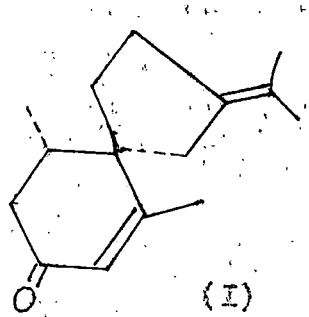
STUDIES IN ALICYCLIC SYSTEMS

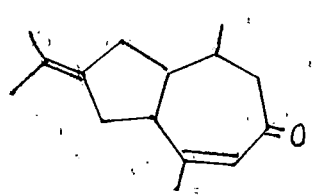
PART II

SYNTHESIS AND REACTIONS OF 1,2-BIS-(2'-OXOCYCLOHEXYL)-ETHANE

Interest in spiro compounds has been revived in recent years largely because a number of spiro compounds have been isolated from natural sources in recent years. The most note-worthy of these is β-vetivone (I) which until 1960's was considered to be a hydrazulene derivative (II). The pioneering work of Marshall[1] unequivocally established the spirodecane structure of this compound. This has had a catalytic effect in the revival of interest in the spiro compounds in general and spiro sesquiterpenes in particular. The number of synthesis that have appeared in literature and their variety bears an ample testimony to this fact.



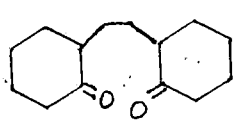
(I)



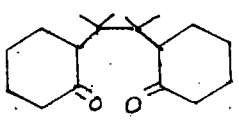
(II)

One of the methods of synthesis of spiranes is by way of condensation of α,ω-dihalo compounds with cyclic ketones. A review of this and other reactions leading to the carboeyclic

spiro compounds has appeared in literature.[2] Christol et al[3] who developed this method of synthesis of spiro compounds - the di- and tetra- alkylations of ketonic substrates with α,ω-dihaloalkanes - have reported that whereas the alkylation of cyclohexanone with 1,3-dibromopropane led to 2-allylcyclohexanone there was no reaction with 1,2-dibromoethane. With other α,ω-dihalocompounds like 1,4-dibromobutane and 1,5-dibromopentane spirocompounds could be obtained. Apparently these authors were looking for spirocompounds only. We were not aware of this work when we attempted the reaction of cyclohexanone with 1,2-dibromoethane in presence of sodium ethoxide in ethanol. We could isolate an appreciable amount of a white crystalline solid m.p. 153°. The compound was found to have been formed by the condensation of two moles of the ketone with one mole of the dibromo compound. A study of the mass spectrum of the compound (m/e 222) clearly showed that the compound is the hitherto unreported 1,2-bis-(2'oxo-cyclohexyl)-ethane (III). The IR spectrum of the compound was almost identical with that of (IV) described by Camps.[4]



(III)



(IV)

Interestingly Camps has prepared the compound (IV) in a nine-step

sequence starting from cyclohexanone as shown in the chart below:

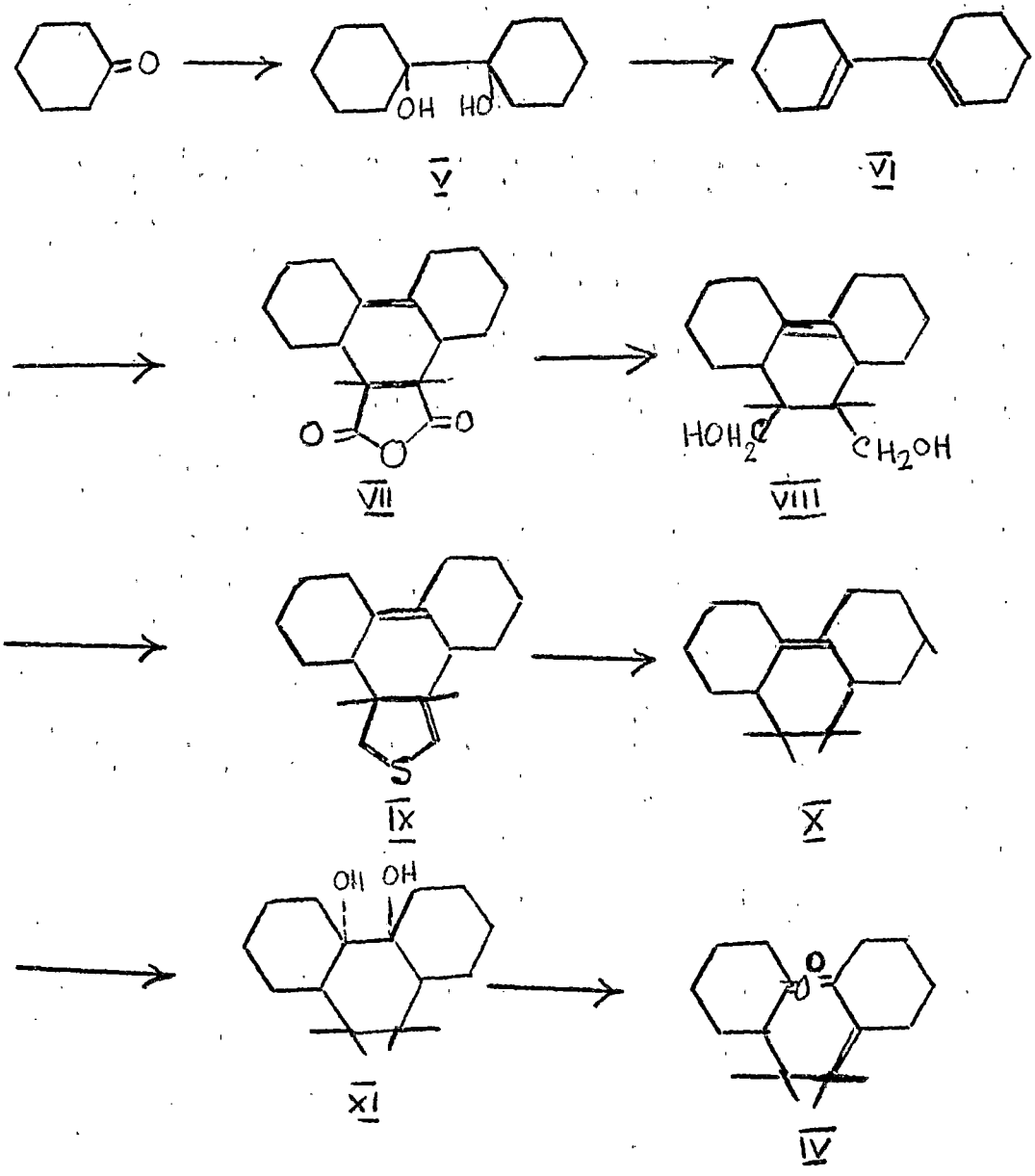
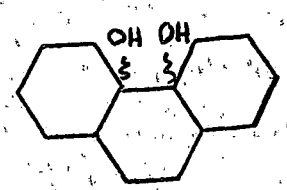


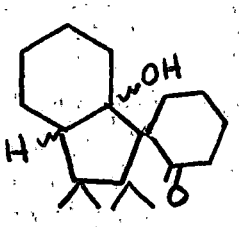
CHART I

Reduction of cyclohexanone with aluminium amalgum in benzene gave the pinacol (V) which on dehydration gave the diene (VI). Diels-Alder reaction with dimethylmaleic anhydride gave the tetracyclic compound (VII) which on reduction with lithium aluminium hydride gave cis 9,10-dimethyl-9,10-di-(hydroxymethyl)-$\Delta^{4a(4b)}$-perhydrophenanthrene (VIII) which was converted to the sulphide (IX) by standard reactions. Desulphurisation with Raney Nickel gave the tetramethyl compound (X) which was hydroxylated with osmium tetroxide to (XI). Oxidation of the diol with lead tetraacetate in benzene gave (IV).

We wanted to study (i) the conversion of the diketone (III) to the perhydrophenanthrenediol (XII) and study the action of acid on it and, (ii) convert the diketone to spiro system by acid/base catalysed aldol condensation. Camps et al have studied the base catalysed aldol condensation of the diketone (IV) with sodium methoxide in methanol and have reported the formation of the spiro ketoalcohol (XIII). They have, however,



(XII)

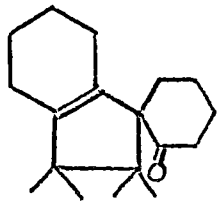


(XIII)

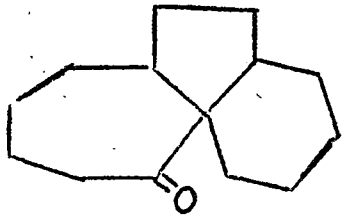
not studied the acid catalysed reaction of the diketone which would have led to the formation of the dehydrated compound (XIV).

1,2-Bis-(2'oxocyxlohexyl)-ethane (III) was treated with sodium amalgum in benzene under nitrogen for three hours to give a white crystalline compound m.p. 145° which in IR showed no carbonyl absorption. The compound showed a broad band at 3400 cm^{-I} indicating the presence of a hydroxyl group. The mass spectrum clearly indicated (m/e 224) that the compound is the hitherto unreported perhydrophenanthrenediol (XII). Though the compound appeared to be homogeneous (TLC), it is quite likely a mixture of various perhydrophenanthrenediols with (perhaps) the trans-anti-trans isomer predominating.

We hoped that the diol (XII) would rearrange to the tricyclic ketone (XV) under the influence of acids. When the



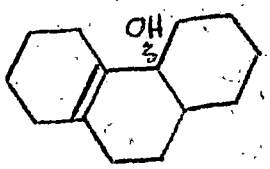
(XIV)



(XV)

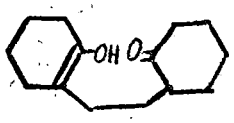
diol was treated with concentrated sulphuric acid, an intense blood-red colour developed. The reaction mixture on working up gave a pleasant smelling oil. The molecular weight (m/e 206) indicated that the compound was formed by the loss of one molecule of water from one molecule of the compound. The IR spectrum indicated the presence of a hydroxyl group (3400 cm^{-1}) though a weak band at 1700 cm^{-1} indicated the presence of a carbonyl function. The compound is probably a mixture of (XV) and (XVI). The extremely small amount of the

compound at our disposal was insufficient to attempt a seperation. Further work is ~~in~~ progress.

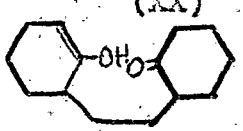


(XVI)

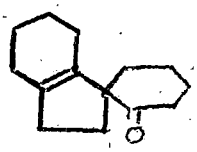
Next, we attempted the acid catalysed aldol condensation of the diketone(III). The compound could lead to the formation of the hitherto unknown compounds (XVII) and/or (XVIII). Clearly (XVIII) which can arise from the thermodynamically less stable enol (XIX) and hence has the unfavourable anti-Bredt structure, cannot be formed. It is therefore more likely that the spiro compound which arises from the thermodynamically



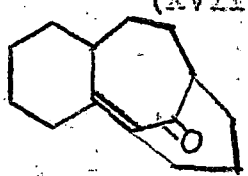
(XX)



(XIX)



(XVII)



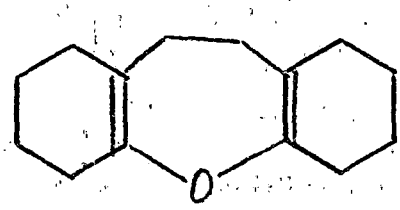
(XVIII)

more stable enol (XX) will be formed in preference to (XVIII).

Treatment of the diketone (III) with Boron trifluoride in acetic acid gave a sweet smelling oil formed by the loss

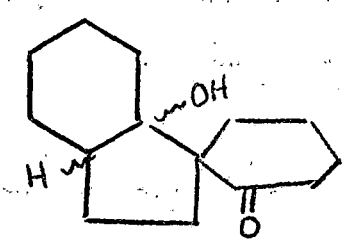
of one molecule of water. In the IR the compound showed strong absorption at 1720 cm^{-1}. The compound has been assigned the structure (XVII).

The possibility of the compound being the tricyclic ether (XXI) which can arise by the loss of one molecule of water from the dienolic form of the diketone was ruled out on the basis of the IR spectrum.



(XXI)

We expected that the diketone (III), would, like its structurally analogous tetramethyl diketone of Camps et al give the keto alcohol (XXII). But even after prolonged treatment with sodium methoxide no (XXII) could be isolated from the reaction mixture. The starting material was completely recovered. We are not able to account for this behaviour. We are attempting the reaction with other bases.



(XXII)

STUDIES IN ALICYCLIC SYSTEMS

PART II

EXPERIMENTAL

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 M Hz / 60 M Hz spectrophotometers. Mass spectra were recorded by Central Drug Research Laboratories, Lucknow and Prof Mitsuo Miyazawa of Kinki University, Japan.

1,2-Bis-(2'oxocyclohexyl)-ethane (VII)

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 23g 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 1,2-bis-(2'oxocyclohexyl)-ethane as a white solid m.p. 153°. Yield 50 g

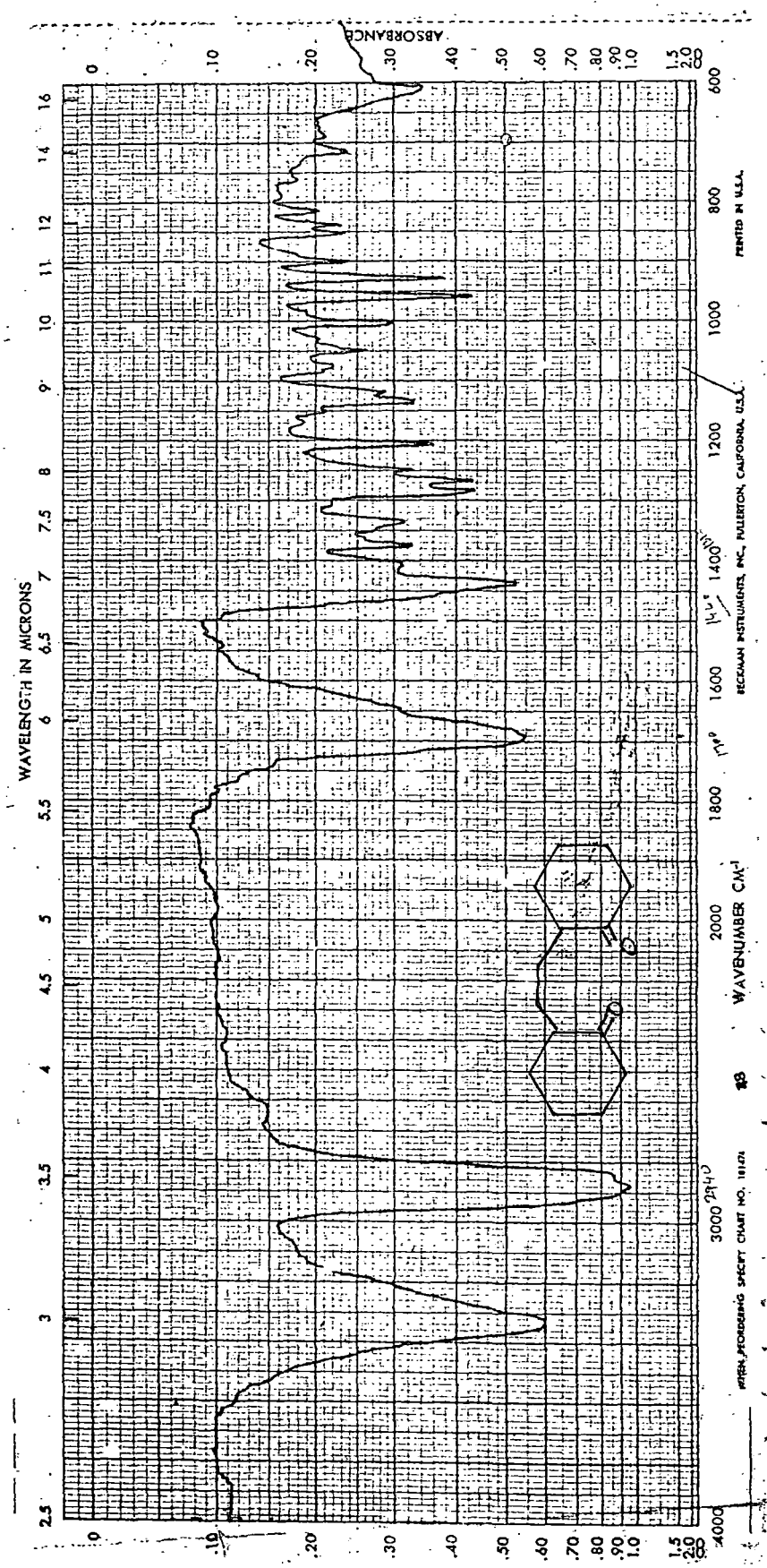
IR in cm^{-1} (nujol) (Spectrum 24)

1700, 1440

PMR (Spectrum 25)

Mass (Spectrum 26)

m/e 222, 139, 190, 125, 98


ABSORBANCE
WAVELENGTH IN MICRONS
WAVENUMBER CM-1
BECKMAN INSTRUMENTS, INC., FULLERTON, CALIFORNIA, U.S.A.
PRINTED IN U.S.A.

SPECTRUM 24

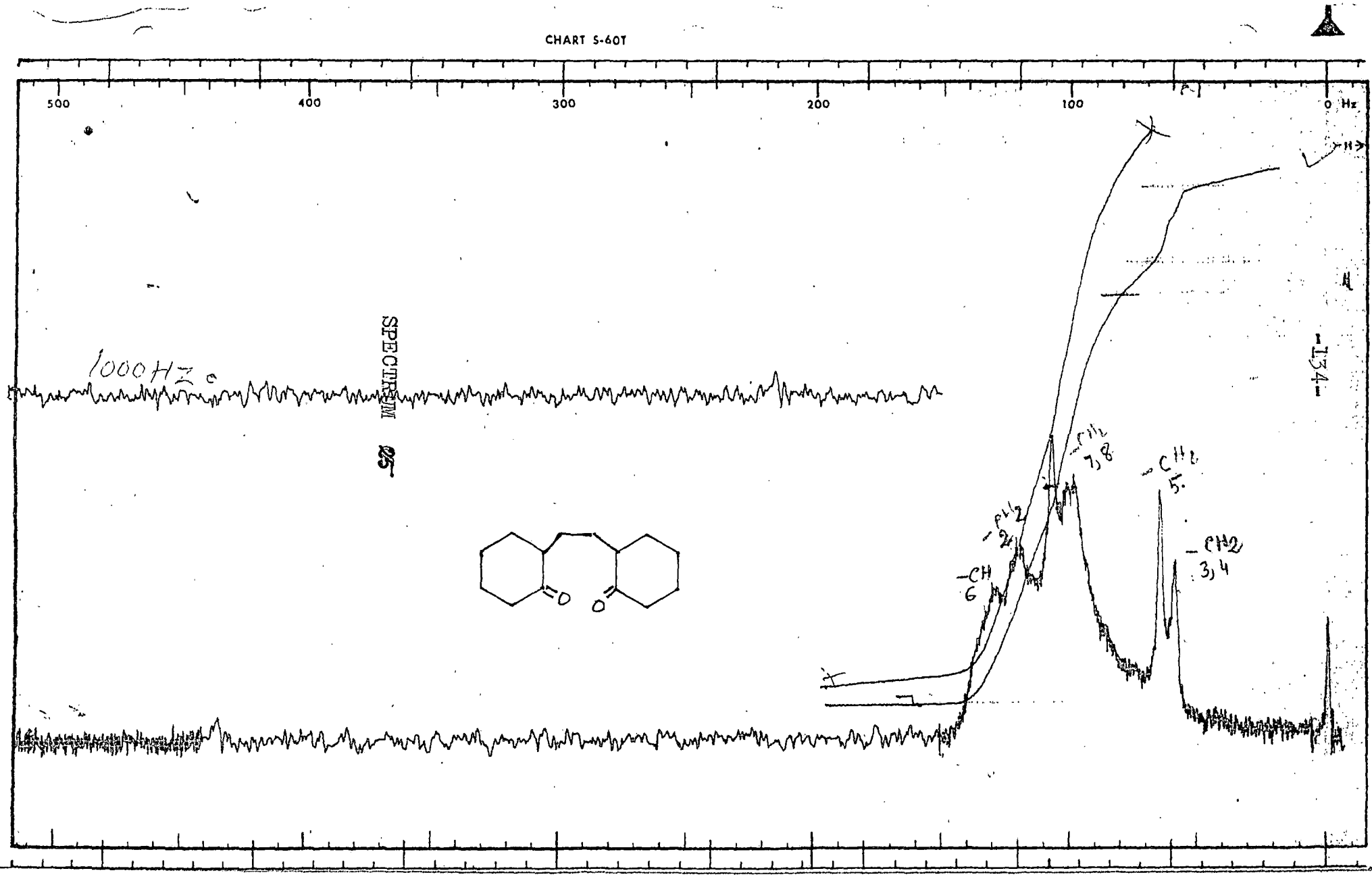
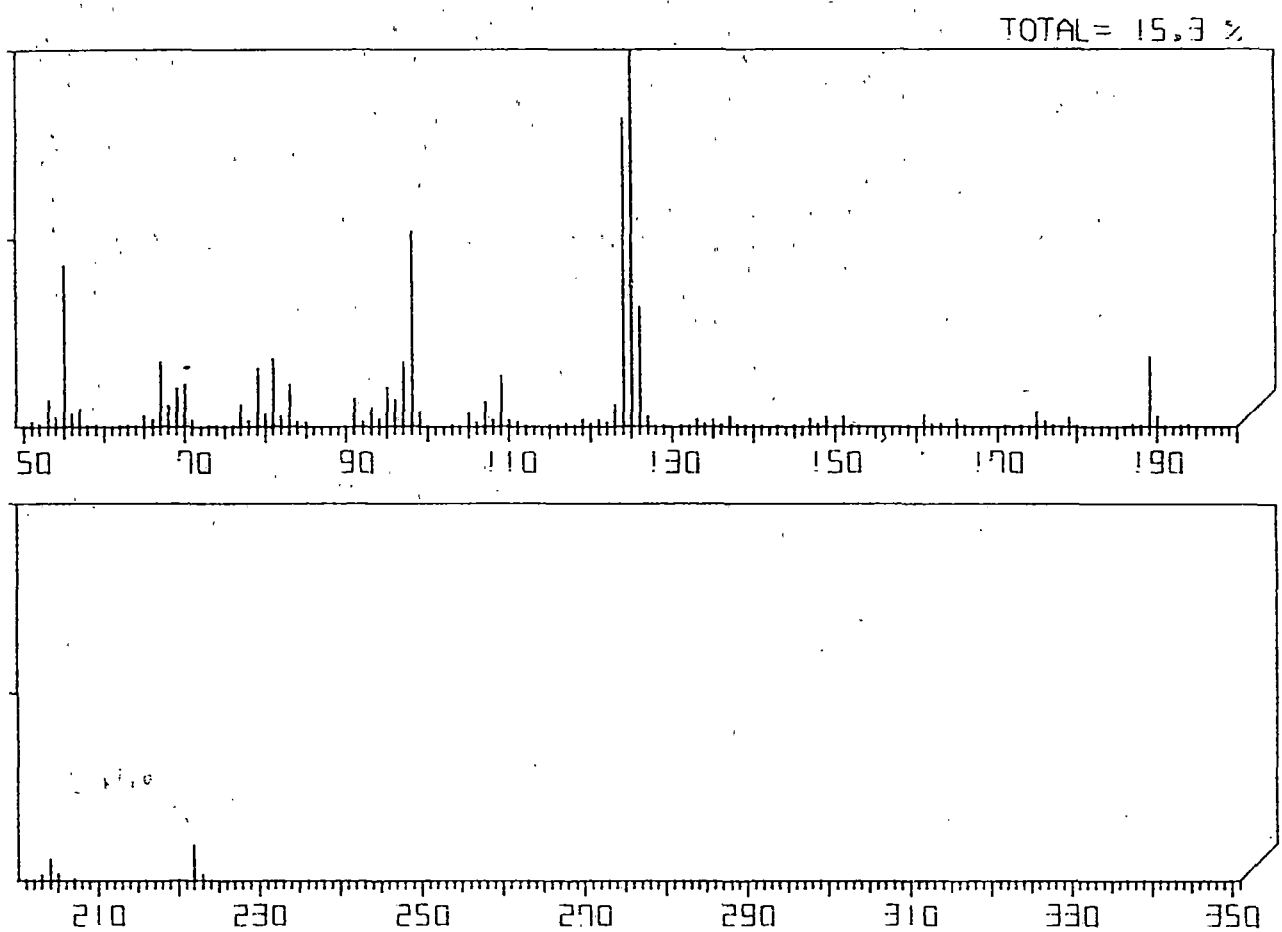


CHART S-60T
500
400
300
200
100
0 Hz
SPECTRUM
1000Hz
-134-
-CH 6
-CH2 2,
-CH2 7,8
-CH2 5.
-CH2 3,4
O
O

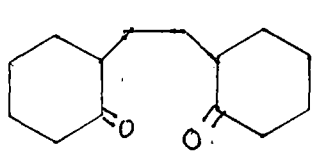
* MODE: EI

HV: 3500 EV: 20 / 70 TRAP: 60
IS TEMP: 270 GAIN: 4 SCAN SPEED: 8
COL TEMP:

DATA NO.	R.T.	PEAK	MASS RANGE	BASE PEAK	TOTAL INT'Y	RAW	B.G.
18(1/2)	.0	164	50.0- 224.0	409500(125.0)	.2667+07	0	0



SPECTRUM 26



Reduction of 1,2-bis(2'oxocyclohexyl)-ethane with Sodium amalgum: Formation of 4a,4b-dihydroxyperhydrophenanthrene (XII)

To sodium amalgum (prepared from 1.8g clean sodium and 10ml mercury) warmed to 50°C was added the diketone (III) (2g) dissolved in absolute alcohol (20 ml) in an atmosphere of nitrogen. Through out the addition the reaction mixture was stirred and after the addition the reaction 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. The dihydroxyperhydrophenanthrene (XII) seperated as a white solid m.p. (from benzene-petroleum ether) 145°

IR (nujol) [in cm^{-1}] (Spectrum 27)

3400 (broad), 1400 (S) 1370 (M)

PMR (ppm) (Spectrum 28)

3.8 (2H), 0.8 - 2.0 (multiplet)

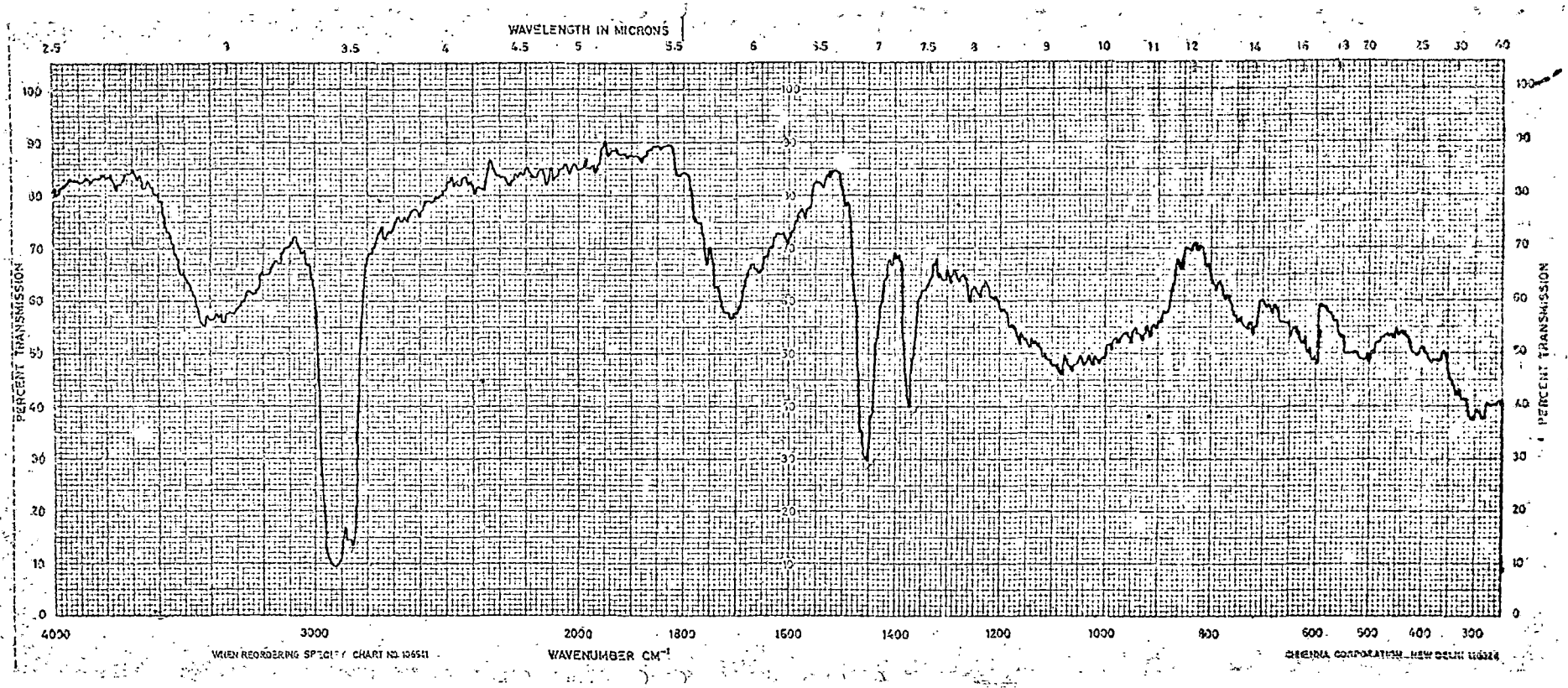
Mass Spectrum (Spectrum 29)

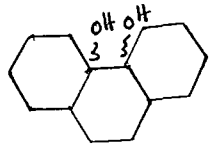
m/e 224, 206, 150, 149, 108 (base peak)

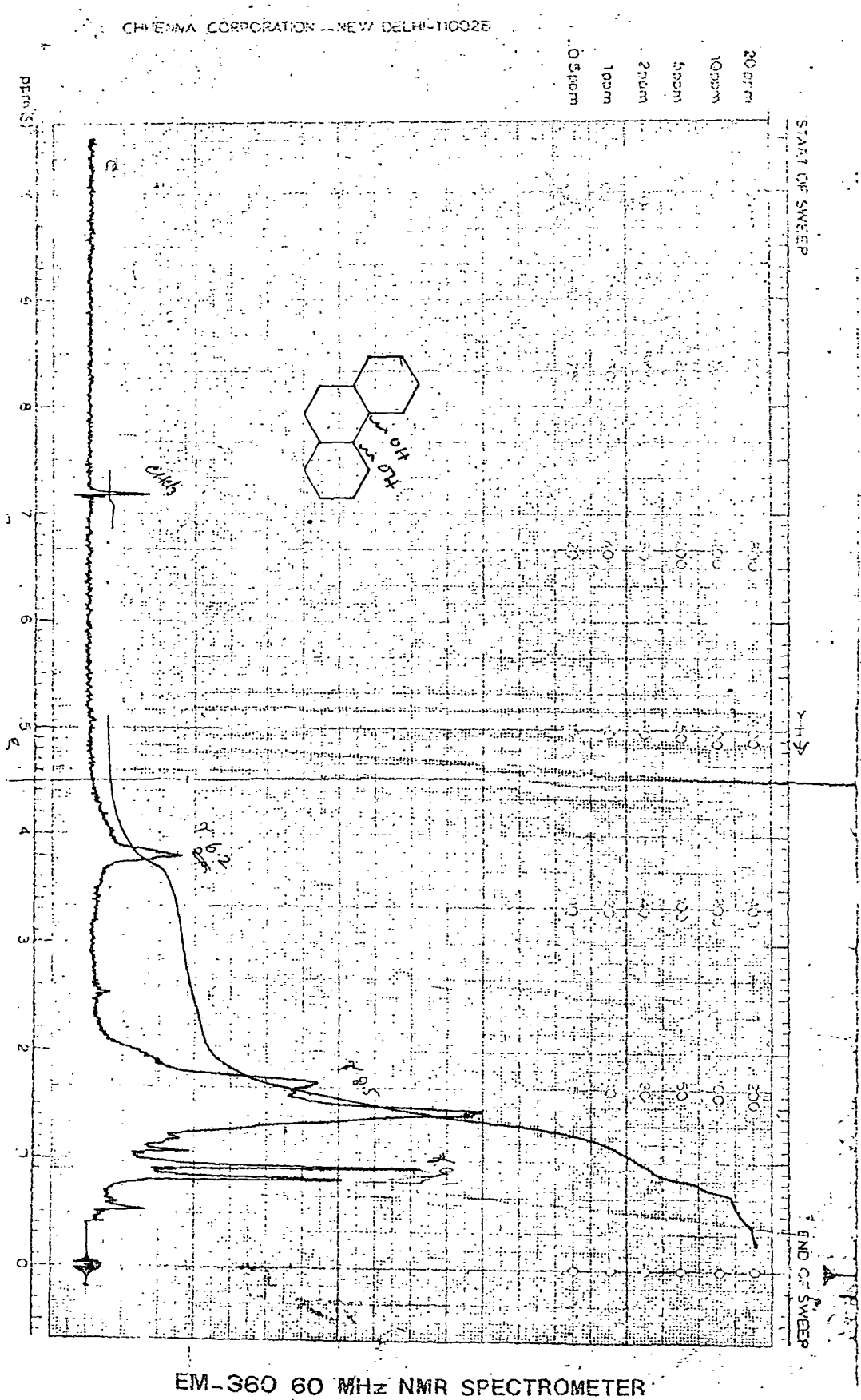
Action of Conc. Sulphuric acid on the perhydrophenanthrene diol (XII). Attempted Pinacol - pinacolone rearrangement

The diol (XII) (1 g) was treated with conc. sulphuric acid (5 ml) and the reaction mixture stirred at r.t. An intense blood-red colour developed. The stirring was continued for

OH SH


WAVELENGTH IN MICRONS
2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 9 10 11 12 14 16 18 20 25 30 40
PERCENT TRANSMISSION
100 90 80 70 60 50 40 30 20 10 0
4000 3000 2000 1800 1600 1400 1200 1000 800 600 500 400 300
WAVENUMBER CM⁻¹


OH
OH
3
5



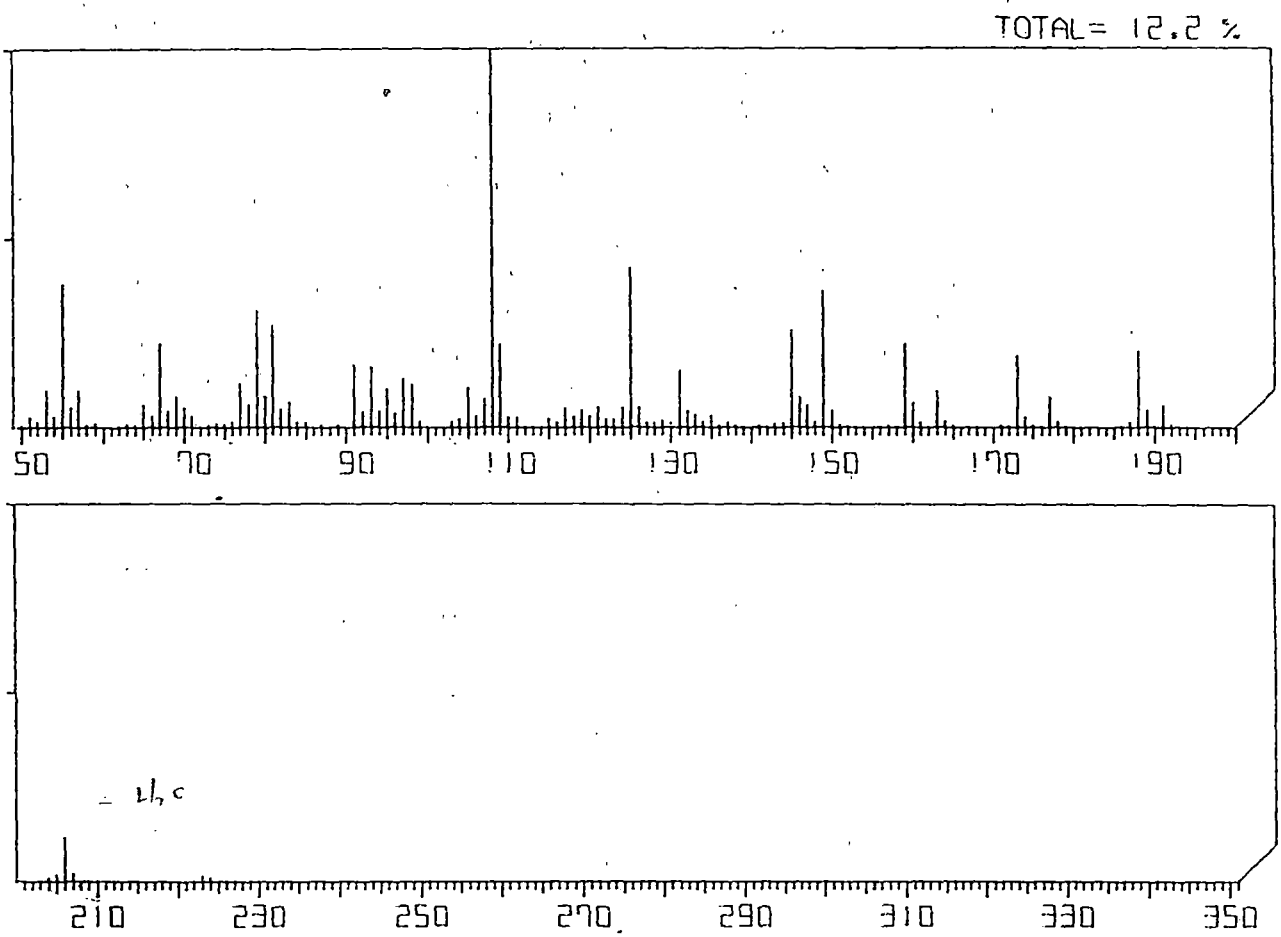
EM-360 60 MHz NMR SPECTROMETER

Spectrum 28

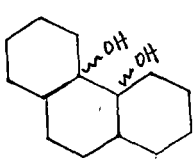
* MODE: EI

HV: 3500 EV: 20 / 70 TRAP: 60
IS TEMP: 270 GAIN: 4 SCAN SPEED: 8
COL TEMP:

DATA NO.	R.T.	PEAK	MASS RANGE	BASE PEAK	TOTAL INT'Y	RAW	B.G.
19(3)	.0	155	50.0- 278.0	195600(108.0)	.1594+07	0	0



Spectrum 29



two hours and the reaction mixture was left overnight at room temperature. Next day 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. 138/1.5 Torr.

IR (liquid film) [in cm^{-1}] (spectrum 30)

3400, 2920, 1700, 1450, 1070

PMR (ppm) (Spectrum 31)

1.2 (multiplet), 3.6

Mass Spectrum (m/e) (Spectrum 32)

206, 188, 173, 159

Treatment of the diketone(III) with Boron trifluoride in Acetic acid. Formation of Spiro compound (XVIII)

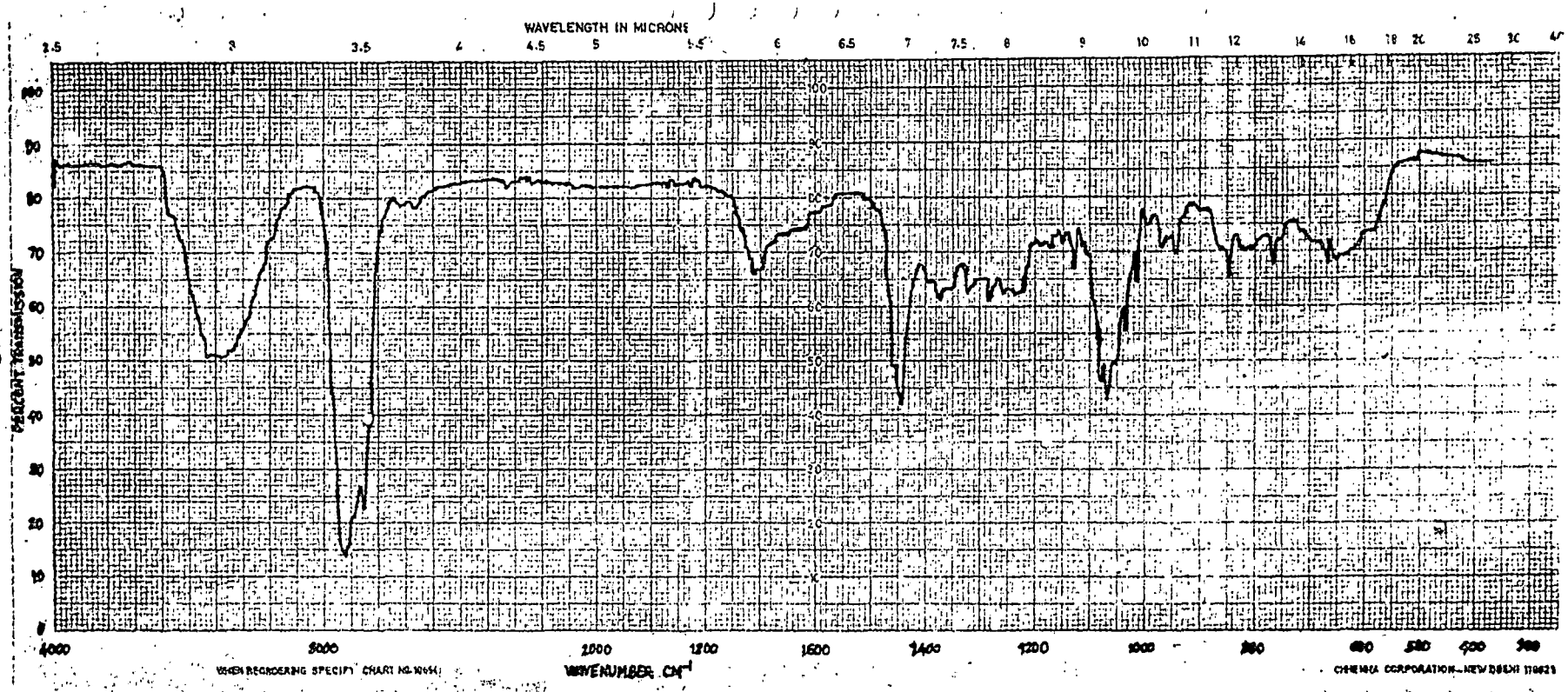
The diketone (III) was dissolved in glacial acetic acid (5 ml) and treated with freshly distilled boron trifluoride in acetic acid (5 ml) and gently refluxed for one hour. The reaction mixture was diluted with water and extracted with benzene. The extract was thoroughly washed free of acid, dried and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

IR (liquid film) (Spectrum 33)

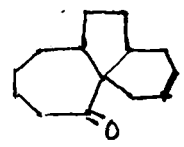
2820, 2900, 1720, 1450, 1250, 1100 cm^{-1}

PMR (ppm) (Spectrum 34)

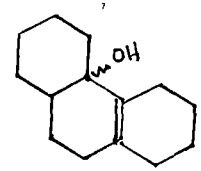
1.7 (multiplet)



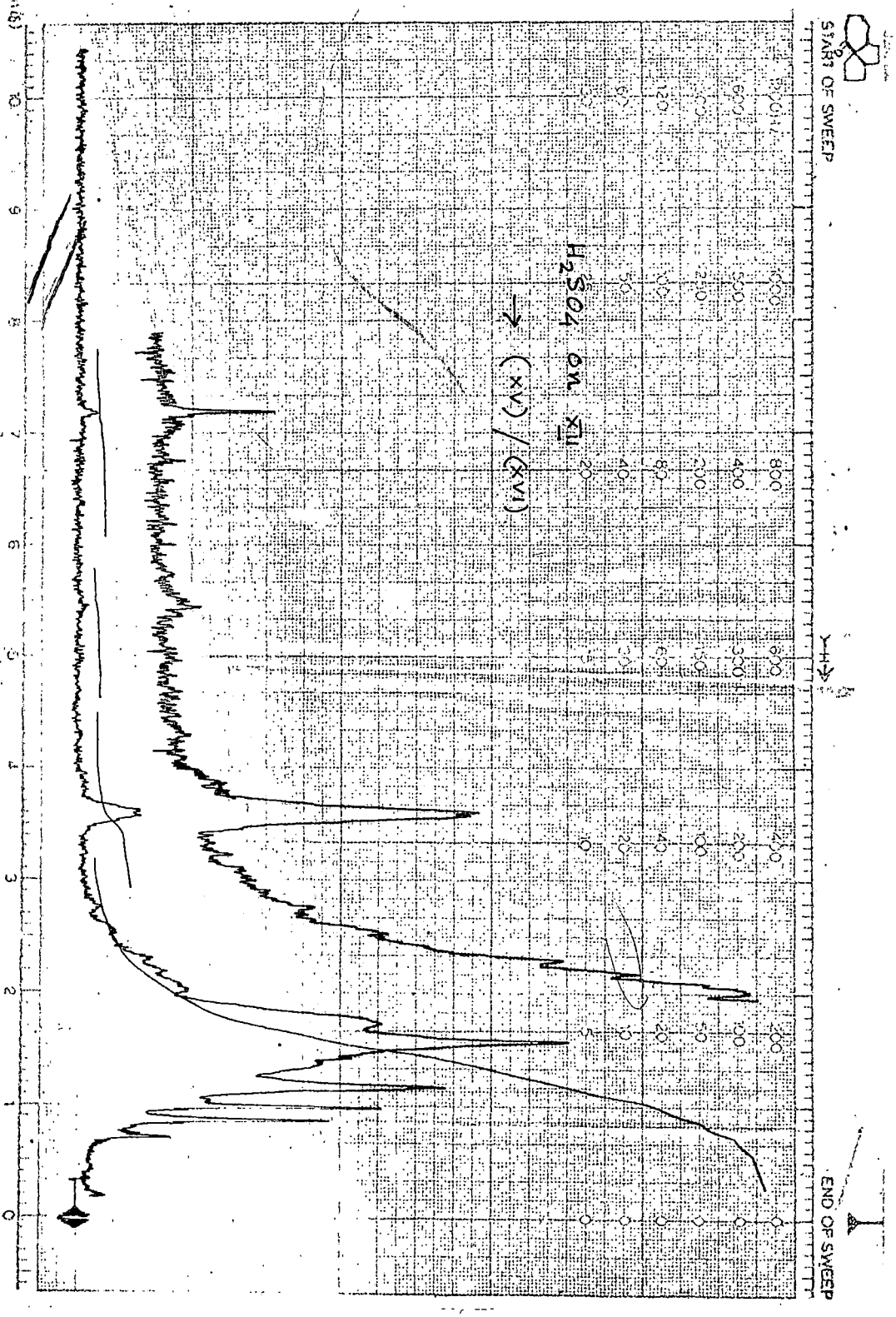
H_2SO_4 ON DIOL XII



XV

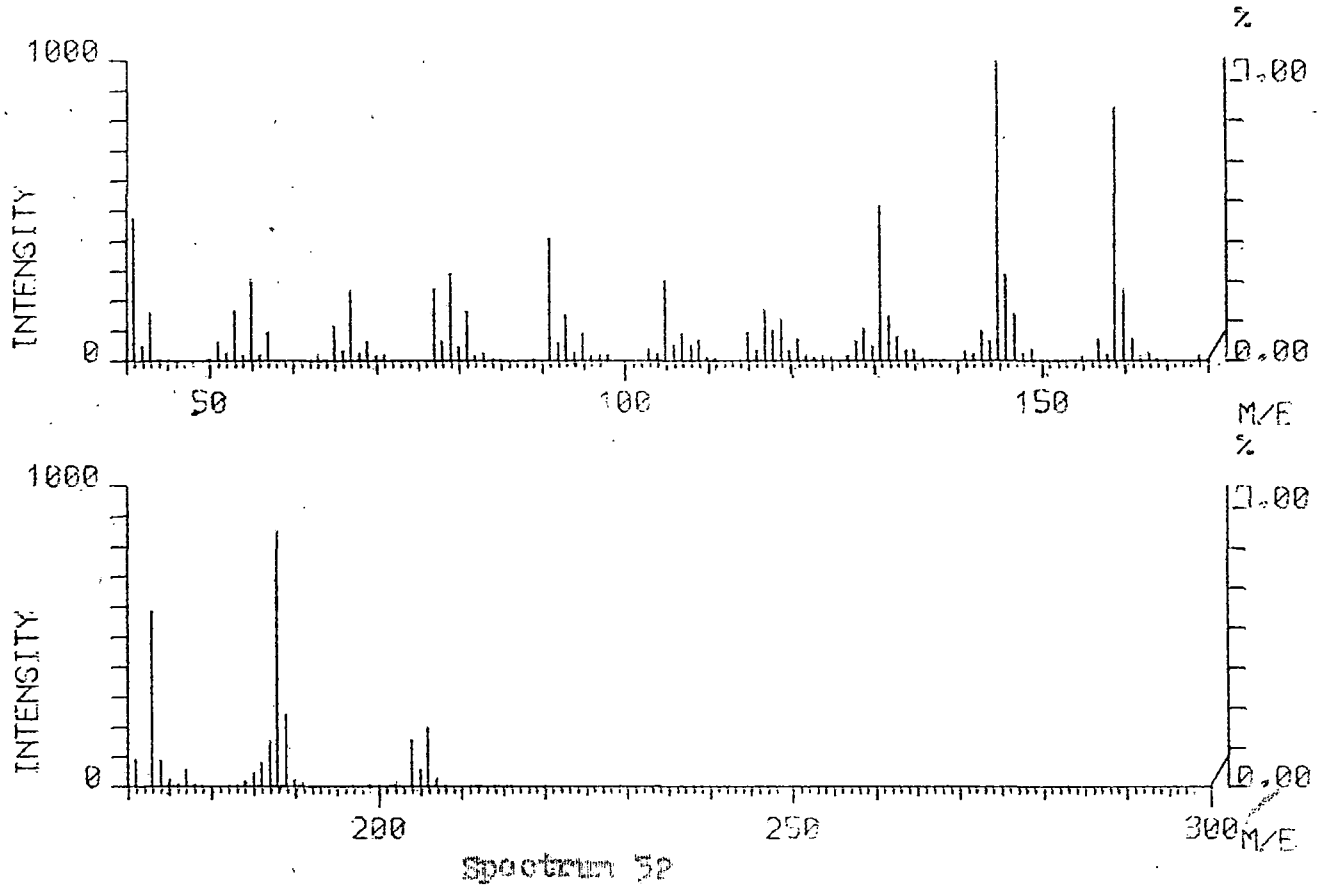


XVI



Spectrum 31

MASS SPECTRUM : (4 TO 5)
SAMPLE CODE NO. NIL,DR(MRS).M.MURTHI,DARJEELING
NOTE :13/12/83
BASE PEAK - M/E 145.0 INT. 454.8



Spectrum 52

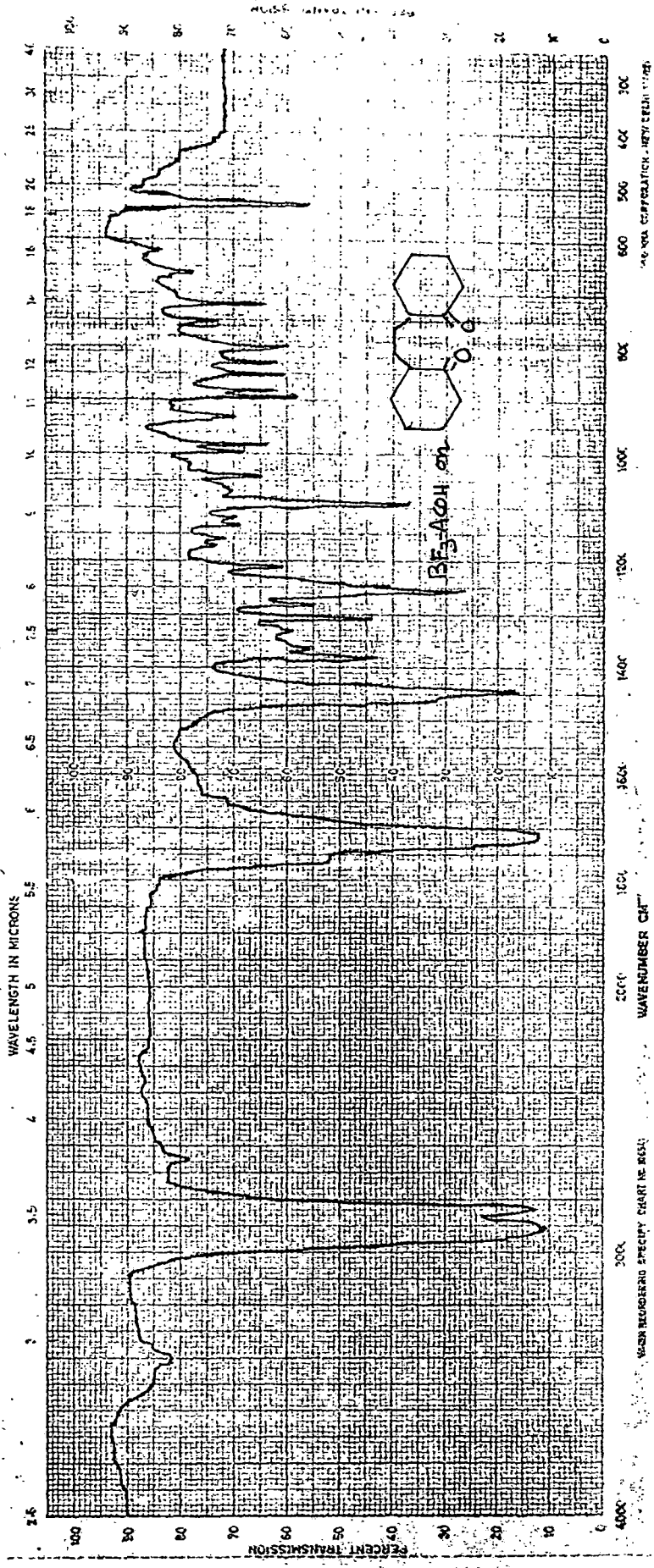
H_2SO_4 on XII

Mass Spectrum (Spectrum 35)

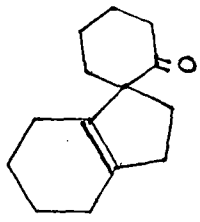
204, 186, 108, 92

Action of Sodium methoxide on diketone (III): Attempted base catalysed aldol condensation

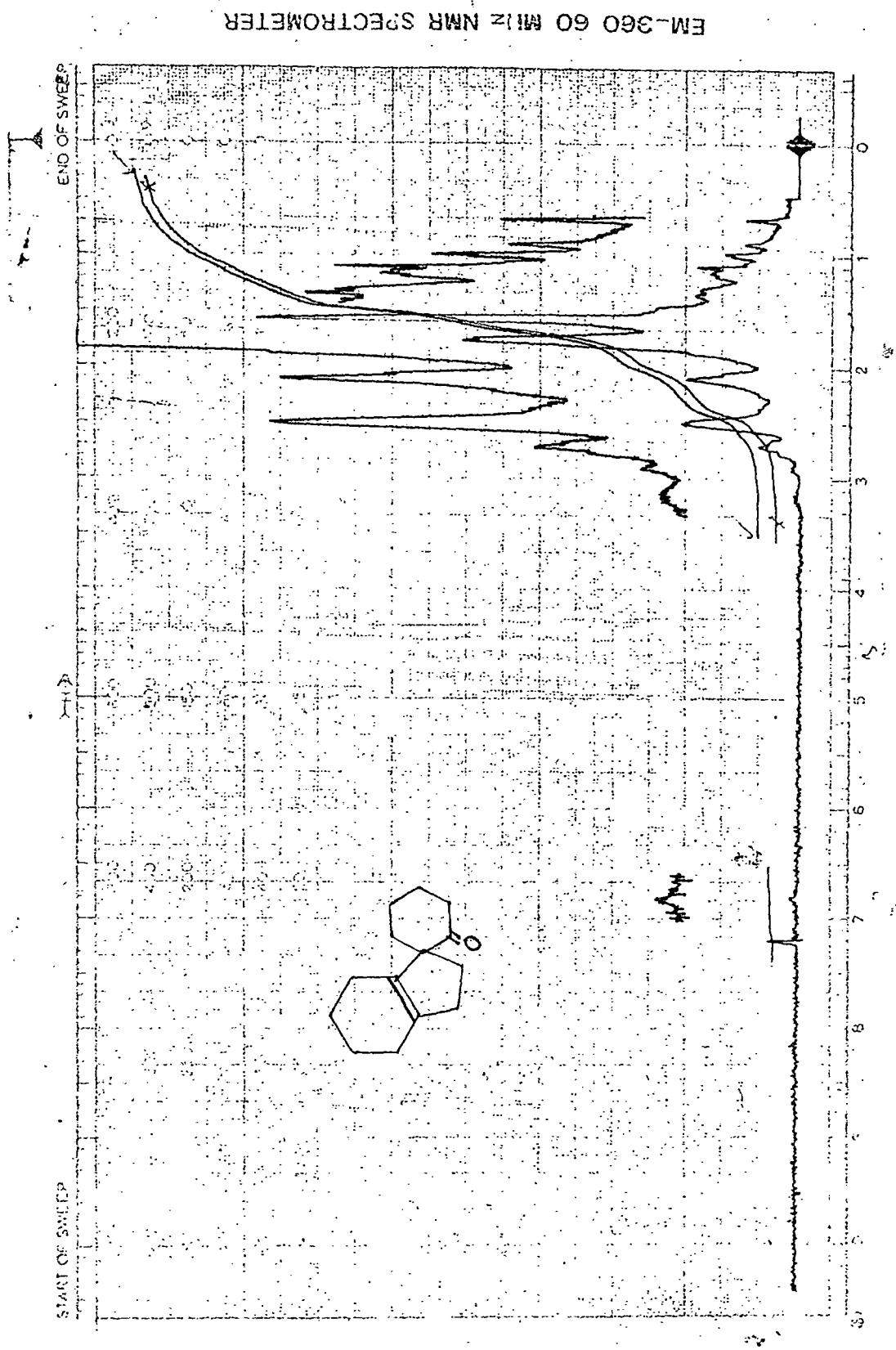
The diketone (III) (2g) was treated with sodium methoxide in methanol (300 mg Sodium in 10 ml methanol) and refluxed for 3 hours. Excess alcohol was distilled off and the residue diluted with water, extracted with benzene, washed the organic extract with water, dried and concentrated. A white solid separated which was found to be identical with the diketone (m.m.p and mixed TLC).



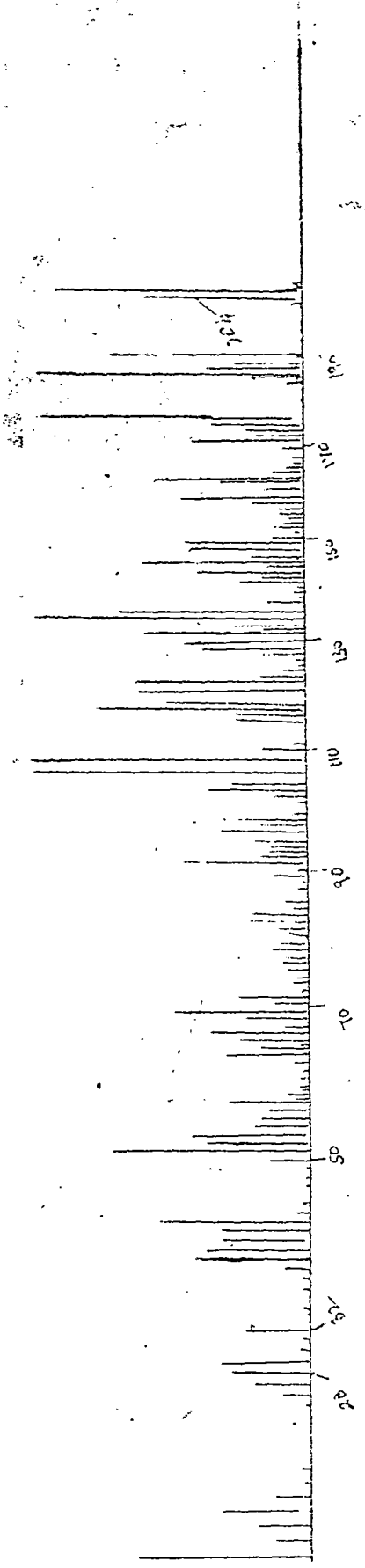
Spectrum 33

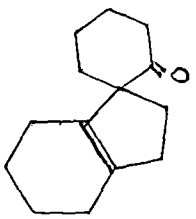


(XVII)


EM-360 60 MHz NMR SPECTROMETER
END OF SWEEP
START OF SWEEP
0
1
2
3
4
5
6
7
8
9
δ
O

Spectrum 34





Spectrum 35

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2. A.P. Krapcho Synthesis, 383 (1974); ibid., 425, (1976)

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