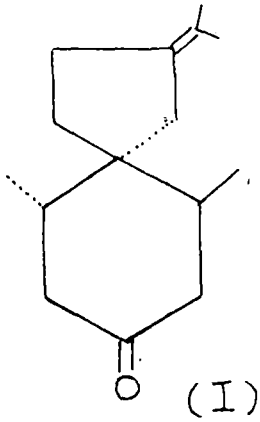
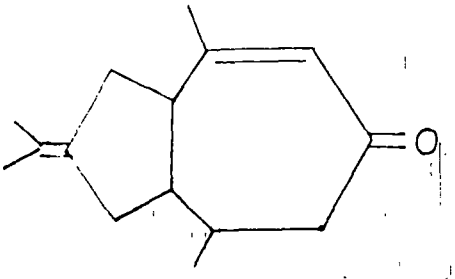
Part - 2

REACTION OF CYCLOHEXANONE WITH DIBROMOETHANE - FORMATION OF A NOVEL SPIRO COMPOUND

The discovery in nature of a large number of spiro esquiterpenes and the elucidation of their structures by classical chemical and modern instrumental methods has revived the interest in spiro compounds. The pioneering work of Marshall *et al*[1] who unequivocally established the structure of β- vetivone(I) which was considered to be a hydrazulene derivative (II) until 1960's had had a catalytic effect in the revival of interest in the field of spiro compounds in general and spiro sesquiterpenes in particular. The number of syntheses of β- vetivone itself that have appeared in literature in recent years bears an ample testimony to this fact.[2]

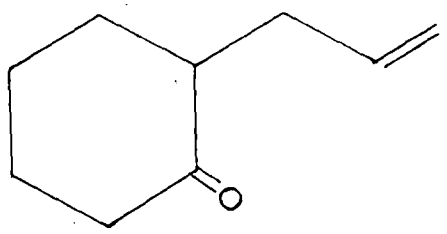


(I)



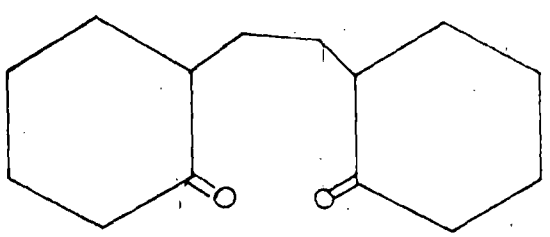
(II)

One of the methods of synthesis of spiranes is by way of 2,2-alkylation of cyclic ketones with α-ω-dihalo alkanes. A review of this and other reactions leading to spiro compounds has appeared in literature[3]. **Christol** *et al*[4] who developed this method of the synthesis of spiro compounds have reported that whereas the alkylation of cyclohexanone with 1,3- dibromo propane led to 2-allyl cyclohexanone(**III**) there was no reaction with 1,2-dibromoethane. With other dihalo compounds like 1,4-dibromobutane or 1,5-dibromo pentane spiro compounds could be isolated.

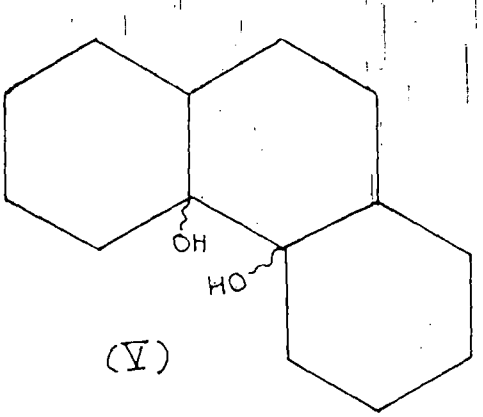


(III)

Interestingly, however when cyclohexanone was reacted with dibromoethane in presence of NaOEt, a white crystalline compound (m.p.153°C) could be isolated in an appreciable yield. The mass spectrum of the compound(m/e 222, significant peaks 204, 189, 125) (fig.3) and the fragmentation pattern suggested that the compound is most likely to be the hither to unreported 1,2-bis-(2'-oxocyclohexyl) ethane(IV). The infrared spectrum indicated the presence of a carbonyl group. The band at ca. 3300 cm^{-1} was taken as an impurity on account of the very high humidity in this region. Reduction of this compound with sodium amalgam gave a white solid m.p. 145°C(Benzene-Petether) which showed no carbonyl absorption in the IR. The mass spectrum (m/e 224, significant fragments 206, 188, 108) (fig.6) suggested that the compound might be the hitherto unreported dihydroxy perhydrophenanthrene (V)

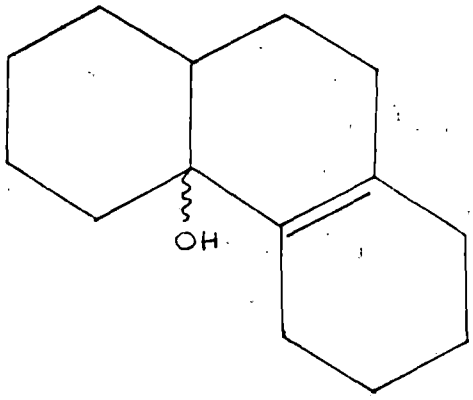


(IV)

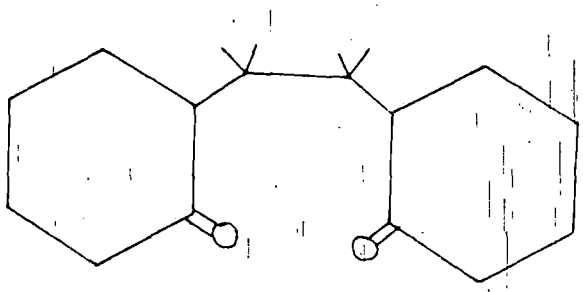


(V)

When (V) was treated with conc. H_2SO_4, the reaction mixture developed an intense red colour. From the reaction mixture could be isolated a sweet smelling liquid b.p. 138°C / 1.5 Torr. The mass spectrum of the compound (m/e 206 significant mass fragments 188, 173, 159, 145, 131)(fig.9) suggested that the compound was formed with the loss of a mole of water. The absence of carbonyl absorption in IR was very significant.The presence of a broad band ca. 3000 cm^{-1} clearly indicated that there was no pinacol-pinacolone rearrangement. The compound was given the structure (VI)

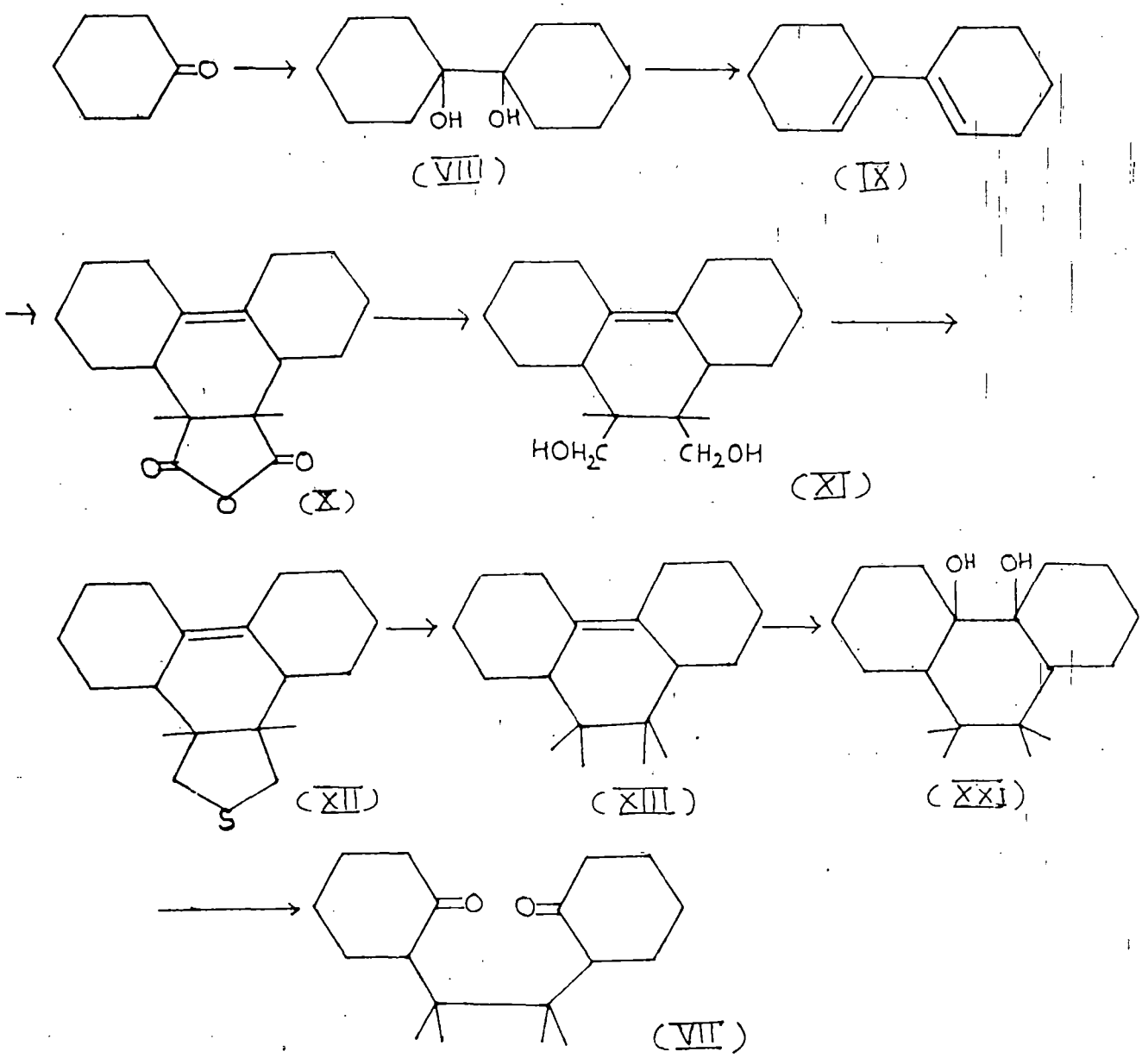


(VI)

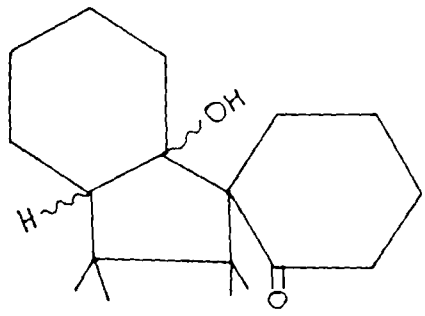


(VII)

At this point it came to our notice that Camps[5] had prepared the diketone(VII) starting from cyclohexanone according to the following scheme.

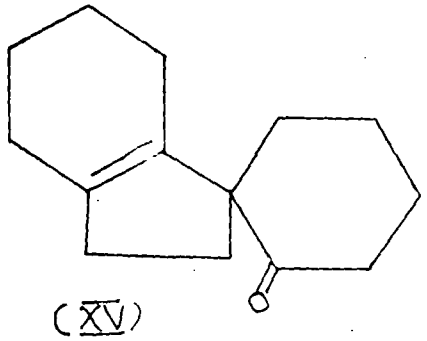


The author had reported that the diketone (**VII**) on heating with NaOMe underwent intramolecular aldol condensation to give the interesting spiro keto alcohol (**XIV**).

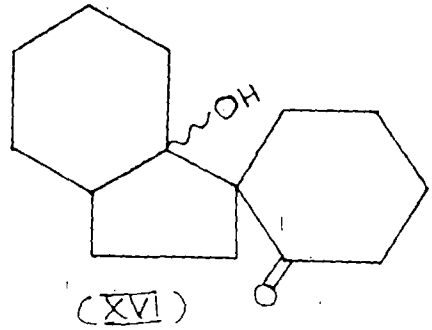


(XIV)

When the initial condensation product of cyclo hexanone and dibromo ethane, (**IV**) was treated under **Camps**[5] conditions, to our utter surprise the starting material was recovered. However when the compound was treated with BF_3-Acetic acid complex a smooth reaction took place and from the reaction mixture we could isolate a pleasant smelling liquid b.p.120^{0}C /1.5 Torr., m/e 204 (significant fragments176, 133) (fig.12). The IR spectrum of the compound indicated the presence of a carbonyl group in the compound. Based on the analogy of Camps spiro keto alcohol (**XIV**), this liquid was assigned the structure (**XV**). The fact that the initial adduct failed to undergo base catalysed aldol condensation prompted us to re-examine the initial adduct. We had made an assumption that the band at ca. 3300 cm^{-1} in the IR was due to moisture. The compound was dried over P_2O_5 in vacuum for 48 hours. Even then the broad band at ca. 3300 cm^{-1} persisted. It appeared that the compound was not a simple ketone but a hydroxy ketone. It might be that the initially formed diketone (**IV**) might have, under the experimental conditions undergone intramolecular aldol condensation to give the spiro keto alcohol (**XVI**)



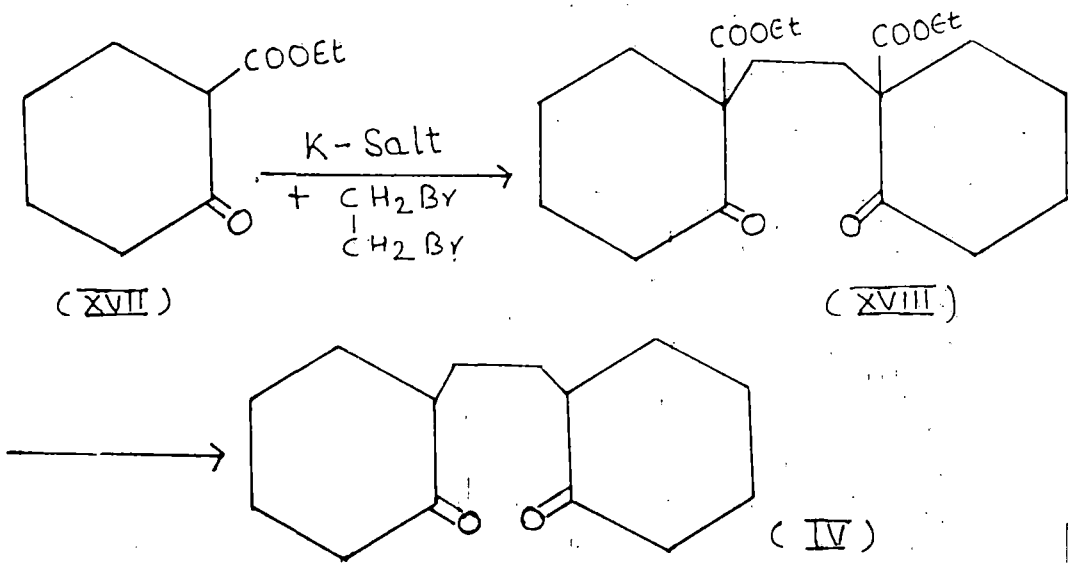
(XV)



(XVI)

The mass spectrum and fragmentation pattern is not likely to be any different from that of diketone (IV).

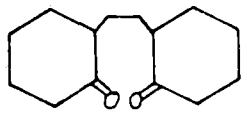
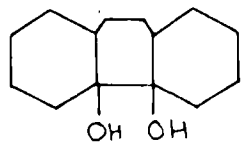
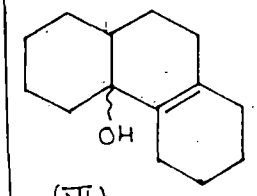
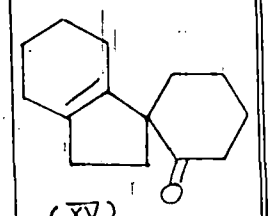
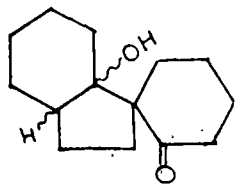
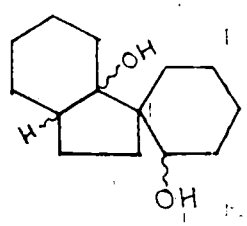
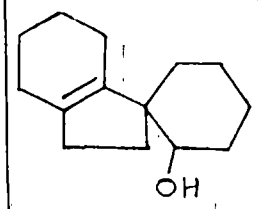
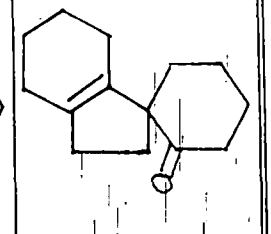
An attempt was made to prepare the diketone by the following scheme.



(XVII) (XVIII) (IV)

Heating of the potassium salt of 2-Carbethoxy cyclohexanone with dibromoethane gave a very small quantity of a crystalline solid m.p. 167^{0}C . Attempted hydrolysis and decarboxylation with dil HCl led to intractible tarry material. Absence of bromine in the compound and negative test for β-keto ester with ferric chloride has prompted us to assign the structure (**XVIII**) to the initial condensation product from 2-carbethoxy cyclohexanone.

Consequent on the revision of the originally assigned structure to the condensation product of cyclohexanone & dibromo ethane from **(IV)** to **(XVI)**, the structures of the various derivatives have been revised as shown below

Structure Originally Assigned	 (IV)	 (V)	 (VI)	 (XV)
Revised Structure	 (XVI)	 (XIX)	 (XX)	 (XV)

Results And Discussion

All melting points and boiling points are uncorrected. Solvents were dried over anhydrous sodium sulphate. IR spectra were recorded on Beckmann IR 20 spectrophotometer. PMR spectra were recorded on Varian 90 MHz/ 60 MHz spectrophotometers. Mass spectra were recorded by Central Drug Research Laboratories, Lucknow and Prof. Mitsuo Miyazawa of Kinki University, Japan.

1-Hydroxy bicyclo (4.3.0) nonane -9- spiro -1'- cyclohexan -2'-one (XVI)

A mixture of cyclohexanone (98 g; 1 mole) and 1,2-dibromoethane (94 g; 0.5 mole) was added in one lot to sodium ethoxide (prepared from 300 ml absolute ethanol and 23 g sodium) and refluxed on a water bath for six hours. Excess alcohol was removed under reduced pressure and the reaction mixture carefully acidified with dilute hydrochloric acid and extracted with benzene, washed dried and concentrated. The gummy residue on trituration with petroleum ether gave 1-Hydroxy bicyclo (4.3.0) nonane -9- spiro -1'- cyclohexan-2'-one as a white solid .

m.p. 153°C. Yield 50 g.

IR (Fig 1) 3340 cm^{-1}; 1722 cm^{-1}; 1440 cm^{-1}.

PMR (Fig 2) 0.9 - 1.1 δ(m,20H,due to $-CH_2$ protons) ; 2.1-2.4 δ(m,3H, due to one $-CH_2$ protons α to CO group and -OH proton)

Mass (Fig 3) m/e 222, 204, 189, 125.

A possible fragmentation pattern is given in page no138 .

Reduction of 1-Hydroxy bicyclo (4.3.0) nonane -9- spiro- 1'- cyclohexan- 2'- one with Sodium amalgum:

To sodium amalgum (prepared from 1.8 g clean sodium and 10 ml mercury) warmed to 50°C was added the compound (XVI) (2 g) dissolved in absolute alcohol (120 ml) in an atmosphere of nitrogen. Through out the addition the reaction mixture was stirred and after the addition the reacion mixture was stirred for an additional hour at room temperature and then refluxed on a water-bath for an hour more. The mixture was cooled. mercury separated, and the residue concentrated and diluted with water. The aqueous solution was extracted with benzene washed, dried and concentrated. 1-Hydroxy bicyclo(4.3.0.)nonane-9-spiro-1'- cyclo hexane - 2'- ol(**XIX**) seperated as a white solid m.p(from benzene-petroleum ether) 145°C.

IR (Fig 4) 3400 cm^{-1}(broad); 1460(s); 1370(m).

PMR (Fig 5) 0.5 - 2.0 δ(m, 21H, due to $-CH_2$ protons) ; 3.7 - 4.05 δ(m, 3H, due to -CH proton and two OH protons)

MS (Fig 6) m/e 224, 206, 188, 108.

A possible fragmentation pattern is given in page 139.

Action of conc. sulphuric acid on the diol (XIX)

The diol (**XIX**) (1g) was treated with conc. sulphuric acid (5ml) and the reaction mixture stirred at room temperature. An intense blood red colour developed. The stirring was continued for two hours and the reaction mixture was left overnight at room temperature. The reaction mixture was diluted with water, extracted with benzene, washed free of acid, dried and concentrated. The residue on distillation gave a sweet smelling oil (500 mg) b.p. 138°C / 1.5 Torr. Structure XX (Revised XXIII)

IR (Fig 7) 3400 cm^{-1}; 2920 cm^{-1}; 1700 cm^{-1}; 1440 cm^{-1}.

PMR (Fig 8) 0.7 - 1.8 (m, 20H, due to $-CH_2$ protons); 2.0-2.4 δ (t, 1H, due to -OH proton); 3.6 δ (t, 1H, due to -CH)

MS (Fig 9) m/e 206; 188; 173; 159; 143.

A possible fragmentation pattern is shown in page 140.

Treatment of the compound (XVI) with boron trifluoride in acetic acid

The compound (XVI) was dissolved in glacial acetic acid (5 ml) and treated with freshly distilled boron trifluoride in acetic acid (5 ml) and gently refluxed for one hour. The reaction mixture was diluted with water and extracted with benzene. The extract was thoroughly washed free of acid, dried and concentrated. Thee residue on distillation gave a pleasant smelling oil b. p. 120°C / 1.5 Torr. Yield 800 mg.

IR (Fig 10) 2900 cm^{-1} ; 2840 cm^{-1} ; 1720 cm^{-1} ; 1450 cm^{-1}.

PMR (Fig 11) 0.7 - 2.3 δ(m, 18H, due to $-CH_2$ protons) ; 2.3 - 3.0 δ (t, 2H,due to $-CH_2$ α to -CO group)

MS (Fig 12) m/e 204, 176, 133.

A possible fragmentation pattern is shown in page 141.

Treatment of the compound (XVI) with sodium methoxide

The compound (XVI) (2 g) was treated with sodium

methoxide in methanol (300 mg sodium in 10 ml methanol) and refluxed for 3 hours. Excess alcohol was distilled off and the residue diluted with wated , dried and concentrated. A white solid separated which was found to be identical with (XV1).

Condensation of 2-carboethoxy cyclohexanone and dibromo ethane followed by attempted Ketonic Hydrolysis to 1,2-bis- (2'- oxocyclohexyl)-ethane(IV)

5.6 g (0.1 mole) KOH is dissolved in 5 ml H_2O and 30 ml of 96% alcohol and the solution cooled to 5 - 10 ^{0}C with an ice salt mixture. With stirring and outside cooling 17.0 g (0.1 mole) of freshly disstilled 2-carbethoxy cyclohexanone is added over a 3 min. period and after 2 min. 50 ml of ether is also added, care being taken that the reaction temperature does not exceed 20 ^{0}C. The pasty precipitate is suction filtered immediately, washed first with a small amount of ice cold 96% alcohol, then with ether . The solid is pressed on clay plates and is dried at 50 - 60 ^{0}C for 2 hours. The product so obtained forms white, glistening, thick scales when recrystallized from alcohol.

A mixture of 20.0 g K-salt (0.1mole) of the ester 9.49 (0.05 mole) and dibromo ethane are stirred and heated for several hours. A white crystalline product was obtained in a low yield after usual work up.

m.p. 167^0 C

Hydrolysis of the adduct with dil. HCl yielded a tarry intractible material.

ADDENDUM

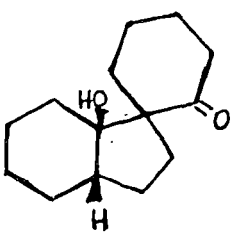
The strcture (XVI) was assigned to the hydroxy ketone on the basis of the following evidences:

(i) the compound was formed by heating a mixture of cyclohexanone and 1,2-dibromoethane with sodium ethoxide in ethanol;

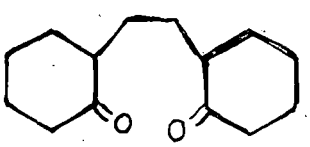
(ii) the ir spectrum indicated the presence of carbonyl and hydroxy groups;

(iii) the mass fragmentation pattern suggested that the compound might be either the diketone (IV) or a hydroxy ketone: in fact Dr. Miyazawa of Kinki University who had recorded the spectrum had suggested the diketone structure;

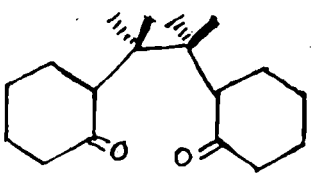
(iv) Camps[5] who had prepared the diketone (VII) had reported that the compound on heating with sodium methoxide gave the spiro ketol (XIV) by way of intramolecular aldol condensation. However, our compound was not affected by the reagent. It was, therefore, concluded that the diketone initially formed must have undergone aldol condensation to give the hydroxy ketone. ^{1}H-NMR spectrum was not of much use in interpreting the structure due to the fact that the different signals were strongly overlapping.



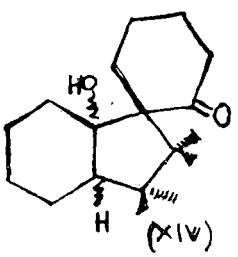
(XVI)



(IV)

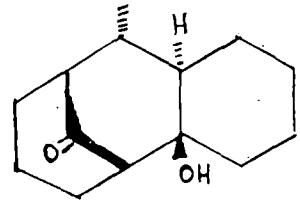


(VII)



(XIV)

The cis hydrindane structure was presumed in view of the known preference of the hydrindane system for cis fusion but this was not confirmed. Dr F. Naf of Firmenich, Geneva was requested to solve this stereochemical problem. He was kind enough to run the various spectra including the 2D inadequate spectrum and has concluded that the hydroxy ketone has the structure (XXI). In fact the compound has been reported in literature[6] and has been characterized by X-ray and 2D NMR. The compound can be obtained by reaction of cyclohexanone with sodium ethoxide. The fact that we had used dibromoethane completely misled us. It may be pertinent to point out that Buchbauer et.al. point out that straight forward assignments of the signals of ^{1}H- and ^{13}C-NMR spectra is not possible due to the fact that the signals of the aliphatic hydrogens are strongly overlapping even at 250MHz. Only the doublet of the CH_3 group at 0.9 ppm in the PMR can be assigned immediately. The ^{13}C-NMR spectrum of the compound reveals a similar situation, although the CO- signal and the resonances at 15.26 (CH_3) and 59.4 ppm (C_1) can be assigned by chemical shift considerations and by their multiplicity obtained from an off-resonance decoupled spectrum. The only way to get an unambiguous assignment of the ^{13}C signals is via a 2D-INADEQUATE experiment which yields the carbon-carbon connectivity. The assignments of the ^{1}H- and ^{13}C-resonances are given in Table 1 and the ^{13}C-^{13}C coupling constants in Table 2.



XXI

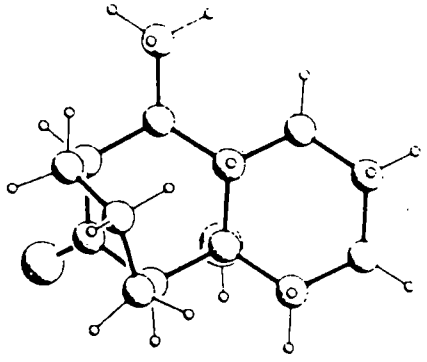
TABLE I

^{13}C	ppm	Multiplicity	^{1}H	ppm
1	59.36	d	1	2.21
2	77.41	s	2	-
3	35.80	t	3	1.40 / 1.75
4	20.68	t	4	1.59 / 1.77
5	25.82	t	5	1.31 / 1.80
6	24.95	t	6	1.30 / 1.71
7	45.48	d	7	1.81
8	37.06	d	8	2.08
9	52.40	d	9	2.25
10	28.72	t	10	1.81 / 2.27
11	19.71	t	11	1.52 / 1.86
12	29.11	t	12	1.90 / 2.11
13	220.78	s	13	-
14	15.26	q	14	1.04

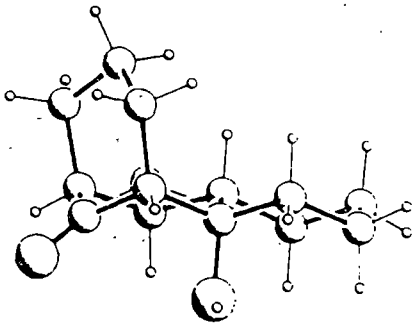
TABLE 2[6]

1-2	31.9 Hz	8-9	30.6 Hz
2-3	34.5 Hz	9-10	30.3 Hz
3-4	33.3 Hz	10-11	32.4 Hz
4-5	33.1 Hz	11-12	32.6 Hz
5-6	30.4 Hz	12-1	30.2 Hz
6-7	34.1 Hz	3-14	36.1 Hz
7-8	34.1 Hz	2-7	34.1 Hz

Crystal structure determination showed the carbon framework consists of three cyclohexane rings, two forming trans-decalin and the third connected in an adamantane-like configuration as shown below.



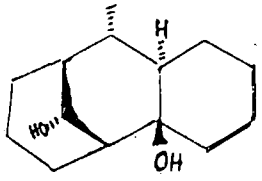
A



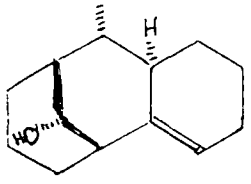
B

Projection of (XXI) perpendicular (A) and parallel (B) to the decalin plane.

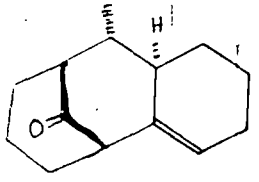
In view of the revision of structure (XVI) of the keto-alcohol to (XXI), the structures (XIX), (XX) and (XV) shown on page 133 of this thesis are revised to (XXII), (XXIII) and (XXIV) respectively.



(XXII)



(XXIII)



(XXIV)

PERKIN ELMER

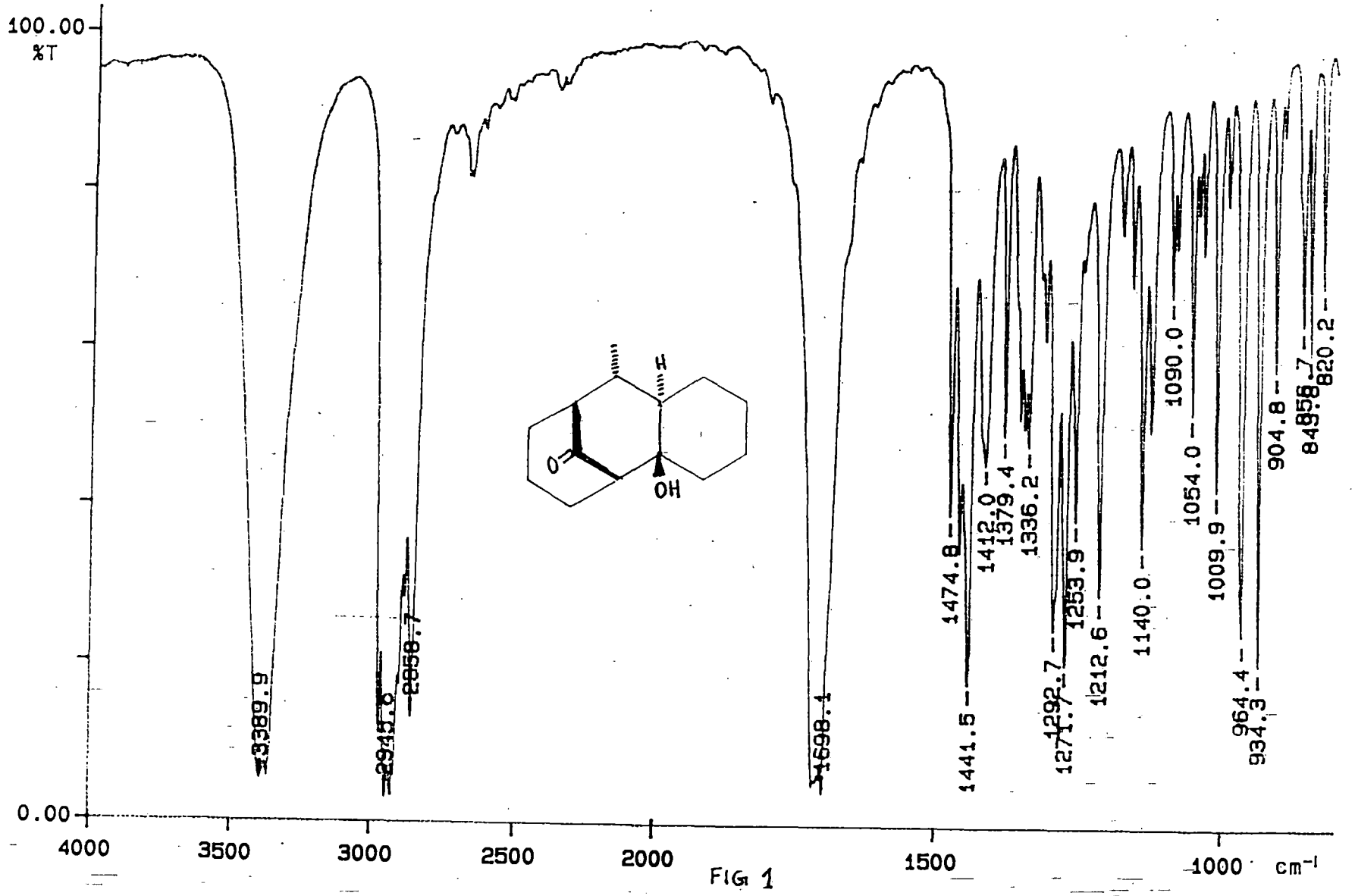


FIG 1

93/12/03 17:06 Firmenich SA / DRAI
X: 16 scans, 4.0cm-1, apod weak, flat, abex
BRM164988 Pastille KBR

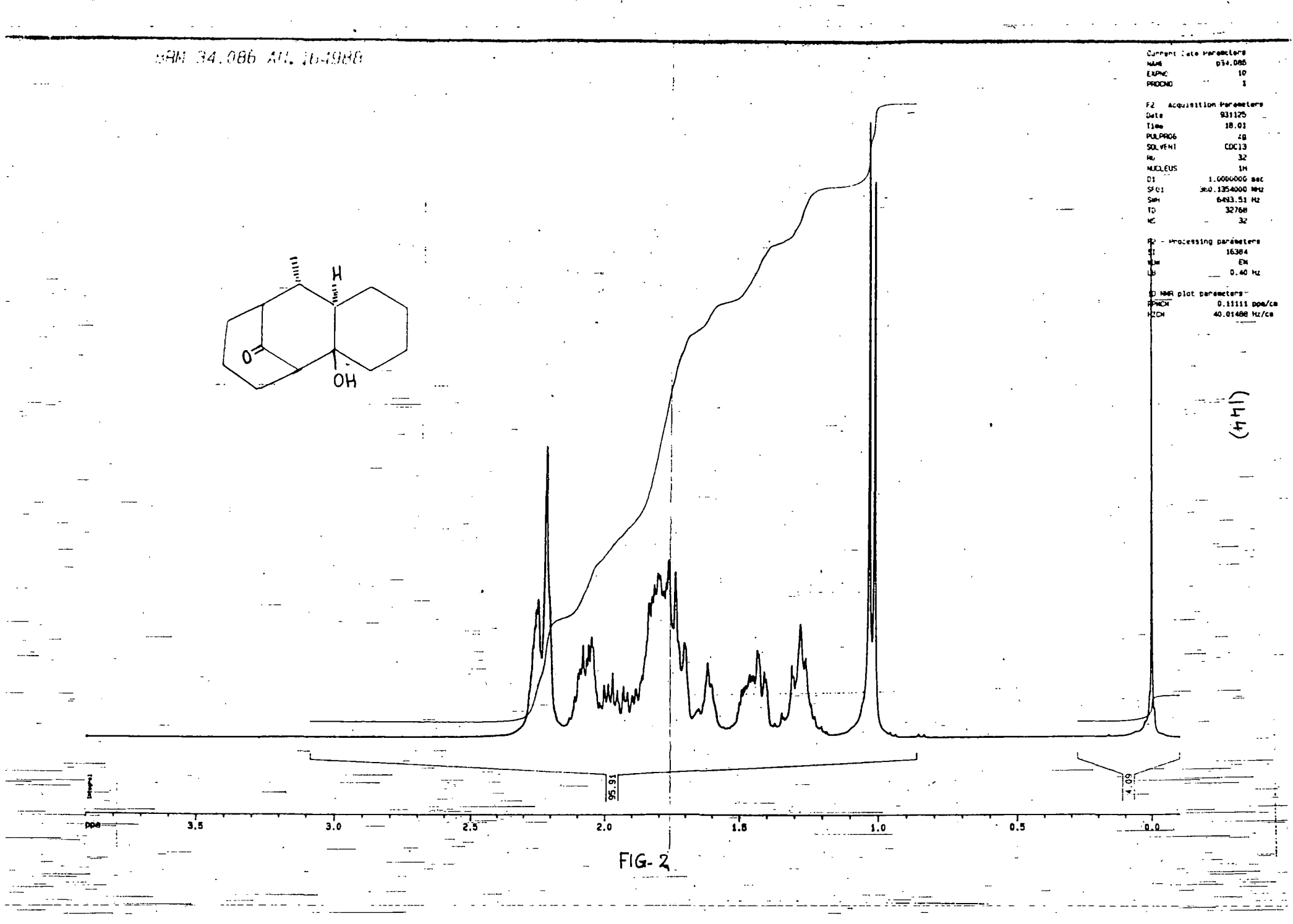

SAM 34.086 AL. 104988
Current Data Parameters
NAME p34.086
EXPNO 10
PROCNO 1
F2 Acquisition Parameters
Date 931125
Time 18.01
PULPROG zg
SOLVENT CDCl3
NS 32
NUCLEUS 1H
D1 1.0000000 sec
SFO1 300.1354000 MHz
SWH 6493.51 Hz
TD 32768
NC 32
F2 - Processing parameters
SI 16384
WDW EM
LB 0.40 Hz
1D NMR plot parameters
PPMCM 0.11111 ppm/cm
HZCM 40.01488 Hz/cm
H
O
OH
95.91
4.09
ppm
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

FIG-2

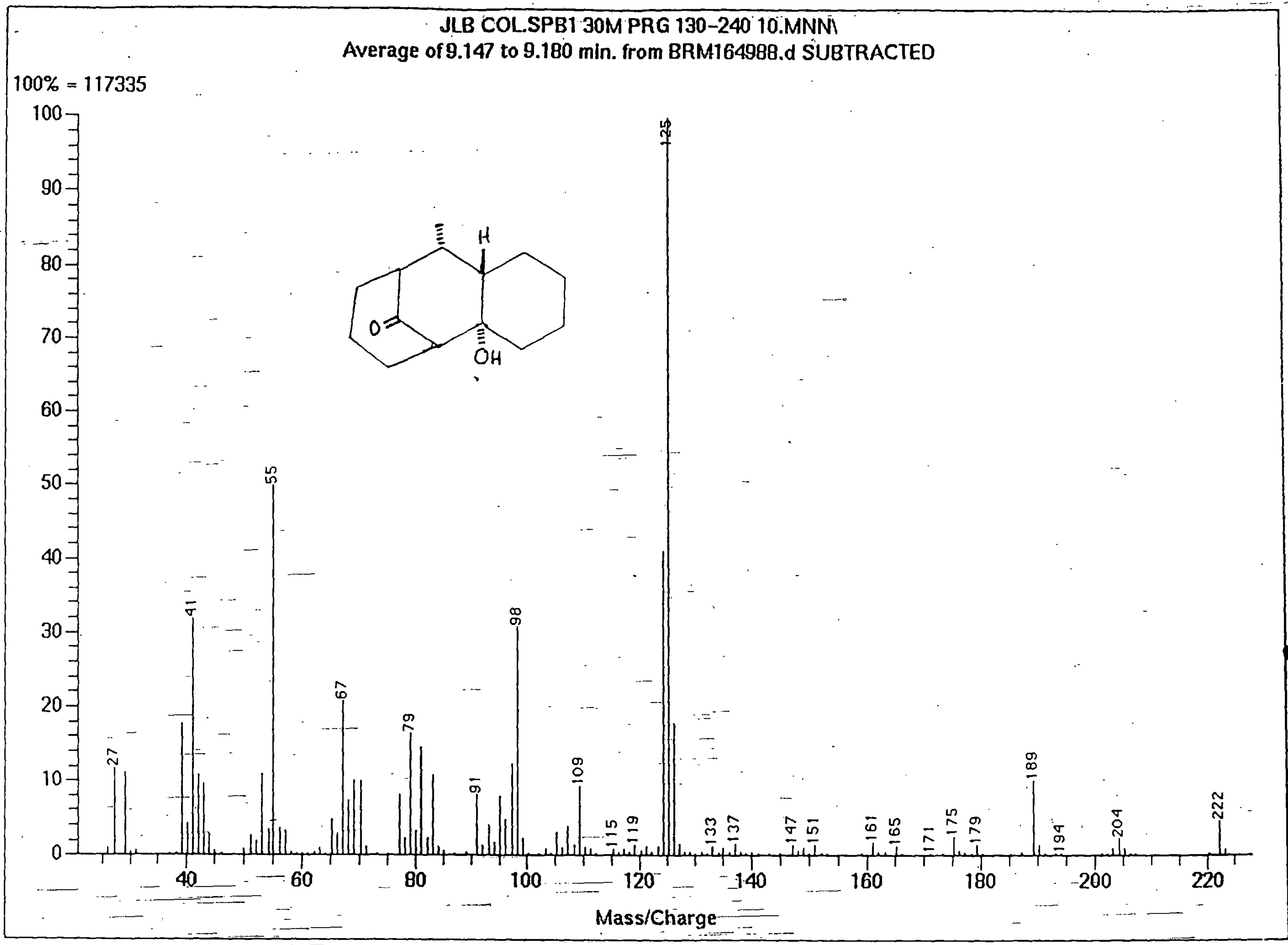
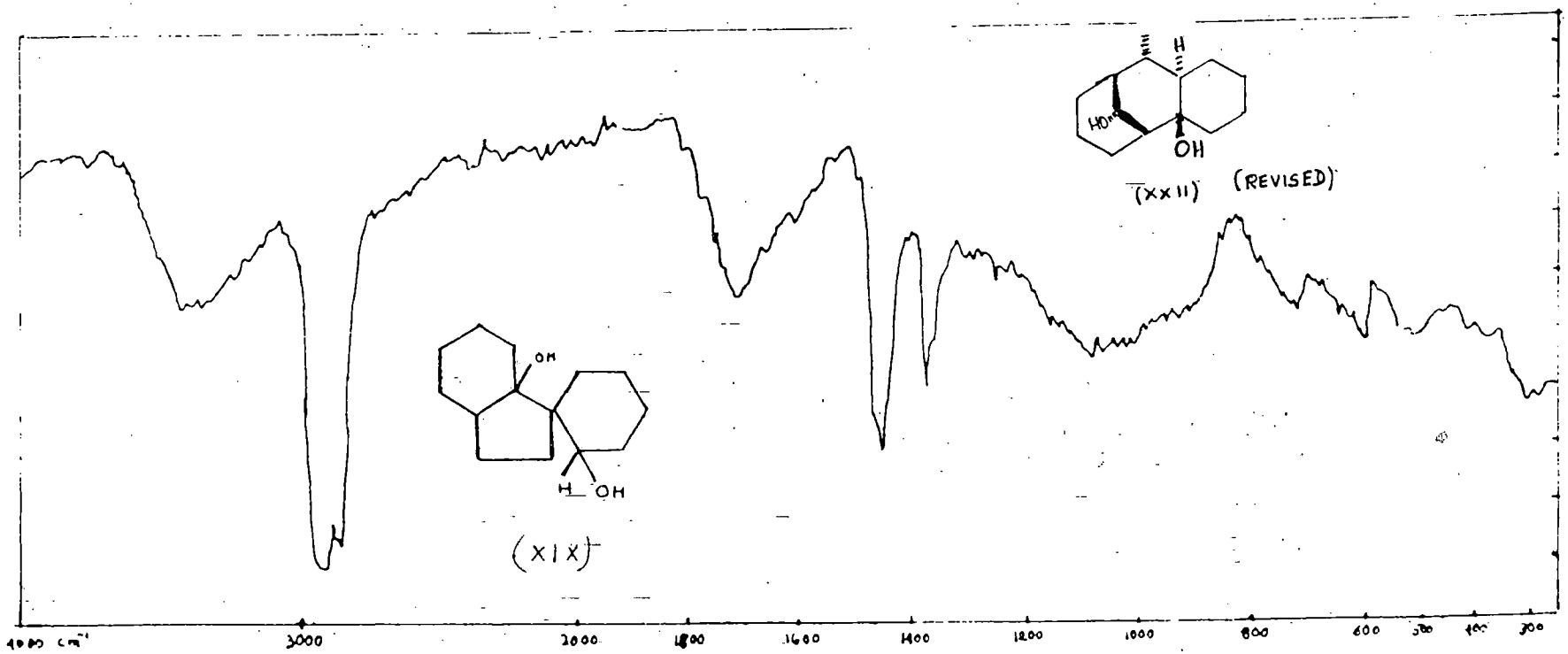

JLB COL.SPB1 30M PRG 130-240 10.MNN\
Average of 9.147 to 9.180 min. from BRM164988.d SUBTRACTED
100% = 117335
H
O
OH
125
55
41
98
67
79
27
109
91
115
119
133
137
147
151
161
165
171
175
179
189
194
204
222
Mass/Charge

FIG 3

Fig. 4


OH
H
OH
(XIX)
H
HO
OH
(XXII) (REVISED)
4000 cm⁻¹
3000
2000
1800
1600
1400
1200
1000
800
600
100
90
80
70
60
50
40
30
20
10
0

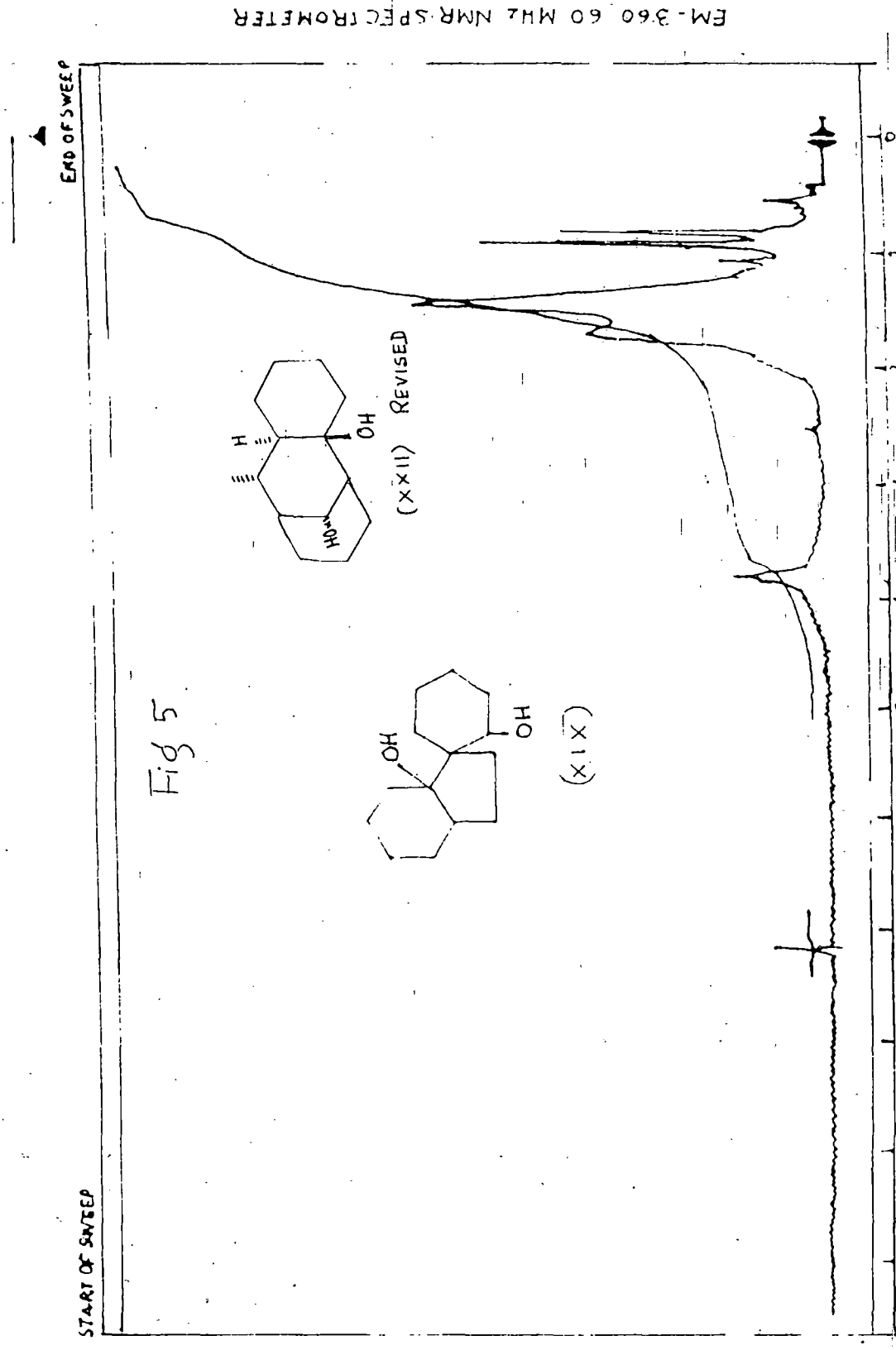

EM-360 60 MHz NMR SPECTROMETER
END OF SWEEP
START OF SWEEP
H
OH
HO
OH
(X11) REVISED
OH
OH
(X1)
0
1
2
3
4
5
6
7
8
9
10

Fig 5

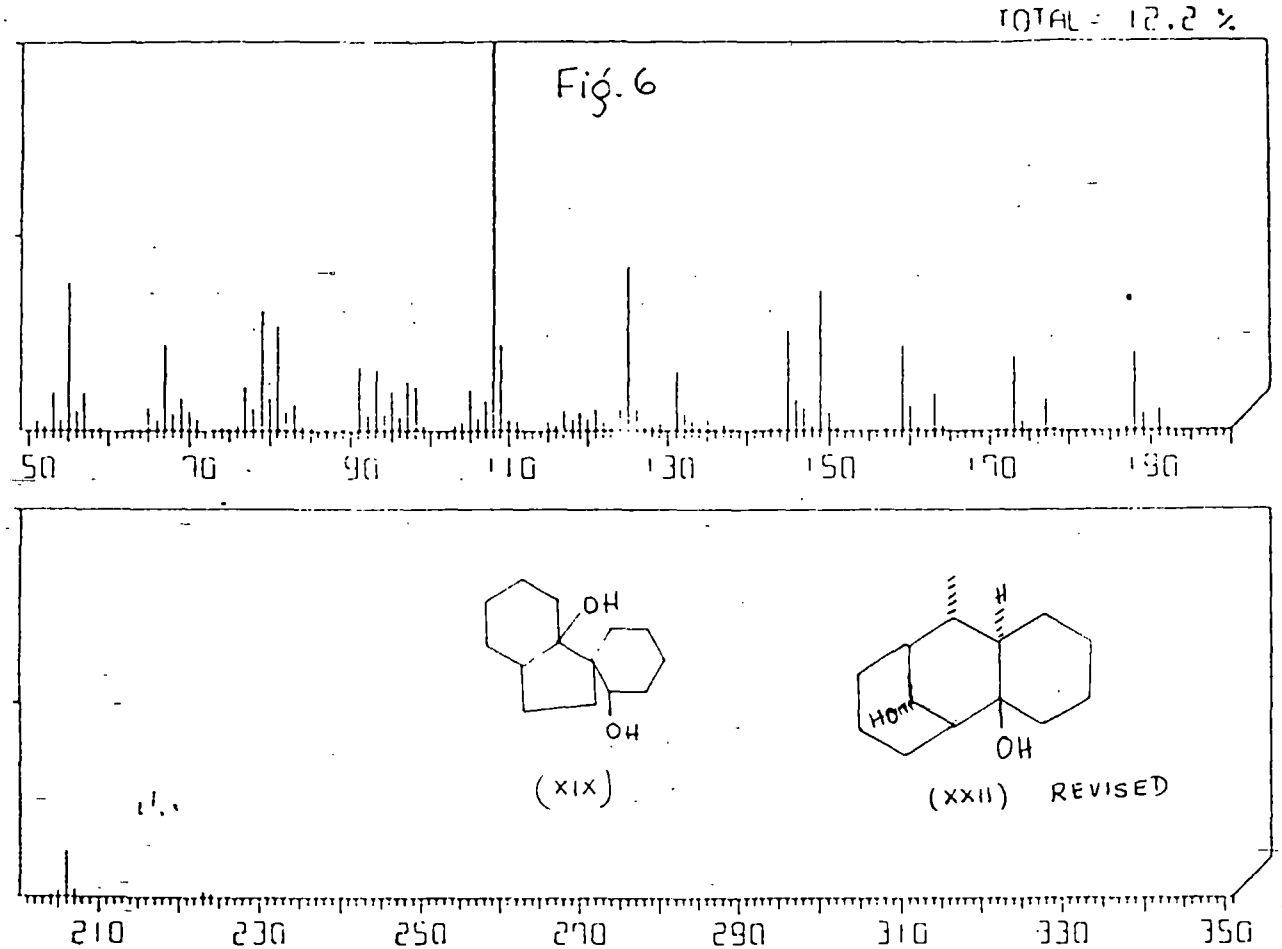
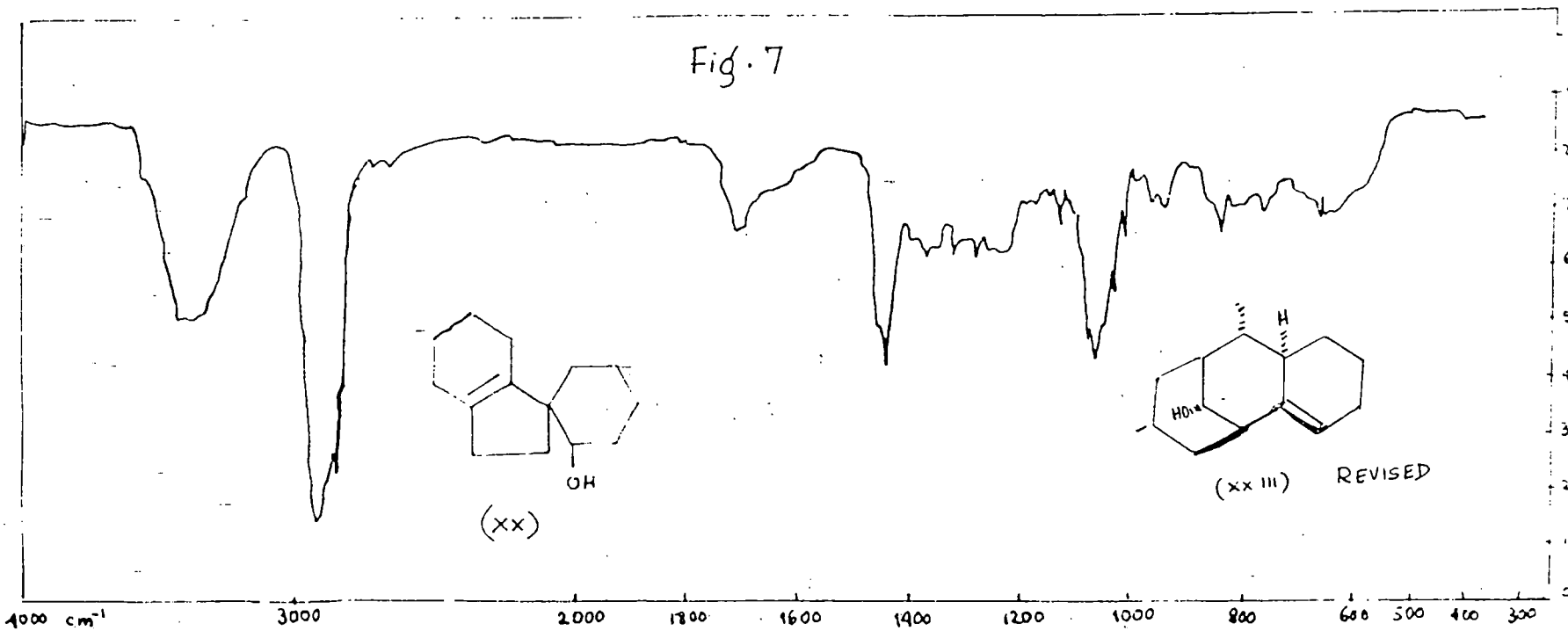


Fig. 6

(XIX)

(XXII) REVISED

Fig. 7



(xx)

(xx III) REVISED

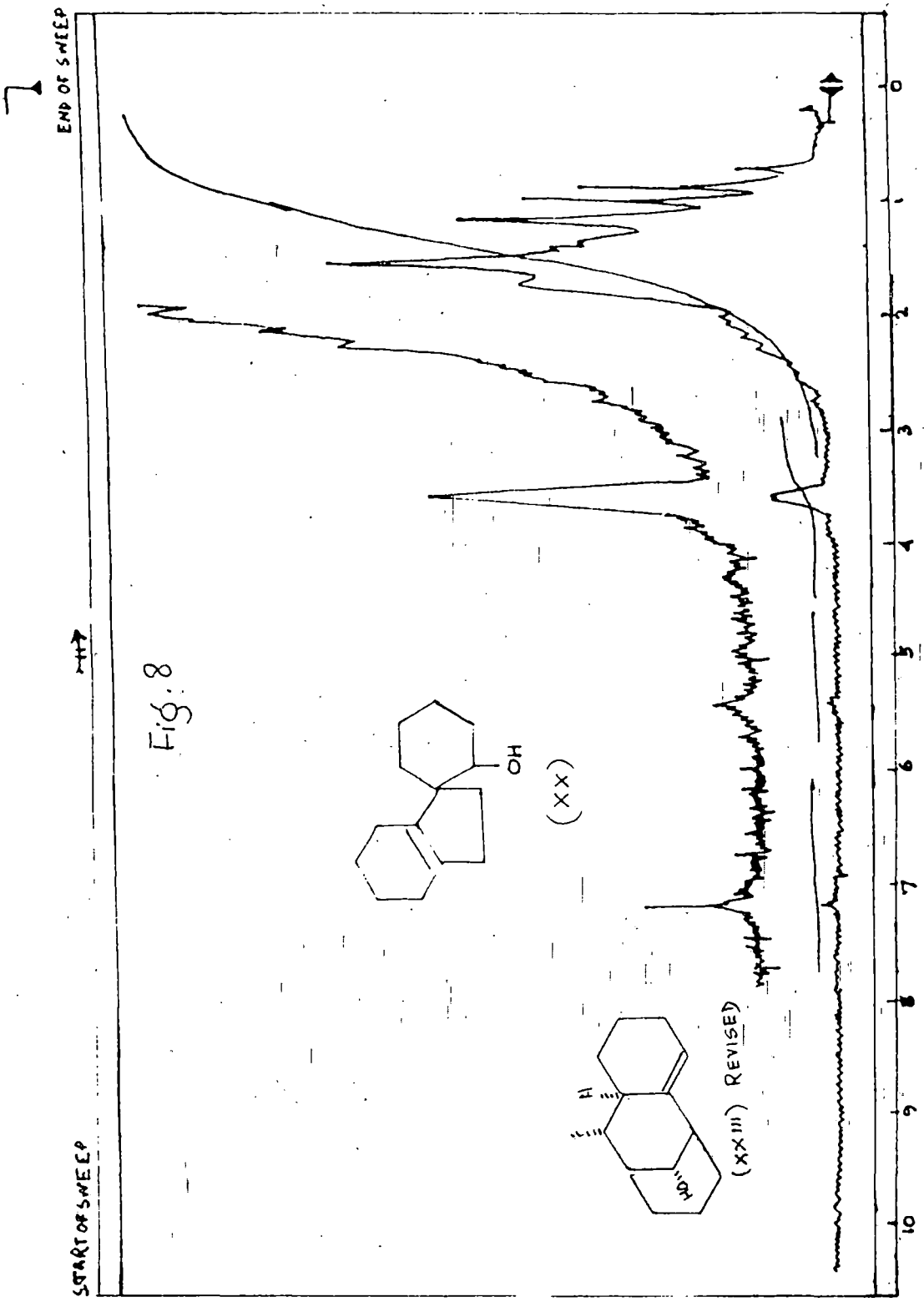
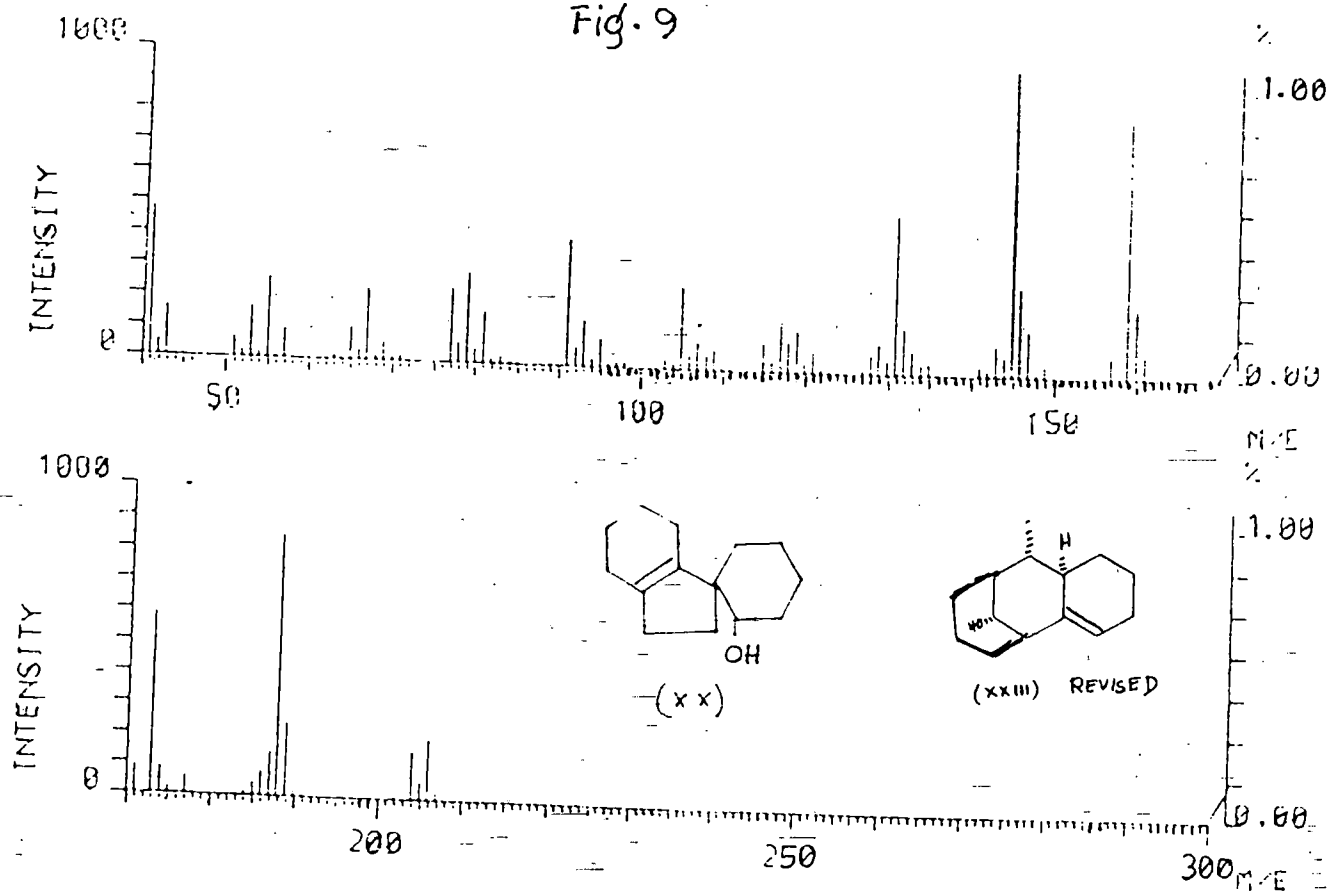

END OF SWEEP
START OF SWEEP
OH
(XX)
(XXIII) REVISED
0
1
2
3
4
5
6
7
8
9
10

Fig. 8

Fig. 9


1000
INTENSITY
0
50
100
150
%
1.00
0.00
M/E
1000
INTENSITY
0
200
250
300
M/E
%
1.00
0.00
OH
(xx)
H
(xxiii) REVISED

150

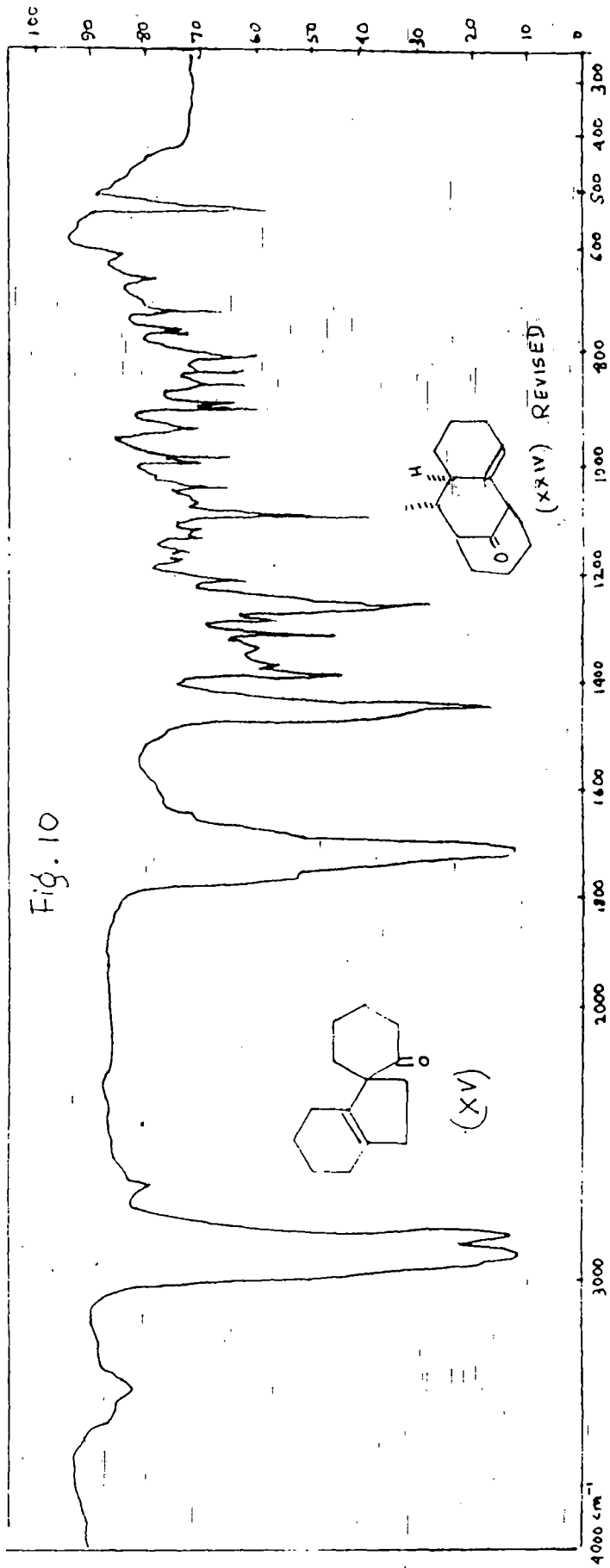

100
90
80
70
60
50
40
30
20
10
0
4000 cm⁻¹
3000
2000
1800
1600
1400
1200
1000
900
800
600
500
400
300
(XV)
(XIV) REVISED

Fig. 10

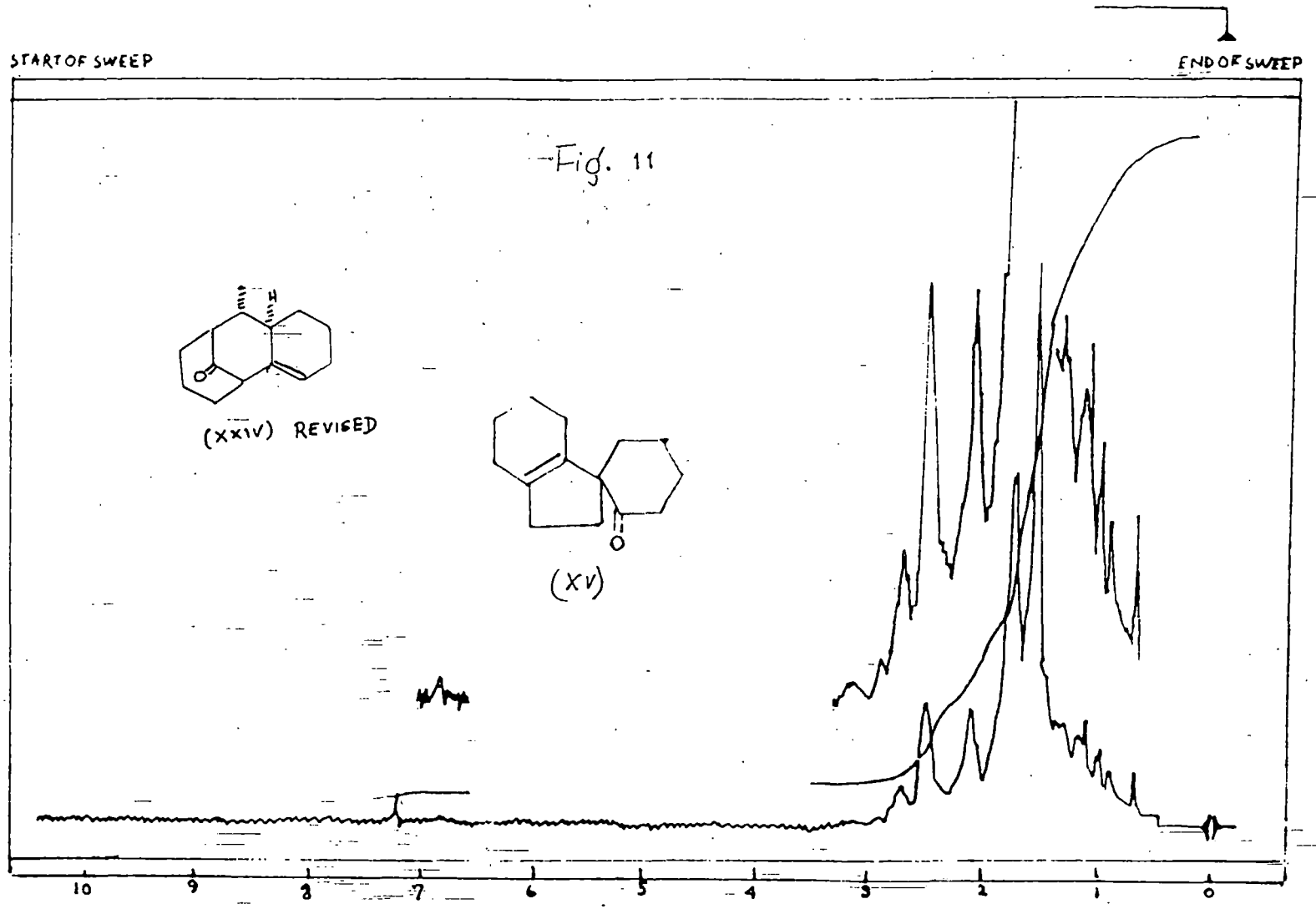
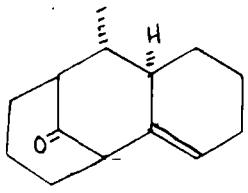


Fig. 11

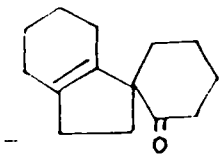
(XXIV) REVISED

(XV)



(XXIV) REVISED

Fig. 12



(XV)

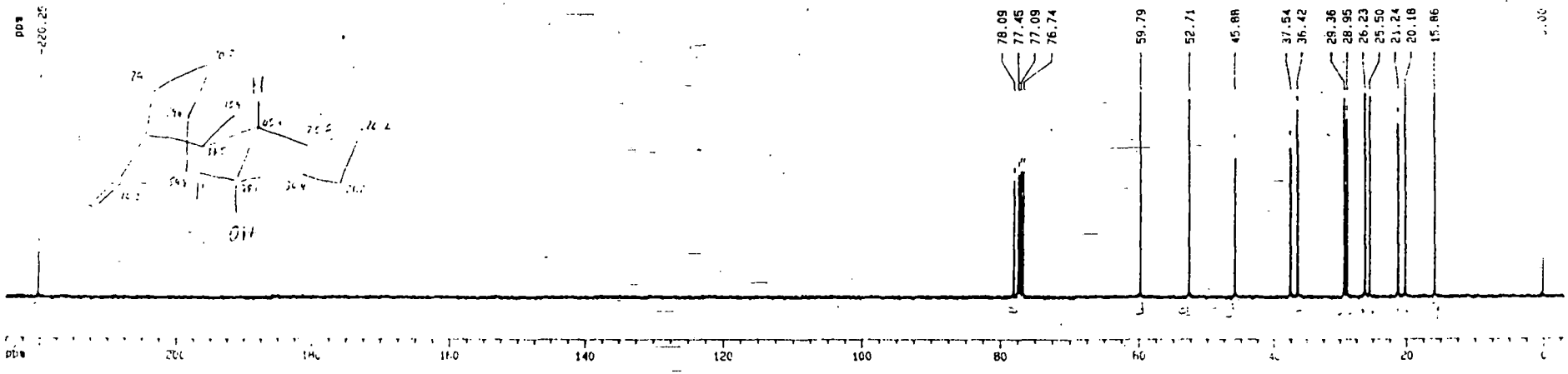


FIG-13 ^{13}C - NMR OF XX1

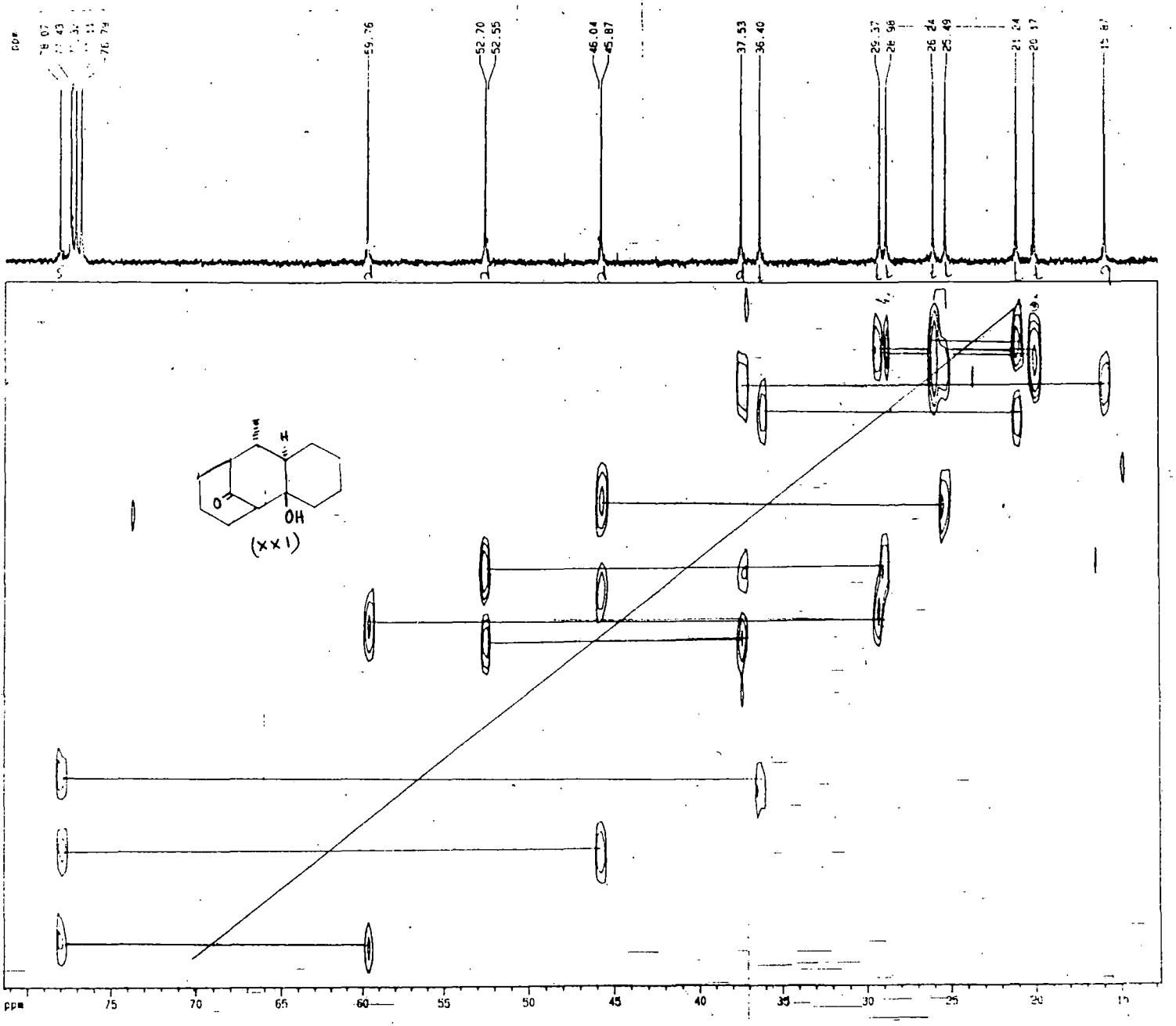
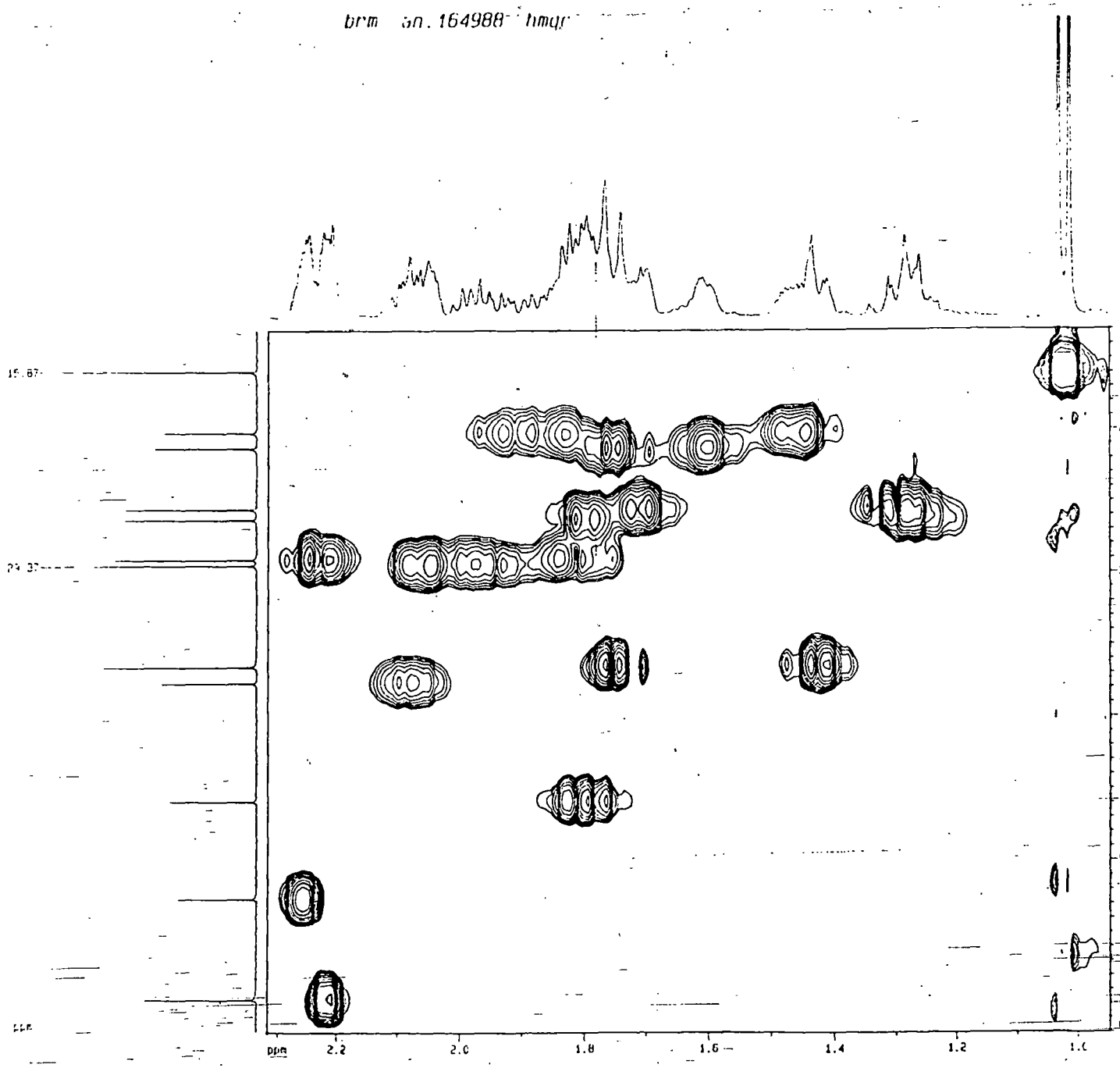


FIG 14. INADEQUATE 2-D NMR


brm sn.164988 hmqc
ppm
2.2
2.0
1.8
1.6
1.4
1.2
1.0
30
40
50

REFERENCES

1. Marshall, J.N. and Johnson, P.C. J.Am. Chem Soc 89, 2750 (1967)

2. Part I of this thesis Pages 27 - 65

3 Arapcho, A.P. Synthesis 313, (1976) Ibid., 425 (1976)

4 Mousseron, M. , Jacquier, R. and Christol, H. Bull. Soc. Chim . (France) 345 (1957)

5 Camps, P. and Pascual, J. Anal Quim. 72, 1032 (1976) Ph.D thesis submitted by Camps,P. to Barcelona University, Spain (1972)

6. Buchbauer, G., Fischlmayr, A., Haslinger, E., Robien, W., Völlenkle, H., and Wassmann, C., Monatsh. Chem. 115, 730 (1984)