CHAPTER-III

JH MIMICS BASED ON BAKUCHIOL

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ABSTRACT

Several derivatives of bakuchiol, a meroterpenoid from *Psoralea corylifolia* Linn., have been prepared and evaluated for insect juvenile hormone activity against *Dysdercus koenigii* nymphs. Almost all of these were found to be more active than the standard farnesyl methyl ether, while some of these proved to be many times more potent.

JH MIMICS BASED ON BAKUCHIOL

The extracts of many plants have been found to exhibit juvenile hormone (JH) activity.[1] Pet. ether extract of seeds of Psoralea corylifolia Linn. was found by Joshi et al.[2] to completely inhibit the metamorphosis of the red cotton bug Dysdercus koenigii. Treatment of the last instar nymphs with a 10 µg/nymph dose of the extract was found to result in the production of supernumerary giant nymphs which failed to develop into mature adults and eventually died. Lower doses of the same extract produced nymph-adults mixtures which never mated or laid eggs. Even when the extract was applied on freshly laid eggs the embryonic development of the latter got disrupted indicating the potential use of the extract as a hormonal chemosterilant.

Bakuchiol (1)[3-5] a meroterpenoid is the chief constituent of the seed extract and was found to be responsible for the JH activity exhibited by the extract.[6] The compound exhibited JH activity more potent than that exhibited by the naturally occurring JH mimic juvabion (9).[7] The structure of bakuchiol is reminiscent of certain synthetic JH mimics (e.g. 5,[8] 6,[8] 7[9] 8,[10]) incorporating a benzene ring in the structure.

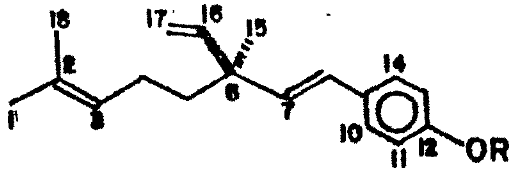
A survey[11] of the structural modifications which tend to enhance JH activity revealed that the presence of oxirane, methoxyl, ethoxyl, hydroxyl or halogen functions enhanced the JH activity of a compound.

Keeping in view the above considerations, bakuchiol was transformed into compounds bearing the JH-activity enhancing functional groups and their activity was evaluated on the red cotton bug, Dysdercus koenigii.

RESULTS

Liberal amounts of bakuchiol could be isolated fairly easily from the seeds of Psoralea corylifolia Linn.[3] The petroleum ether extract of seeds contained bakuchiol as the major component which could be obtained in pure form by column chromatography of the extract over silica gel (overall yield, 1.6% on the dry weight of seeds).

Eleven derivatives (2-4; 10-17) based on bakuchiol (1) and four each (19-22; 24-27), derived from 7,8-dihydrobakuchiol methyl ether (18) and 7,8,16,17-tetrahydrobakuchiol methyl ether (23) were synthesised.



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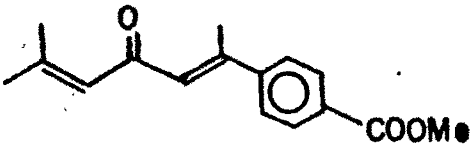
2: R = Me

3: R = Et

4: R = *n*-Pr



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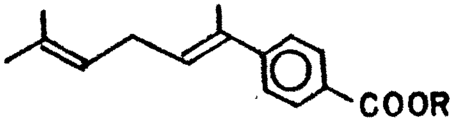

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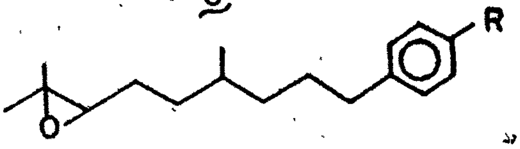

R = Et, *iso*-Pr

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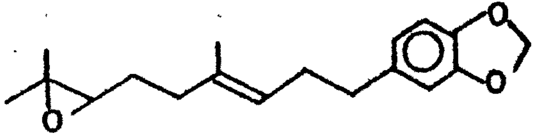

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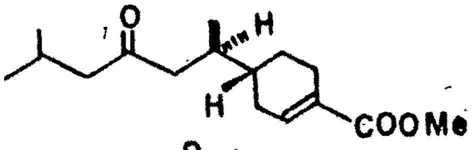

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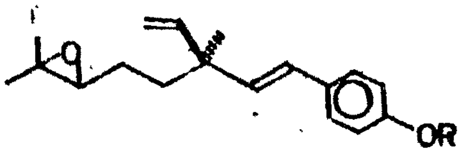
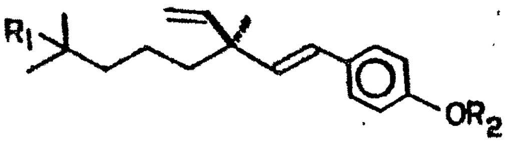
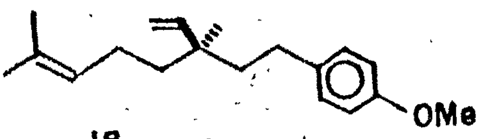


10 : R = Me
11 : R = Et
12 : R = n - Pr



	R_1	R_2
13	Cl	Me
14	OH	Me
15	OMe	Me
16	OH	Et
17	OH	n-Pr



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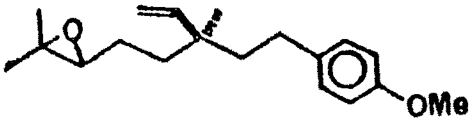

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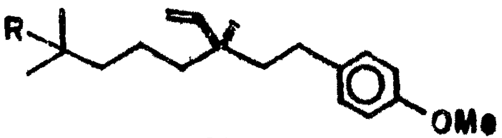
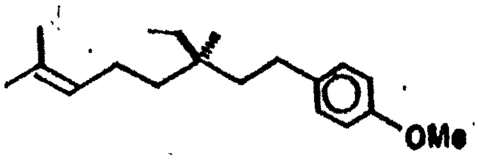


20 : R = Cl
21 : R = OH
22 : R = OMe



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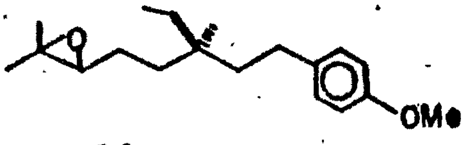

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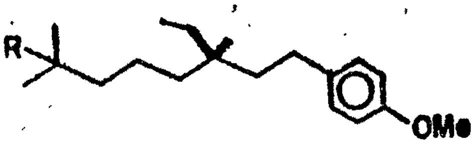

25 : R = Cl
26 : R = OH
27 : R = OMe

Alkylations of bakuchiol were carried out using sodium hydride/THF with the appropriate alkylating agent[12] and the alkyl ethers isolated in the usual manner. Dev et al.[3] had prepared 7,8-dihydrobakuchiol by H_2/Pd-C/EtOH method. However, it was more conveniently prepared by reduction with sodium-ammonia[13]. t-Butanol was found the best solvent for both selectivity as well as the completion of the reaction. 7,8,16,17-Tetrahydrobakuchiol required for the preparation of (23) was obtained by hydrogenation of bakuchiol in ethanol over 5% Pd-$CaCO_3$ catalyst,[3] and the product purified by chromotography over silver nitrate impregnated silica gel (to separate the tetrahydro product from some hexahydro product).

Selective epoxidation of the 2,3-olefinic linkage could only be achieved by the action of molar equivalent of perbenzoic acid (PBA) in benzene solution[14] while PBA in chloroform or aq. peracetic acid gave, in general, complex mixtures. The oxiranes were taken as the starting material for the synthesis of 2-hydroxy derivatives (14, 16, 17, 21, 26). This was achieved by the reduction of the oxirane with lithium aluminium hydride in tetrahydrofuran.[15]

The corresponding 2-methoxy derivatives were next prepared by the O-methylation of the C-2 hydroxyl group with sodium hydride and iodomethane in tetrahydrofuran.

The 2-chloro derivatives (13, 20, 25) were obtained by the addition of the calculated amount of hydrogen chloride to the substrate. This was achieved by generating HCl *in situ* by addition of calculated amounts of acetyl chloride to a solution of absolute methanol in glacial acetic acid.

The structures of compounds thus synthesised are fully borne out by their spectral (UV, IR, PMR & Mass) and analytical data which have been summarised in Tables I-IV.

TABLE I. UV AND IR SPECTRA OF BAKUCHIOL DERIVATIVES

Structure	λ_{max}^{EtOH} nm(ε)	$\nu_{CCl_4}^{max}$ (cm^{-1})		
		$-CH{=}CH_2$	$-CH{=}CH-$	others
2	262(22930)	916	972	1610, 1525, 1252, 1180, 1040, 825
3	265(17750)	910	970	1605, 1505, 1242, 1170, 1120, 1046
4	266(22926)	905	970	1602, 1504, 1450, 1245, 1110
10	262(23120)	916	972	1610, 1530, 1252, 1180, 1040
11	265(18326)	910	962	1602, 1502, 1240, 1170, 1110, 1040
12	265(22570)	908	968	1602, 1505, 1460, 1375, 1240, 1170, 1110
13	262(15220)	915	972	1605, 1510, 1246, 1175, 1035, 740
14	262(24590)	910	970	3400, 1615, 1510, 1246, 1175, 1035
15	262(25166)	900	960	1596, 1500, 1238, 1166, 1070, 1025
16	264(15923)	900	960	3330, 1600, 1500, 1240, 1162, 1036
17	265(19812)	905	970	3330, 1600, 1500, 1235, 1162
18	230(6547); 280(1940) 287(1637)	920	-	1615, 1510, 1460, 1250, 1178, 1045
19	231(4050); 278(1830)	920	-	1615, 1510, 1465, 1246, 1042
20	230(6869); 280(1954) 287(1639)	920	-	1615, 1515, 1250, 1049, 730
21	229(4930); 279(2071)	920	-	3430, 1616, 1512, 1470, 1245, 1044
22	230(5341); 279(1910)	920	-	1618, 1515, 1470, 1255, 1090, 1060
23	230(6532); 281(1973) 288(1655)	-	-	1615, 1515, 1470, 1245, 1180, 1045
24	227(6842); 278(1793)	-	-	1614, 1510, 1465, 1380, 1250, 1180, 1045
25	230(2702); 280(1581)	-	-	1620, 1518, 1472, 1252, 1182, 1049, 730
26	229(5369); 281(1494)	-	-	3600, 1612, 1510, 1470, 1248, 1176, 1040
27	228(2516); 282(628)	-	-	1610, 1510, 1465, 1365, 1380, 1245, 1178, 1084, 1040

TABLE II. PMR SPECTRAL CHARACTERISTICS[a] OF BAKUCHIOL DERIVATIVES

Structure	Ar-H 4H,AA'BB' (Δν/J)	Δ^7 2H,AB-q J=16cps	Δ^{16} 3H,ABC-type	C-3(H)	C-6(Me) (s)	C-2(Me's)	Ar-OMe or Ar-OCH_2R	Other signals
2	6.96(4.43)	6.06	4.85-6.05	∼5.1	1.18	1.56,1.65	3.78(3H,s)	-
3	6.92(4.59)	6.04	4.85-6.05	∼5.1	1.18	1.56,1.65	3.94(q,J=7)	
4	6.91(4.55)	6.05	4.82-6.00	∼5.1	1.18	1.55,1.65	3.83(t,J=6)	-
10	6.98(4.43)	6.10	4.88-6.02	2.52 (t,J=6)	1.23	1.20(6H)	3.77(3H,s)	-
11	6.90(4.55)	6.04	4.85-5.97	2.47 (t,J=6)	1.20	1.17(6H)	3.95(q,J=7)	-
12	6.91(4.55)	6.05	4.85-6.00	2.48 (t,J=5)	1.20	1.16(6H)	3.85(t,J=6)	-
13	6.95(4.45)	6.09	4.85-6.05	-	1.19	1.52(6H)	3.76(3H,s)	-
14	6.95(4.53)	6.08	4.85-6.05	-	1.18	1.13(6H)	3.75(3H,s)	-
15	6.95(4.53)	6.08	4.85-6.05	-	1.18	1.06(6H)	3.77(3H,s)	OMe(C-2): 3.07(s)
16	6.92(4.57)	6.05	4.85-6.00	-	1.17	1.12(6H)	3.94(q,J=7)	-
17	6.91(4.57)	6.05	4.85-6.00	-	1.17	1.13(6H)	3.85(t,J=6)	-
18	6.79(2.76)	-	4.85-6.00	∼5.1	1.10	1.57,1.65	3.68(3H,s)	ArCH_2: 2.40(m)
19	6.81(2.69)	-	4.80-5.90	∼2.45	1.04	1.20,1.23	3.71(3H,s)	ArCH_2: 2.40(m)
20	6.80(2.79)	-	4.75-5.90	-	1.03	1.52(6H)	3.71(3H,s)	ArCH_2: 2.40(m)
21	6.82(2.65)	-	4.80-5.95	-	1.03	1.15(6H)	3.73(3H,s)	ArCH_2: 2.42(m)
22	6.79(2.69)	-	4.75-5.90	-	1.01	1.06(6H)	3.70(3H,s)	ArCH_2: 2.38(m) OMe(C-2): 3.05(s)
23	6.81(2.79)	-	-	5.05 (t,J:7)	0.85	1.60,1.67	3.71(3H,s)	ArCH_2: 2.40(m)
24	6.82(2.75)	-	-	∼2.45	0.90	1.23,1.25	3.74(3H,s)	ArCH_2: 2.43(m)
25	6.81(2.75)	-	-	-	0.88	1.54(6H)	3.72(3H,s)	ArCH_2: 2.38(m)
26	6.81(2.75)	-	-	-	0.88	1.17(6H)	3.72(3H,s)	ArCH_2: 2.40(m)
27	6.83(2.75)	-	-	-	0.88	1.10(6H)	3.73(3H,s)	ArCH_2: 2.41(m) OMe(C-2): 3.11(s)

[a] Chemical shifts in ppm; s(singlet), t(triplet), q(quartet), m(multiplet)

TABLE III. MASS SPECTRA[a] OF BAKUCHIOL DERIVATIVES

Structure	m/e(%)	1	2	3	4	5	6	7	8	9	10
2	270(21.3)	227(7.3)	201(13.1)	188(18.0)	187(100)	172(12.3)	159(14.8)	158(11.4)	135(10.6)	129(10.6)	121(36.9)
3	284(23.0)	272(15.3)	201(84.6)	187(19.0)	163(20.5)	161(25.6)	145(18.0)	135(43.5)	134(47.4)	121(100)	107(25.6
4	298(37.0)	216(20.6)	215(100)	173(37)	158(10.5)	149(29.6)	145(18.5)	121(11.1)	120(9.8)	107(28.4)	93(10.5)
10	286(16.3)	188(15.4)	187(100)	185(7.2)	172(11.8)	159(14.4)	158(9.0)	129(9.0)	128(7.7)	121(30.9)	115(6.3)
11	300(5.2)	201(52.6)	189(18.4)	135(18.4)	134(15.9)	122(16.9)	121(100)	107(10.5)	105(9.2)	59(11.8)	55(10.5)
12	314(72.0)	299(17.0)	298(63.0)	216(42.2)	215(100)	173(53.9)	155(20.1)	149(37.0)	145(20.1)	107(23.3)	105(35.0)
13	306(1.5)	270(23.8)	188(15.8)	187(79.3)	159(14.2)	134(38.0)	122(11.0)	121(100)	119(11.0)	115(9.0)	91(16.6)
14	288(9.8)	270(2.1)	199(4.8)	188(16.6)	187(100)	172(9.1)	159(9.5)	158(7.0)	129(4.8)	121(22.2)	91(4.8)
15	302(10.0)	270(4.6)	199(5.4)	188(15.9)	187(100)	172(8.4)	159(8.4)	158(6.2)	121(21.7)	115(4.6)	83(5.4)
16	302(12.8)	284(3.0	215(18.0)	202(18.0)	201(100)	173(18.5)	158(7.0)	145(13.5)	135(8.5)	107(17.0)	91(5.7)
17	316(3.0)	298(60.6)	216(20.2)	215(100)	173(35.3)	149(19.1)	145(18.1)	107(29.3)	95(10.5)	91(10.0)	81(10.0)
18	272(18.3)	187(15.8)	135(23.7)	134(53.4)	122(10.8)	121(100)	91(5.8)	83(4.9)	81(4.9)	69(11.8)	55(9.8)
19	288(14.8)	255(5.8)	203(12.2)	187(32.2)	135(54.8)	134(95.4)	122(27.0)	121(100)	105(14.8)	96(17.5)	91(18.0)
20	308(3.5)	272(9.4)	270(2.0)	187(16.4)	135(31.7)	134(78.8)	122(9.0)	121(100)	69(18.5)	55(14.1)	43(15.2)
21	290(12.3)	272(5.3)	187(17.7)	135(31.7)	134(78.8)	121(100)	95(4.4)	91(5.3)	81(14.1)	59(15.0)	
22	304(9.4)	272(21.3)	187(27.3)	135(32.4)	134(65.8)	122(11.9)	121(100)	91(7.3)	81(13.6)	73(91.4)	
23	274(13.7)	246(3.6)	245(18.3)	190(5.5)	189(37.1)	187(7.3)	135(7.3)	134(9.1)	122(10.6)	121(100)	91(6.3)
24	290(8.3)	261(6.2)	232(4.8)	205(7.6)	189(19.4)	161(4.8)	137(7.0)	135(8.3)	134(14.5)	122(13.9)	121(100)
25	310(12.0)	274(5.2)	245(9.5)	189(15.2)	135(6.8)	134(6.3)	122(11.0)	121(100)	83(4.2)	77(3.7)	73(5.2)
26	292(2.8)	290(4.6)	274(3.2)	245(8.0)	189(27.2)	161(4.6)	147(5.0)	137(5.0)	135(7.4)	122(12.5)	121(100)
27	306(2.7)	274(9.9)	245(16.4)	189(41.7)	135(7.1)	134(10.9)	122(10.0)	121(100)	83(10.4)	73(85.7)	71(5.4)

[a] Ten most abundant ions, besides molecular ion, are given.

TABLE IV. PHYSICAL PROPERTIES AND ELEMENTAL ANALYSES OF BAKUCHIOL DERIVATIVES

Structure	Molecular formula	B.P (°C/mm)	n_D^{25}	$[\alpha]_D^{25}$[c] (c)	Analyses Found (%) C		Calc. (%) C	
					C	H	C	H
2	$C_{19}H_{26}O$	133-35/0.4[a]	1.5402[b]					
3	$C_{20}H_{28}O$	144-45/0.1[a]	1.5338	+29.47(1.7)	84.20	9.78	84.45	9.92
4	$C_{21}H_{30}O$	140-42/0.2[a]	1.5294	+26.62(3.6)	85.00	10.09	84.51	10.13
10	$C_{19}H_{26}O_2$	190-95/0.2	1.5300	+33.84(2.5)	79.27	9.26	79.68	9.15
11	$C_{20}H_{28}O_2$	180-98/0.4	1.5314	+34.03(3.6)	80.04	8.97	79.95	9.39
12	$C_{21}H_{30}O_2$	178-84/0.1	1.5228	+25.55(3.1)	80.69	9.34	80.21	9.41
13	$C_{19}H_{27}OCl$	-	1.5341	+15.39(5.1)	-	-	-	-
14	$C_{19}H_{28}O_2$	175-80/0.3	1.5340[b]	+35.40(1.3)	78.81	10.14	79.12	9.78
15	$C_{20}H_{30}O_2$	155-66/0.3	1.5231[b]	+33.37(1.3)	79.36	10.16	79.42	9.99
16	$C_{20}H_{30}O_2$	185-90/0.1	1.5324	+43.82(1.1)	79.91	9.99	79.42	9.99
17	$C_{21}H_{32}O_2$	184-90/0.3	1.5292	+29.17(4.6)	80.11	9.69	79.70	10.19
18	$C_{19}H_{28}O$	144-46/0.8[a]	1.5130[b]	+9.90(2.7)	84.20	9.90	83.77	10.35
19	$C_{19}H_{28}O_2$	165-70/0.3	1.5076[b]	+16.73(1 5)	78.70	9.36	79.12	9.78
20	$C_{19}H_{29}OCl$	-	1.5078	+11.69(1.1)	-	-	-	-
21	$C_{19}H_{30}O_2$	175-80/0.3	1.5095	+21.72(2.0)	78.13	9.97	78.57	10.41
22	$C_{20}H_{32}O_2$	165-70/0.6	1.4964[b]	+14.95(2.7)	78.75	10.42	78.90	10.59
23	$C_{19}H_{30}O$	142-44/1.0[a]	1.5032	±0	82.96	10.50	83.15	11.01
24	$C_{19}H_{30}O_2$	140-45/0.2	1.5140	±0	78.77	9.93	78.57	10.41
25	$C_{19}H_{31}OCl$	-	1.5015	±0	-	-	-	-
26	$C_{19}H_{32}O_2$	170-75/0.2	1.5018	±0	77.66	10.49	78.03	11.00
27	$C_{20}H_{34}O_2$	140-45/0.1	1.4921	±0	78.72	10.93	78.38	11.18

[a] Uncorrected boiling points. The remaining entries indicate the temp. of the bath (bulb distillations).

[b] These measurements are at 30°C.

[c] Specific rotations in chloroform solution.

Juvenile Hormone Activity

The activity of these compounds has been tested on 4 hr. old last instar nymphs of red cotton bug, *Dysdercus koenigii*, using 10, 1.0 and 0.1 ug of each compound in acetone as a topical application and evaluating the results in terms of inhibition of metamorphosis. Farnesyl methyl ether was used as a reference compound. Summery of these results is given in Table V.

From an analysis of the JH-activity data (Table V), it is clear that bakuchiol (1) provides a valuable model for JH-mimics. Ethers (2, 3, 4) are more potent than the corresponding free phenol (1), 2-hydroxy (14, 21, 26) are more potent than the 2-methoxy (15, 22, 27) analogues. 2,3-Epoxy derivatives (10, 19. 24) are in general, more potent than the corresponding 2-chloro (13, 20, 25), 2-hydroxy (14, 21, 26) or 2-methoxy (15, 22, 27) analogues. Both Δ^7 and Δ^{16} appear to be essential for good activity (2-4 and 10-17 as compared to 18-27). 2,3-Epoxybakuchiol propyl ether (12) is most potent of the compounds investigated in the present study and deserves further detailed exploration of its activity in other systems.

TABLE V. JUVENILE HORMONE ACTIVITY OF SOME BAKUCHIOL DERIVATIVES

Compound	Dose/nymph		
	10	1	0.1
	Score[a]		
Farnesyl methyl ether	1.5	0.0	-
2	4.0	1.4	-
3	4.0	4.0	1.5
4	4.0	3.4	0.0
10	4.0	4.0	-
11	4.0	4.0	2.0
12	4.0	4.0	2.9
13	4.0	1.5	-
14	4.0	3.7	-
15	4.0	0.7	-
16	4.0	4.0	1.8
17	4.0	4.0	1.2
18	1.5	0.0	-
19	4.0	0.1	-
20	4.0	0.0	-
21	3.1	0.3	-
22	2.7	0.0	-
23	1.5	0.0	-
24	4.0	0.1	-
25	3.0	0.0	-
26	2.5	0.3	-
27	1.8	0.0	-
Bakuchiol[b]	3.0	1.0	-

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[a] Score represents the mean of two experiments, each of which was carried out using three replicates of 15 nymphs each. Nymphs which successfully moulted were characterised and scored as: normal adults (0), adult-nymphs (1), intermediates (2), nymph-adults (3), and sixth instar nymphs (4).

[b] From ref. 8

EXPERIMENTAL

For general remarks, see Chapter II, Experimental.

Purity of each new compound was ascertained by thin layer chromatography of the material on 0.3 mm layers of silica gel (solv. 20% EtOAc in benzene, unless stated to the contrary.

Bakuchiol (1)

Whole seeds (670 gms) of Psoralea corylifolia Linn. (with pericarp intact) were extracted with pet. ether (60-80) in a soxholet apparatus. Removal of solvent furnished the extract (16.2 gms). Bakuchiol was obtained by chromatography of the extract on silica gel (IIA, 117 gms; column: 11 x 2 cm) and following fractions were collected.

Chromatogram

Fr. No.	Eluent	Vol. of eluent	Wt/gms
1	Pet. ether (60-80)	100 x 8 ml	0.1231
2	5% ether in pet. ether	100 x 3 ml	0.0047
3	25% ether in pet. ether	100 x 11 ml	13.1265
4	50% ether in pet. ether	100 x 3 ml	0.2661
5	Ether	100 x 6 ml	2.4052
		Total	15.9256

Fraction 3, a mixture of three compounds was re-chromatographed on silica gel (IIA, 180 gms, column; 42 x 3 cm).

Chromatogram

Fr. No.	Eluent	Vol. of eluent/ml	Wt./gms
1	Pet. ether (60-80)	500 x 8	-
2	5% ether in pet. ether	100 x 12	-
3	10% ether in pet. ether	100 x 8	10.3974
4	25% ether in pet. ether	100 x 4	1.4321
5	Ether	100 x 8	2.7211
		Total	14.5506 gms.

Fraction 3 was distilled 184^{0}(bath)/4 mm to give bakuchiol (1) as golden yellow oil (1.6% overall yield) having spectral characteristics identical with those reported earlier.[3] Dev *et al.*[3] had reported an overall yield of 7.2% bakuchiol (on the dry weight of seeds). The low yield obtained in the present study may be due to the fact the seeds were in storage for a long time before being extracted.

7,8-Dihydrobakuchiol

Sodium pieces (1.3 g; 0.056 g atom) were added to a stirred solution of t-butanol (50 ml) and liquid ammonia (300 ml). The deep blue solution was stirred for 10 mins. followed by cautious addition of solid NH_4Cl (2.0 gms). Ammonia was allowed to evaporate to half the volume when the reaction mixture was cautiously diluted with water (50 ml). After leaving the solution overnight at room temperature it was extracted with ether (25 x 4 ml) and the ether extract washed with water (25 x 6 ml) and brine (25 x 2 ml). Solvent removal gave a reddish oil which was distilled to give pure (tlc solvent, 40% diethyl ether in hexane) 7,8-dihydrobakuchiol[3] (4.32 g; yield, 86%).

7,8,16,17-Tetrahydrobakuchiol

Bakuchiol (2.77g) dissolved in absolute ethanol (25 ml) was hydrogenated over 5% Pd-$CaCO_3$ (372 mg) at 730 mm pressure and at 29°C until two equivalent of hydrogen (560 ml) was absorbed. The product which contained some hexahydrobakuchiol was purified by column chromatography (10% $AgNO_3$-SiO_2, 100 g; column, 24 x 3.5 cm).

Chromatogram

Fr. No.	Eluent	Vol. of eluent/ml	Wt./gms
1	Pet. ether (60-80)	200 x 5	-
2	5% Ether in pet. ether	200 x 5	0.8102
3	10% ether in pet. ether	200 x 20	1.8414
4	Ether	500 x 2	0.0021
		Total	2.6537

Fraction 2 was identified as hexahydrobakuchiol while Fraction 3 was pure (tlc: 5% $AgNO_3$-SiO_2; solvent: 20% ether-hexane) 7,8,16,17-tetrahydrobakuchiol[3] (1.84 g).

Alkylation of phenols

The following is illustrative of the general procedure followed for alkylation of bakuchiol (1) and its dihydro and tetrahydro derivatives.

Bakuchiol (3.2 g; 12.5 mmole) dissolved in dry THF (10 ml) was injected into a suspension of sodium hydride (6.0 g as oil dispersion; washed with ether; NaH, 3.0 g; 130 mmol) in THF (10 ml) and ethyl iodide (20.28 gm, 130 mmol). The mixture was stirred at room temperature for 0.5 hr and at reflux for 6 hrs. The excess hydride was decomposed by cautious addition of water (20 ml). The organic layer was separated and the aqueous layer extracted with ether (25 ml x 3). The combined organic layer was washed with water (20 ml x 3) and brine (15 ml x 2), dried (Na_2SO_4) and freed from solvent to give a residue which on distillation gave bakuchiol ethyl ether (3.72 g; yield 91%). Methyl and n-propyl iodide were used for the preparation of the corresponding alkyl ethers; yields varied 87-91%.

Epoxidation of 2,3-olefinic linkage

Epoxidations were carried out as illustrated below. A chilled solution of perbenzoic acid (0.97 g; 7.0 mmol) in benzene (23 ml) was added dropwise to bakuchiol ethyl ether (2.0 g; 7.0 mmol) and the solution was kept 0-5°C for 14 hrs. The mixture was diluted with ether (10 ml) and washed with water (5 ml), aqueous sodium carbonate (5%; 15 ml x 3), water (25 ml x 4) and brine (25 ml x 2). It was dried (Na_2SO_4), freed from solvent and the residue was purified by I DCC[16] (SiO_2, 250 g; column, 25.0 x 4.7 cm; solvent, 11% EtOAc in benzene) and distilled to give pure 2,3-epoxybakuchiol ethyl ether (1.77 g; yield, 85%)

Reduction of 2,3-epoxy derivatives to 2-hydroxy compounds

The following is illustrative of the general procedure used for the reduction of 2,3-epoxybakuchiol derivatives to the corresponding 2-hydroxy compounds. 2,3-Epoxybakuchiol methyl ether (1.43 g; 5 mmol) in THF (5 ml) was added dropwise to a stirred suspension of LAH (0.19 g; 5 mmol) in THF (5 ml) at 0^{o} under N_2 blanket and the mixture was stirred for 0.5 hr at $0^{o}C$; and at reflux for 4 hrs. The excess hydride was decomposed with a saturated solution of Rochelle salt (25 ml). The organics were separated and aqueous portion extracted with ether (25 ml x 3). The combined organic layer was washed with water (25 ml x 5) and brine (25 ml x 2) and dried (Na_2SO_4). Removal of solvent gave a colourless viscous residue which was distilled to give pure 2-hydroxybakuchiol methyl ether as a colourless oil (1.22 g; yield 87%).

O-Methylation of 2-hydroxy derivatives

O-Methylation of 2-hydroxy derivatives was typically carried out as follows. 2-Hydroxybakuchiol methyl ether (0.288g; 1 mmol) in dry THF (5 ml) was injected slowly (10 mins) with stirring to a suspension of sod. hydride (4.8 g, oil dispersion washed with ether; NaH, 2.4 g, 100 mmol) in THF (5 ml) and methyl iodide (2 ml) under

N_2 blanket. The mixture was stirred for 1.5 hr at room temperature and 1.0 hr at reflux. The excess hydride was decomposed with water (40 ml) added dropwise. The aqueous layer was separated and extracted with ether (20 ml x 2). The combined organic layers were washed with water (30 ml x 3) and brine (25 ml x 2), dried (Na_2SO_4) freed from solvent and residue distilled to give 2-methoxy bakuchiol methyl ether as a colourless oil (0.274 g; yield, 91%), homogenous by tlc (solvent: 40% diethyl ether in hexane).

Addition of HCl to bakuchiol derivatives

Addition of HCl across the 2,3-double bond of bakuchiol derivatives was typically carried out as follows: Acetyl chloride (0.39 g; 5.0 mmol) was added to a solution of absolute methanol (0.16 g; 5.0 mmol) in glacial acetic acid (10 ml) at 16-17°C and the mixture was allowed to stand for 0.5 hr. This solution (1 ml: 0.5 mmol HCl) was added to bakuchiol methyl ether (0.135 g; 0.5 mmol) at 0°C and the solution allowed to stand at 0-5°C for 14 hrs. The reaction mixture was diluted with water (5 ml) and extracted with ether (10 ml x 3). The ether extract was washed with aqueous sodium bicarbonate (5%; 10 ml x 2), water (20 ml x 6) and brine (10 ml x 2), dried (Na_2SO_4)

and freed from solvent. The residue (0.15 g) was purified by IDCC (SiO_2, 20g; column, 25 x 1.5 cm; solvent, 20% EtOAc in benzene) to give pure (tlc) 2-chlorobakuchiol methyl ether (0.121 g; yield 79%.).

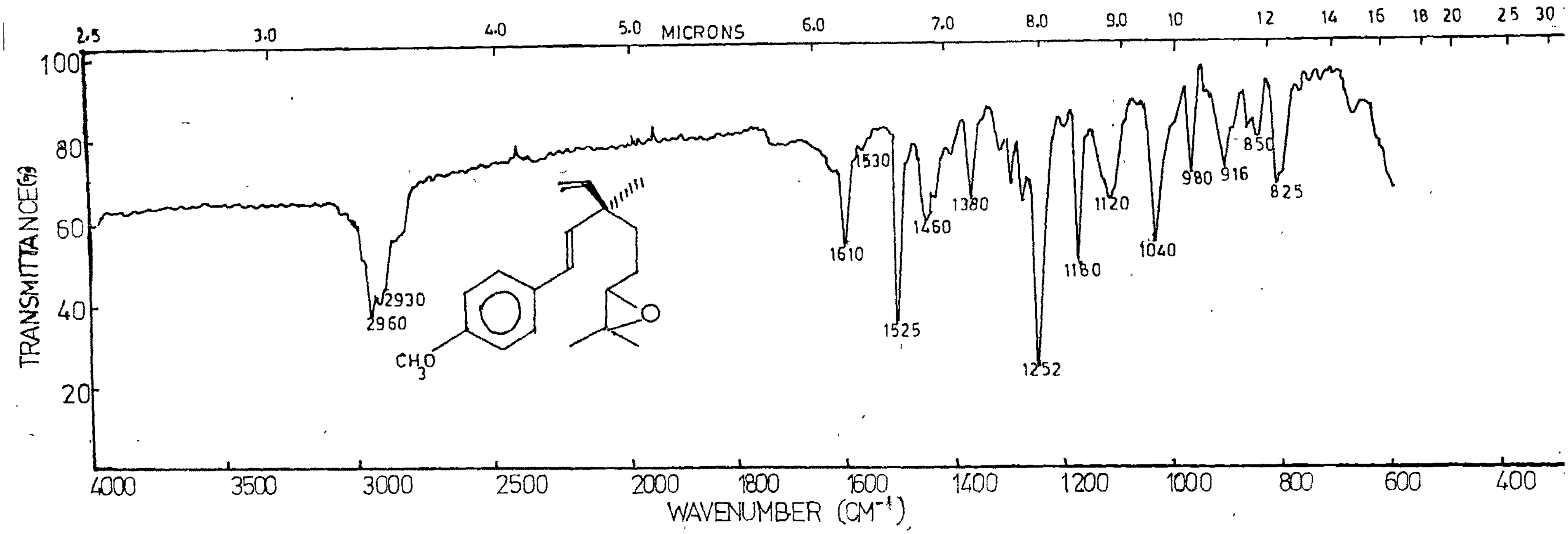


FIG. III-1: IR SPECTRUM OF 2,3-EPOXY BAKUCHIOL METHYL ETHER (10)

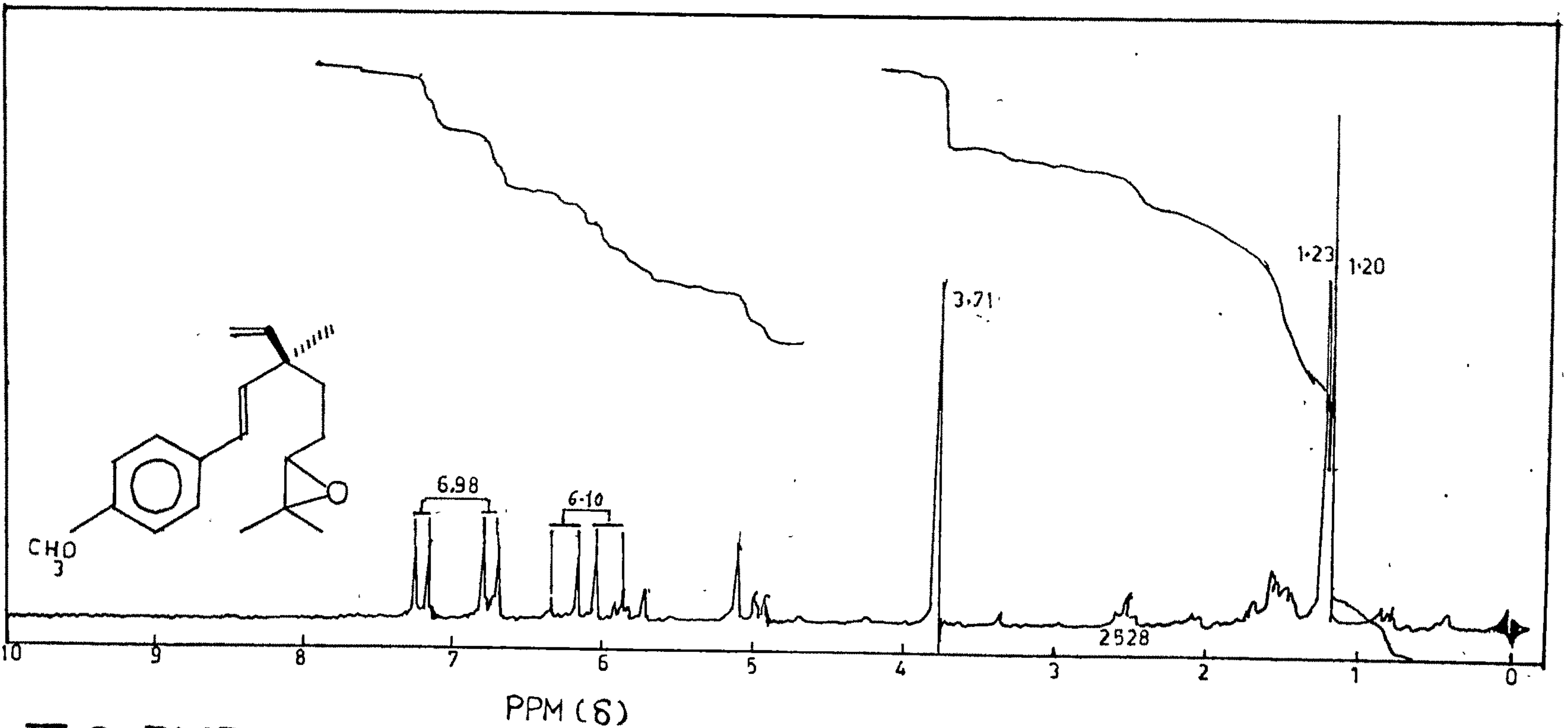


FIG. III-2: PMR SPECTRUM OF 2,3-EPOXY BAKUCHIOL METHYL ETHER (10)

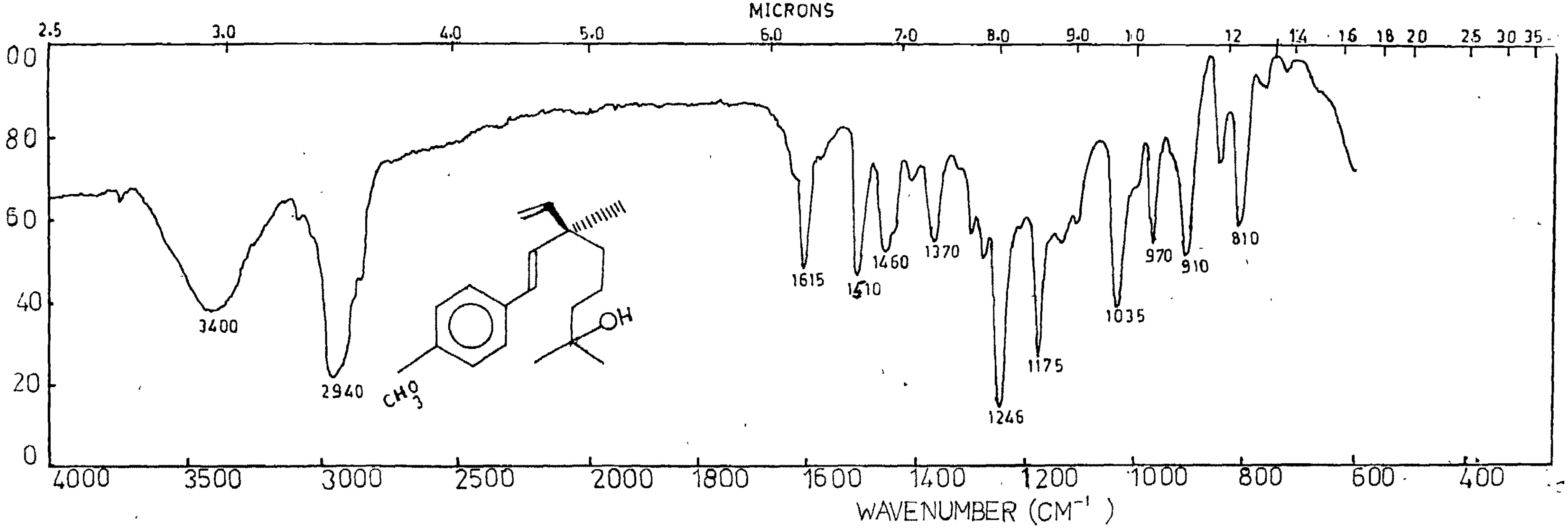


FIG.III-3: IR SPECTRUM OF 2-HYDROXY BAKUCHIOL METHYL ETHER (14

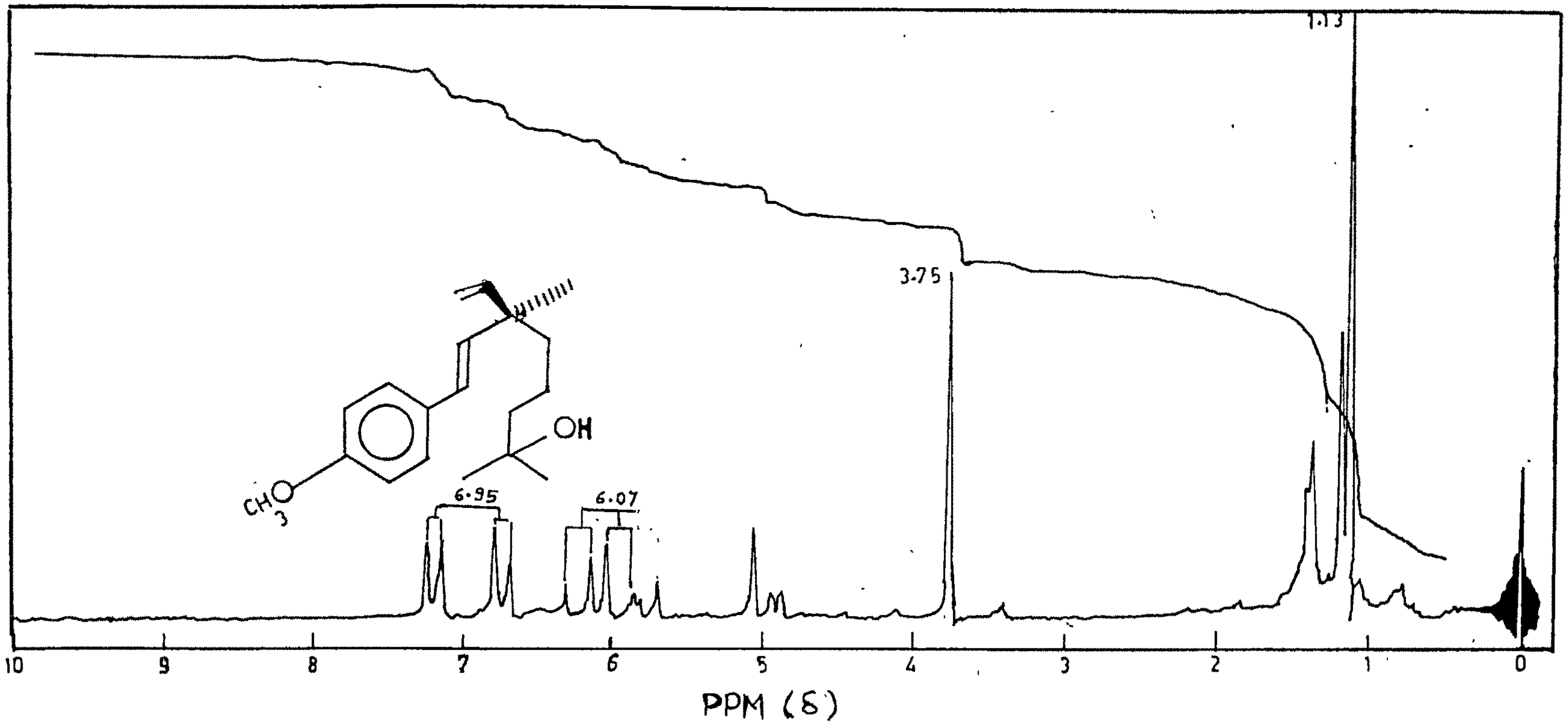


FIG. III-4: PMR SPECTRUM OF 2-HYDROXY BAKUCHIOL METHYL ETHER (14)

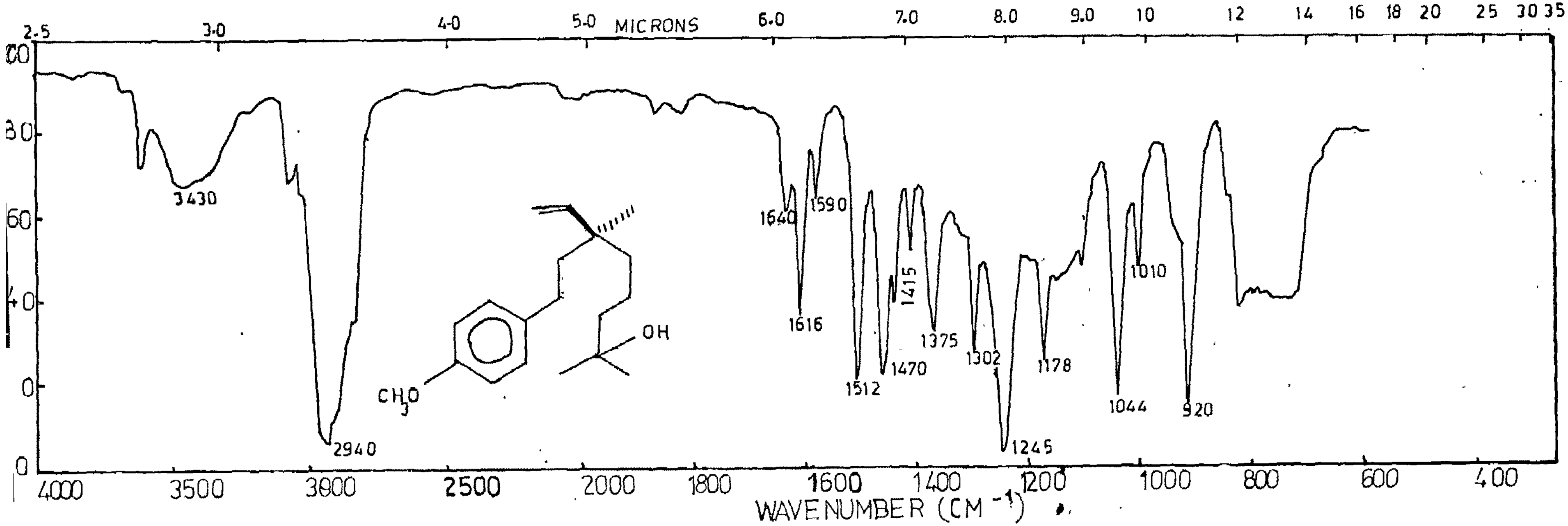


FIG. III-5: IR SPECTRUM OF 2-HYDROXY-7,8-DIHYDRO BAKUCHIOL METHYL ETHER (21)

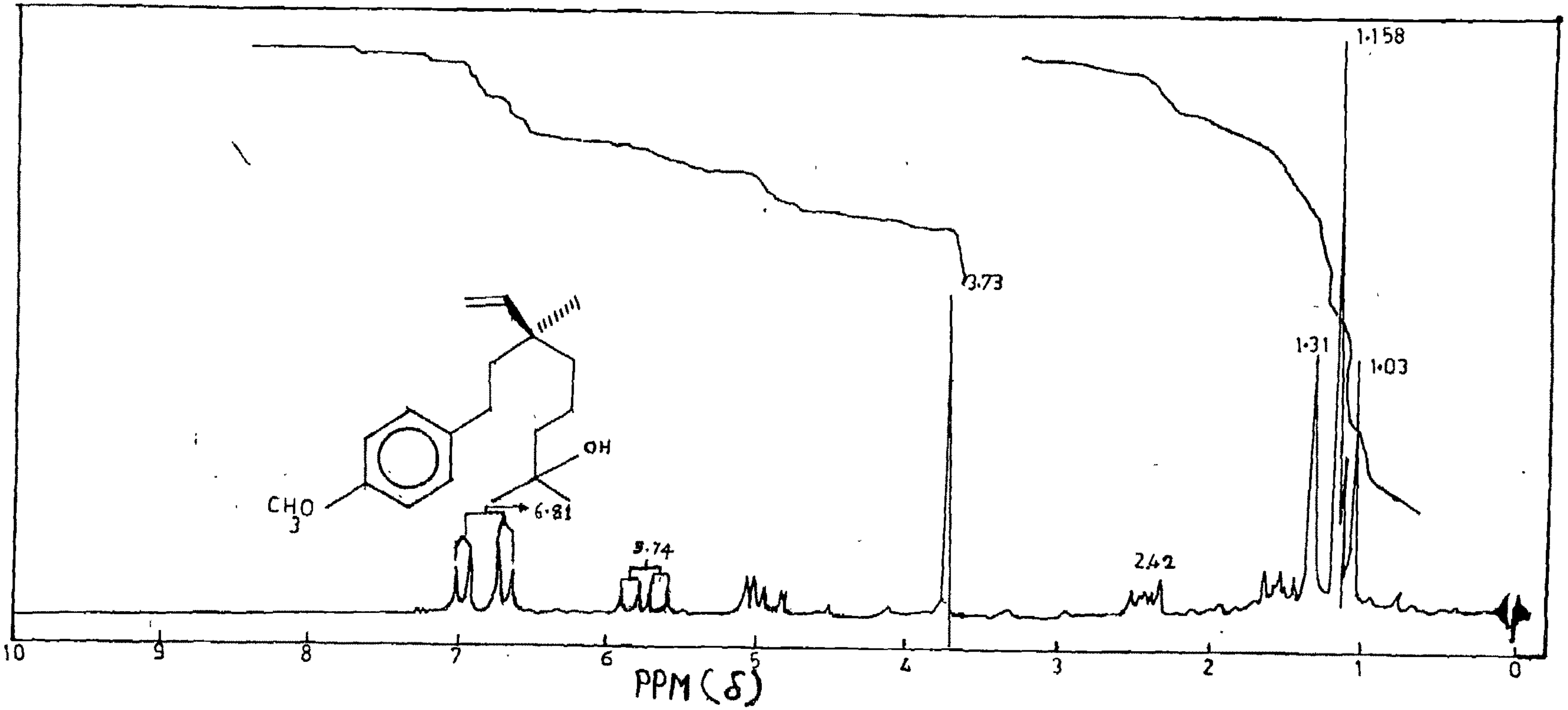


FIG. III-6: PMR SPECTRUM OF 2-HYDROXY-7,8-DIHYDRO BAKUCHIOL METHYL ETHER (21)

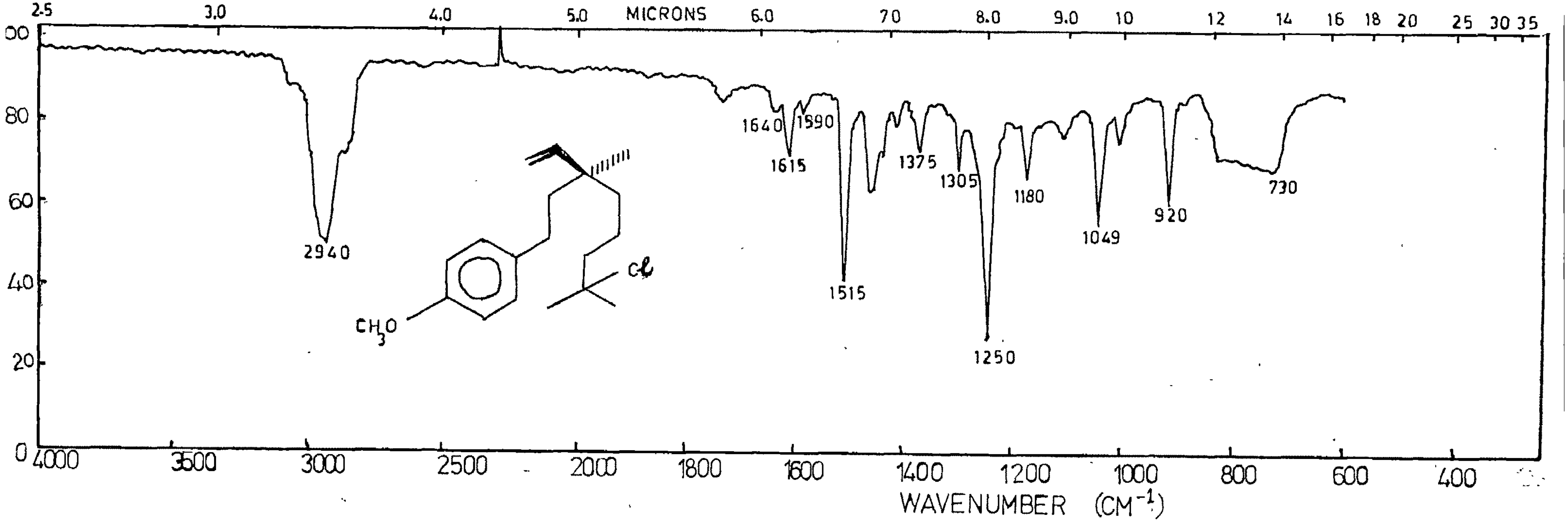


FIG. III 7: IR SPECTRUM OF 2-CHLORO-7,8-DIHYDRO BAKUCHIOL METHYL ETHER(20)

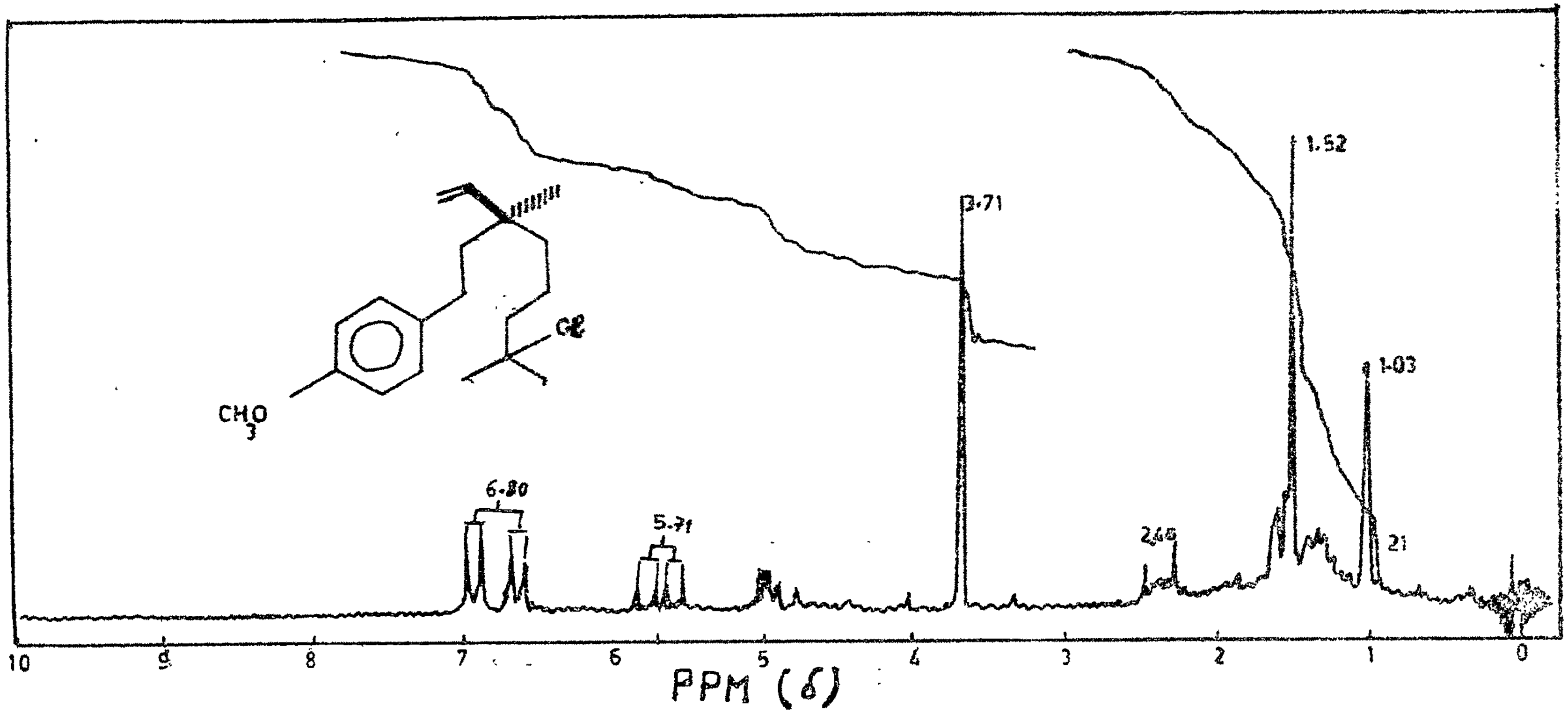


FIG.III-8: PMR SPECTRUM OF 2-CHLORO-7,8-DIHYDRO BAKUCHIOL METHYL ETHER(20)

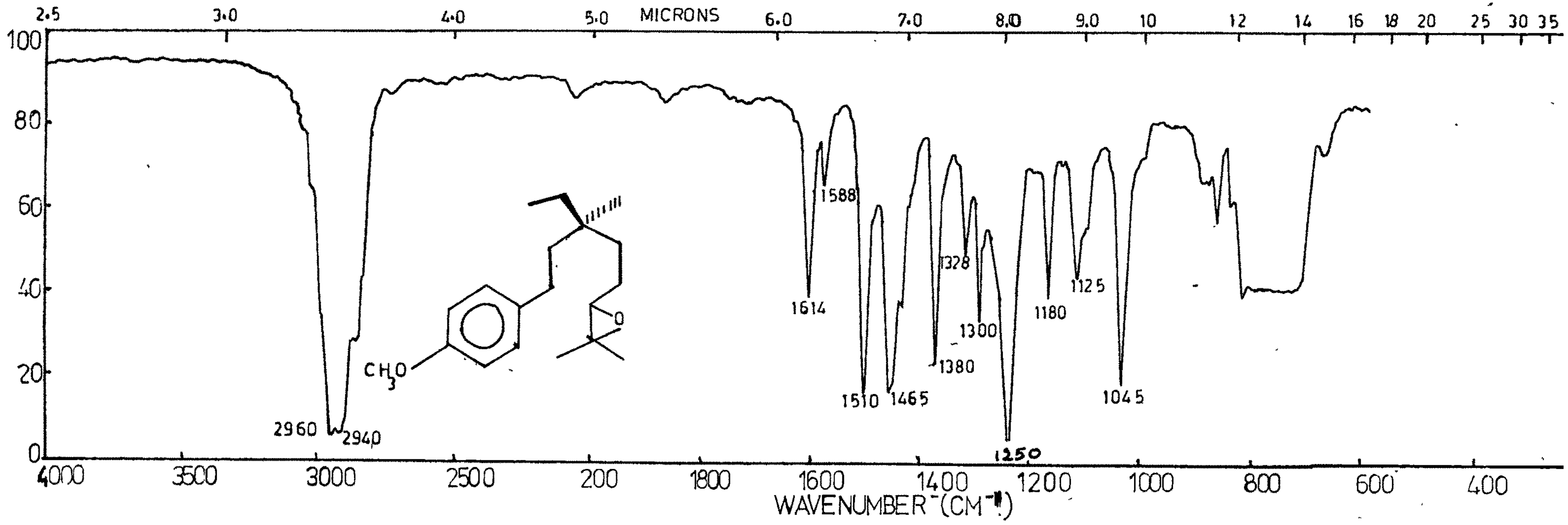


FIG.III-9: IR SPECTRUM OF 2,3-EPOXY-7,8,16,17-TETRAHYDRO BAKUCHIOL METHYL ETHER (24)

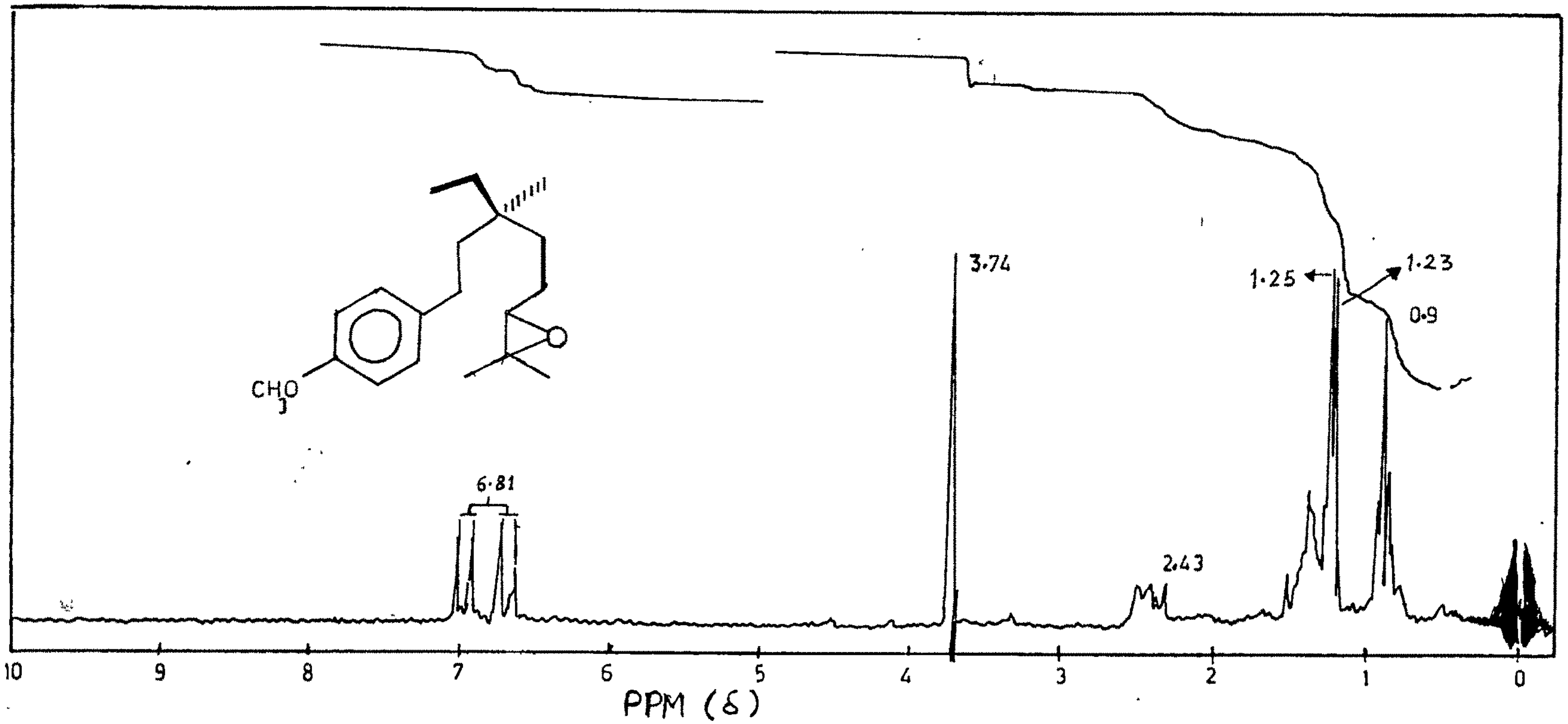


FIG. III-10: PMR SPECTRUM OF 2,3-EPOXY-7,8,16,17-TETRAHYDRO BAKUCHIOL METHYL ETHER (24)

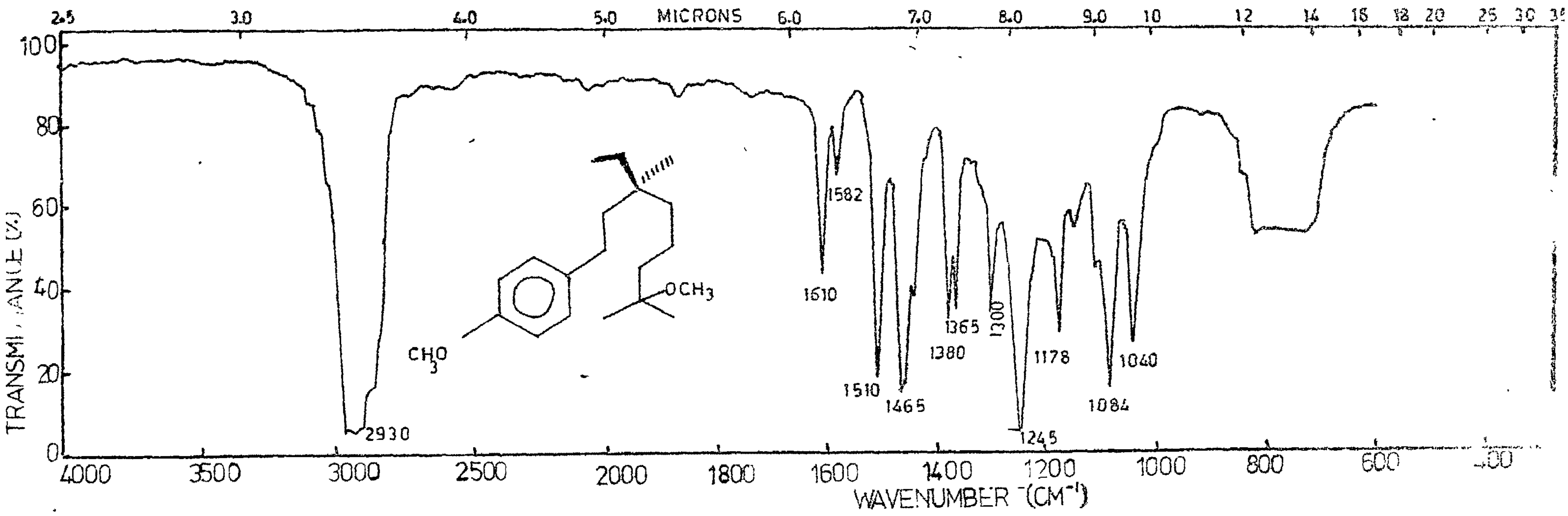
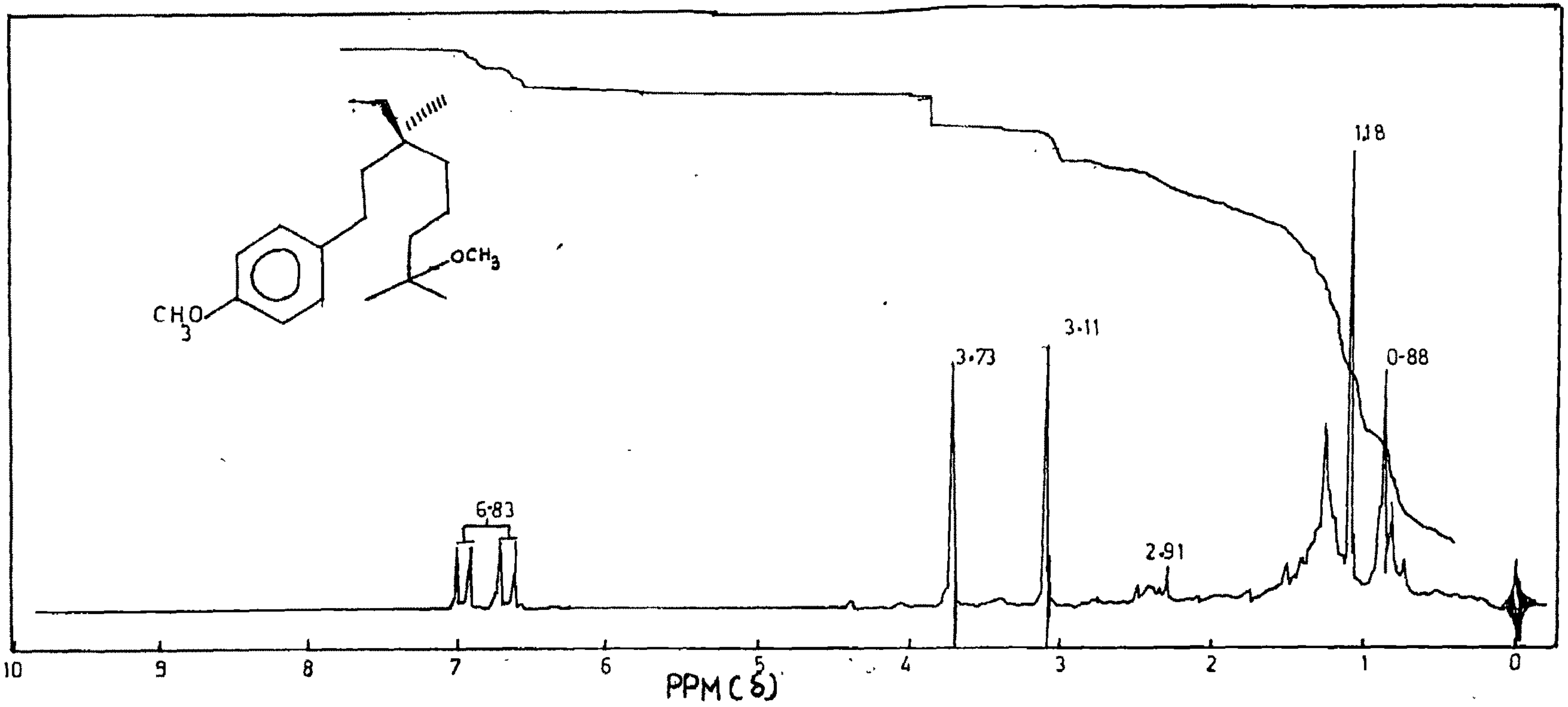


FIG. III-11: IR SPECTRUM OF 2-METHOXY-7,8,16,17-TETRAHYDRO BAKUCHIOL METHYL ETHER (27)



IG. III-12: PMR SPECTRUM OF 2-METHOXY-7,8,16,17-TETRAHYDRO BAKUCHIOL METHYL ETHER(27)

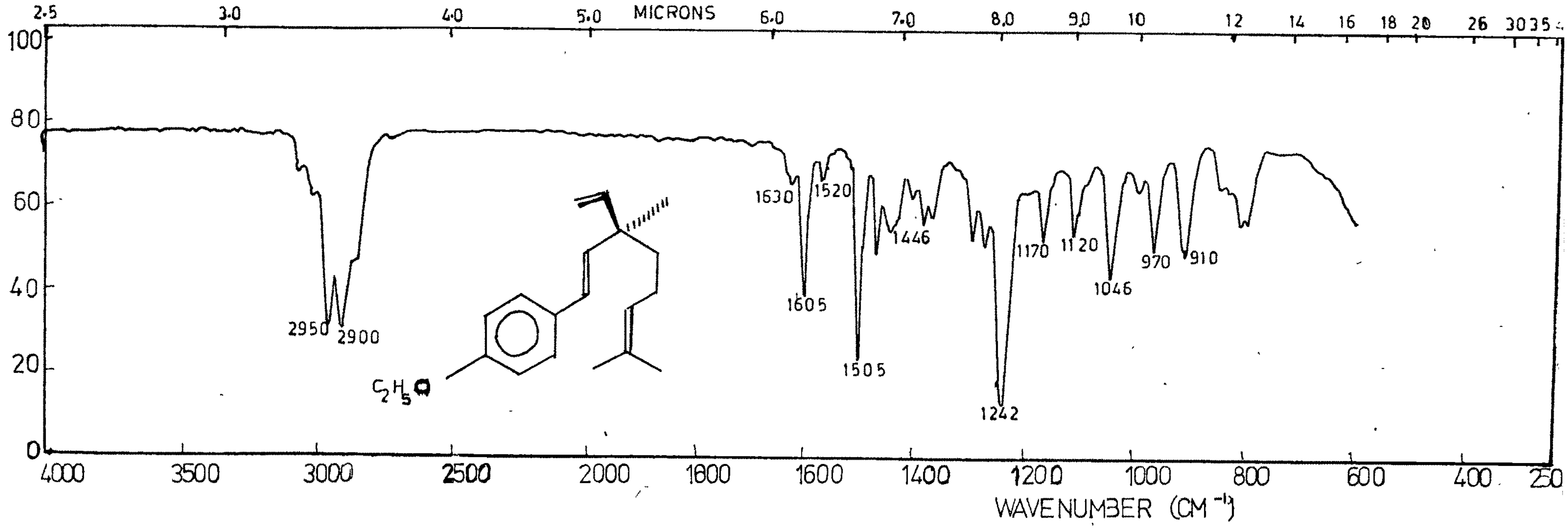


FIG. III-13: IR SPECTRUM OF BAKUCHIOL ETHYL ETHER (3)

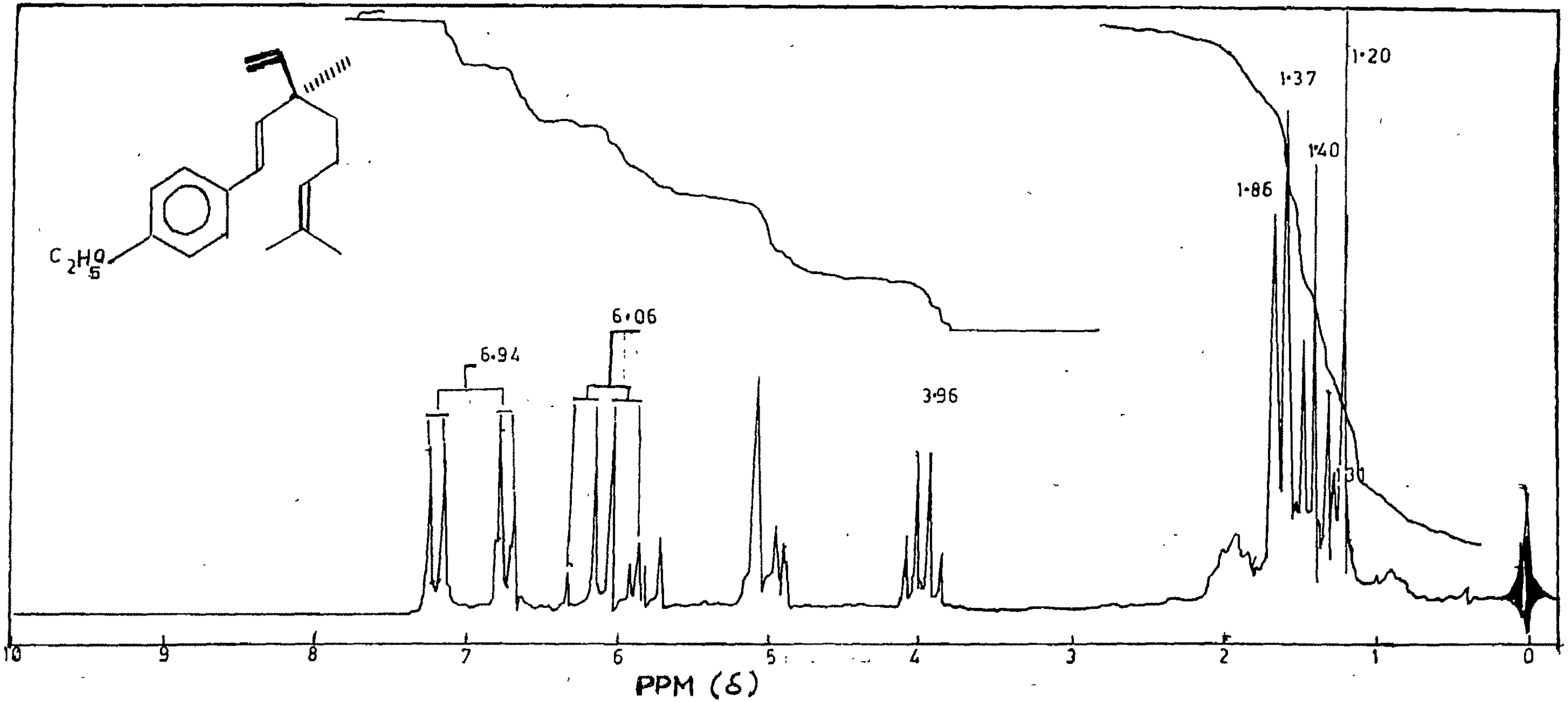


FIG. III-14: PMR SPECTRUM OF BAKUCHIOL ETHYL ETHER (3)

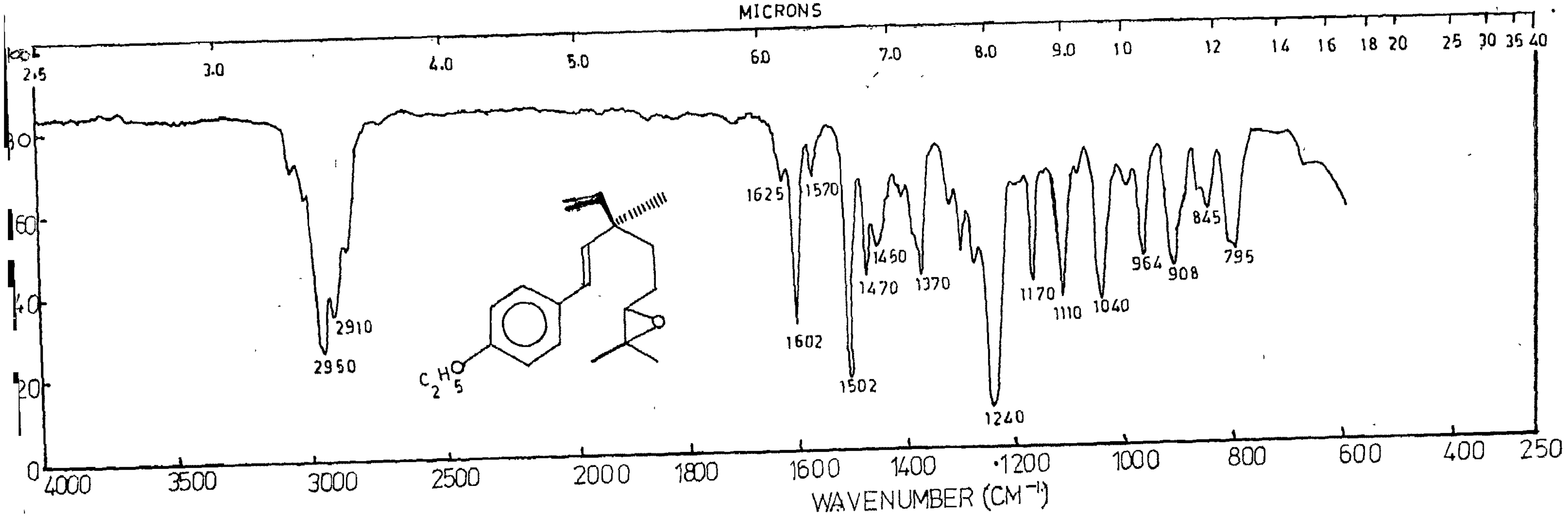


FIG.III-15: IR SPECTRUM OF 2,3-EPOXY BAKUCHIOL ETHYL ETHER(II)

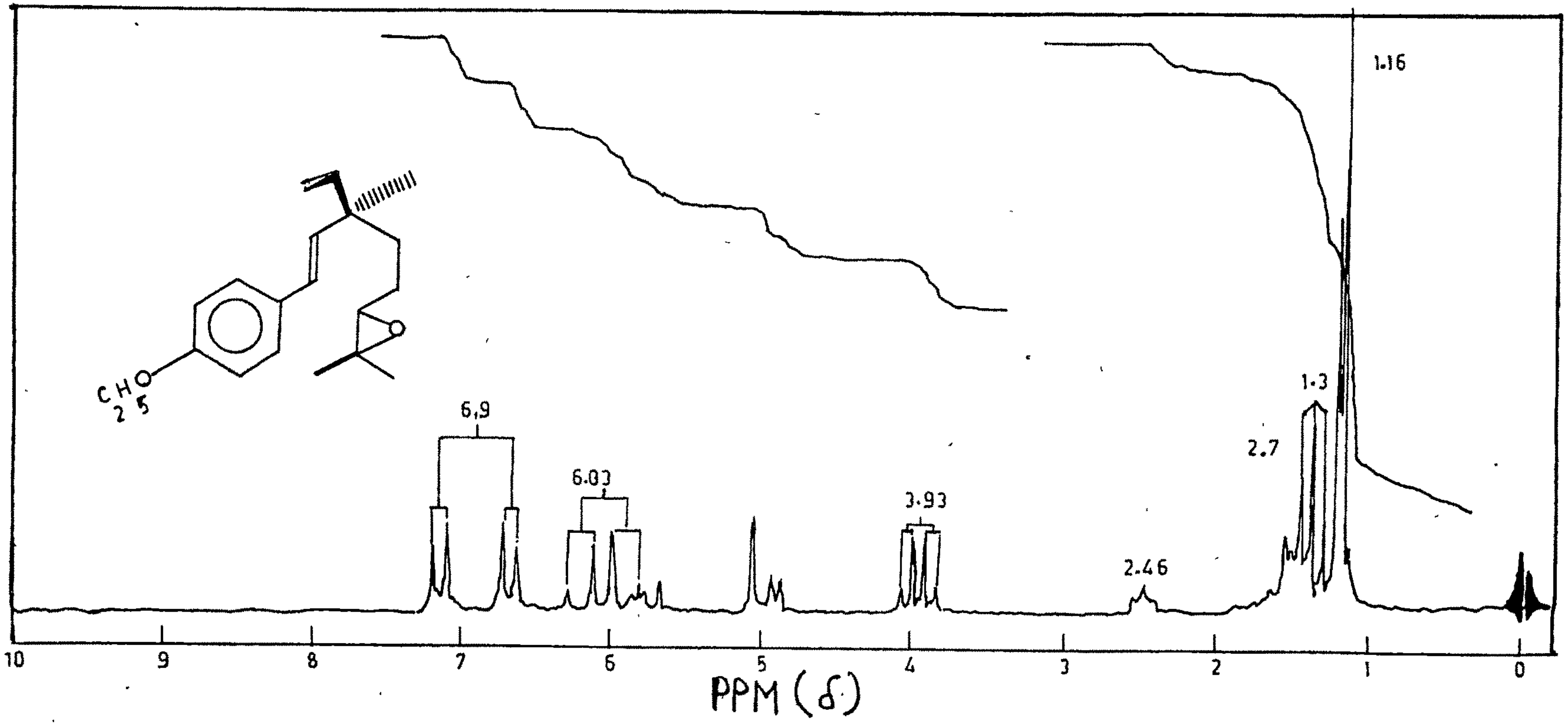


FIG. III-16: PMR SPECTRUM OF 2,3-EPOXY BAKUCHIOL ETHYL ETHER (II)

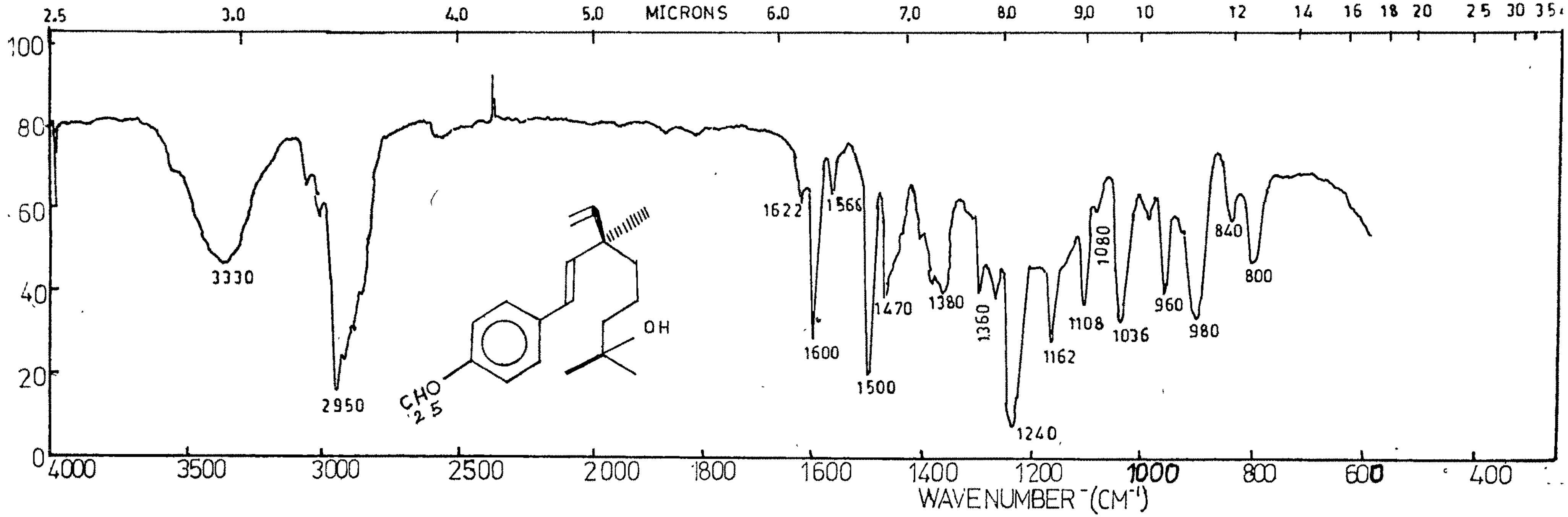


FIG.III-17: IR SPECTRUM OF 2-HYDROXY BAKUCHIOL ETHYL ETHER (16)

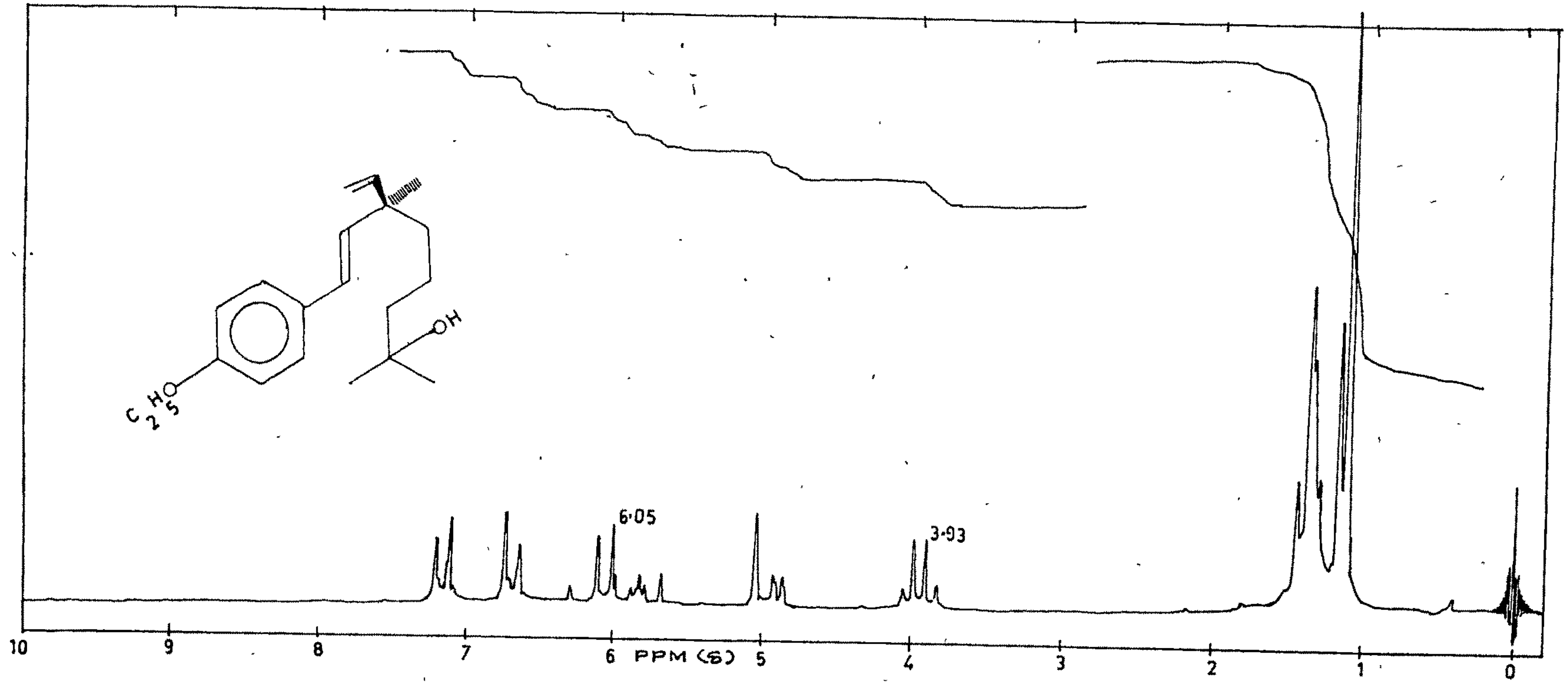


FIG III-18 : PMR SPECTRUM OF 2-HYDROXY BAKUCHIOL ETHYL ETHER (16)

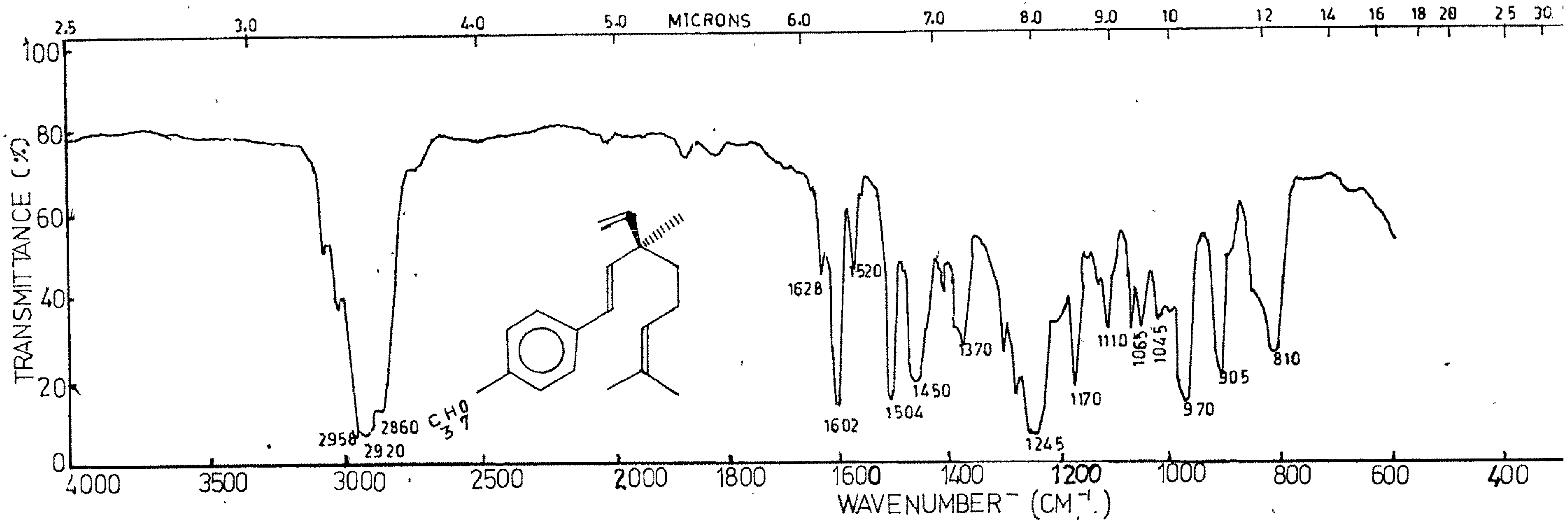


FIG. III-19: IR SPECTRUM OF BAKUCHIOL PROPYL ETHER (4)

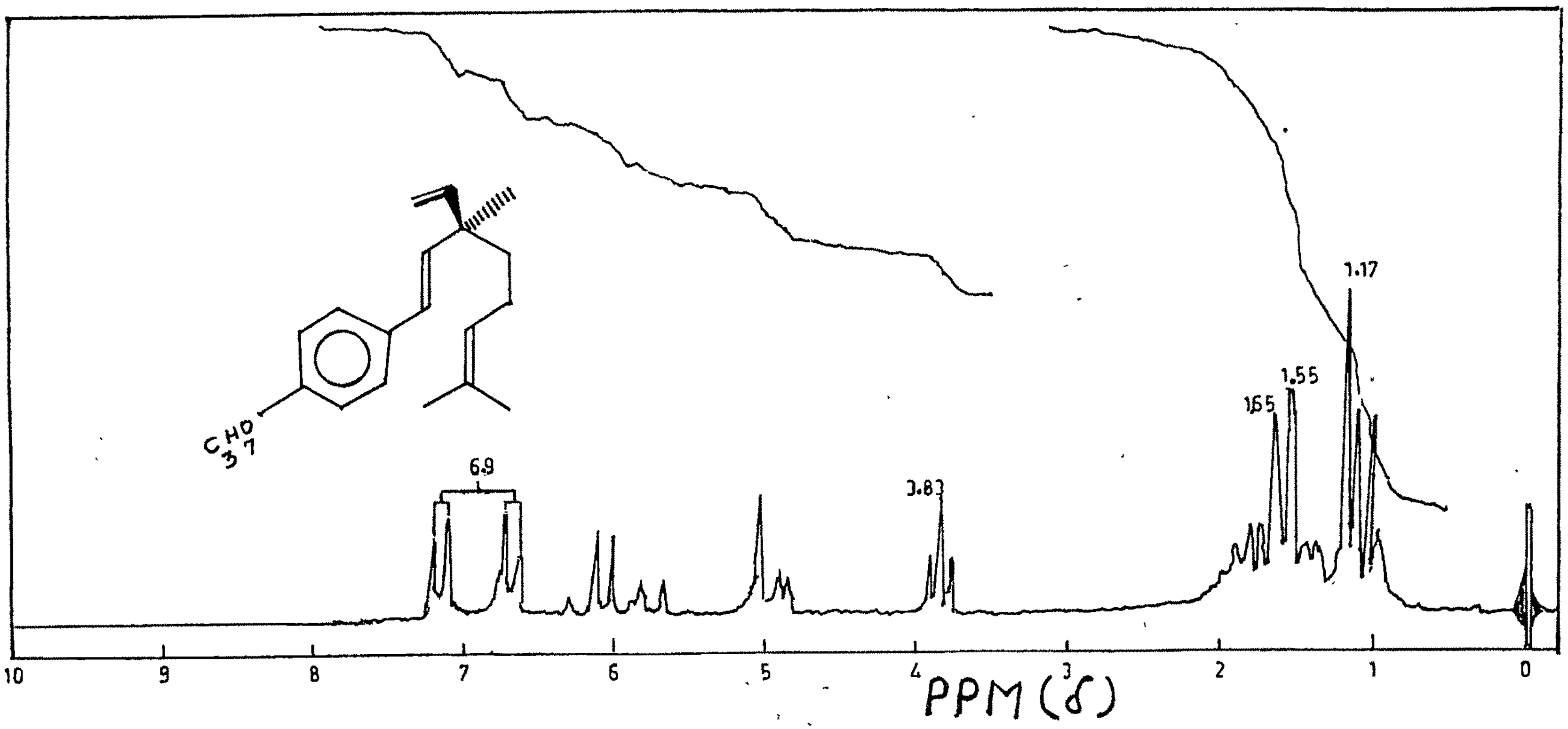


FIG. III-20: PMR SPECTRUM OF BAKUCHIOL PROPYLETHER (4)

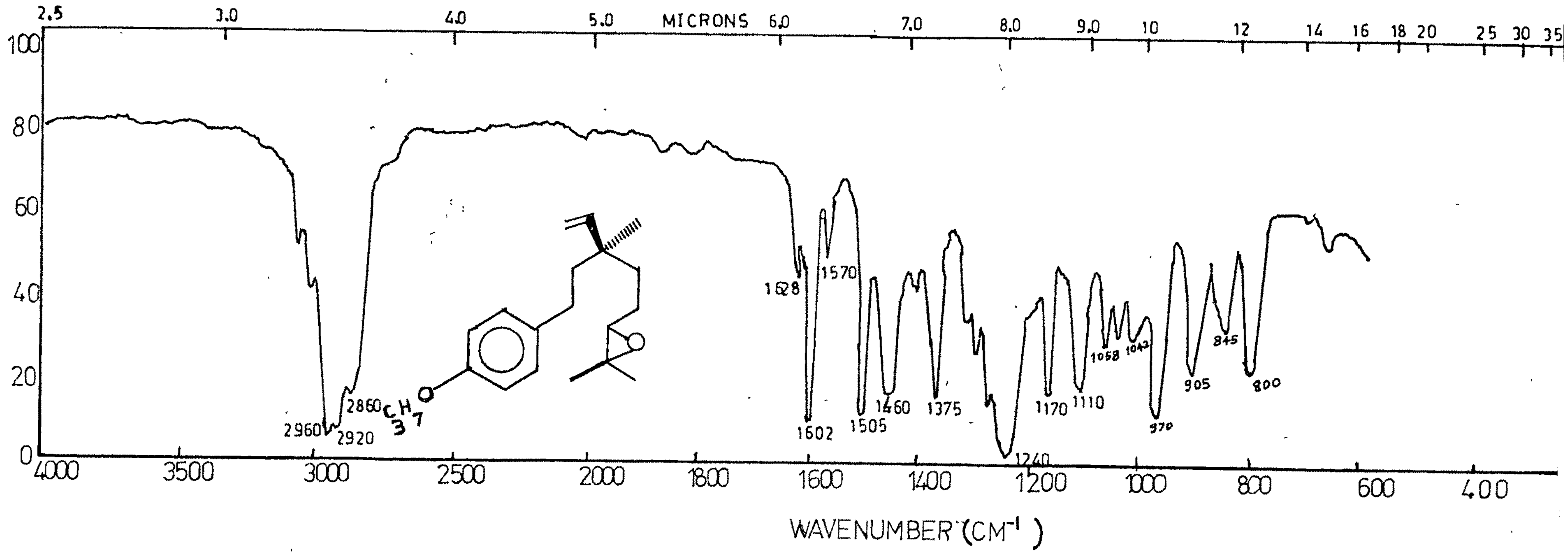


FIG. III-21: IR SPECTRUM OF 2,3-EPOXY BAKUCHIOL PROPYLETEHR (12)

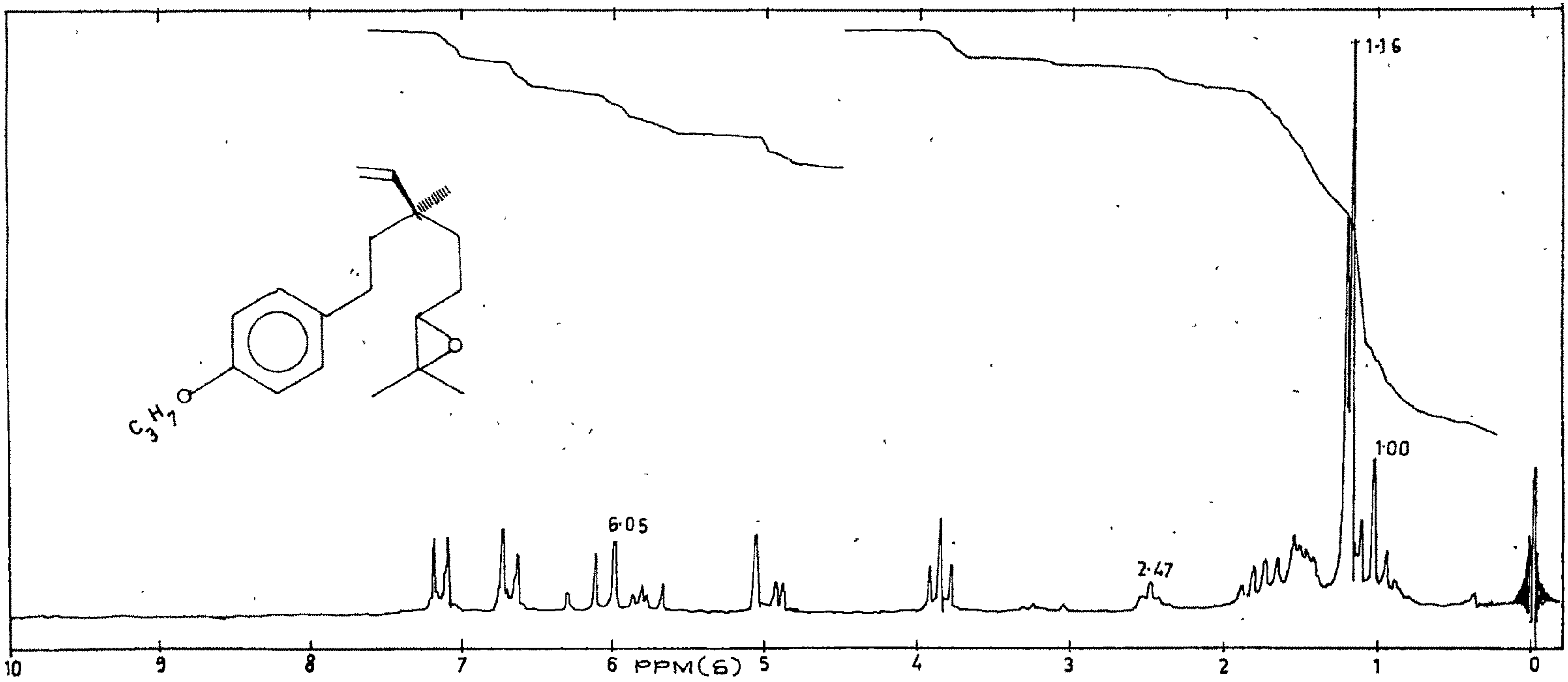


FIG III-22: PMR SPECTRUM OF 2,3-EPOXY BAKUCHIOL PROPYL ETHER (12)

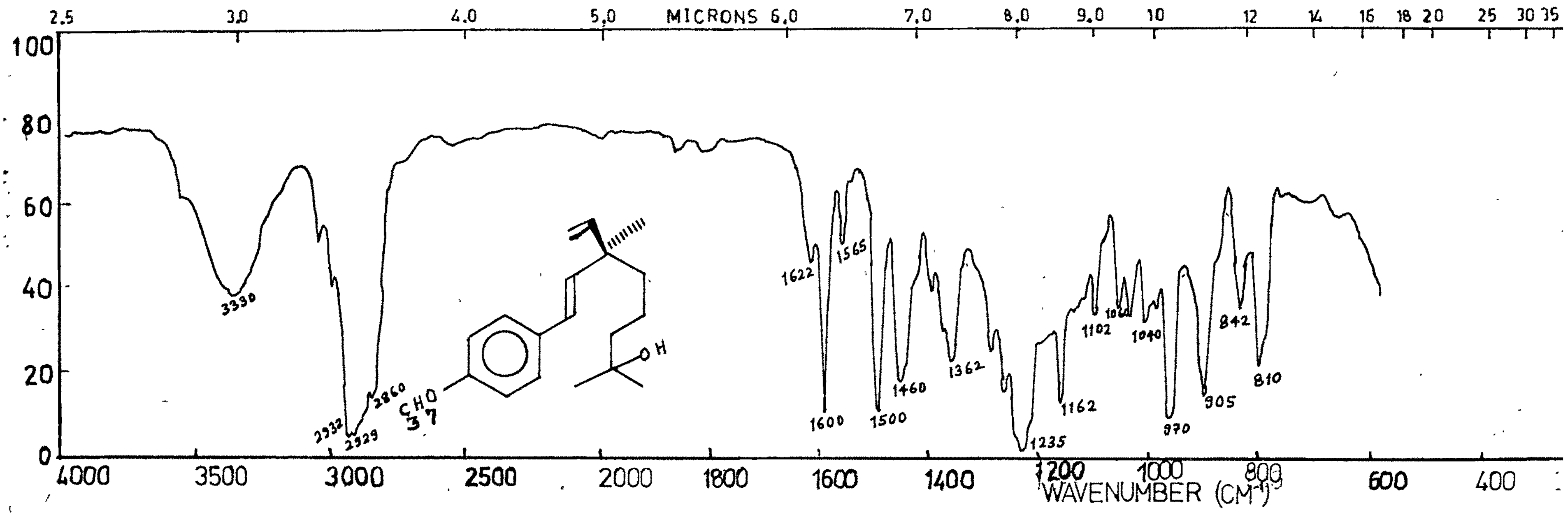


FIG. III-23: IR SPECTRUM OF 2-HYDROXY BAKUCHIOL PROPYL ETHER (17)

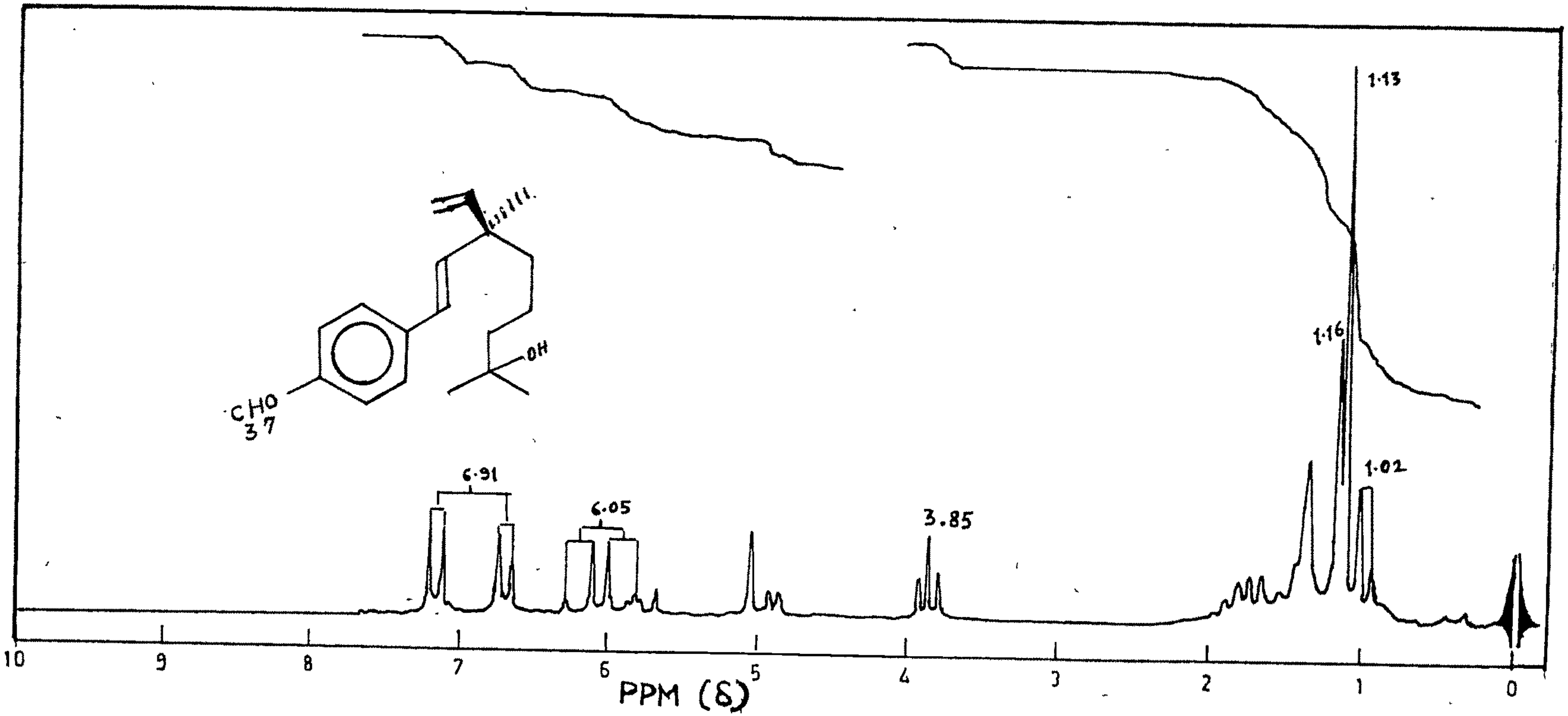


FIG. III-24: PMR SPECTRUM OF 2-HYDROXY BAKUCHIOL PROPYL ETHER (17)

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