m, 3.94 ppm) and Ar$\underline{H}$(4H, AA'BB' quartet centered at 7.53 ppm).

The failure of these two reductions to get jaeschkeanadiol prompted us to switch over to another route. Here it was envisaged that if the tosylate function is displaced by halide, then the resulting halide should yield jaeschkeanadiol on reduction with either LAH or tri-n-butyltinhydride[7]. The latter reagent was the preferred one as the reduction with this reagent is a free radical chain process and hence the formation of products arising out of intermediacy of carbonium ions would be subdued.

Tosylate of the hydroxy carbonate, when treated with NaI in acetone[8] failed to give the desired iodide and only the starting tosylate was recovered back (TLC, PMR). Next, the displacement reaction was attempted using HMPT[9] as a solvent, but in this case too, no displacement was observed even after leaving the reactants for as many as 150 hr at room temp.

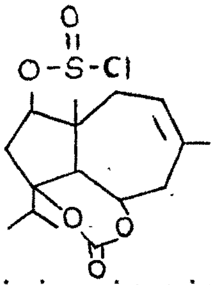
The failure of these displacement reactions might be attributed to two factors. a) the configuration of the C_8 hydroxyl is such that back side attack of nucleophile is terribly hindered and b) the neo-pentylic nature of C_8 carbon atom. In an effort to see, whether the stereochemistry of C_8 OH could be reversed to get an epimeric jaeschkeanatriol, c (in which case it might be possible to carry out SN_2 displacement reaction), ketocarbonate (6) was reduced with LAH The product obtained from this reduction was identical in all respect (m.p., mixed m.p., IR, PMR) with the naturally occuring jaeschkeanatriol. Reduction with $NaBH_4$ also yielded jaeschkeanatriol.

Having failed to get the desired halide, attention was next focused on the dehydrotosylation. The idea was to obtain an olefin from the tosylate and then reduce selectively the disubstituted double bond in the presence of tri-substituted double bond by using Wilkinson catalyst[10] Tris (triphenylphosphine) chlororhodium . The use of collidine[11], pyridine[12], alumina[13] and potassium tert. butoxide[14] for the dehydrotosylation reaction is well documented in the literature.

Reaction of the tosylate with pyridine and collidine under refluxing conditions gave the starting material back. With alumina (gr.I), a mixture of atleast three compounds was obtained, from which the major compound was obtained pure by chromatography over SiO_2-gel. The examination of the spectral data (IR, PMR) of this compound revealed that in this compound only the carbonate linkage had opened up, while the sulfonate ester moiety was intact. The treatment of the tosylate with potassium tert.butoxide resulted in the formation of a complex mixture, from which only one compound was obtained pure by chromatography. It was also found to be the one in which only the carbonate linkage had opened up (IR, PMR).

The failure of these reactions prompted us to devise an alternative route. In this case, it was thought worthwhile to get halide directly from the hydroxy carbonate. The combination of pyridine and thionyl chloride[15] has been known to be excellent for preparation of alkyl chloride from alcohol. Thus when a mixture of hydroxy carbonate and thionyl chloride in benzene was heated in presence of pyridine, a mixture of atleast three compounds was obtained, from which two compounds were obtained pure by chromatography over silicagel. The major compound was found to be the starting hydroxy carbonate (TLC, IR, PMR). The minor compound did not show any OH function in its IR spectrum and showed -O-CO-O absorption (1760 cm^{-1}). Its PMR indicated presence of -C-M̲e, -CHM̲e$_2$(9H, m, between 0.95 and 1.07 ppm)-C=CM̲e (3H, s, 1.83 ppm), -C=CH̲ (1H, m, 5.43 ppm) and a broad multiplet integrating for two protons at 4.33 . Thus there is a downfield shift of 0.65 of the C_8 proton. Thinking that we had the desired chloride in hand, we treated it with LAH in anhy. ether. The compound obtained after usual work up was found to be jaeshkeanatriol(TLC, IR, PMR).

The fact that the compound obtained from the above reduction was jaeshkeanatriol, and not the desired jaeshkeanadiol clearly proves that the reaction of hydroxy carbonate with thionyl chloride and pyridine gave alkyl chlorosulphite (9) and not the chloride.



(9)

This is not surprising in view of the fact that formation of the chloride from alcohol using thionyl chloride-pyridine involves this intermediate. No change in the product formation was observed when the reaction of hydroxy carbonate and thionyl chloride was carried out at higher temperatures.

In another set, reaction of hydroxy carbonate and thionyl chloride was carried out in presence of HMPT[16], but in this case, it failed to react and only the starting material was recovered back after work up (IR, PMR).

The combination of triphenylphosphine and carbon tetrachloride is very versatile for converting primary and secondary alcohols into the corresponding chlorides under mild and essentially neutral conditions[17]. Thus, when hydroxy carbonate was treated with a mixture of triphenylphosphine and carbon tetrachloride, a mixture of atleast three compounds was obtained after work up. Of these the desired chloride (10) was separated pure by column chromatography over SiO_2-gel (the other two compounds being unreacted triphenyl phosphine and triphenyl phosphine oxide), IR: (Fig.XVIII) no OH absorption, -O-CO-O (1740 cm^{-1}) and C-Cl (790 cm^{-1}); PMR:(Fig.IXX)-C-$\underline{Me}$ (3H, s, 1.2 ppm),-CH$\underline{Me}_2$(6H, two doublets, centered at 1.05 and 1.14 ppm, J=7Hz each), -C=C-$\underline{Me}$ (3H, s, 1.86 ppm)-C$\underline{H}$-O-CO-O and -C$\underline{H}$Cl (2H, m, centered at 4.37 ppm) and -C=C$\underline{H}$ (1H, m, 5.52 ppm). The compound analysed for $C_{16}H_{23}O_3Cl$ (M^+ at m/e 298 , Fig. XX)

Thus having obtained the required chloride, next step was to reduce it to get jaeshkeanadiol. The reduction was carried out by using LAH in diglyme[18]. A complex mixture

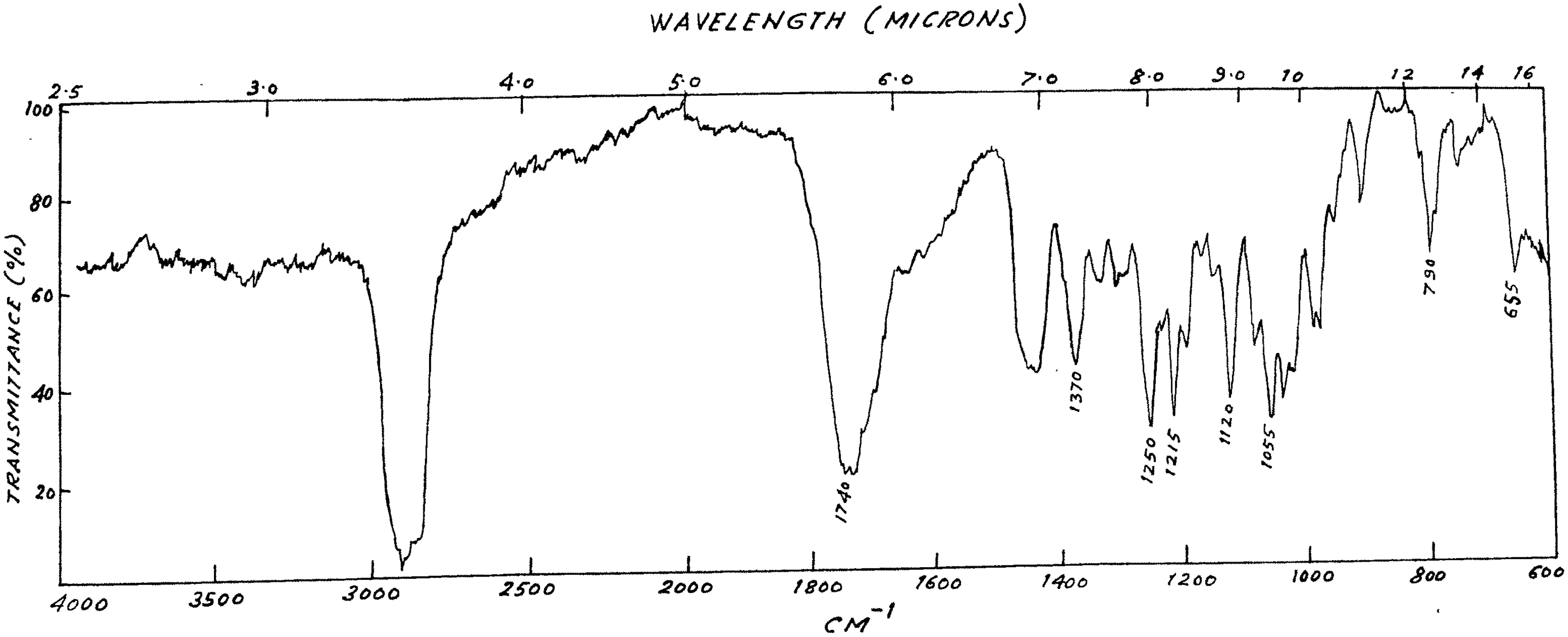


FIG. XVIII. IR SPECTRUM OF CHLORIDE (10)

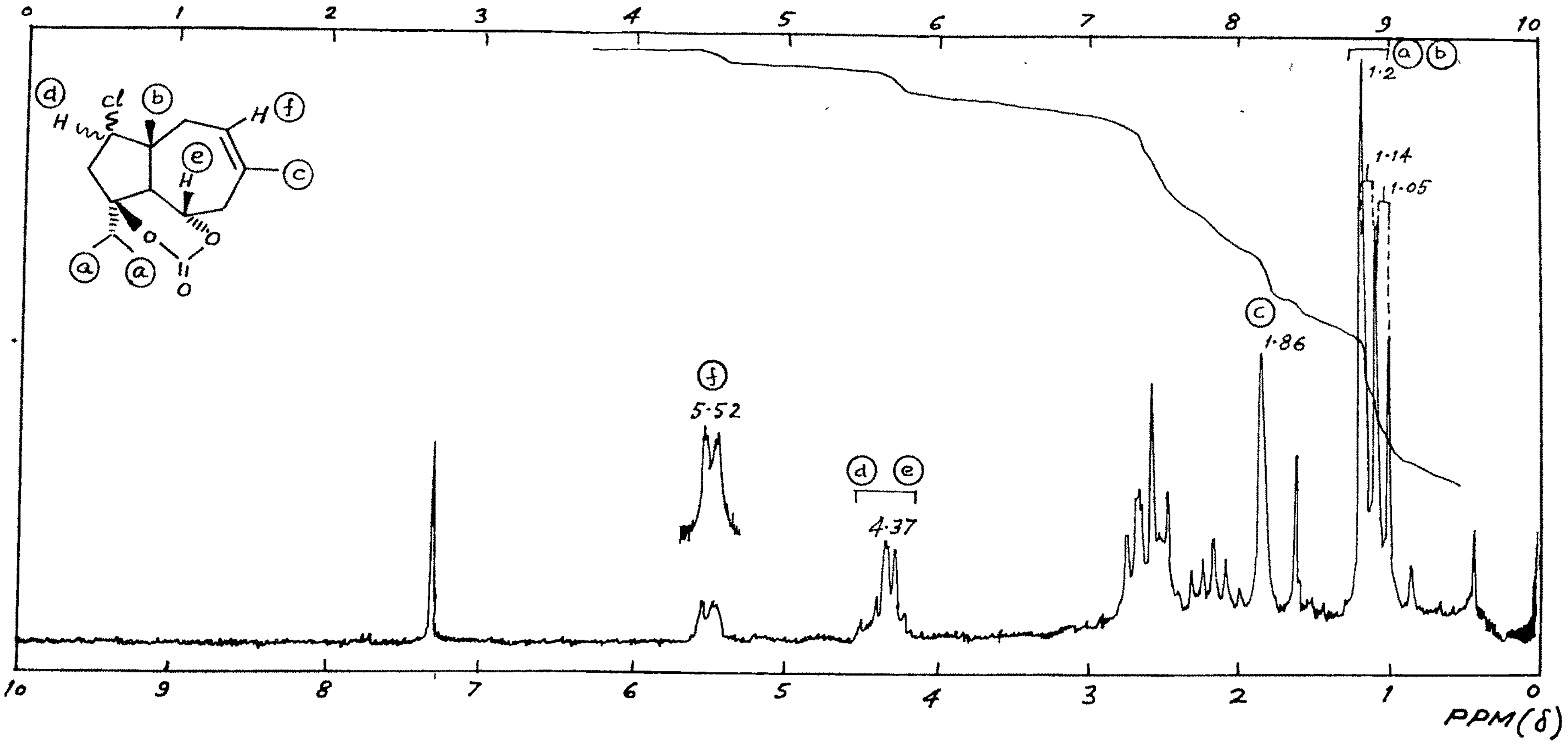
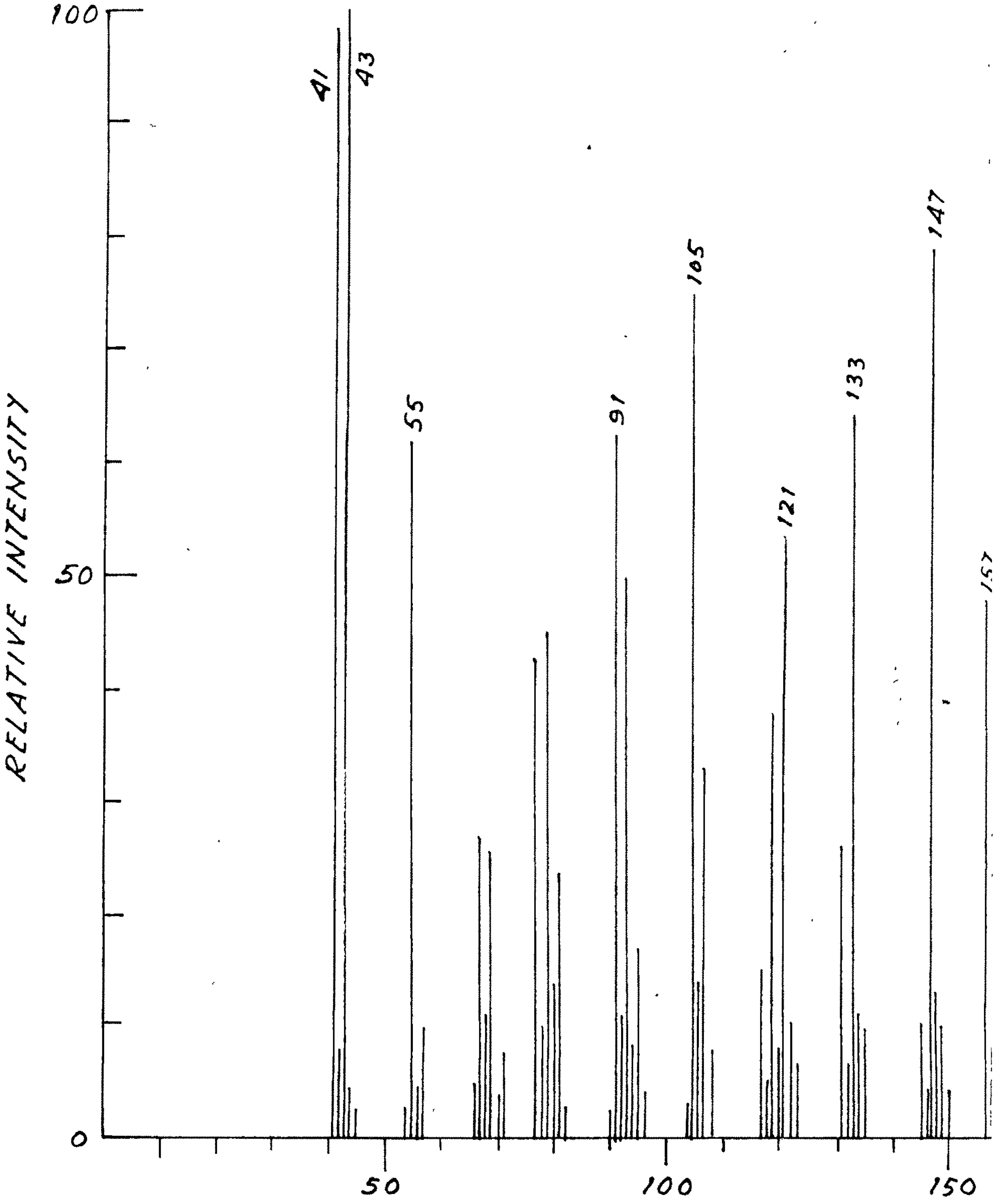


FIG. IXX. PMR SPECTRUM OF CHLORIDE (10)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RELATIVE INTENSITY
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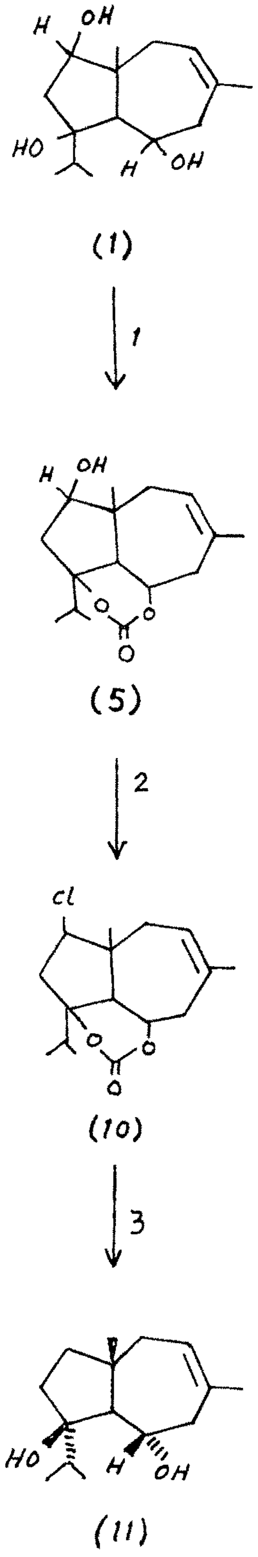

REAGENTS-

1. $COCl_2$/PYRIDINE
2. ϕ_3P/CCl_4
3. LAH/DIGLYME

FIG. XXI

was obtained from the above reduction, from which the desired jaeschkeanadiol was obtained pure by chromatography over silica gel. It was identical in all respects (GLC, IR, PMR) with the authentic jaeschkeanadiol (11). (Fig. XXI)

The obtention of jaeschkeanadiol from jaeschkeanatriol also clarifies the stereochemistry at all centres in jaeschkeanatriol except that at C_8 centre.

EXPERIMENTAL

General remarks

All melting points and boiling points are uncorrected. Light petroleum refers to the fraction having the boiling range 60-80°. Optical rotations were measured at room temperature (27±2°) in chloroform (except when otherwise stated) on a Carl-Zeiss or a Perkin-Elmer (model 141) or Schimdt-Haensch spectropolarimeter model polatronic I. UV spectra were taken on a Perkin-Elmer spectrophotometer model 402 in ethanol solution. IR spectra were taken on a Perkin-Elmer Infracord, model 137 E or 267 as nujol mulls (solids) or smear (liquids) unless stated other wise. PMR spectra were taken in 10-20% solution in CCl_4 or $CDCl_3$ unless mentioned otherwise with TMS as internal standard on a Varian A-60 or T-60 spectrometer or Perkin-Elmer spectrometer, model R-32, signals being recorded in (ppm) values, relative to TMS as zero. Mass spectra were recorded on a CEC Mass spectrometer Model 21-110B or Varian CH-7 using an ionizing voltage of 70 eV and a direct inlet system. GLC was carried out on Hewlett-Packard 5712A and 7624A gas chromatographs (Column:360 cm x 5 cm, 5%, 6';10%,12'; Carbowax 20M and 3% 6' SE-30 on Chromosorb W, 60-80; H_2 as carrier gas).

Silica gel for column chromatography (100-200 mesh) was activated at 125-30°/6-8 hr and standardised according to Hernandez *et al.*[19] TLC was carried out on silica gel (∽200 mesh) layers (0.25 mm) containing 10% gypsum;

visualisation of spots was carried out with 1% vanillin in H_3PO_4 aq (50%) or 1% vanillin in H_2SO_4 or 20% H_2SO_4 in methanol mixture spray followed by heating at ~120°/10 min. The neutral alumina used for column chromatography was activated to grade I by heating at 400-460° for 6 hr and suitable grades were prepared according to Brockmann and Schodder[20]. TLC with 5-10% Ag^+-silica gel was carried out according to Gupta and Sukh Dev[21].

All the solvent extracts were washed with brine and dried over anhydrous sodium solfate before evaporating solvent. All reactions were monitored by TLC.

ISOLATION OF VARIOUS CONSTITUENTS

The roots of Ferula jaeschkeana*(5.9 kg) which are quite fibrous, were cut into small pieces and extracted in a percolator with acetone. A total of 312.5 g(~11.5%) of the acetone extract (dark brown gum) was obtained.

The acetone extract (105 g) was dissolved in ether (1 litre) extracted with saturated $NaHCO_3$ aq(75 ml x 7) to remove free acids (3.85 g) in the usual manner and the residue (101.15 g) hydrolysed by refluxing with aq methanolic KOH (5%, 1.5 litre) for 4 hr (N_2). This was worked up in the usual manner to give acidic (46.96g) and neutral (47.62g) portions.

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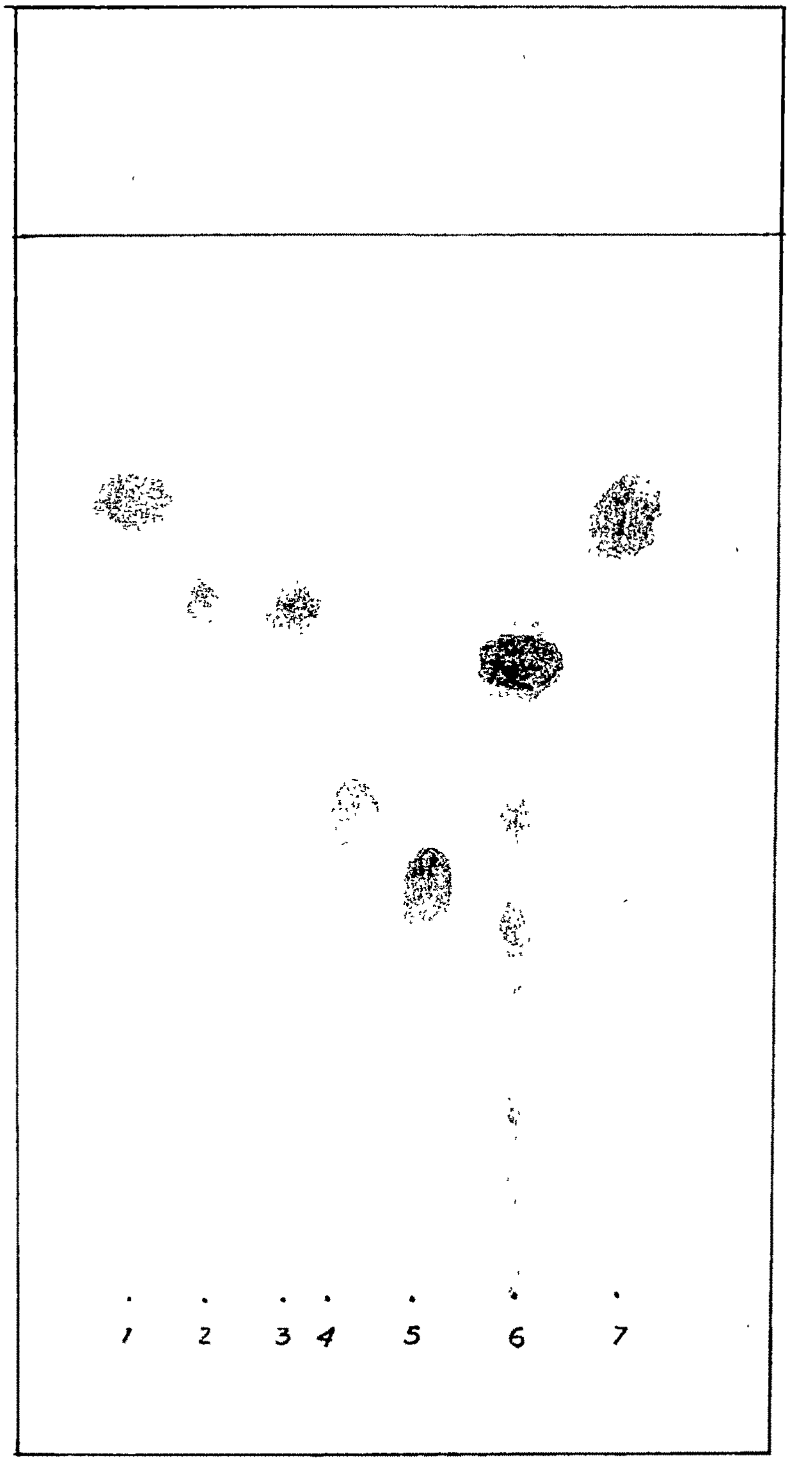
*We are grateful to Dr.C.K.Atal of the Regional Research Laboratory, Jammu for the supply of these roots.

Thus, there is a loss of 6.56g of material in the hydrolysis step. This can be attributed to two factors: either some highly volatile components are present in the extract or there are some water soluble compounds present. To check the latter probability, 5 g of total acetone extracts were taken up in ether (100 ml) and the ether solution was repeatedly washed with water (15 ml x 5). On evaporation of the water from the washings there was obtained 0.201 g of material. Removal of the ether from dried extract gave compound (4.4990 g). The water soluble material was not investigated further.

The above neutral fraction (65 g) was chromatographed on silica gel (IIB, 1400 g) using a modified column. A column having three sections of diameters 5.2, 6.7 and 7.6 cm (in the discending order) was employed. The objective behind this approach was to minimise the tailing effect of the bands.



(SILICA GEL G PLATE)

SOLVENT SYSTEM : BENZENE (70%)-ETHYL ACETATE (30%)

VISUALISATION : 1% VANILIN IN H_2SO_4 SPRAY

(1) DYE (SUDAN YELLOW) (2) NEOJAESCHKEANADIOL

(3) JAESCHKEANADIOL (4) EPOXYJAESCHKEANADIOL

(5) JAESCHKEANATRIOL (6) TOTAL NEUTRALS (SAPONIFIED ACETONE EXTRACT)

(7) DYE (SUDAN YELLOW)

FIG. XXII. THIN LAYER CHROMATOGRAM OF THE NEUTRAL CONSTITUENTS OF FERULA JAESCHKEANA (FROM SAPONIFIED ACETONE EXTRACT)

CHROMATOGRAM I

Fr.	1	Light petroleum	10x500 ml	1.95g	Hydrocarbons
Fr.	2	C_6H_6	14x500 ml	2.38g	Complex mixture
Fr.	3	C_6H_6	1x500 ml	4.97g	Mixture rich in alcohols.
Fr.	4	C_6H_6-10% acetone	7x500 ml		
Fr.	5	-do-	2x500 ml	33.03g	Rich in jaeschkeanadiol
Fr.	6	-do-	4x500 ml	2.46g	Complex mixture
Fr.	7	-do-	3x500 ml	3.65g	Rich in epoxy jaeschkeanadiol
Fr.	8	C_6H_6-20% acetone	8x500 ml		
Fr.	9	-do-	2x500 ml	3.24g	Complex mixture
Fr.	10	-do-	2x500 ml	7.0 g	Rich in jaeschkeanatriol
Fr.	11	Methanol	2x500 ml	2.8 g	Polar compounds

<u>Frac</u>. 5 was crystallised from light petroleum to give fine needles of jaeschkeanadiol, m.p. 91-2°

<u>Frac</u>.10 on crystallisation from acetonitrile gave jaeschkeanatriol as fine prisms, m.p. 164-5°, $[\alpha]_D$+20°. Mass:m/e 236($M-18^+$, 20%), 211(100%), 193(78%), 175(40%), 167(43.5%), 147(48.5%), 133(43.5%), 121(64%), 107(47.5%), 71(45.5%), 55(31%), 43(58%). (Found:C, 71.17; H 10.43. $C_{15}H_{26}O_3$ requires: C, 70.87; H, 10.23%).

<u>Frac</u>. 7 and 8 were combined and (1 g) was further chromatographed on silica gel (IIB, 45 g, 60x1.5 cm).

CHROMATOGRAM II

Fr. 1	C_6H_6	10x50 ml	-	-
Fr. 2	C_6H_6-20% $CHCl_3$	5x50 ml	-	-
Fr. 3	C_6H_6-40% $CHCl_3$	5x50 ml	-	-
Fr. 4	C_6H_6-60% $CHCl_3$	5x50 ml	-	-
Fr. 5	C_6H_6-80% $CHCl_3$	5x50 ml	-	-
Fr. 6	$CHCl_3$	5x50 ml	-	-
Fr. 7	$CHCl_3$-5% EtOAc	6x50 ml	0.255g	Complex mixture.
Fr. 8	-do-	20x50 ml	0.518g	Epoxyjaeschkeanadiol
Fr. 9	Methanol	3x50 ml	0.1g	Polar compounds.

Frac. 8 was crystallised from ether-petroleum ether (40-60°) to give fine needles of epoxyjaeschkeanadiol, m.p. 102-103°, $[\alpha]_D$+23.33°(c, 1.14). Mass:m/e 236($M-18^+$ 2.5%), 211(7%), 193(56%), 175(11.5%), 156(10%), 151(12.5%) 125(26%), 83(12.5%), 74(56%), 43(50%). (Found:C, 70.62; H, 10.35. $C_{15}H_{26}O_3$ requires: C, 70.87; H, 10.23%).

Frac. 3 and 4 from chromatogram I were mixed together and further chromatographed on $AgNO_3$ impregnated SiO_2-gel. (200g, 55 x 3.5 cm).

CHROMATOGRAM III

Fr.	1	Light petroleum	2 x 250 ml	-	-
Fr.	2	Light petroleum -50% C_6H_6	2 x 250 ml	-	-
Fr.	3	C_6H_6	6 x 50 ml	0.594g	Mixture
Fr.	4	-do-	14 x 50 ml	2.197g	Complex Mixture of alcohols
Fr.	5	-do-	5 x 50 ml	0.86 g	Mixture
Fr.	6	C_6H_6-2% acetone	9 x 50 ml		
Fr.	7	Acetone	-	0.513g	Polar compounds.

Frac. 5 and 6 were combined and further chromatographed (0.8 g) on $AgNO_3$-SiO_2 gel (50 g, 55x1.8 cm)

Fr.	1	C_6H_6	2x100 ml	0.044g	Rejected
Fr.	2	-do-	1x100 ml	0.069g	Complex mixture
Fr.	3	-do-	3x100 ml	0.413g	Rich in neojaeschkeanadiol
Fr.	4	-do-	1x100 ml	0.037g	Rejected.
Fr.	5	C_6H_6-10% $CHCl_3$	8x100 ml	0.074g	Neojaeschkeanadiol
Fr.	6	C_6H_6-50% $CHCl_3$	5x100 ml	0.08 g	Polar compounds.

Frac. 5 was distilled, b.p. 150-60°(bath temp)/0.8 mm to give neojaeschkeanadiol, $[\alpha]_D$+9.85°(c,2.03). Mass:m/e 220 ($M-18^{+}$, 12.5%), 205(19%), 177(62.5%), 162(34%), 159(28%), 135(41%) 121(100%), 107(50%), 93(62.5%), 79(41%), 43(50%).

(Found:C, 75.30; H, 10.90. $C_{15}H_{26}O_2$ requires:C, 75.51; H, 11.0%).

Frac. 3 from the above chromatography was further chromatographed on $AgNO_3$-SiO_2gel (25x1 cm) to get more of neojaeschkeanadiol.

Fr. 1	C_6H_6	3 x 50 ml	-	-
Fr. 2	C_6H_6-50% $CHCl_3$	6 x 50 ml	-	-
Fr. 3	$CHCl_3$	6 x 50 ml	-	-
Fr. 4	$CHCl_3$-5% EtOAc	2 x 50 ml	0.007g	Rejected
Fr. 5	-do-	7 x 50 ml	0.117g	Neojaeschkeanadiol
Fr. 6	-do-	2 x 50 ml	0.092g	Neojaeschkeanadiol with polar impurities.
Fr. 7	$CHCl_3$-10% EtOAc	4 x 50 ml	0.075g	Polar compounds.

Acetylation of jaeschkeanatriol

Jaeschkeanatriol (100 mg), acetic anhydride (2 ml), pyridine (2 ml) were mixed and left overnight at room temperature. Solvent removal followed by the usual work up furnished the hydroxy diacetate (110 mg), which was crystallised from ether-light petroleum as stout needles, m.p. 119-20°, $[\alpha]_D = -19.81°$(c, 2.1%), (Found:C, 67.16; H,9.34. $C_{19}H_{30}O_5$ requires: C, 67.43; H, 8.94%). Mass:m/e 338(M^+, 0.5%), 320(1%), 295(12%), 235(10%), 175(56%), 147(32%), 132(25%), 105(16%), 71(36%), 43(100%).

Dihydrojaeschkeanatriol

Jaeschkeanatriol (1.0g) was hydrogenated over pre-reduced PtO_2(80 mg) in glacial AcOH (15 ml), 25°/710 mm, hydrogenation was complete after uptake of one mole equivalent of H_2(3 hr). The catalyst was filtered, the solvent flashed off and the residue was diluted with water (20 ml). Ether extraction (3x30 ml) followed by the usual work up gave the dihydroderivative (1.040 g) which was crystallised from acetonitrile as fine prisms, m.p. 153-54°, $[\alpha]_D$+21.81°(EtOH, C,2.2%)(Found: C, 70.53; H, 11.29. $C_{15}H_{28}O_3$ requires: C, 70.27; H, 11.01%). IR:OH 3400, 1060 cm^{-1}; PMR(in pyridine):-CH$\underline{Me}$(3H, d, 1.15 ppm, J=6 Hz),-C-$\underline{Me}$(3H, s, 1.35 ppm),-CH($\underline{Me}$)$_2$(6H, 2d centered at 0.93 and 1.025 ppm, J=7 Hz each), two C$\underline{H}$OH (1H each, m, 4.6 and 3.75 ppm) Mass: m/e 256(M^+, 0.2%), 238(0.4%), 213(64%), 195(100%), 177(23.5%), 153(56.4%) 123(92%), 95(70%), 71(99%), 55(47%).

CrO_3 oxidation of dihydrojaeschkeanatriol (3)

To a solution of dihydrojaeschkeanatriol (0.5 g) in acetone (15 ml) Jones reagent was added drop by drop at 15° till a reddish brown colour persisted (1.8 ml). After 30 min. the excess reagent was destroyed by adding a few drops of methanol and diluted with water (25 ml). It was then extracted with ether (3x35 ml) and the ether extract was washed with 10% $NaHCO_3$ aq (2x15 ml), water, brine and dried. The crude diketone (.480 g) obtained after solvent removal was passed through a column of silica gel (15x1.5 cm) and the chloroform eluted material (.45 g) was distilled at 185-90° (bath temp)/1.5 mm, $[\alpha]_D$ -20.61° (c, 1.2%), n_D^{25} 1.4915 (Found: C, 71.57; H, 9.90, $C_{15}H_{24}O_3$ required: C, 71.39; H, 9.59%)

PMR: $M\underline{e}_2CH$(6H, d, 0.925 ppm, J=7Hz), -CH$\underline{Me}$(3H, d, 1.04 ppm, J=7Hz) -C-$\underline{Me}$(3H, s, 1.1 ppm). HO-C-C$\underline{H}$-C=O(1H, s, 3.2 ppm)

Mass: m/e 234(M-18$^+$, 28%), 209(80%), 191(58%), 163(26%), 149(76%), 139(100%), 121(82%), 109(76%), 95(84%), 69(72%).

α,β-Unsaturated ketone (4)

Hydroxy diketone (0.1 g) was refluxed (N_2) with 5% ethanolic KOH (10 ml) for 30 min. The solvent was flashed off and the residue was diluted with water (15 ml). Ether extraction followed by the usual work up gave the

α,β -unsaturated ketone (0.84 g), which was distilled at 140-45°(bath temp.)/0.2 mm. (Found:C,76.44; H, 9.69. $C_{15}H_{22}O_2$ requires: C,76.88; H, 9.46%). Mass: m/e 234 (M^+, 72%), 219(5%), 206(72%), 191(100%),163(40%), 138(40%), 123(28%), 61(80%), 43(99%).

Cyclic carbonate of jaeschkeanatriol(5)

Jaeschkeanatriol (0.1 g) was dissolved in chloroform (alcohol free, 15 ml) containing pyridine (1 ml). The mixture was cooled to 0°C. A solution of phosgene in toluene (20%, 2.5 ml) was added dropwise into the cooled mixture and the mixture was stirred for 75 min. It was left overnight in refrigerator (12 hr). Excess of phosgene was destroyed by addition of ice cold water. After extraction with ether (3 x 25 ml), the ether extract was washed successively with 2N HCl aq(2 x 10 ml), 5% Na_2CO_3 aq (2x10 ml) water (3x10 ml) and finally with brine. The dried extract on evaporation of the solvent gave the solid carbonate (0.125 g) which was crystallised from methylene chloride-light petroleum, m.p. 124-5°, $[\alpha]_D$-34.85°(c,2.89), IR:OH 3480 cm^{-1}, O-CO-O 1765, 1255 cm^{-1}, PMR:-C-Me (3H, s, 1.01 ppm)-$CHMe_2$ (6H, 2d at 0.98 and 1.04 ppm, J=7 Hz each) -C=C-Me(3H, s, 1.82 ppm), one CHOH(1H, m, 3.68 ppm), -OCO-C-H (1H, triplet of doublets at 4.42 ppm, $J_1=J_3=5$ Hz, $J_2=10$ Hz) and -C=C-H (1H, m, 5.46 ppm)(Found:C, 68.35; H, 8.30 $C_{16}H_{24}O_4$ requires: C, 68.57; H, 8.57%)

Oxidation of hydroxycarbonate(6)

Hydroxycarbonate (0.05 g) was dissolved in acetone (methanol free, 2 ml) and was cooled thoroughly(ice-salt). Jones reagent was added gradually till the brown colour persisted($\sim$0.05 ml). It was then left under cold (ice-water) for about 45 min., diluted with water and extracted with ether (3 x 15ml). The product obtained after usual work up (0.04g) was crystallised from methylene chloride-light petroleum, m.p. 125-26°. IR:CO 1740 cm^{-1}, O-CO-O 1765 and 1250 cm^{-1}. PMR: -C-$\underline{Me}$(3H, s, 1.24 ppm),-CH$\underline{Me}_2$ (6H, 2d, 0.85 and 1.06 ppm, J=7Hz each)-C=C-$\underline{Me}$(3H, s, 1.86 ppm) -O-CO-O-C$\underline{H}$ (1H, triplet of doublets 4.55 ppm, J_1=J_3=5 Hz, J_2=10 Hz) and -C=C-$\underline{H}$ (1H, m, 5.53 ppm) Mass: m/e 278(M^+,11%), 262(16%),233(8%), 190(8%), 165(100%), 150(32%), 148(16%), 120(43%), 90(24%) and 40(62%)

(Found: C, 69.13; H, 8.17. $C_{16}H_{22}O_4$ requires: C,69.07; H, 7.914%)

Treatment of ketocarbonate (6) with alkali

Ketocarbonate (0.201 g) was dissolved in ethanol 6-7 ml). To this solution was rapidly added a solution of KOH(0.15 g in 0.3 ml of water) under N_2 atmosphere. The reaction mixture was stirred at room temp. for 3½ hr (N_2). Excess of solvent was evaporated under suction at room temperature and the residue was taken up in ether (20 ml) after dilution with water(5 ml). The ether solution was washed with water (4x5 ml), brine and dried. Evaporation of the solvent furnished compound(0.149 g) which was found to be a mixture of atleast three compounds on TLC (solvent: C_6H_6-10% acetone). It was chromatographed on silica gel (IIB, 3.5 g, 16 x 0.9 cm)

Fr. 1	C_6H_6	5 x 15 ml	0.06g	Liquid Rf 0.65
Fr. 2	C_6H_6-2% EtOAc	6 x 10 ml		Nil
Fr. 3	C_6H_6-4% EtOAc	4 x 15 ml		Nil
Fr. 4	C_6H_6-8% EtOAc	5 x 15 ml	0.038g	Liquid Rf 0.4

<u>Frac</u>. 1 was distilled, b.p. 170-80°(bath temp)/0.8 mm; λ max at 214, 241 and 342 nm (ε, 2880,8930,8498 resp.) IR: C=O 1698, C=C 1610 cm^{-1}, PMR:-C-$\underline{Me}$(3H, s, 1.04 ppm) -CH$\underline{Me}_2$ (6H, 2d at 1.2 and 1.22 ppm, J=7Hz each)-C=C-$\underline{Me}$ (3H, s, 1.9 ppm), -C=CH-CO and -C=C$\underline{H}$ (3H, m,5.97 ppm)

(Found: C, 83.86; H, 9.43. $C_{15}H_{20}O$ requires: C,83.33; H, 9.25%) On the basis of these data the comound was assigned structure (7).

<u>Frac</u>. 4 was distilled, b.p. 180-90° (bath temp.)/1-1.5mm, λ max: 233 nm(ε,8853) IR: OH 3420, C=0 1685 and C=C 1600 cm^{-1} PMR: -C-Me (3H, s, 1.62 ppm)-CH$\underline{Me}_2$(6H,2d at 1.16 and 1.24 ppm, J=7 Hz each)-C=C-$\underline{Me}$ (3H, s, 1.62 ppm), one C$\underline{H}$OH (1H, m, 4.68 ppm),-C=C$\underline{H}$ (1H, m, 5.35 ppm) and -C=C$\underline{H}$-C=0 (1H, s, 6.04 ppm)

(Found: C, 75.73; H,9.399. $C_{15}H_{23}O_2$ requires:C,75.63;

H, 9.663%) Structure (8) is in full agreement with above spectral data.

Tosylate of the hydroxycarbonate

Hydroxycarbonate (0.05 g) was dissolved in anhydrous pyridine (1.1 ml) and the mixture was cooled to 0°. To this cooled solution was added freshly crystallised p-toluenesulfonyl chloride (0.15 g). The mixture was left at room temp. for 10-12 hr. It was then decomposed with ice and water, extracted with ether (2 x15 ml) and the ether solution was washed with cold 1:1 HCl aq (2x5ml), water, brine and dried. Solvent removal under vacuo afforded compound (0.051 g) which was crystallised from ether-pet.ether(40-60°), m.p. 120-1°, $[\alpha]_D$-42.4° . IR: O-CO-O 1760, C-SO_2-O-C 1380 and 1185 cm^{-1}, PMR:-C-<u>Me</u> (3H, s, 1.06 ppm),-CH<u>Me</u>$_2$ (6H, 2d at 0.91 and 0.98 ppm, J=7 Hz each), -C=C-<u>Me</u>(3H, s, 1.82 ppm),Ar-<u>Me</u>(3H, s, 2.5 ppm), -O-CO-O-C<u>H</u> and -C<u>H</u>-O-SO_2-C-(2H, bm, centered at 4.37 ppm),-C=C<u>H</u>(1H, m, 5.42 ppm) and Ar<u>H</u>(4H, a typical AA'BB' quartet centered at 7.63 ppm).

Reduction of the tosylate

(A)-With lithium aluminium hydride

To a stirred slurry of lithium aluminium hydride (0.2g) in ether(5 ml) was added gradually under cooling (ice-salt) a solution of tosylate (0.06g) in ether (5 ml) over a period of 5 min. The reaction mixture was then stirred for an additional six hr (10-20°)

Excess of hydride was destroyed by careful addition of water (0.3 ml) followed by 15% aq NaOH(0.3 ml) and water (1 ml). The white grannular solid was filtered off and washed with ether (20 ml). Removal of the ether from filtrate afforded compound (0.025g) which was identified as jaeschkeanatriol from its PMR spectrum.

(B) With sodium borohydride

Sodium borohydride (0.014 g) was added to a solution of tosylate (0.05 g) in dimethylsulfoxide (3 ml) at room temp. The reaction mixture was first stirred at room temperature for 4 hr and then at 80-90°(bath) for additional 4 hr. After cooling to room temperature, water(5 ml) was added to it and the aqueous phase extracted with ether (2 x 15 ml). The ether extract was washed thoroughly with water (4 x 5 ml) brine and dried. Evaporation of the solvent afforded an oily residue (0.0429 g). Its TLC showed it to be a mixture of atleast three compound from which the major component (Rf 0.18) was separated by PLC (solvent: C_6H_6-3% EtOAc., yield 0.028 g)
IR: OH 3520, C-SO_2-O-C 1370 and 1180 cm^{-1} C=CH (aromatic) 1600 cm^{-1}, PMR:-C-Me(3H, s, 0.95 ppm), -CHMe_2(6H, 2d centered at 0.83 and 0.93 ppm, J=7Hz each),-C=C-Me (3H, s, 1.75 ppm), Ar-Me (3H, s, 2.46ppm), CHOH(1H, m, at 3.41 ppm), CH-O-SO_2-(1H,m,3.94 ppm),-C=CH(1H, m, 5.34 ppm) and ArH (4H, a typical AA'BB' 'quartet' centered at 7.53 ppm).

The above data indicate the compound to be dihydroxy tosylate.

Treatment of tosylate with sodium iodide

(A) Tosylate (0.05 g) was dissolved in anhy. acetone (10ml), NaI(0.022g) was added to it and the mixture was mechanically shaken for 24 hr. Excess of the solvent was removed under vacuo, the residue diluted with water (3 ml) and extracted with ether (2x15 ml). The ether solution was washed with 10% aq $NaHSO_3$ (2 x 5ml), water, brine and dried. Sovent evaporation at room temp. gave compound (0.045 g) which was extablished to be the starting tosylate from its IR and PMR spectral data.

(B) In another set the displacement reaction was carried out at higher temperature. Thus a mixture of tosylate (0.05 g), NaI (0.022 g) and acetone(10 ml) was refluxed for 50 hr, cooled and worked up as above to get compound (0.043 g). It was found to be unchanged tosylate (IR, PMR).

(C) Tosylate (0.05 g) was dissolved in HMPT(hexamethyl phosphorous triamide, 5 ml). NaI (0.02 g) was added to it and the mixture was left at room temp. for 150 hr. After diluting with water the usual work up gave starting tosylate (0.046 g)(IR,PMR)

Reduction of ketocarbonate (6) with LAH

To a suspension of LAH (0.1 g) in ether (5 ml) was added a solution of ketocarbonate (0.05 g) in ether(5 ml) at 0°. After stirring the reaction mixture for 2 hr, excess of hydride was decomposed in an usual manner. The white grannular sold was filtered off and washed with ether(5 ml). Removal of the ether from combined filtrate gave compound (0.042) which was crystallised from acetonitrile, m.p. 164-65°. It was identical in all respects m.p.,mixed m.p., IR, PMR with the naturally occuring jaeschkeanatriol.

The reduction of the ketocarbonate was also carried out with $NaBH_4$, but here too jaeschkeanatriol was obtained.

Reaction of tosylate with pyridine

Tosylate (0.05 g) was dissolved in anhy. pyridine (6 ml) and the solution was refluxed for 2½ hr. After cooling, it was diluted with water (5 ml) and extracted with ether.(3 x 10 ml). The ether extract was washed with 2N HCl aq (3 x 5 ml), with water till neutral and finally with brine and dried. Solvent was evaporated from the dried extract to yield compd. (0.045 g) It was found to be starting tosylate from its IR and PMR spectral data.

In the same manner the above reaction was carried out with collidine as solvent, but in this case too, only the starting tosylate was recovered back(IR, PMR)

Treatment of tosylate with alumina

Tosylate (0.1 g) in benzene (6.6 ml, 2/3 v/w of alumina) was loaded on dry packed column (10 x 1 cm) of alumina (N/I, 10 g). At the end of 32 hr., the compound was eluted out as a gum with benzene containing 2% methanol , (0.08 g). It was found to be dihydroxytosylate from its IR and PMR spectral data (described aarlier).

Reaction of tosylate with potassium tert.butoxide

Tosylate (0.1 g) in DMSO(3 ml) was added to a solution of potassium tert.butoxide (0.112 g) in DMSO (6 ml) at 20-25°. The reaction mixture was then stirred at this temp. for 4 hours. After leaving it for 12 hours at 15-20°, it was decomposed with ice and water and extracted with ether (3 x 15 ml). The ether extract was washed with 2N HCl aq (2 x 5 ml), water (4 x 5 ml) and brine. The dried extract on solvent removal furnished compound (0.15g) which was found to be a complex mixture on TLC (solvent: C_6H_6-10% acetone). It was chromatographed over silica gel (IIB, 5 g, 22 x 1 cm).

Fr 1	C_6H_6	10 x 15 ml	0.005g Mixture
Fr 2	C_6H_6	11 x 15 ml	0.045g Semi solid
Fr 3	C_6H_6-2% EtOAc	10 x 15 ml	0.029g Complex mixture

<u>Frac</u>.2 was found to be dihydroxytosylate (PMR,IR)

Reaction of hydroxycarbonate (5) with $SOCl_2$/pyridine

Hydroxycarbonate (0.1 g), thionyl chloride (0.77 ml), pyridine (0.03 ml) were mixed together in benzene (6ml) and refluxed for 24 hr. After cooling and decomposing with ice-water, the reaction mixture was extracted with ether (3 x 20 ml). The ether solution was washed with 2N HCl aq (2x5 ml). 5% Na_2CO_3 aq (2 x 5 ml), water (3x5 ml) brine and dried. Solvent removal gave compound (0.1 g). It was found to be mixture of atleast two compounds. Separation was affected over silica gel column(12 x 0.9cm)

Fr.	1	C_6H_6	5 x 10 ml	Nil	-
Fr.	2	C_6H_6-2% EtOAc	7 x 10 ml	0.0152 g	Gummy solid
Fr.	3	C_6H_6-5% EtOAc	8 x 10 ml	0.060 g	Solid

Frac. 2 IR: no OH absorption , O-CO-O 1760 cm^{-1}, PMR: -C-Me and $-CHMe_2$ (9H, m, between 0.95 and 1.07 ppm), -C=C-Me(3H, s, 1.83 ppm),-C=C-H (1 H , m, 5.43 ppm) and a two proton broad multiplet at 4.33δ. The compound gets decomposed giving tarry residue on distillation at 120°-30° (bath temp.)/0.8 mm

Frac. 3 was crystallised from methylenechloride-light petroleum, m.p. 124-5°. It was found to be hydroxycarbonate (IR, PMR)

Reduction of fraction 2

Fraction 2 (0.03 g) from above reaction was dissolved in ether (4 ml) and this was added under cooling to a slurry of LAH (0.1 g) in ether (5 ml). After stirring for two hr at room temp. the solution was cooled to 10° and excess of hydride was destroyed by careful addition of water (0.1 ml), 15% aq NaOH(0.1 ml) and water (0.3 ml). The white grannular solid was filtered off and washed with ether (10 ml). The combined filtrate on evaporation of solvent gave compound (0.024 g) which was crystallised from acetonitrile, m.p. 164-3°. It was established to be jaeschkeanatriol on the basis of PMR.

Reaction of hydroxycarbonate with triphenylphosphine-carbontetrachloride

Hydroxycarbonate (0.5g) was dissolved in anhydrous carbontetrachloride (25 ml). Triphenylphosphine(1.9127g, dried over P_2O_5) was added to this solution and it was refluxed for six hr. Excess of the solvent was flashed off and the residue was extracted with benzene (3 x 10 ml). Removal of benzene gave compound (1.5 g) which was chromatographed on silicagel (IIB, 30 g, 30 x 1.5 cms)

Fr. 1 light petroleum	4 x 50 ml	0.040 g	Triphenyl phosphine
Fr. 2 ⌬ C_6H_6	10 x 50 ml	0.305 g	Solid
Fr. 3 Methanol	-	1.0 g	Triphenyl phosphine oxide.

Frac. 2 was crystallised from petroleum ether(40-60°) m.p. 151-2°, $[\alpha]_D$+14.12°(c, 1.35), IR:O-CO-O 1740 and C-Cl 790 cm^{-1}. PMR: -C-<u>Me</u> (3H, s, 1.2 ppm)-CH<u>Me</u>$_2$(6H, 2d at 1.05 and 1.14 ppm, J=7Hz each)-C=C-<u>Me</u> (3H, s, 1.86 ppm), -C<u>H</u>-Cl and C<u>H</u>-O-CO-O(2H, m, 4.37 ppm), -C=C-<u>H</u> (1H, m, 5.52 ppm) Mass:m/e 298(M^+,27%), 211(100%) 183(30%),175(77%),169(48%),157(48%),147(79%), 133(64%), 121(53%), 105(75%), 91(62%), 55(62%), 43(99%). (Found: C, 63.83; H, 7.77. $C_{16}H_{23}O_3Cl$ requires: C,64.33; H, 7.7%)

<u>Reduction of chlorocarbonate</u> (10)<u> with LAH</u>

Chloride (0.2 g) in diglyme (freshly distilled over LAH, 5 ml) was added to a suspension of LAH (0.4361g) in diglyme (10 ml) and the mixture was stirred (N_2) for 15 hr at 110-20° (bath temp). Excess of hydride was then decomposed by careful addition of water (1 ml), 15% aq NaOH (1 ml) and water (3 ml) to the cooled reaction mixture (5°C). More water was then added (10 ml) and the aqueous phase was extracted with ether (3 x20 ml). The ether solution was washed with water (4 x 5 ml), brine and dried. Solvent was flashed off to get compound (0.121 g) which was found to be complex mixture on TLC (solvent: C_6H_6-25% EtOAc). It was chromatographed over silica gel (IIB, 4.5 g, 22x0.9 cm)

Fr.	1	C_6H_6	5 x 10 ml	0.009 g	Rejected
Fr.	2	C_6H_6	10 x 10 ml	0.019 g	Jaeschkeanadiol
Fr.	3	C_6H_6	14 x 10 ml	0.013 g	Mixture of jaeschkeanadiol and chlorodiol
Fr.	4	C_6H_6-5% EtOAc	4 x 10 ml	0.06 g	Polar compounds rich in chlorodiol

<u>Frac</u>. 2 solidified on trituration with petroleum ether (40-60°). It was established to be jaeschkeanadiol on the basis of its IR and PMR spectral data which is identical with that of authentic sample of jaeschkeanadiol.

<u>Frac</u>. 3 was found to be mixture of jaeschkeanadiol and chlorodiol from the PMR of the crude mixture.

SUMMARY

Jaeschkeanatriol, the second major component of *Ferula jaeschkeana* is shown to possess structure (1). Its stereochemistry has been established by a direct chemical correlation with jaeschkeanadiol (11)

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