CHAPTER IV

Fragmentation of Homoallylic Alcohols : Effect of Ring Strain

FRAGMENTATION OF HOMOALLYLIC ALCOHOLS: EFFECT OF RING STRAIN

Abstract——The synthesis of 6-hydroxy-2-methylenebicyclo [2,2,2] octane by two different routes is described. The details of the fragmentation reactions of this homoallylic alcohol and isopulegol are presented. It is concluded that a certain amount of ring strain in the molecule is indispensable for clean fragmentation reaction.

FRAGMENTATION OF HOMOALLYLIC ALCOHOLS: EFFECT OF RING STRAIN

INTRODUCTION

In the preceding Chapter, the geometric requirements of the fragmentation of homoallylic alcohols in bicyclo [2,2,1] heptane system were established. It is only reasonable to assume that strain introduced in any molecule by structural or steric factors would provide some of the driving force for the fragmentation process. Removal of such a strain by suitably modifying the molecular structure, should make the fragmentation process less facile. In bicyclo [2,2,1] heptane, the cyclohexane ring is forced into a boat form which is further deformed by the methylene bridge which brings carbon atoms 1 and 4 closer than would normally be for an undeformed boat form. As a result, considerable Bayer strain (estimated[1] to be $\sim$20 k.cal/mole) is introduced. In contrast, bicyclo [2,2,2] octane has no Bayer strain because the bridge is formed by two methylene groups and the valence angles are not deformed, but steric strain due to nonbonded interaction of eclipsed substituent does exist. In the case of cyclohexane, there is no Bayer strain and nonbonded interactions are also minimised in the chair conformation in which it exists.

The steric energy of a molecule is believed to arise from four potential energy functions of structural parameters, namely, bond angle(θ), torsional angle(ϕ), bond length (r), and non-bonded distance(d). Certain structural features are recognized as "normal or strain free" and deviation from these values leads to an increase in the strain energy[2]. The magnitude of these potential energy functions in the three ring systems is recorded in Table I. The enhanced strain in bicyclo[2,2,1] heptane as compared to bicyclo[2,2,2] octane and cyclohexane is obvious by comparison of bond angle (θ), bond length(r), and nonbonded distance (d) values. Table II shows strain energy differences and enthalpies of the three systems.

Table I: Experimental and calculated values of bond angle(θ), torsional angle (Ø), bond length (r,A) and nonbonded distance(d,A) for cyclohexane, bicyclo[2,2,1] heptane and bicyclo[2,2,2] octane

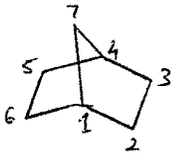
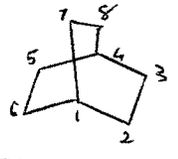
Alkane	Structural parameter	Expt.[2]	Calcd.		
			Allinger's[3]	Schleyer's[4]	Ermer's[2]
Cyclohexane 	θ	111.7	111.3	111.0	-
	Ø	55.9	56.4	55.3	-
	r(CC)	1.528	1.530	1.533	-
Norbornane 	θ ($C_1C_7C_4$)	93.1	93.1	93.3	92.1
	r (C_1C_2)	1.539	1.535	1.533	1.553
	r (C_2C_3)	1.557	1.538	1.533	1.552
	r (C_1C_7)	1.560	1.531	1.522	1.566
	d ($C_1 \ldots C_4$)	2.260	2.22	2.21	-
Bicyclo[2,2,2] octane 	θ($C_1C_2C_3$)	109.7	109.5	110.1	109.9
	r (C_1C_2)	1.542	1.529	1.536	1.538
	r (C_2C_3)	1.552	1.533	1.540	1.539
	d ($C_1 \ldots C_4$)	2.592	2.555	2.595	-

Table II: Experimental and calculated Enthalpies and strain energies[4](k.cal/mole)

Alkane	$\triangle H_7$(gas 25°)			Strain energy calcd.	
	Exptl	calcd.			
		Allinger	Schleyers	Allinger	Schleyers
Cyclohexane	-29.50	-29.93	-29.35	1.21	1.43
Norbornane	-12.42	-13.48	-12.99	16.78	16.98
Bicyclo[2,2,2] octane	-23.75	-24.22	-22.15	11.33	12.95

Thus, the enthalpy of bicyclo[2,2,1] heptane is lower by 11 k.cal/mole and 17 k.cal/mole compared to bicyclo[2,2,2]octane and cyclohexane respectively.

Clearly, the strain energies of the three ring systems follow the order, bicyclo[2,2,1]heptane > bicyclo[2,2,2]octane > cyclohexane.

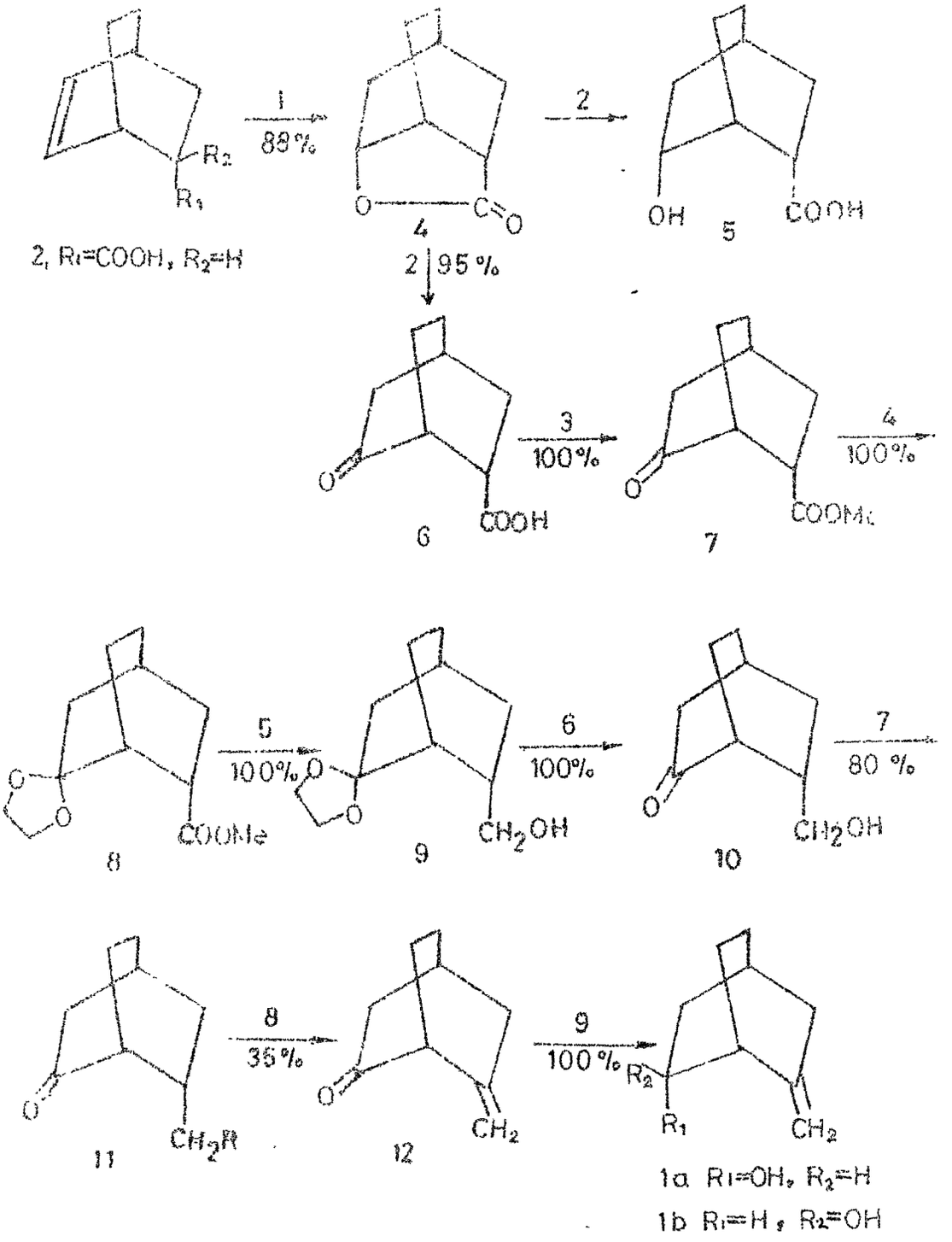
It has been observed (Chapter II) that bicyclo [2,2,1] heptane undergoes facile fragmentation. In order to assess if the ring strain contributes to the ease of fragmentation, the corresponding reactions were studied with homoallylic alcohols incorporated in bicyclo [2,2,2] octane and cyclohexane systems.

2. SYNTHESIS OF 6-HYDROXY-2-METHYLENE BICYCLO[2,2,2]OCTANE (1)

The homoallylic alcohol 1 has been synthesised by two different routes as described below. Route I did not give the desired product in satisfactory yield. This necessiated developing a second route, which gave better yield of 1 .

ROUTE-I

It was envisaged that, a potential route to the alcohol 1 could proceed *via* the dehydration of 2-hydroxymethyl-6-oxo-bicyclo [2,2,2] octane 10, which can be obtained by deketalisation of the known ketal alcohol 9[5], readily available from γ-lactone 4[5] (Fig-1). Gerveties *et al*[5] synthesised the ketal alcohol 9 starting from the known γ-lactone 4[6]. Acid hydrolysis



REAGENTS (1) 30% H_2SO_4 ; (2) NaOH ; RuO_4 ; (3) CH_2N_2 ; (4) $HO(CH_2)_2OH$ / PTSA
(5) LAH; (6) $BF_3.Et_2O$, (7) CS_2 - NaOH - CH_3I ; (8) A_3; (9) $NaBH_4$

FIG. 1 : SYNTHESIS OF 6-HYDROXY-2-METHYLENEBICYCLO [2,2,2] OCTANE (ROUTE - ONE)

of 4 gave the hydroxy acid 5, which was esterified, oxidised and ketalised to give the ketal ester 8 . LAH reduction of 8 gave the ketal alcohol 9. The γ-lactone 4 was originally synthesised by Bohme et al[7]. Diels-Alder reaction of 1,3-cyclohexadiene and acrylic acid at 160° for 12 hr. gave epimeric acids 2 and 3 in 45% yield, which were lactonised by 30% H_2SO_4 to γ -lactone in 75% yield.

We followed the above sequence of reactions to make the ketal alcohol 9 by making appropriate modification wherever needed. In our hands Diels-Alder reaction of 1,3-cyclohexadiene and acrylic acid, according to the method of Bohme et al, did not give more than 35% yield. We could improve the yields upto 80-85% by increasing the reaction temperature from 160 to 180° and time from 12 to 20 hr. However, all our attempts to isolate the hydroxy acid 5 by basic hydrolysis of 4 followed by acidification were unsuccessful and only led to the isolation of the starting material. This was not totally unexpected, since Brown et al[8] have observed that usually γ -hydroxy acids exist largely as lactones at room temperature.

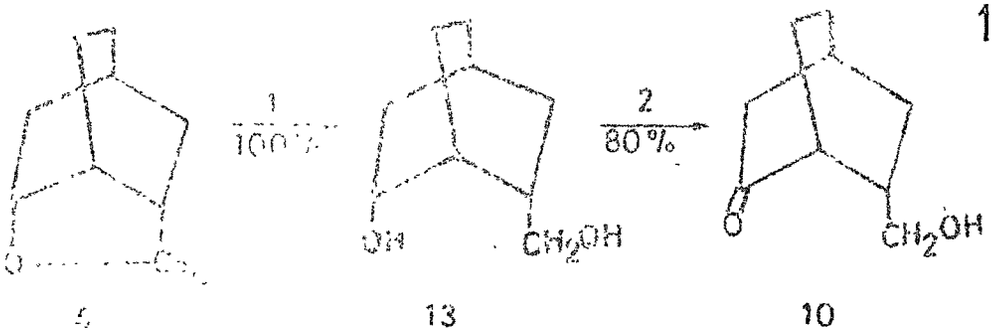
Since hydroxy acid though formed, could not be isolated, a reagent capable of carrying out oxidation of secondary alcohols under neutral or basic conditions was needed. Recourse was taken to the oxidation of hydroxy acid in basic medium with ruthenium tetraoxide by the method described by Montory *et al*[9]. Accordingly, the lactone 4 was hydrolysed with one equivalent of sodium hydroxide and subsequently oxidised with RuO_4 to yield the sodium salt of 6 which upon neutralisation with 10% dil aqueous hydrochloric acid gave the keto acid 6.

The above keto acid 6 was converted to the hydroxy ketone 10 by the following sequence of reactions. The keto-acid 6 was esterified (CH_2N_2) and ketalised to the ketal ester 8. The latter on reduction with LAH was smoothly converted to the ketal alcohol 9, which on exposure to BF_3-Et_2O gave the desired 2-hydroxy methyl-6-oxobicyclo[2,2,2]octane 10. The structure of the hydroxy ketone 10 is consistent with its spectral data: IR(FIG 13): (Nujol): OH 3560,1100 cm^{-1}; six-membered C=O 1720 cm^{-1}. PMR (FIG 14) ($CDCl_3$): CH_2-OH, (2H, m, 3.1 to 3.5 ppm).

The hydroxy ketone 10 was also prepared more conveniently by an alternate route (FIG.2). Lactone 4 was quantitatively converted by LAH to the diol 13, which was selectively oxidised by Bromine-HMPT[10] to the desired keto alcohol 10 in an over all yield of 90%.

The next step was the dehydration of the ketal alcohol 9 or ketone alcohol 10 into olefin 12. Several methods are available for dehydration of the primary alcohol[11]. In the first instance it was planned to convert ketal alcohol 9 into its tosylate and then carry out the elimination of the tosyl group. However, the reaction of ketal alcohol 9 with p-toluene sulphonyl chloride in pyridine furnished only a hydroxy ethyl ether 14. The structure of 14 was deduced by correlation with the known compound 10, by cleavage[12] of the ether linkage of the compound 14 with TsCl-pyridine and NaI-Zn. The plausible mechanism of formation of 14 from 9 is shown in FIG.3.

Next the dehydration of ketone alcohol 10 was investigated. When 10 was refluxed with p-toluene sulphonyl chloride in pyridine, a method useful for the dehydration of primary alcohol[13], a tarry product



5 13 10

REAGENTS: (1) LAH (2) Br_2/HMPT

FIG. SYNTHESIS OF 2-HYDROXYMETHYL-6-OXOBICYCLO[2,2,2]OCTANE (10)

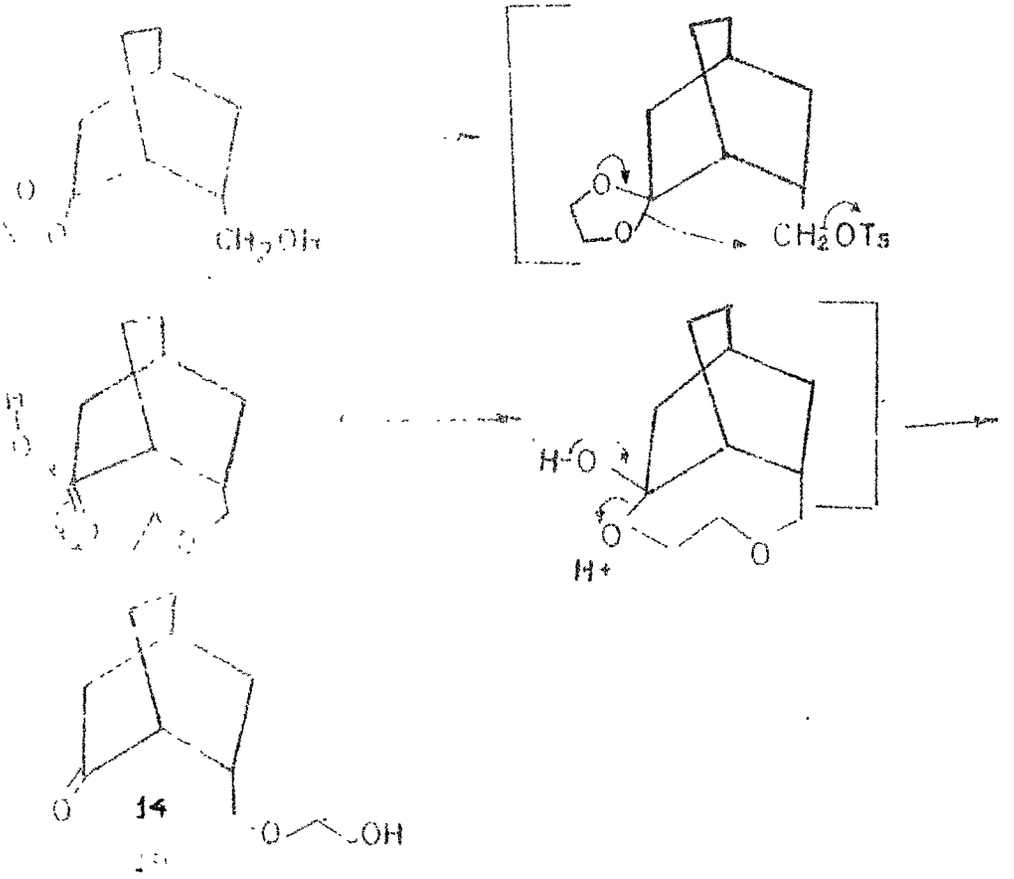


FIG. 3 POSSIBLE FORMATION OF HYDROXYETHYL ETHER - 14

was obtained. Treatment with the same reagent at room temperature, however gave the expected tosylate 11 (R=OTs) in a quantitative yield. Attempts to convert the tosylate 11 (R=OTs) to the required olefin 12 were unsuccessful with alumina[13]; it got hydrolysed back to the hydroxy ketone 10. Attempts to dehydrate 10 by refluxing in HMPT[14] were equally unsuccessful and once again only a tar was obtained. Finally, the pyrolysis of the xanthate ester 11 (R=OCSMe) of 10 at 220° gave the keto olefin 12* in 35% yield. IR(CCl_4) (FIG 19); six membered ketone 1725 and 1024 cm^{-1}; $C=CH_2$ 1645 and 893 cm^{-1}. PMR(CCl_4)(FIG 20): $C=CH_2$ (2H, s, 4.8 and 4.92 ppm); $CH-C=CH_2$ (1H, m, 2.7 to 2.9 ppm).

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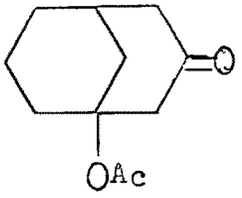
*House et al obtained this keto olefin 12 in 42% yield together with the monocyclic ketone 16 and several minor products by pyrolysis of tertiary acetate 15 at 580-600°. Obviously this method could not be useful as a preparative method.



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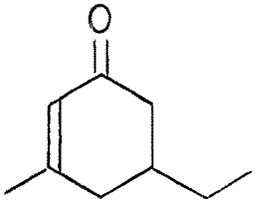

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Reduction of 12 with $NaBH_4$ gave a mixture of homoallylic alcohols 1a and 1b in the ratio of 8:2, which were inseparable by TLC and GLC but clearly distinguishable by their PMR spectra. The separation of these two alcohols in pure form was not attempted.

The structural assignment of the two isomers 1a and 1b was easily made on the basis of difference in chemical shift of olefinic protons in their PMR spectra. These protons in 19 appear down field (4.9 δ) compared to 1b (4.72 δ) because of anisotropic effect of the hydroxyl group. These assignments are further supported by the aniticipated preferential attack by the hydride ion from the side, opposite to the terminal methylene group, to give 1a.

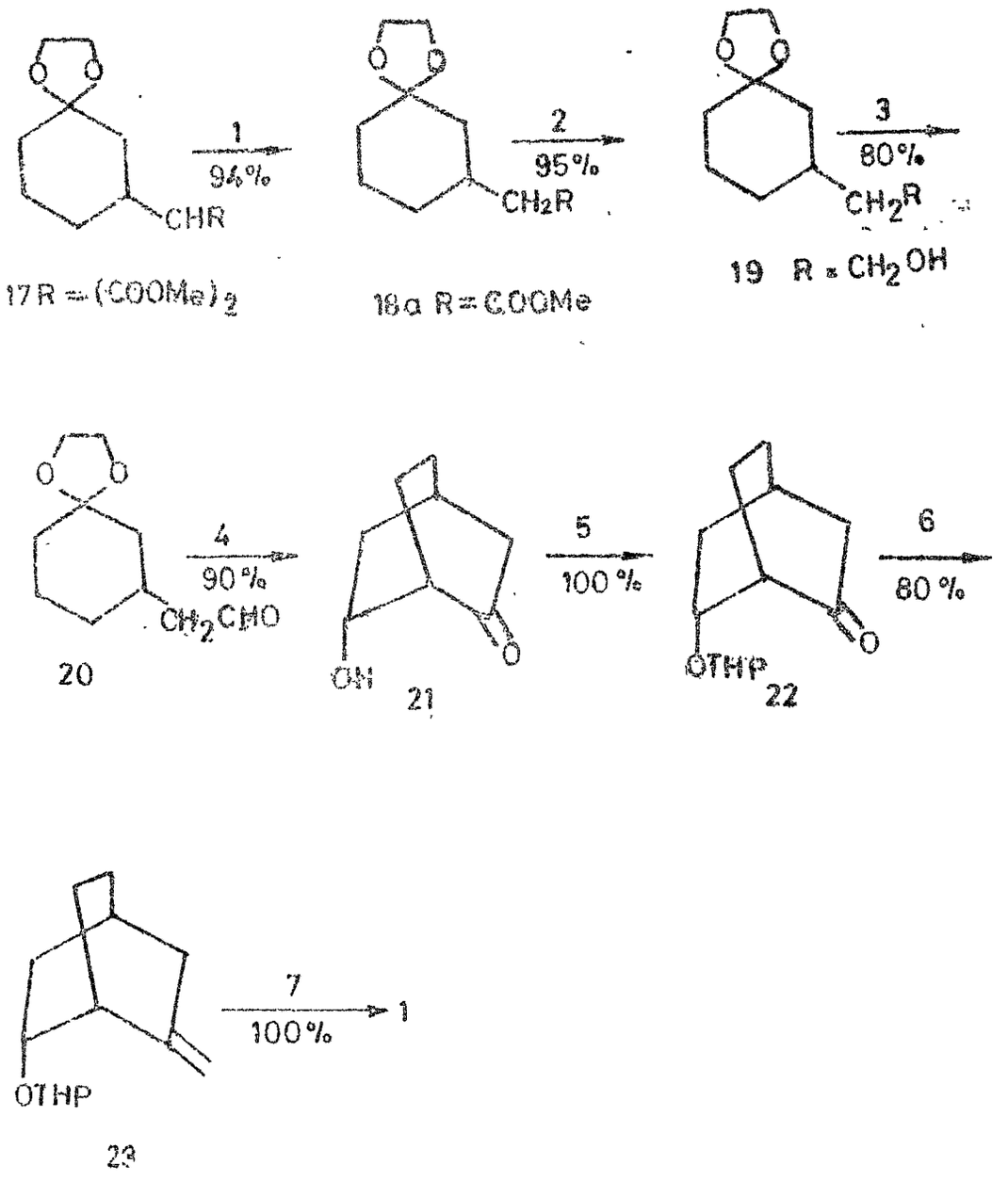
The over all yield by the above sequence was poor ($\sim$20%). Hence it was found necessary to develop a better preparative method and this could be achieved by the method described below in Route-II.

ROUTE-II

It was envisaged that the desired homoallylic alcohol 1 can be more conveniently made starting from the known[16] 2-oxo-6-hydroxymethyl bicyclo[2,2,2]octane 21

by Wittig reaction after protecting the hydroxyl group (FIG.4). The known procedure[16] for the synthesis of 21 involves the reduction of methyl(3,3-ethylenedioxycyclohexyl)acetate 18 to the alcohol 19, which is oxidised to aldehyde 20, the aldol condensation of which gives 2-oxo-6-hydroxybicyclo[2,2,2]octane, but the overall yield from cyclohexenone is < 20%.

The above sequence of reactions was reinvestigated and the conditions optimised to get consistently good yields of 21 (70%). Ethyl(3,3-ethylenedioxycyclohexyl) malonate 17 was prepared from cyclohexenone according to a reported procedure[17]. The older method[18] for the conversion of 17 to ethyl(3,3-ethylenedioxycyclohexyl) acetate 18 ($R=C_2H_5$) involved the half hydrolysis of diester followed by decarboxylation at higher temperature, but the yield reported was less than 50%. The treatment of 17 with NaCl-DMSO-H_2O[18] at 160° under nitrogen atmosphere for 18 hr furnished 18 ($R=C_2H_5$) in 90% yield. The ketal ester 18 ($R=C_2H_5$) was converted into the hydroxy ketone by the following sequence of reactions. Reduction of 18 with LAH to 19 followed by oxidation of 19 by CrO_3-pyridine in dichloromethane gave the aldehyde 20 in 80% yield. The aldehyde 18 was converted into 21 by aldol condensation with aqueous phosphoric acid in 80% yield.



REAGENTS : (1) NoCl - DMSO - H_2O ; (2) LAH; (3) CrO_3-PYRIDINE; (4) 15% H_3PO_4 ; (5) DHP/PTSA, (6) ϕ_3P - CH_3I - BASE; (7) H^+.

FIG. 4: SYNTHESIS OF HOMOALLYLIC ALCOHOL 1 (ROUTE- TWO)

The above hydroxy ketone 21 was converted into a mixture of isomeric tetrahydropyranyl ethers 22 (90% yield), by treatment with dihydropyrane/p-toluene sulphonic acid in ether at room temperature. Tetrahydropyranyl ethers were subjected to Wittig reaction with methylene triphenyl phosphorane in THF. Subsequent cleavage of tetrahydropyranyl ether with acid gave a mixture of homoallylic alcohols 1a and 1b in a ratio of 9:1, which were not separated. The overall yield of the homoallylic alcohol by this route is 60%.

3. RESULTS

Fragmentation of homoallylic alcohol 1

Treatment of alcohol 1 in carbontetrachloride with molar equivalent of bromine in presence of sodium carbonate gave a complex mixture of products in almost quantitative yield. The PMR spectrum of this product shows a broad signal at 5.87 ppm(C=CH) and a triplet at 9.7 ppm($J=1.5H_2$). Its IR spectrum shows a carbonyl frequency at 1730 cm^{-1} and an absorption at 2720 cm^{-1} assignable to an aldehyde function. This product gives strong yellow colour with tetranitro methane indicating the presence of unsaturation. The products are unstable and even at room temperature ($\sim 30^{\circ}$) slowly tend to decompose to a coloured mass. PMR spectrum of this mixture clearly reveals that the expected fragmentation product 25 (FIG 5) is present only as a minor component. Further attempts to isolate it were not made due to paucity of the material.

Similarly 1 on treatment with mercuric acetate, undergoes the normal oxymercuration which on sodium borohydride reduction gives a mixture of diols 26, the latter on dehydration give back a mixture of starting alcohols 1 (FIG.5).

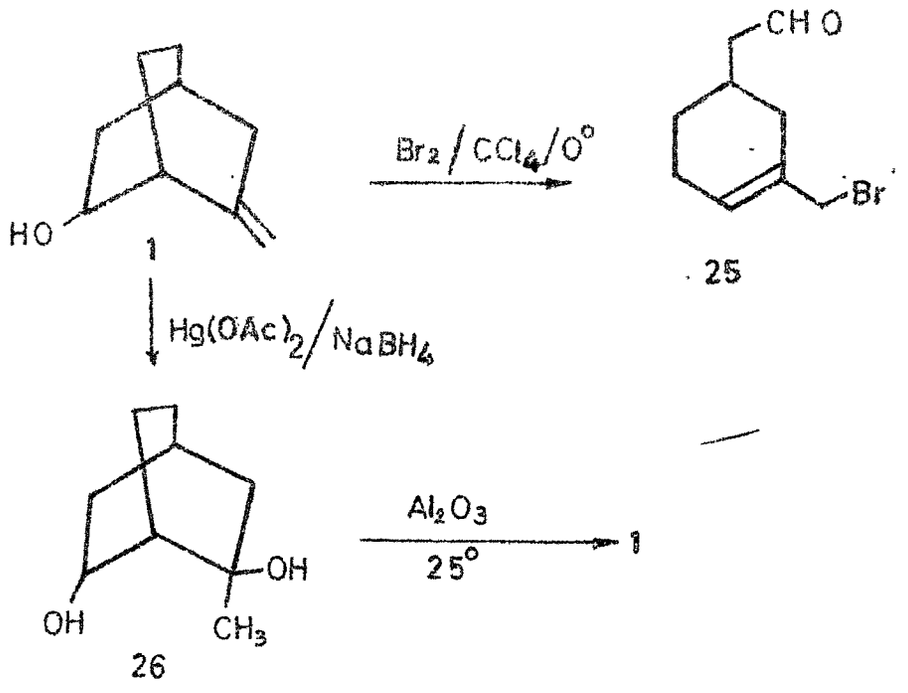


FIG 5. REACTION OF HOMOALLYLIC ALCOHOL 1 WITH BROMINE AND MERCURY(II) ACETATE

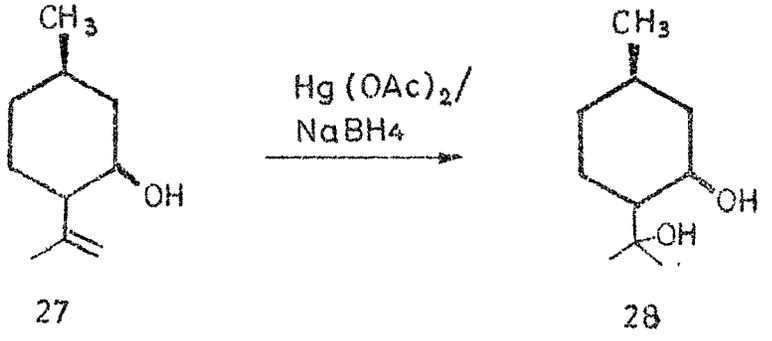


FIG 6 REACTION OF ISOPULEGOL WITH MERCURY(II) ACETATE

Fragmentation of Isopulegol (27)

Similarly, isopulegol 27[19] on treatment with mercuric acetate, undergoes the normal oxymercuration which on $NaBH_4$ reduction gives diol 28 (FIG 6).

4. DISCUSSION

Thus the two homoallylic alcohols 1 and 27 did not undergo a clean fragmentation reaction. In the reaction of 1 with bromine, the fragmentation product 26 is only a minor component in an intractable mixture. In either case, there was no fragmentation at all with $Hg(OAc)_2$ but normal oxymercuration of double bond was observed. As already discussed in Chapters II and III, similar system in bicyclo[2,2,1]heptane series unaergoes clean fragmentation.

This study, thus indicates that a certain amount of Bayer strain in the molecule is indispensable for a clean fragmentation reaction. Further studies on this reaction are in progress.

EXPERIMENTAL

For general remarks see Chapter II of this thesis.

Bicyclo[2,2,2]oct-5-ene-2-carboxylic Acids (2 and 3)

A mixture of 1,3-cyclohexadiene (8.0g, 0.1 mole), acrylic acid (7.2 g; 0.1 mole) and hydroquinone(0.25 g) was heated in a sealed glass tube at 180° for 24 hrs. Distillation of the reaction mixture gave the mixture of *exo* and *endo* acids 2 and 3 (13.50g, 88.8%); b.p. 145-150°/20 mm (lit[6] b.p. 140-150/20 mm).

6-*endo*-Hydroxybicyclo[2,2,2] octane-2-*endo*-carboxylic Acid γ -Lactone (4)

A mixture of acids 2 and 3 (10g; 70mmol) in 30% H_2SO_4(v/v, 72 ml) was stirred and heated at 110° for 1 hr. The mixture was cooled to room temperature (≈30°) and poured onto crushed ice (30 g) and extracted with chloroform (25 ml x 3). The chloroform extract was washed with 10% $NaHCO_3$ (10 ml x 3) and water (10 ml x1) and dried. Removal of the solvent and crystallization of the residue from benzene furnished lactone 4 (7.5 g, 75%); m.p. 205-206° (Lit[6]. m.p. 207-208°); IR($CHCl_3$):-C=O 1760 cm^{-1}; PMR ($CDCl_3$): 4.67 ppm(m,1H,C_6-exoH).

Saponification of 4

The lactone 4 (151 mg, 0.001 mole) in methanol(10 ml) was mixed with 20% NaOH (15 ml). The mixture was refluxed for 2 hr, cooled to room temperature and diluted with water (25 ml). It was acidified with molar equivalent conc. HCl, extracted with ether (30 mlx3) and ether extracts were washed with water and dried. Removal of the solvent and crystallization of the residue from benzene gave back the starting γ-lactone 4 m.p.205-206°.

Methyl-6-oxobicyclo[2,2,2]octane-2-endo-carboxylate (6)

The γ-lactone 4 (1.51 g, 0.01 mole) was dissolved in NaOH aq.(0.04 g, 0.01 mole in 25 ml of water). When the solution become homogeneous (2 hr,100°C), it was cooled and found to be neutral to phenolpthalein. To the neutral aqueous solution of sodium salt or the hydroxy acid, was added 50 mg of RuO_2. The solution was cooled ($\sim$20°) and vigorously stirred while a solution containing approximately 10% of stoichiometric amount (2.14 g,0.01 mole) of $NaIO_4$ was added. The solution developed a yellow colour indicating the presence of RuO_4. Upon the appearance of the black ruthenium dioxide precipitate another aliquot of $NaIO_4$ was added. Each successive addition required more time for the disappearance of

the yellow colour of the tetroxide. After total addition (~3 hr) of the periodate, isopropyl alcohol (0.5 ml) was added and the reaction mixture was stirred for an additional 5 min. It was acidified with 10% hydrochloric acid aqueous and extracted with ethyl acetate (20 ml x3). The extracts were combined and dried. The solvent was removed under reduced pressure (20 torr) and crystalisation of the residue from acetone/pet.ether gave keto acid 6 (1.42 g, 87.5%); m.p. 107-109°(Lit[21] m.p. 108-109°).

The keto acid 6 was converted into its methyl ester 7 by treatment with diazomethane in ether. The ether was flashed off to give methyl 6-oxobicyclo[2,2,2]octane-6-endo-carboxylate 7 (1.324 g, 88.3%) b.p.130-140°/5 mm (Lit[21] b.p. 160°/20 mm). IR (CCl_4)(Fig 7): C=O, 1720 cm^{-1}; $COOCH_3$ 1740, 1075 cm^{-1}; PMR (CCl_4)(FIG.8): $COCH_2$(2H,bs; 2.2 ppm); COCH (1H,m, 2.7-2.9 ppm); $-COOCH_3$(3H,s,3.6 ppm). Found 65.92; H, 7.682. $C_{10}H_{14}O_3$ requires C, 65.93; H, 7.692%).

Methyl 6,6-ethylenedioxybicyclo[2,2,2]octane-6-*endo*-carboxylate (8)

The keto ester 7 (0.516 g, 3 m mole) in benzene(30 ml) was mixed with ethylene glycol (0.2 g) and p-toluene-sulphonic acid (10 mg). The mixture was refluxed with continuous removal of water for 7 hr. The cooled reaction mixture was poured into 50 ml water, the organic layer was separated, and the aqueous layer was extracted with benzene (25ml x2). The combined organic layers were washed with brine and freed of solvent. The residue was distilled in vacuo to give 8 (0.589 g, 88%); b.p.120-125°/2-3 mm. IR(CCl_4) (Fig.9): $COOCH_3$ 1725, 1170,1075 cm^{-1}; PMR (CCl_4)(Fig.10): $COOCH_3$ (3H, s, 3.61 ppm); O-CH_2-CH_2-O (4H, m, 3.7 to 3.9 ppm). (Found: C, 63.70; H, 7.96. $C_{12}H_{18}O_4$ requires C,63.71; H,7.964%).

2-*endo*-Hydroxymethyl-6,6-ethylenedioxybicyclo[2,2,2]octane(9)

A solution of 8 ketal ester 8 (113 mg, 0.5 m mole) in dry ether (15 ml) was added dropwise to a stirred suspension of LAH (40 mg) in dry ether (50 ml) kept below 10° by external cooling. After the addition, the mixture was stirred for 2.5 hr at room temperature and then refluxed for 30 min. At the end of this period, the mixture was cooled in an ice bath and the excess LAH was destroyed by cautious addition of water. The ethereal solution was separated and the aqueous layer was extracted with ether (10 ml x 2). The combined ether extracts were washed with water(10 ml x1), dried and concentrated. The residue

was distilled to give 9 (120 mg, 95%); b.p. 118-120°C/ 2-3 mm. IR (CCl_4)(Fig. 11): OH 3300, 1110 and 1090 cm^{-1}. PMR (CCl_4)(Fig.12): -O-CH_2-CH_2-O (4H, m, 3.7 to 4.05 ppm); -CH_2OH(2H, m, 3.23 to 3.51 ppm).

2-endo-Hydroxymethyl-6-oxobicyclo[2,2,2]octane (10)

The BF_3 etherate (0.1 ml) was added to a stirred solution of 9 (1.94 mg, 0.01 mole) in ether (20 ml) at 0°C. The mixture was stirred for additional 30 minutes, diluted with water (30 ml) and extracted with dichloromethane (20 ml x3). The combined extracts were washed with brine, dried and concentrated. The residue was distilled to give 10 (1.52 g, 100%), b.p. 130-135°(bath)/2-3 mm.IR.(CCl_4) (Fig 13): OH 3500,1100,1070 cm^{-1}; C=O 1720 cm^{-1}. PMR(CCl_4) (Fig.14): CH_2-OH (2H, m, 3.1 to 3.5 ppm); COCH (1H, m, 2.17 to 2.28ppm); $COCH_2$(2H, bs, 2.12 ppm). (Found: C,76.10; H,9.090. $C_9H_{14}O_2$ requires C, 76.12; H, 9.09%).

2-endo-Hydroxy-6-endo-hydroxymethylbicyclo[2,2,2]octane (13)

A solution of γ -lactone 4 (0.4569, 3 m mole) in dry ether (25 ml) was added dropwise to a stirred suspension of LAH (40 mg) in dry ether (50 ml) kept below 10° by external cooling. After the addition, the mixture was stirred for 2.5 hr at room temperature. At the end of this period, the mixture was cooled in an ice bath and the

excess LAH was destroyed by cautious addition of water. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, dried and concentrated. The residue was distilled to give 13 (0.460 g,100%); b.p. 140-150°(bath)/2-3 mm . IR(Nujol)(Fig.15): OH 3600,1010, 995 cm^{-1}. PMR ($CDCl_3$)(Fig.16): C<u>H</u>OH (1H, m, 3.68-3.9 ppm); $C\underline{H}_2OH$ (2H, d, 3.5 ppm, J= 5Hz).(Found C, 69.27; H,10.15. $C_9H_{16}O_2$ required C, 6.29; H, 10.25%).

Selective oxidation of diol (13) with Bromine-HMPT

A solution of bromine was added dropwise to a vigorously stirred heterogeneous mixture of diol 9 (152 mg, .001 mole), HMPT(1 ml), dichloromethane(10 ml) and 8% sodium hydrogen carbonate aqueous (10 ml) at ~5°. Stirring was continued till no more alcohol could be detected by tlc. After decantation of the reaction mixture, the aqueous phase is extracted with dichloromethane (25 ml x 3). The combined extracts were washed with brine, dried and concentrated at diminished pressure (20 torr) to give a residue which, when filtered through a small bed of silica gel, yielded 2-endo-hydroxymethyl-6-oxobicyclo[2,2,2] octane 10 (130 mg, 83.8%). IR and PMR spectra of this compound were identical with that of the reaction product obtained from deketalisation of 9 by BF_3-Et_2O.

Rearrangement of ketal alcohol (9)

A mixture of 9 (0.226 g, 1 m mole) and p-toluene-sulphonyl chloride (0.3 g) in pyridine (5 ml) was refluxed for 24 hr. The mixture was cooled to room temp. and poured with stirring into ice cold water(20 ml) and extracted with ether (50 ml x 3). The ether extract was washed and dried. Removal of solvent gave a residue which, when filtered through a small bed of alumina, yielded hydroxyl ether 14 (50 mg). IR (CCl_4)(Fig. 17): C=O 1720 cm^{-1}; OH 3500, 1050 cm^{-1}. PMR(CCl_4)(Fig. 18): $-CH_2-O-CH_2-CH_2-OH$ (6H, m, 3.2 to 3.6 ppm); COCH-(1H, bs, 2.5 ppm); $COCH_2$(2H, bs, 2.18 ppm).

Transformation of 14 to keto alcohol 10

A mixture of 14 (40 mg) and p-toluene sulphonyl chloride (100 mg) in pyridine (5 ml) was kept at room temperature ($\sim 30^{\circ}$) for 4 hrs. The mixture was poured with stirring into ice cold water(20 ml) and extracted with ether (50 ml x 3). The ether extracts were washed and dried. Removal of solvent gave expected crude tosylate (65 mg).

To a stirred solution of this crude tosylate in anhydrous 1,2-dimethoxyethane(15 ml) was added under nitrogen Zn-pwder (100 mg) followed by powdered sodium iodide (100 mg). The mixture was refluxed with stirring for 90 min. The cooled reaction mixture was filtered into 5% sodium thiosulphate aqueous (20ml) and the insoluble material was extracted with ether (20 ml x 3). The combined organic extracts were washed with 1% sodium thiosulphate (10 ml),water (10 ml), saturated $NaHCO_3$ (10 ml) and brine (10 ml). The evaporation of solvent gave the hydroxy ketone 10(20 mg).

6-oxo-2-methylenebicyclo[2,2,2] octane (12)

A mixture of hydroxy ketone 10 (304 mg, 2 m mole), finely pulverized sodium hydroxide (80 mg, 2 m mole), carbon tetrachloride (1 ml) and ether (30 ml) were stirred for 30 minutes and then carbondisulphide (152 mg, 2 m mole) was added, followed, by methyl iodide(300 mg, 2.1 m mole). The reaction mixture was stirred for another 10 minutes and worked up in the usual manner to afford xanthate 11 (450 mg, ~ 100%).

The crude xanthate 11 without further purification was pyrolysed by distilling it form a small bulb at 220° (bath)/100 mm. The distillation was complete in 2 hr. The yellowish distillate (250 mg) was chromatographed on a column of silica gel (II, 17 x 0.7 cm).

Fr.1	Pet.ether	20 ml x 1	80 mg,discarded
Fr.2	1% EtOAc in Pet-ether	1 ml x 8	20 mg,discarded
Fr.3	2% EtOAc in Pet.ether	1 ml x 10	90 mg, (pure 12,GLC,PMR)
Fr.4	5% EtOAc in Pet.ether	2 ml x 5	20 mg, xanthate based on TLC
Fr.5	Ethyl acetate	15 ml	15 mg discarded

Fraction 3 was distilled; b.p. 130-140°(bath)/1.5 mm to give ketone olefin 12. IR(CCl_4)(Fig.19); C=O 1725,1024 cm^{-1}; $C=CH_2$ 1645, 893 cm^{-1}. PMR (CCl_4) (Fig.20): $C=CH_2$ (2H, 2s, 4.8, 4.92 ppm); $\underline{C}H-C=CH_2$(1H, m, 2.7 to 2.9 ppm).

6-exo and endo-Hydroxy-2-methylenebicyclo[2,2,2] octanes (1a and 1b)

A mixture of ketone olefin 12 (41 mg, 3 m mole)and $NaBH_4$ (100mg, 2.5m mol)in EtOH (5 ml) was stirred for 3 hrs.,

at room temperature (32±1°) under nitrogen. Excess of $NaBH_4$ was destroyed by adding 15% aqueous acetic acid (1 ml); then it was diluted with water (10 ml) and extracted with ether (15 ml x 3). The combined extracts were washed with water (10 ml x2) till neutral and dried. Removal of solvent furnished a mixture of alcohols 1 a and 1 b (9:1) (39 mg, 100%). IR (CCl_4)(Fig.21): OH 3400, 1050 cm^{-1}; $C=CH_2$ 1600 cm^{-1}. PMR(CCl_4)(Fig.22): $C=CH_2$ (2H, s, 4.9 ppm for 1a, 4.72 ppm for 1b); CHOH(1H, m, 3.8 to 4.0 ppm to 1a, 3.4 to 3.53 ppm 1b).(Found C, 79.22; H, 10.28. $C_9H_{14}O$ requires C, 79.41; H, 10.29%).

Ethyl-(3,3-ethylenedioxycyclohexyl)acetate(18)

A solution of ethyl-(3-oxocyclohexyl)malonate 17 (0.768 g, 0.03 mole), ethylene glycol(2.0 g, 0.032 mole) and p-toluenesulphonic acid(60 mg) in 70 ml of dry benzene was refluxed with continuous removal of water for 6 hr . The cooled reaction mixture was poured into 50 ml water, the layers were separated, and the aqueous layer was extracted with benzene (50 ml). The combined organic layers were washed with brine and freed of solvent. There remained ketal diester (8.8 g, 90%) as an oil.

The crude ketal diester (8.8 g,1.8 m mole) was added in a single portion under nitrogen to a solution of sodium chloride (1 g) in water (1 ml) and DMSO(25 ml). The mixture was heated at 165° for 12 hrs. The mixture was cooled to room temperature and solvent was removed under diminished pressure (20 mm) and residue poured into cold water. Aqueous layer was extracted thoroughly with ether (50 ml x 3). The combined organic layers were washed to neutrality with brine, dried and freed of solvent. The residue was distilled to give 18 (6.4 g,94%); b.p.118-119°/2.3 mm (lit[18] 110°/0.15 mm).

β-(3,3-ethylenedioxycyclohexyl)ethanol (19)

A solution of 18 (4.56 g, 0.02 mole) in dry ether (30 ml) was added dropwise to a stirred suspension of LAH (1.0 g) in dry ether (100 ml) kept below 10° by external cooling. After addition the mixture was stirred for 2.5 hr at room temperature and for 30 min. under reflux . At the end of this period the mixture was cooled in an ice bath and the excess of LAH was destroyed by cautious addition of water. The ethereal solution was separated and the aqueous layer was extracted with ether (20 ml x2). The combined ether extracts were washed with water (10 ml), brine(10 ml), dried and concentrated.

The residue was distilled to give 19 (3.56 g, 95%);b.p. 118-119°/2mm (Lit.[18] 110°/0.15 mm). IR.(CCl_4): OH 3400,1150 1010 cm^{-1}. PMR(CCl_4): $\underline{CH_2}OH$(2H, t, 3.35 ppm); -O-$\underline{CH_2}$-$\underline{CH_2}$-O (4H,s, 3.85 ppm).

3,3-Ethylene dioxycyclohexylacetaldehyde (20)

Chromium trioxide (12.0 g, 120 m mole) was added to a magnetically stirred solution of pyridine (18.82 g, 120 m mole) in dichloromethane(150 ml). The flask was stoppered with drying tube and solution was stirred for 15 minutes at room temperature. At the end of this period, a solution of alcohol 19 (3.6 g, 20 m mole) in small volume of dichloromethane (20 ml) was added in one portion and stirred for 30 minutes at 25±2°. Then it was filtered through celite and concentrated in vacuo. The residue was mixed with ether and filtered through celite. The ethereal solution was concentrated and the residue was distilled to give 20 (3.6 g, 80%);b.p. 106-7°/ 3 mm (Lit.[18] b.p. 104-5°/3 mm). IR (CCl_4):CHO 2110,1710 cm^{-1}. PMR(CCl_4): O-$\underline{CH_2}$-$\underline{CH_2}$-O (4H,s,3.95 ppm); $\underline{CH}$O(1H,t,9.73 ppm).

Bicyclo[2,2,2]octane-2-ol-6-one (21)

The aldehyde 21 (1.8 g, 0.01 mole) was added dropwise to dilute phosphoric acid (15% v/v, 30 ml) at 110°. The

mixture was heated at 110° for 2 hr, cooled and extracted with ether (25 ml x 3). The ethereal solution was washed with brine, dried and concentrated to give crystalline 21 (1.4 g-90%); m.p. 198-200°(Lit[16] m.p.201°). IR($CHCl_3$) (Fig.23):OH 2400, 1090 cm^{-1}; C=O 1710 cm^{-1}. PMR ($CDCl_3$) (Fig.24): CHOH (1H, m,4.1-4.25 ppm).

6-Tetrahydropyranoxybicyclo[2,2,2]octane-2-one(22)

A mixture of hydroxy ketone 21 (0.144 g, 1 m mole) in anhydrous ether (20 ml), dihydropyrane (127 g, 1.5 mole) and p-toluene sulphonic acid (10 mg) was stirred for 7 hr at room temperature. At the end of this period, the mixture was diluted with water (30 ml) and extracted with ether (20 ml x 3). Combined ether extracts were washed with 10% $NaHCO_3$ (10 ml x 3) and water (10 ml x3), dried and concentrated. The residue was distilled in vacuo to give 22 (210 mg, 90%); b.p. 130-140(bath)/0.5 mm. Mass: M/e 224(M^+, 14.19%), 139(61.24%); 123(11.61%), 122(29.03%), 110(16.12%),95(35.48%), 85(100%),79(41.93%),78(22.58%). IR (CCl_4)(Fig.25): C=O 1735 cm^{-1}; O-C ether 1355,1150 cm^{-1}. PMR(CCl_4)(Fig.26): CH-OTHP(1H, m, 3.9-4.3 ppm); $COCH_2$ (2H,bs, 2.15 ppm).(Found C,69.62; H, 8.918. $C_{23}H_{20}O_3$ requires C, 69.64; H, 8.92%).

6-Tetrahydropyranoxy-2-methylenebicyclo[2,2,2]octane (23)

6-Tetrahydropyranoxybicyclo[2,2,2]octane-2-one 21 (4.48%, 0.2 mole) in dry THF (distilled from LAH, 10 ml) was added to a suspension of triphenyl phosphonium methyl iodide (8.8 g,0.06mole) and freshly prepared potassium ter-butoxide (2.7 g, 0.22 mole) in dry THF (10 ml) under an atmosphere of nitrogen. After the addition was complete (~10 min), the product was stirred for another 1 hr at 45-50°. After leaving for 12 hrs at room temperature, the THF from the reaction mixture was removed by distillation on a water bath. The residue was cooled, diluted with water (50 ml) and extracted with ether (50 ml x 3). The ether extracts were washed with water (10 ml x 3), brine (10 ml x 1) and dried. The removal of solvent furnished a product which was chromatographed over alumina (II, 20 cm x 1.5 cm). Eluation with pet.ether(60-80°) gave 6-tetrahydropyranoxy-2-methylenebicyclo[2,2,2] octane 23 (3.36 g,80%); b.p. 135-140(bath)/0.5 mm). Mass m/e 222(M^+, 1.3%), 178(6.6%), 123(4.8%), 93(4.8%),86(6.6%),85(100%), 78(6.6%), 67(10%). IR (CCl_4)(Fig.27): $C=CH_2$ 1665, 920 and 870 cm^{-1}. PMR(CCl_4)(Fig.28):$C=CH_2$ (2H, m, 4.55 to 4.9 ppm), CHOTHP(2H,m, 3.9 to 4.3 ppm).(Found C,75.57, H,9.90. $C_{14}H_{22}O_2$, requires, C, 75.67; H, 9.90%).

6-*exo*-and 6-*endo*-2-Methylenebicyclo[2,2,2]octanes (*1a* and *1b*)

A mixture of 6-tetrahydropyranoxy-2-methylenebicyclo [2,2,2]octane *24* (0.222 mg, 0.001 mole) in methanol-water (50:50, 10 ml) and 10 N HCl (0.1 ml) was stirred at 25° for 6 hr. The reaction mixture was diluted with water (20 ml) and extracted with ether (25 ml x 3). The ether extracts were washed successively with water (10 ml x 4) and brine (10 ml) and dried. The removal of solvent offered a mixture of alcohols *1a* and *1b* in the ratio of 9:1 respectively (130 mg, ~ 100%).

Synthesis of Isopulegol (*26*)

This alcohol was prepared from citronellal according to the procedure reported in literature[21].

Cleavage of Homoallylic alcohol 1

1) With bromine: To a cooled solution (internal temp. -5 ± 2^{o}) of homoallylic alcohol 1 (136 mg, 1 m mole) in carbon tetrachloride (10 ml) containing Na_2CO_3 (300 mg) was introduced a cold solution of bromine in CCl_4 (5 ml, 160 mg , 1 m mole) during 5 minutes, keeping the temperature -5 ± 3^{o}. The yellow colour of bromine was discharged immediately as the addition of bromine was over. Then Na_2CO_3 was filtered off and washed with CCl_4 (2 ml x2). The solvent was evaporated at 10 ± 2^{o} under reduced pressure to get a residue of a complex mixture, the PMR of which shows -CHO (1H, bs, 9.7 ppm) and C=CH (1H, bs, 5.87 ppm) corresponding to the fragmentation product 25.

2) With-Mercury(II)acetate: To mercury(II)acetate (318 mg, 1 m. mole) in THF (5 ml) and water (2.5 ml) was added a solution of alcohol 1 (136 mg, 1 m. mole) in THF (2.5 ml). The yellow colour disappears in 10 min. and the reaction mixture was stirred at room temperature for 1 hr. The organomercuric acetate reduced in situ by stirring with 3N NaOH (5 ml) and 0.5M $NaBH_4$ in 3M NaOH (5 ml) for 2 hr at room temperature. The reaction mixture was extracted with solvent ether (20 ml x3). The combined ether extracts were washed with brine (5 ml) and dried. Removal of solvent gave the mixture of epimeric diols 26 (130 mg). The crude diol mixture was loaded on dry

packed column of neutral alumina (I, 10 g, 12 x 1.5 cm). At the end of 12 hr , 6-hydroxy-2-methylenebicyclo[2,2,2]octane 1 was eluated out with petroleum ether (100 ml).

Reaction of isopulegol (27) with mercury(II)acetate:

To mercury(II)acetate(318 mg, 1 m mole) in water(5 ml) and THF (2.5 ml) was added a solution of isopulegol 27 (172 mg, 1 m mole) in THF (2.5 ml). The reaction mixture was stirred at room temperature for 1 hr. The organomercurial acetate was reduced in situ by stirring with 3N NaOH (5 ml) and 0.5 M $NaBH_4$ in 3 M NaOH (5 ml). The reaction mixture was extracted with solvent ether (20 ml x 3). The combined ether extracts were washed with brine (5 ml), dried and concentrated. The residue was distilled to give 28 (150 mg, 90%); b.p.118-120° (bath)/2.3 mm. I.R.($CHCl_3$)(Fig.29):OH 3500, 1050 cm^{-1}; PMR($CDCl_3$)(Fig 30): C-CH_3(3H, d, 0.92 ppm, J = 5 Hz), O-CCH_3 (6H, s, 1.25 ppm), C<u>H</u>OH(1H, m, 3.5 to 3.72 ppm). (Found C, 69.75; H, 11.61. $C_{10}H_{20}O_2$ requires C,69.76, H, 11.62%).

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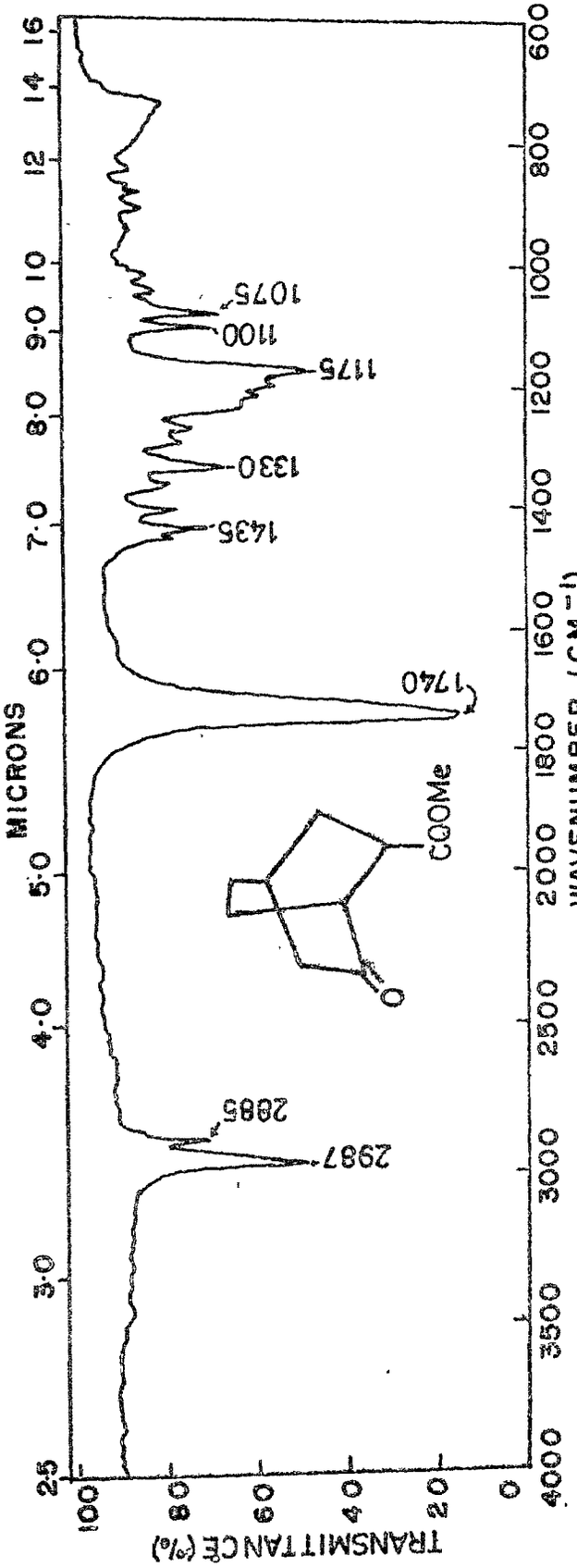


FIG.7: IR SPECTRUM OF METHYL 6-OXOBICYCLO[2,2,2] OCTANE-2-ENDO-CARBOXYLATE (6)

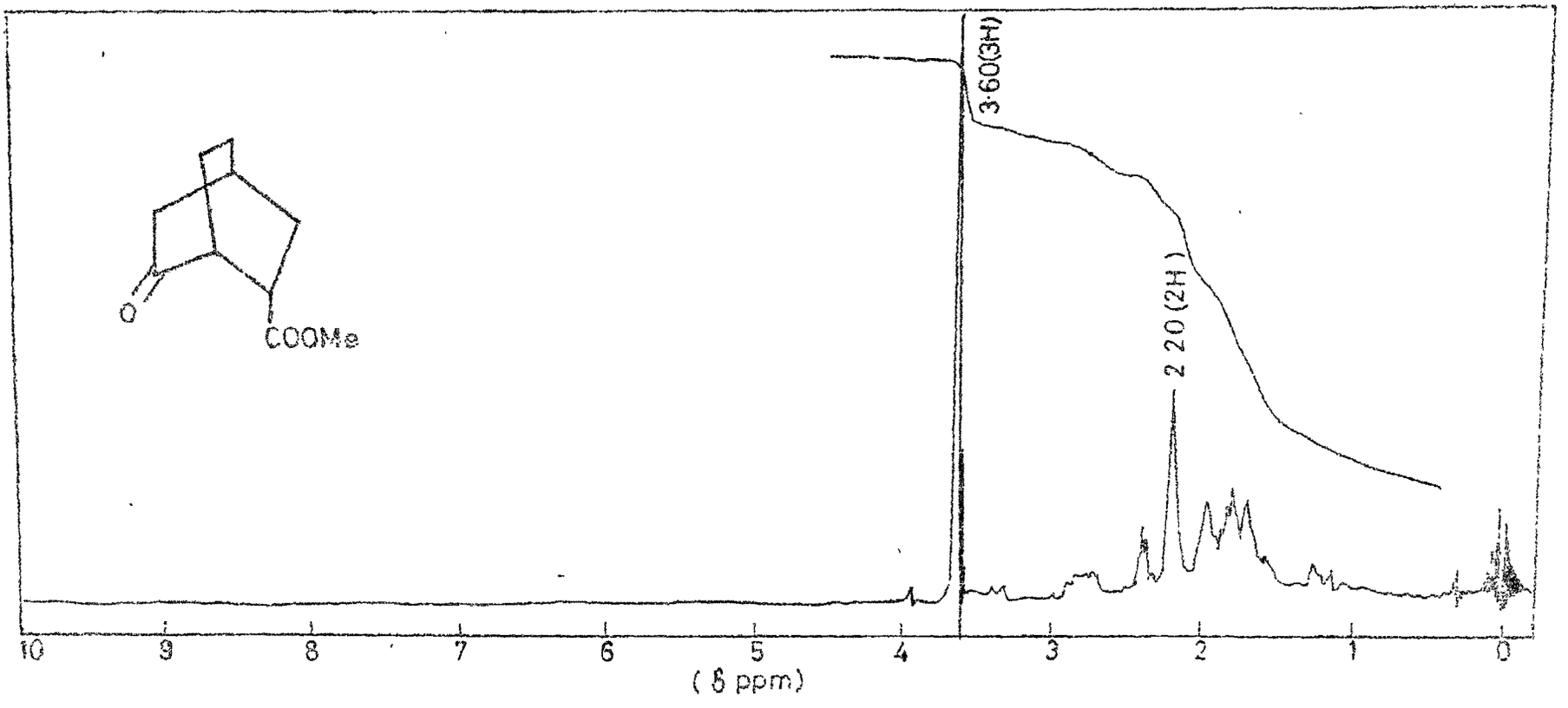


FIG. 8: PMR SPECTRUM OF METHYL 6-OXOBICYCLO[2, 2,2]OCTANE-2-ENDO-CARBOXYLATE (6)

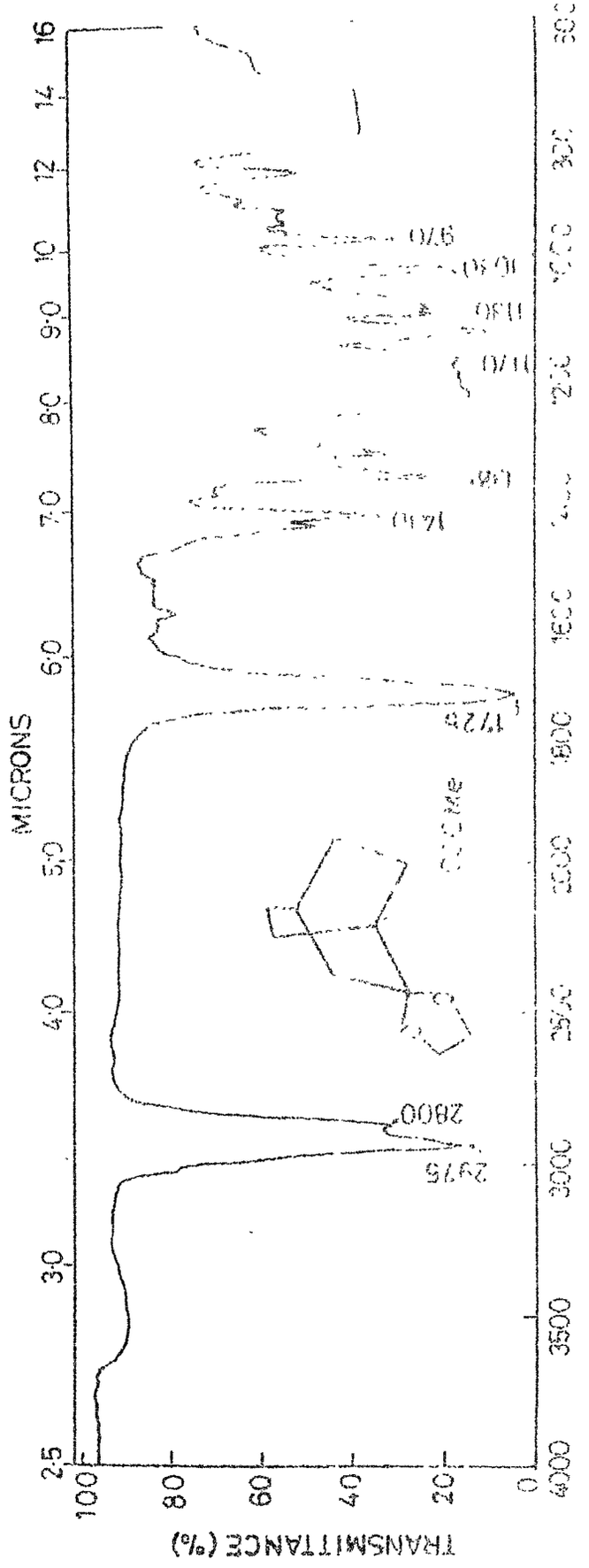


FIG. 61 IR SPECTRUM OF METHYL 5,6-ETHYLENEDIOXYBICYCLO[2.2.2]OCTANE-2-ENDO-CARBOXYLATE (58)

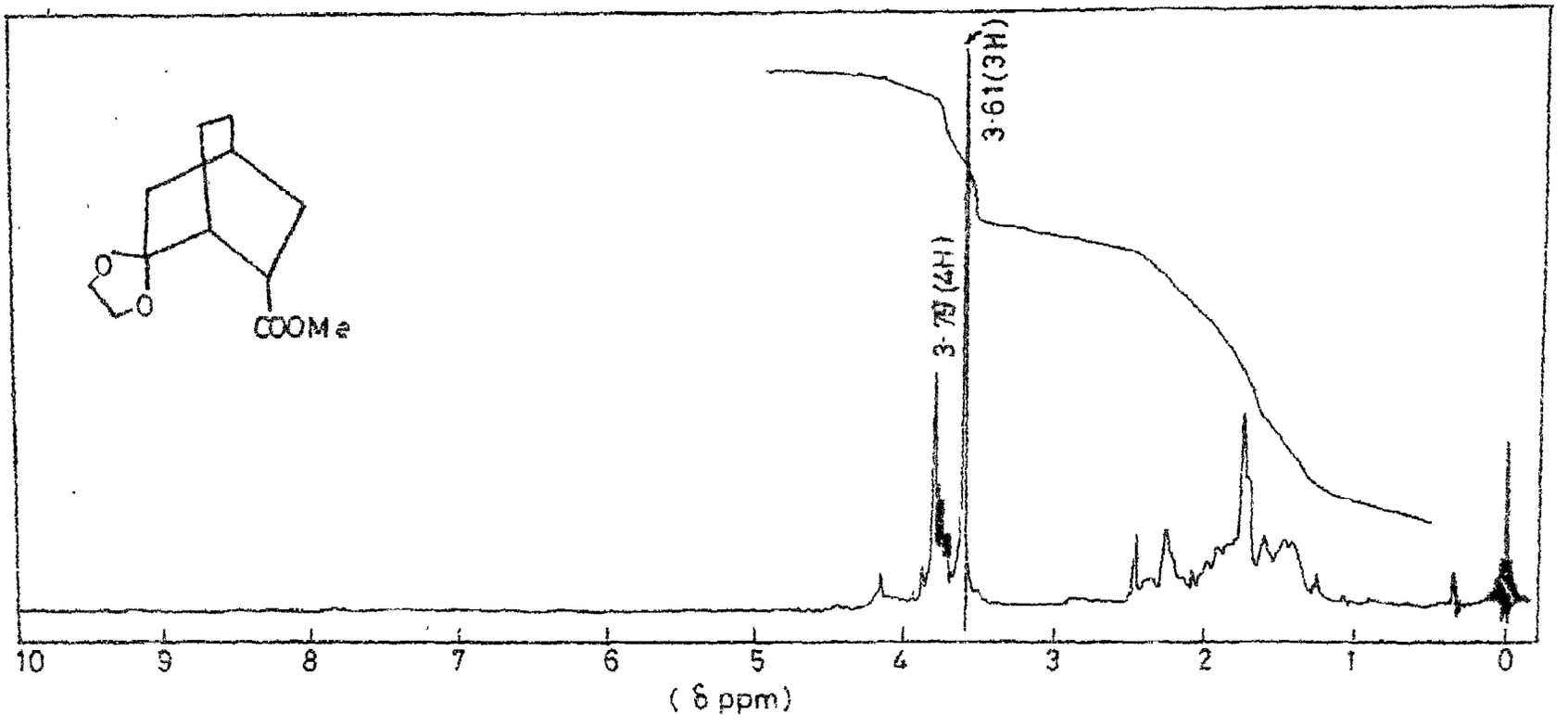


FIG. 10: PMR SPECTRUM OF METHYL 6,6-ETHYLENEDIOXYBICYCLO [2,2,2] OCTANE-2-ENDO - CARBOXYLATE (8)

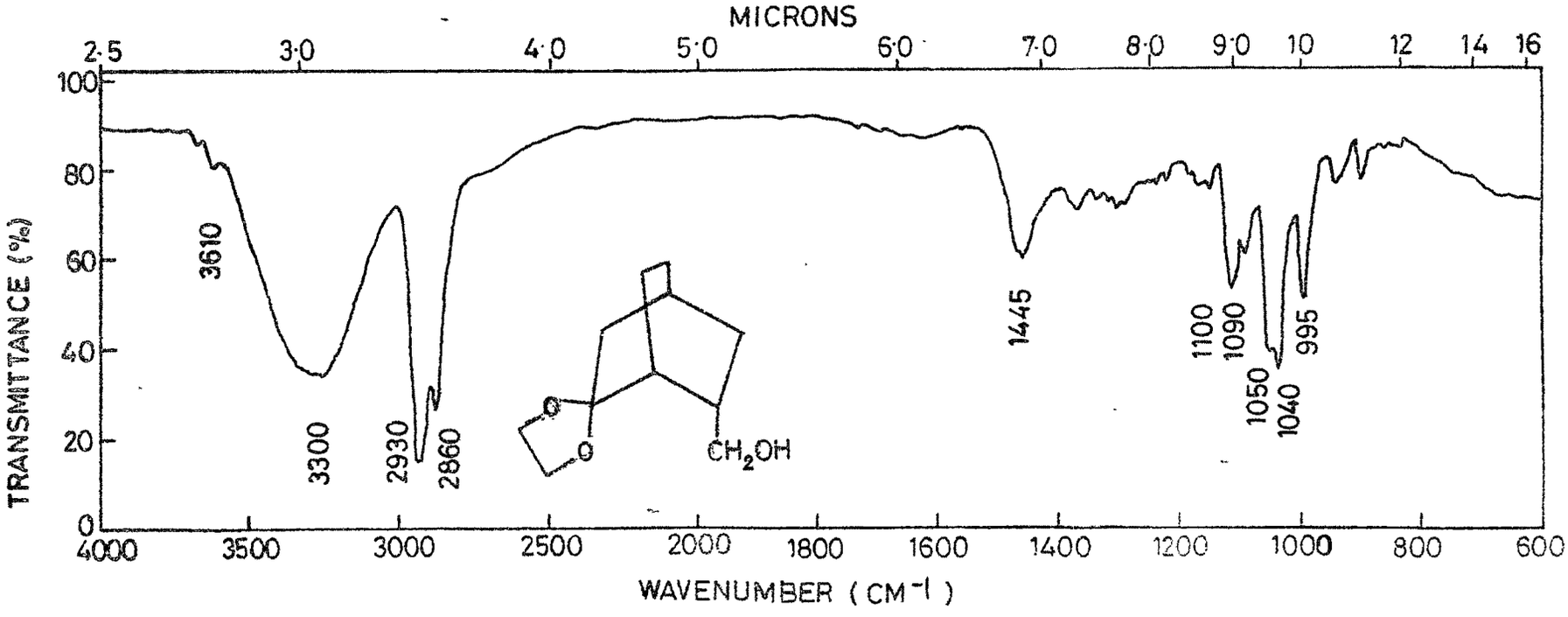


FIG.11: IR SPECTRUM OF 2-ENDO-HYDROXYMETHYL-6,6-ETHYLENEDIOXYBICYCLO-[2,2,2] OCTANE (9)

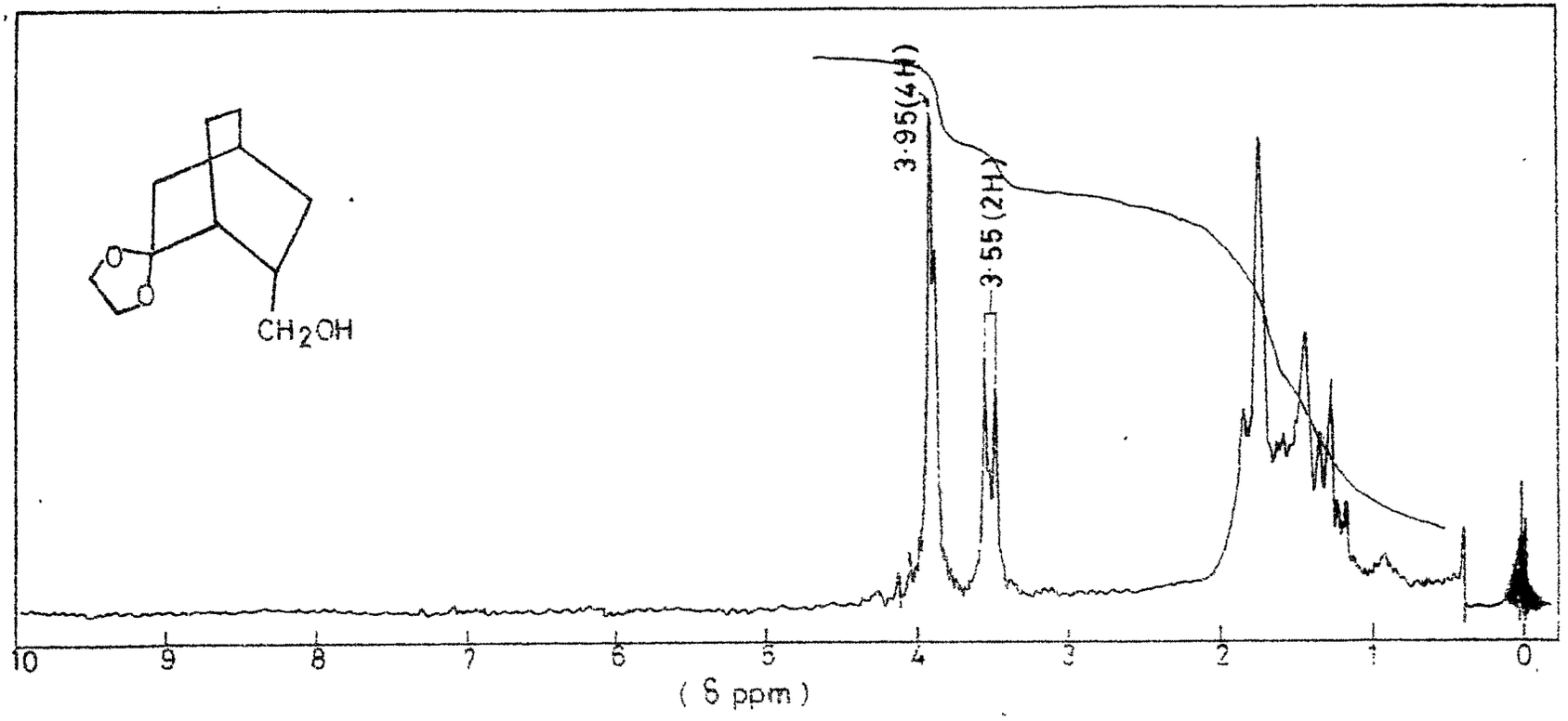
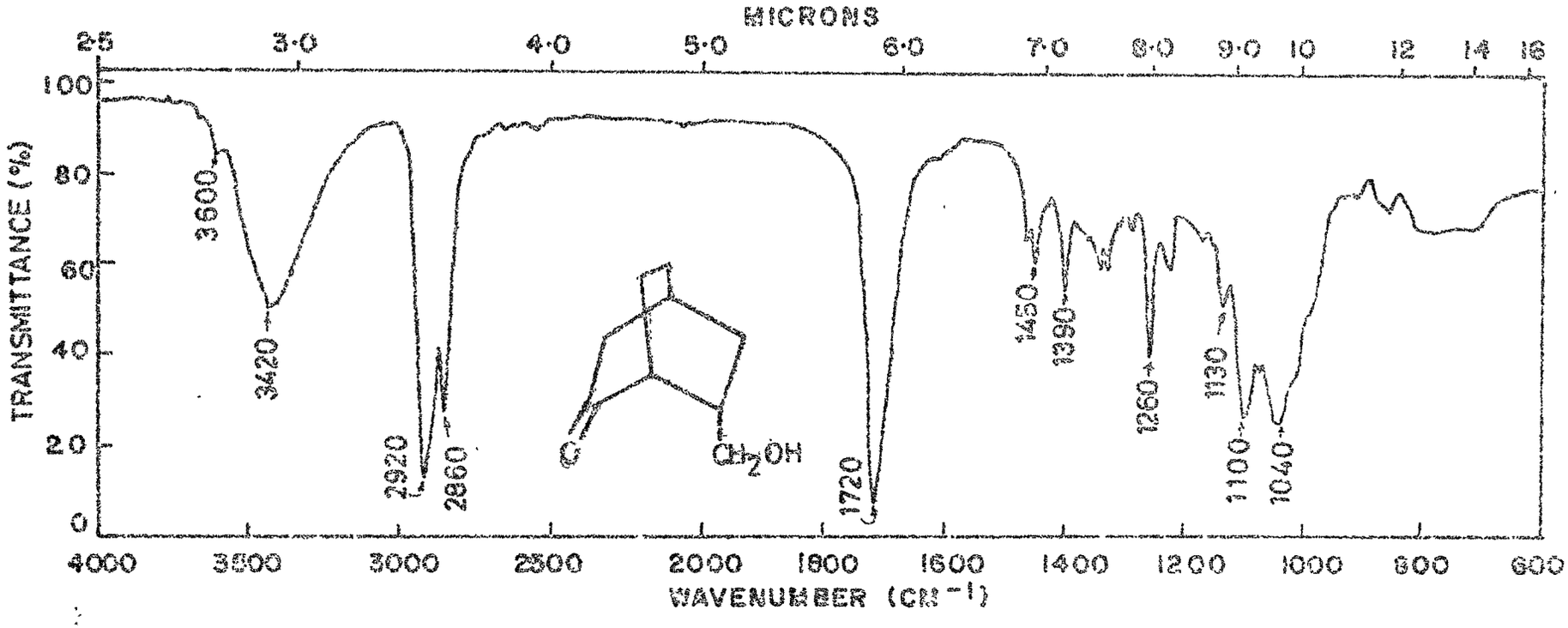


FIG. 12: PMR SPECTRUM OF 2-ENDO- HYDROXYMETHYL-6,6-ETHYLENEDIOXY-BICYCLO[2,2,2] OCTANE(9)



FIG·13: IR SPECTRUM OF 2-ENDO-HYDROXYMETHYL-6-OXOBICYCLO[2,2,2]OCTANE (10)

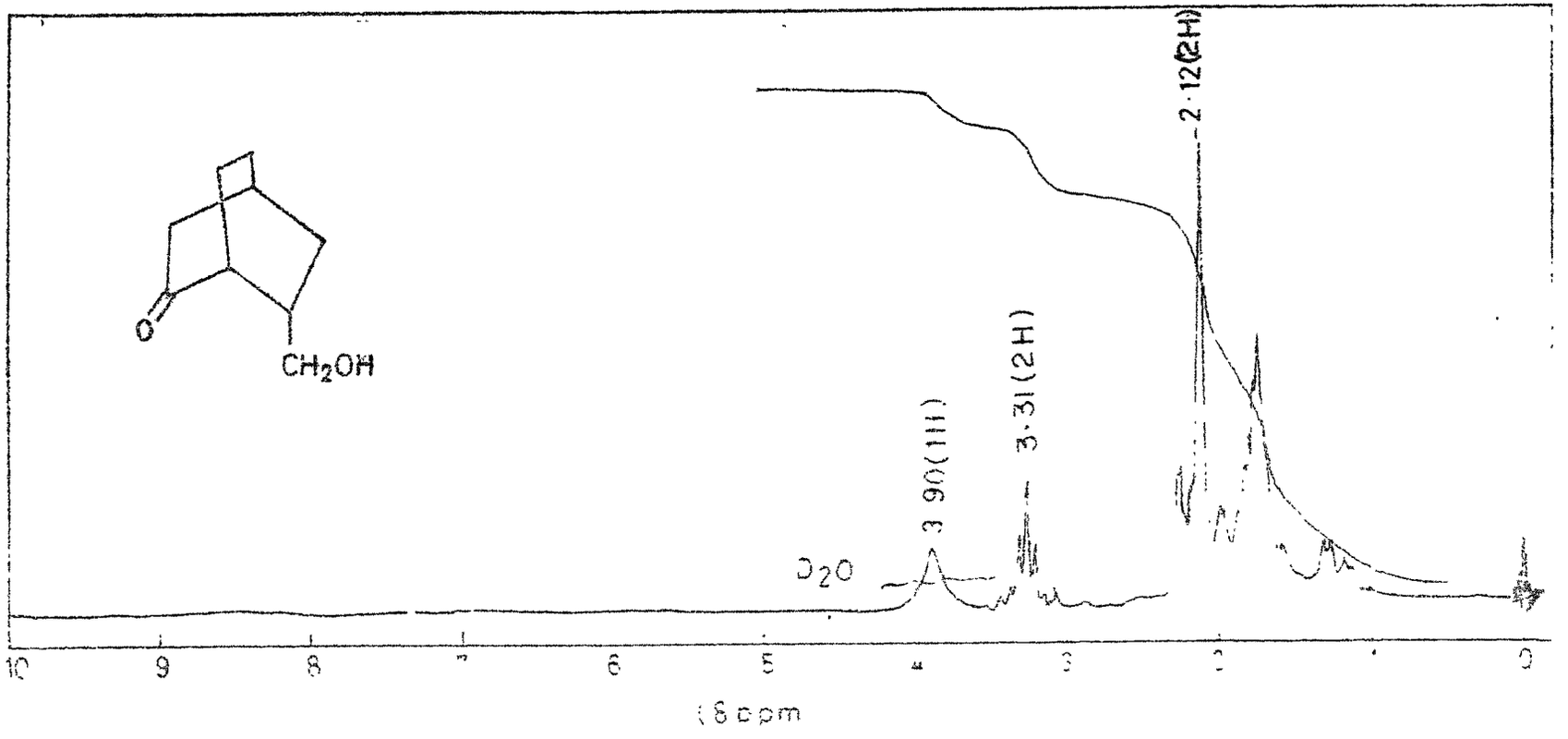


FIG. 14: PMR SPECTRUM OF 2-ENDO-HYDROXYMETHYL-6-OXO-BICYCLO [2,2,2] OCTANE (10)

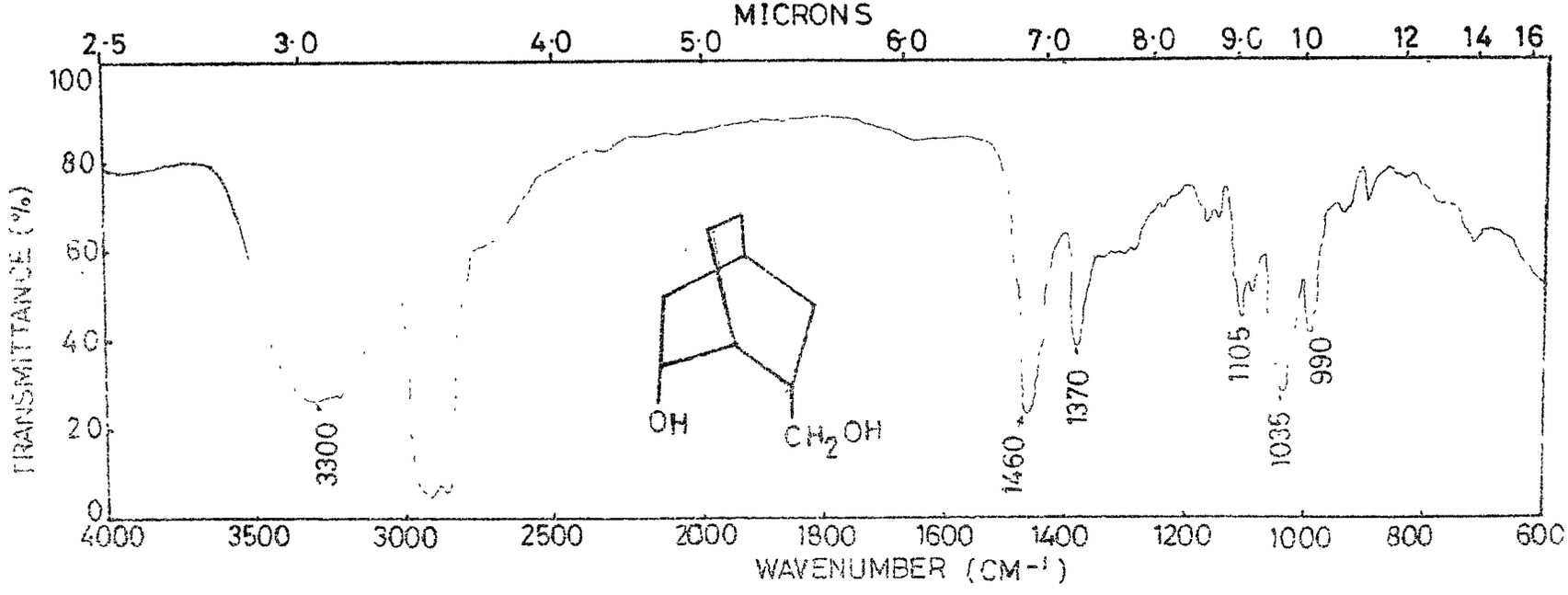


FIG. 15: IR SPECTRUM OF 2-ENDO-HYDROXY-6-ENDO-HYDROXYMETHYLBICYCLO-[2,2,2] OCTANE (13)

3·68(1H)
3·55(J=5Hz)(2H)
CH2OH
OH
H
10
9
8
7
6
5

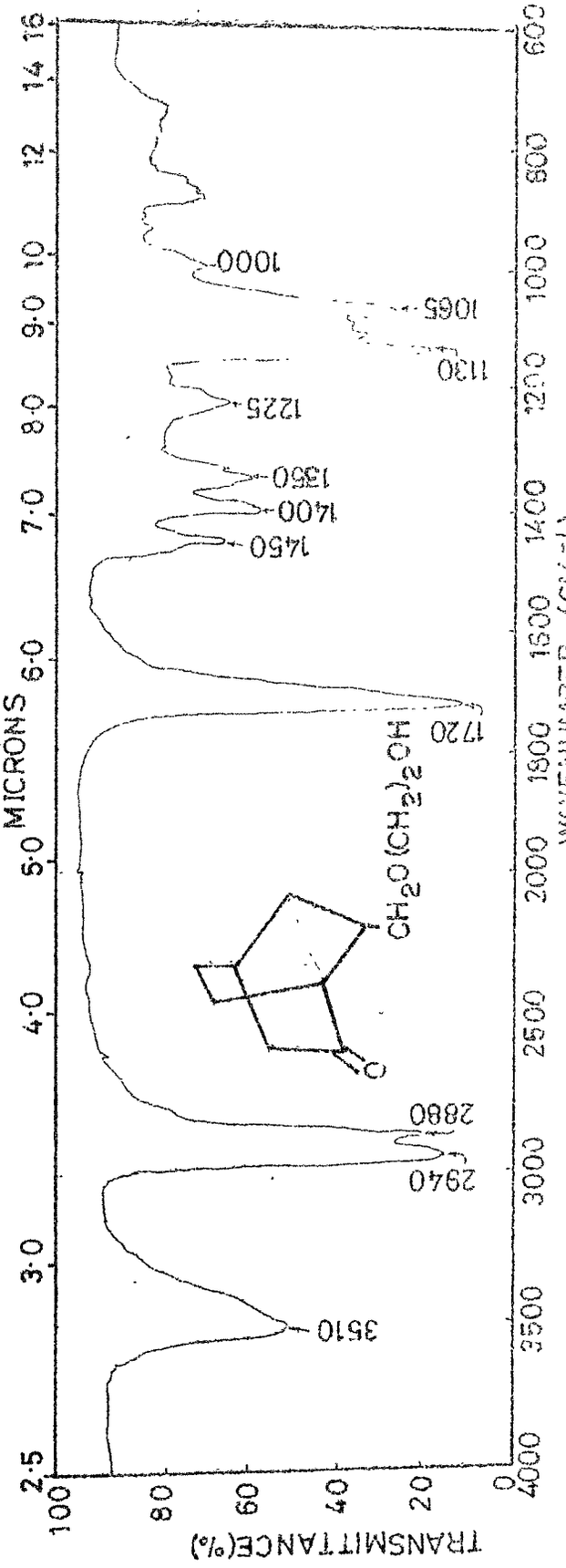


FIG-17 : IR SPECTRUM OF HYDROXYETHYLCOUMARIN (4)

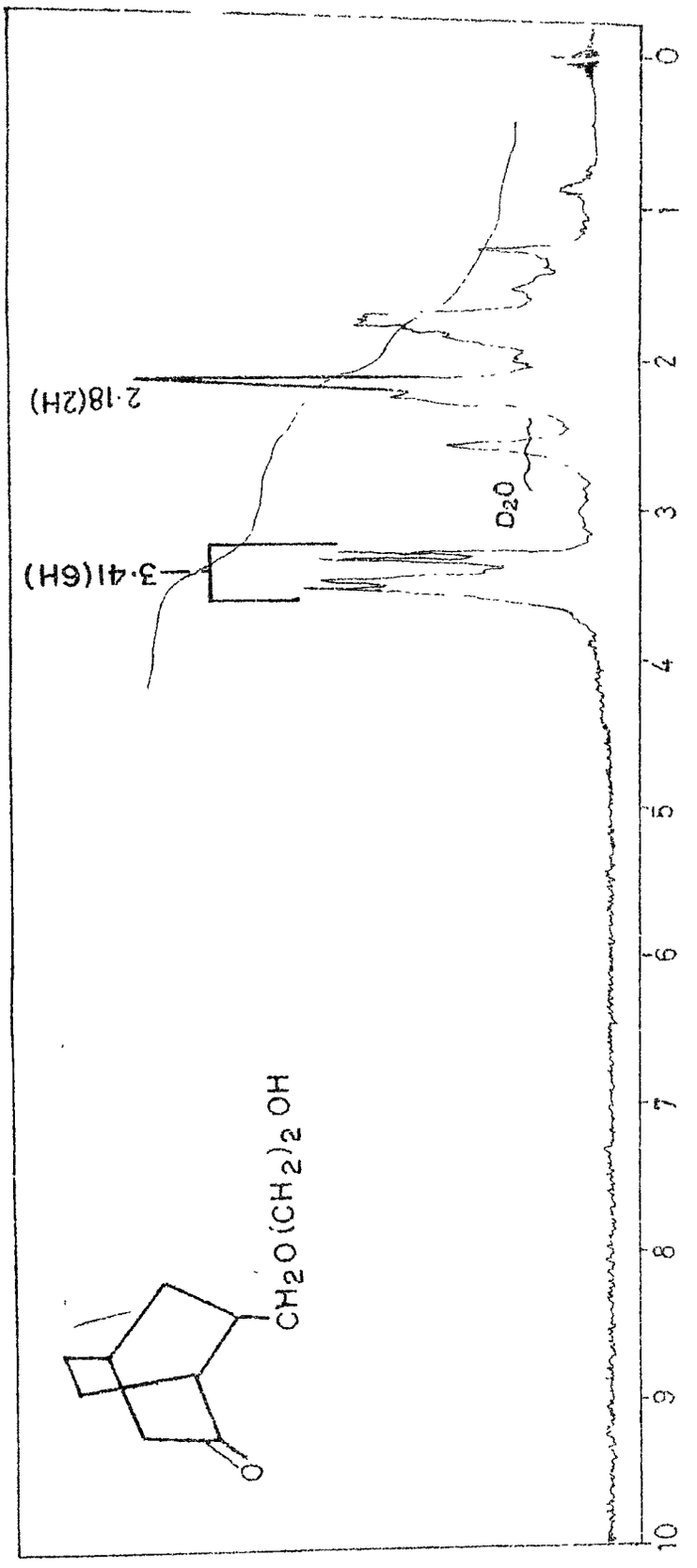


FIG. 18 · PMR SPECTRUM OF HYDROXYETHYLCETHER (14)

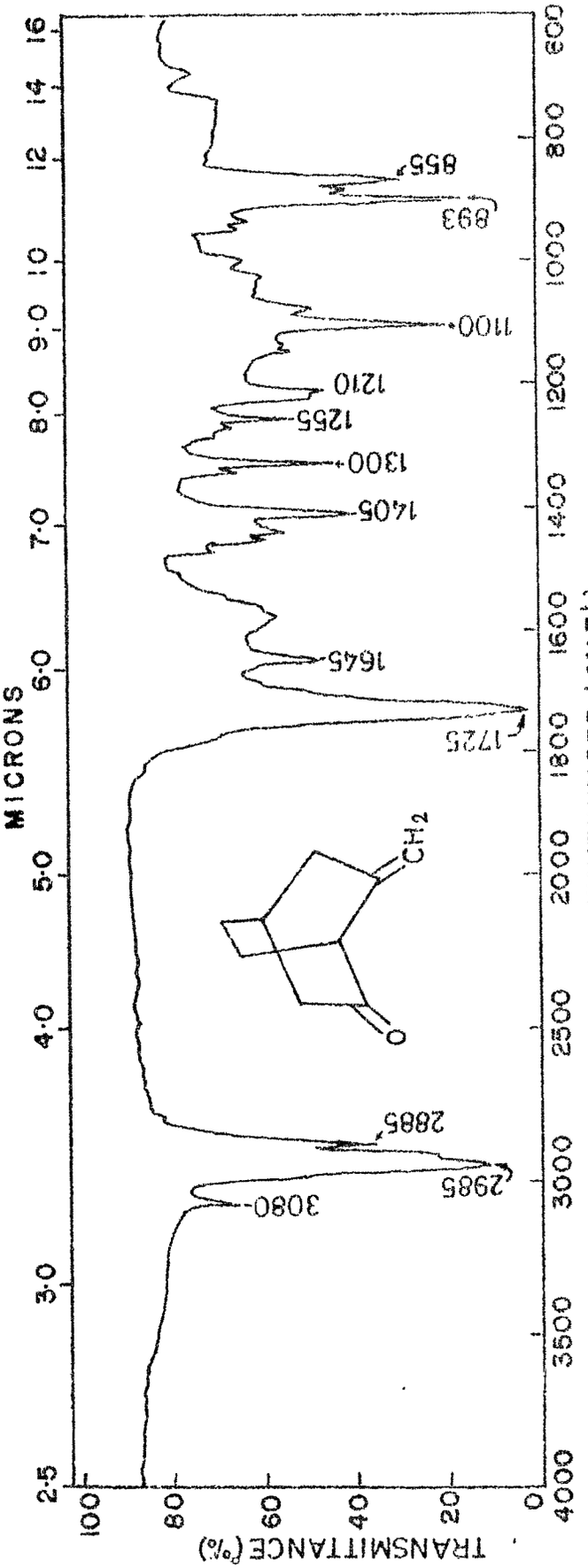


FIG 19: IR SPECTRUM OF 6-OXO-2-METHYLENEBICYCLO [2,2,2] OCTANE (12)

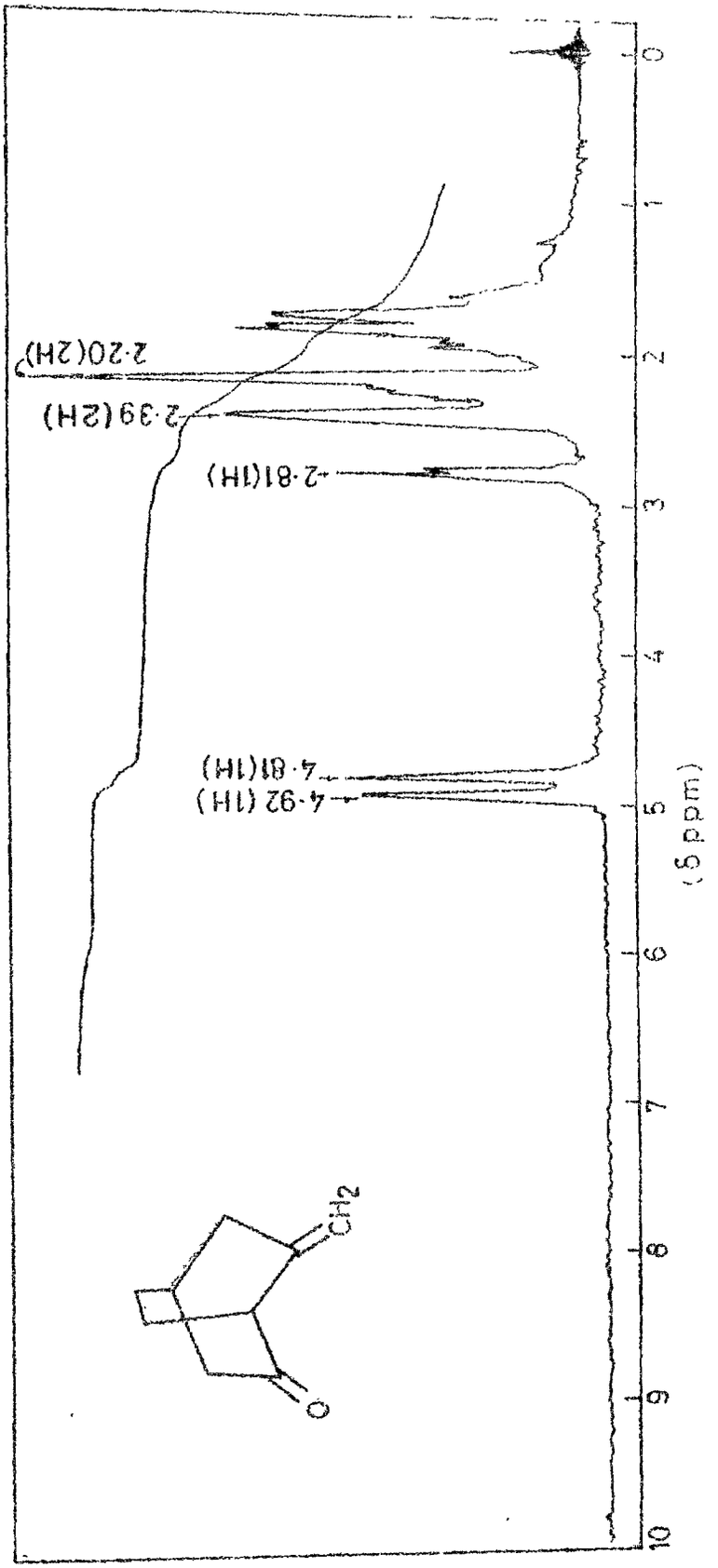


FIG. 20: PMR SPECTRUM OF 6-OXO-2-METHYLENE BICYCLO [2,2,2] OCTANE (12)

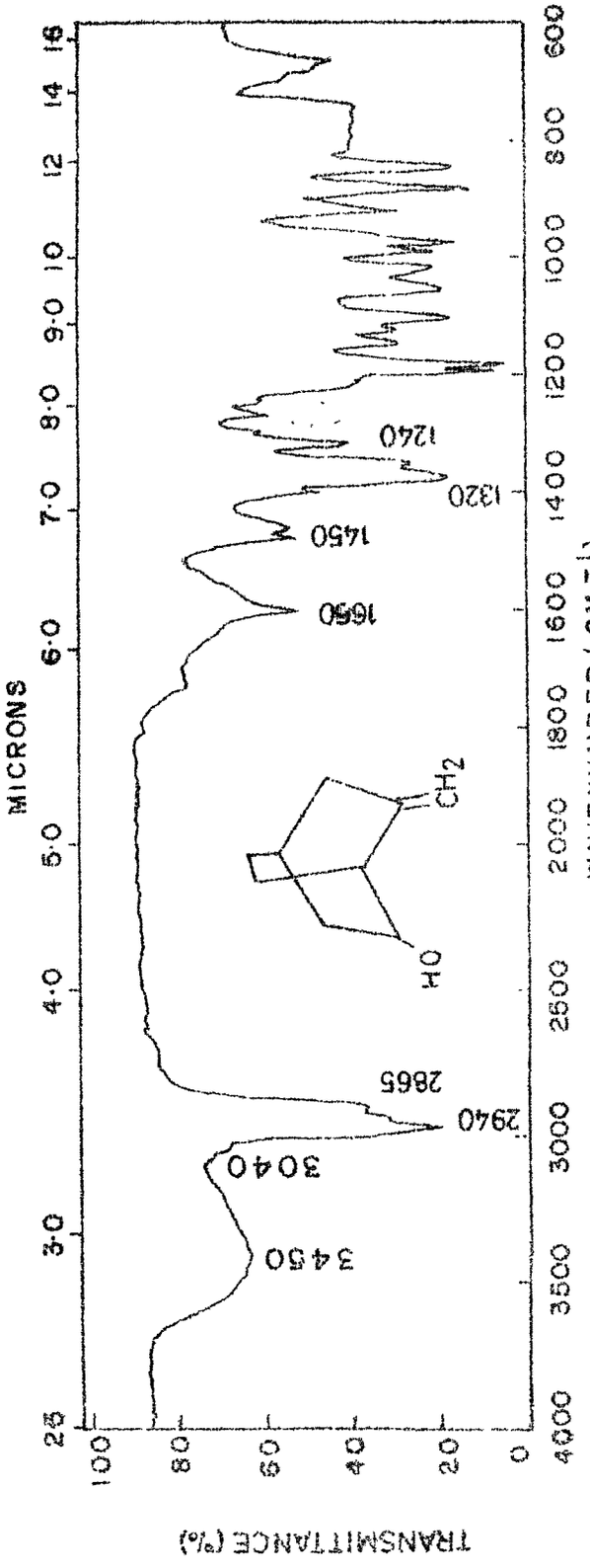


FIG. 21: IR SPECTRUM OF 6-HYDROXY-2-METHYLENEBICYCLO[2.2.2]OCTANE (1)

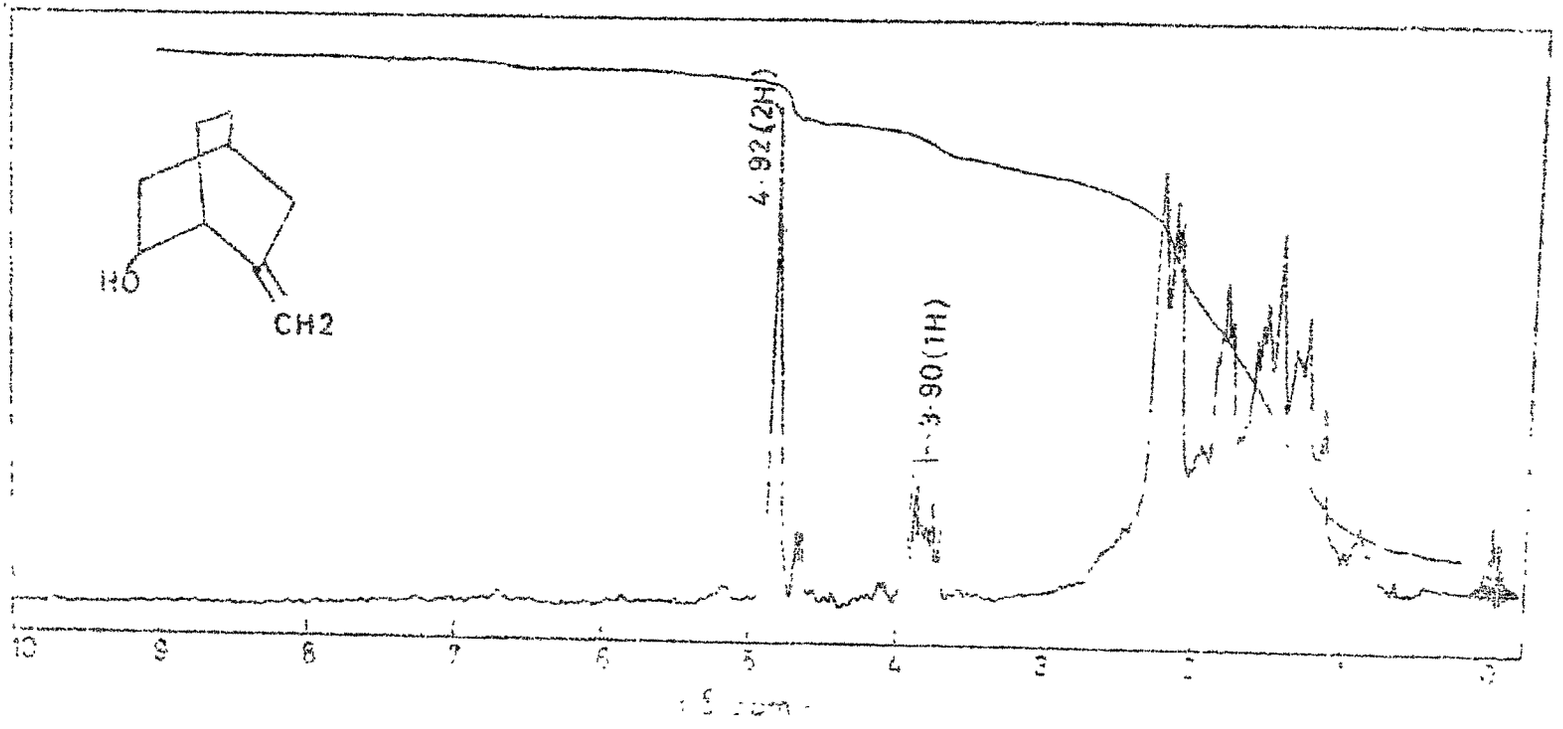


FIG. 22 PMR SPECTRUM OF 6-HYDROXY-2-METHYLENE-BICYCLO [2.2.2] OCTANE(I)

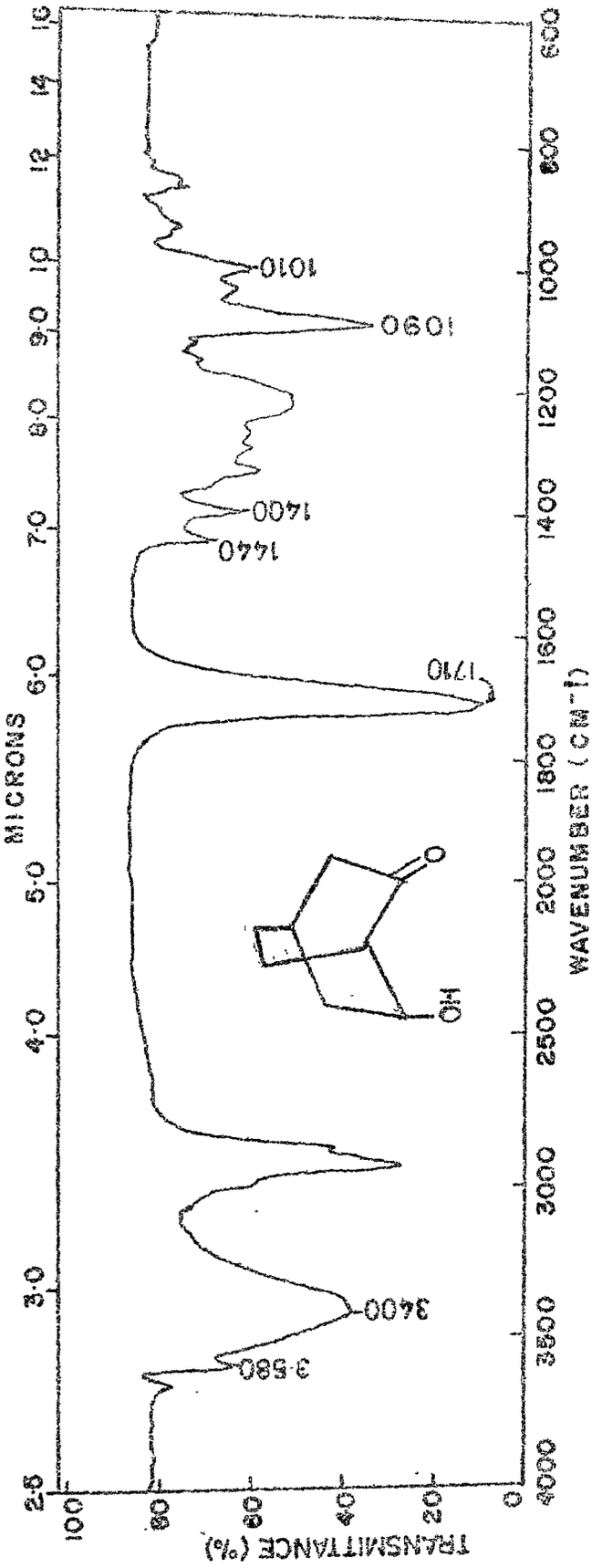


FIG.23: IR SPECTRUM OF BICYCLO[2,2,2]OCTAN-2OL-6-ONE (21)

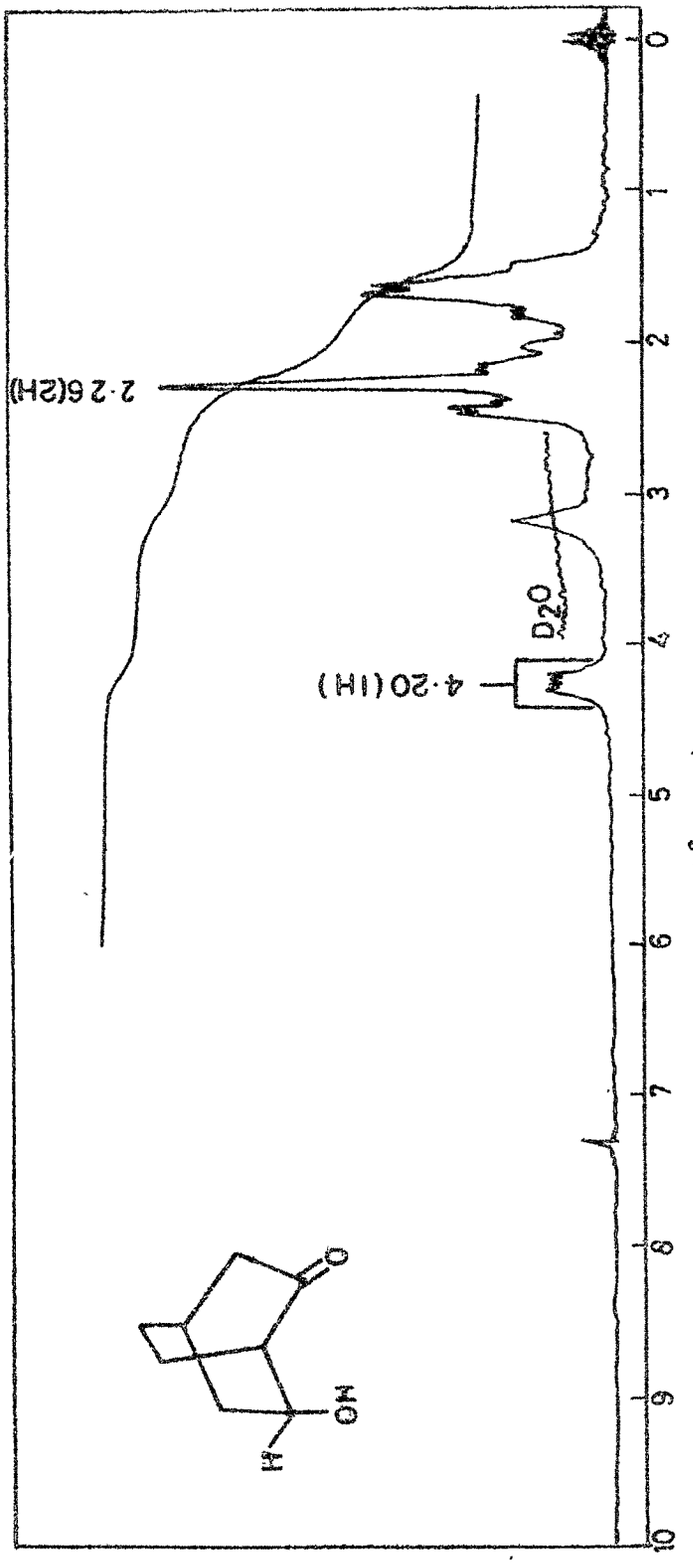


FIG. 24: PMR SPECTRUM OF BICYCLO [2,2,2] OCTANE-2-OL-6-ONE (21)

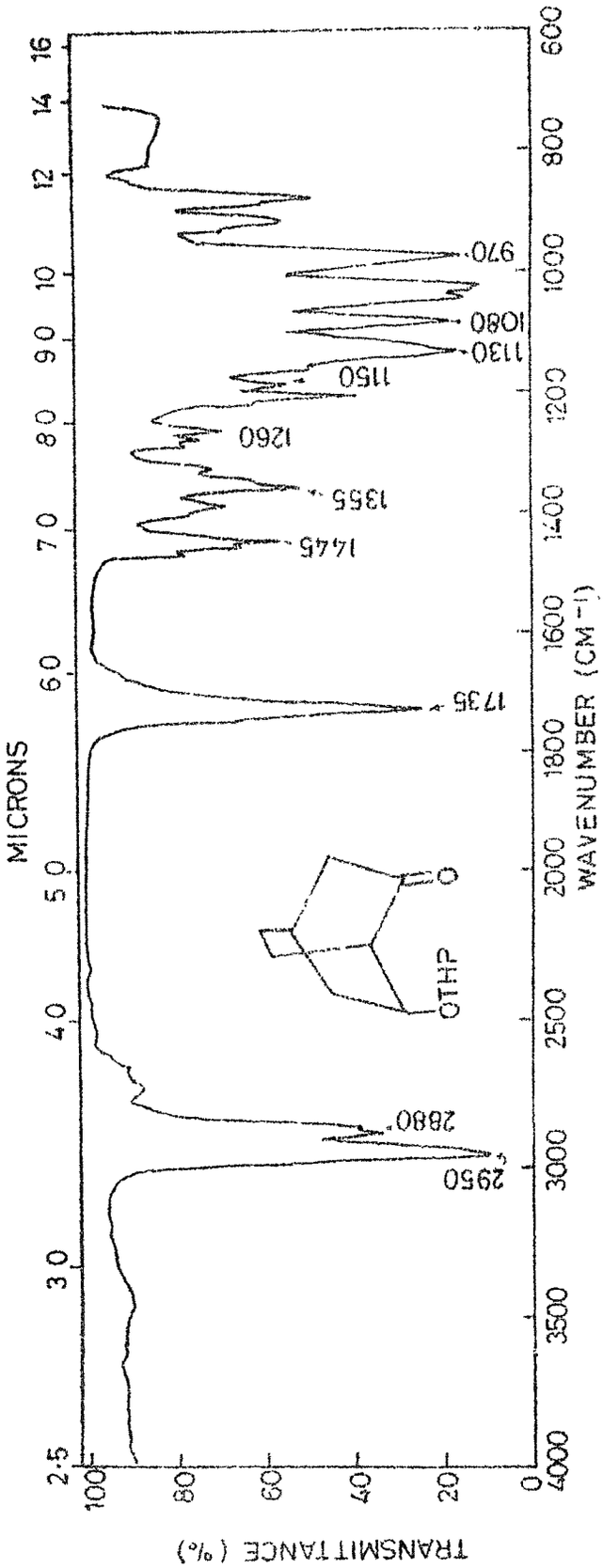


FIG. 25: IR SPECTRUM OF 6-TETRAHYDROPYRANOXYBICYCLOE 2,2,2]OCTANE-2-ONE (22)

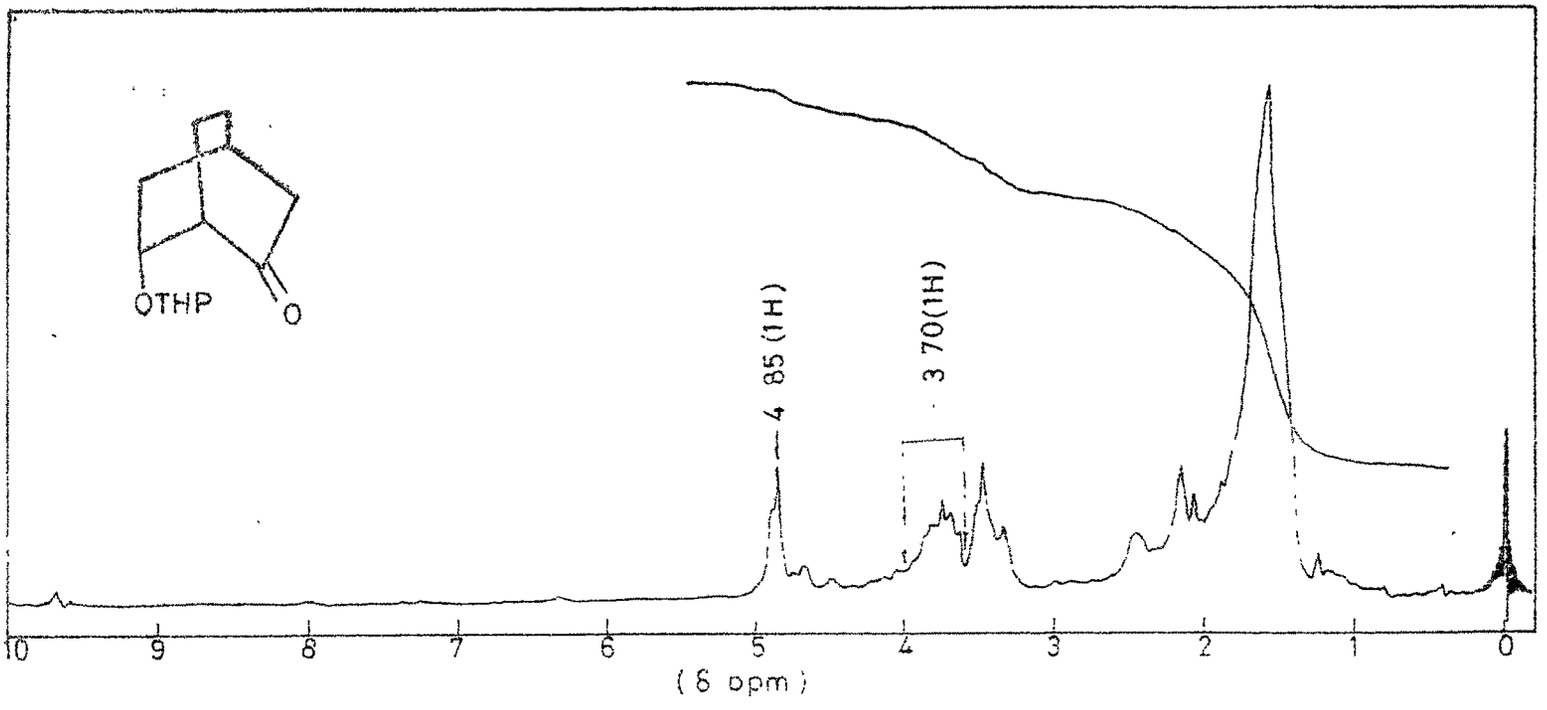


FIG 26: PMR SPECTRUM OF 6-TETRAHYDROPYRANOXY⊃BICYCLO[2,2,2] OCTAN--2-ONE (22)

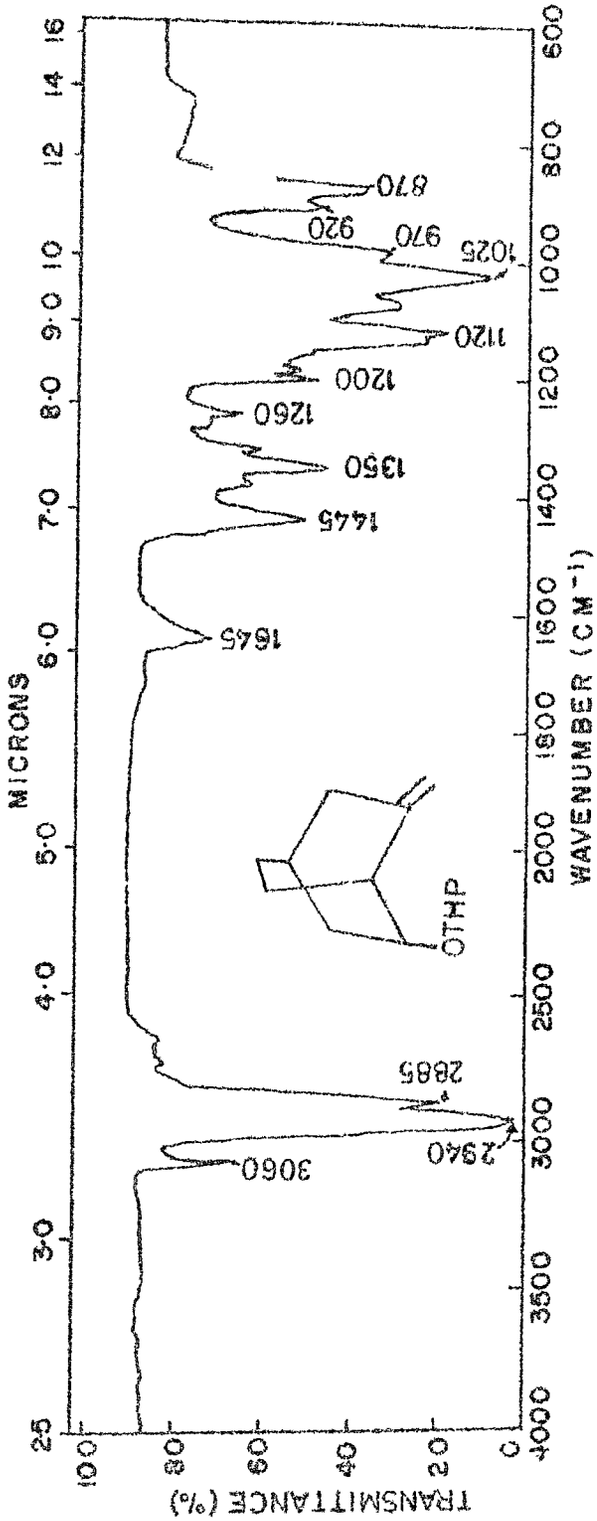


FIG. 27: IR SPECTRUM OF 6-TETRAHYDROPYRANOXY-2-METHYLENEBICYCLO [2.2.2] OCTANE (23)

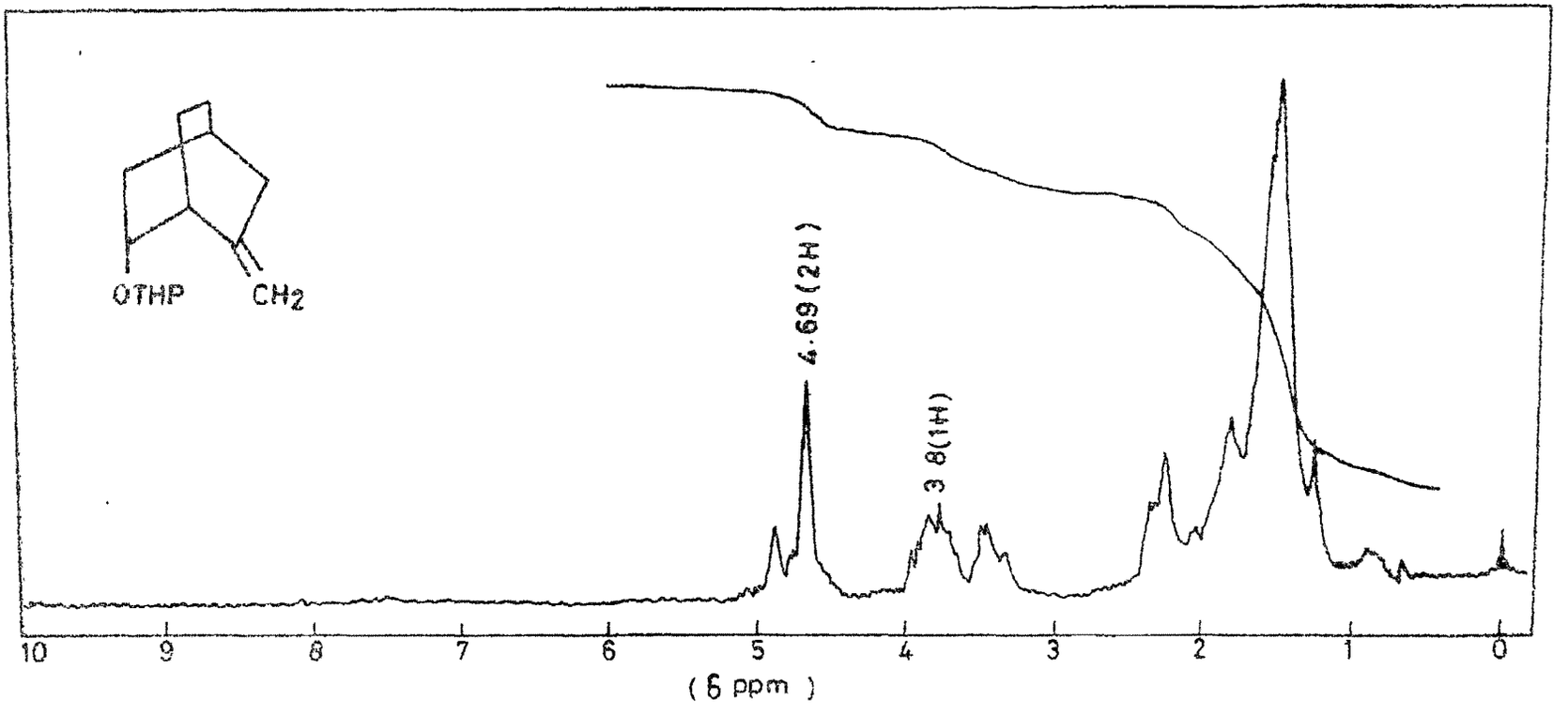


FIG.28: PMR SPECTRUM OF 6-TETRAHYDROPYRANOXY-2-METHYLENE-BICYCLO [2,2,2] OCTANE (23)

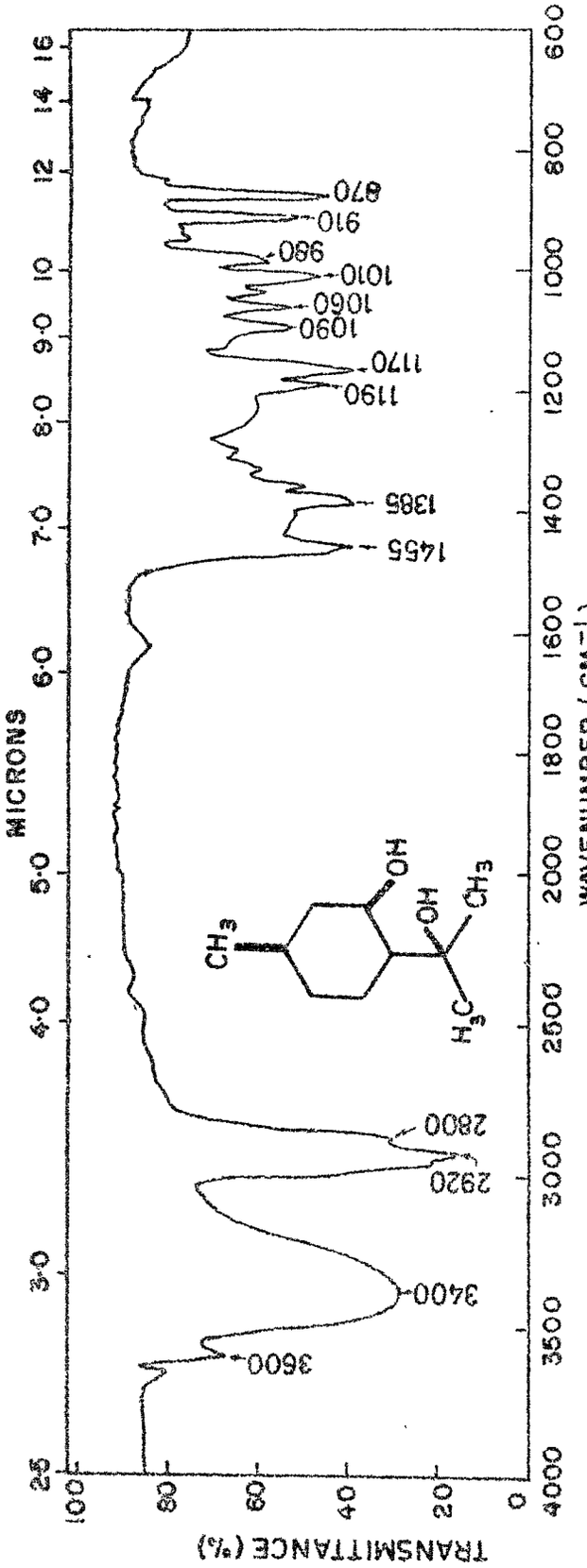


FIG. 29: IR SPECTRUM OF 3,8-DIHYDROXY-P-MENTHANE (28)

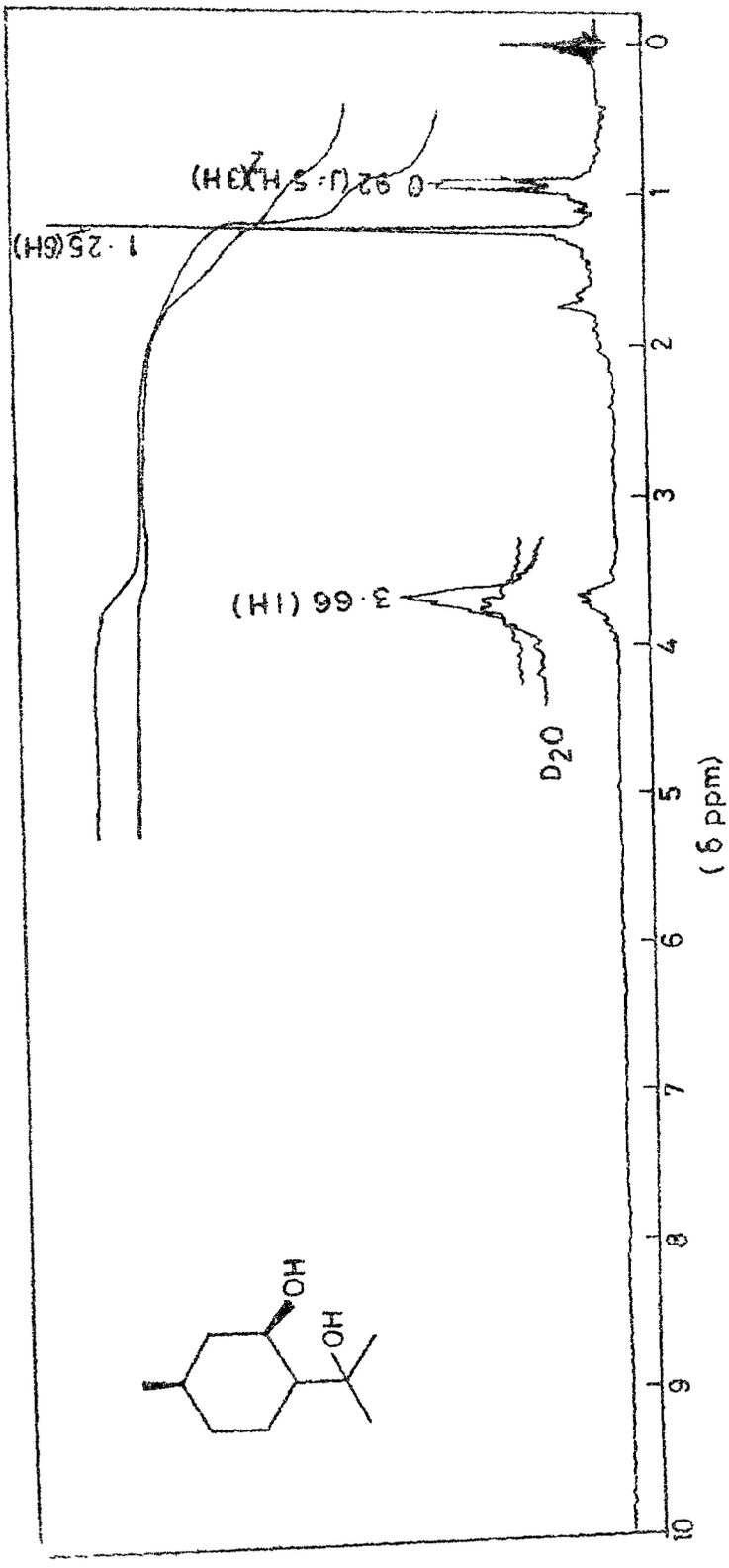


FIG. 30: PMR SPECTRUM OF 3,8-DIHYDROXY-P-MENTHANE (28)