CHAPTER TWO

EXPERIMENTAL AND SPECTRAL INTERPRETATION OF THE COMPOUNDS

EXPERIMENTAL

The experimental work has been divided into four parts :

Part I : The synthesis of N-Propylamino-2,5-dimethyl-3-phenyl indole and its derivatives.

Part II : The synthesis of N-Propylamino-2,3-dihydro-5-methyl indole and its derivatives.

Part III : The synthesis of N-Propylamino-2-methyl-3-phenyl indole and its derivatives.

Part IV : The synthesis of N-Propylamino-2,3-dihydro indole and its derivatives.

General Remarks :

i) Percentage yield, physical constants (MP/BP) elemental analysis (found and calculated) and spectral characteristics of the compounds have been reported.

ii) MP/BP were determined by open capillary method and are uncorrected.

iii) UV spectra were recorded in 95% ethanol on a Hitachi UV-visible spectrophotometer.

iv) IR spectra were recorded in KBr pellets/nujol on a "Perkin-Elmer 297" spectrophotometer.

v) NMR spectra were recorded on "Perkin-Elmer R-32 Spectrometer using T.M.S. as an internal reference and CCl_4/TFA as solvent. The chemical shifts (δ -values) are reported in ppm.

vi) Mass spectra were recorded on "El-MS" computor" system.

vii) The purity of the compound was checked by TLC using silica gel as adsorbent.

SYNTHESIS OF N-PROPYLAMINO-2,5-DIMETHYL-3-PHENYL INDOLE(4)

In this part of the dessertation the synthesis of some indole derivatives has been reported. The strategy employed for the synthesis of desired compound involved the reaction of substituted aromatic amine with acrylonitrile in the presence of Cu-acetate or glacial acetic acid to form corresponding N-cyanoethylamine followed by the reaction of substituted phenacyl bromide in the presence of triethylamine and P_2O_5 in xylene to give N-cyanoethyl-2,5-dimethyl-3-phenyl indole with excellent yield. The disappearance of quartet due to methine proton at 5.2 δ, ppm and apperance of C_2-CH_3 protons at 2.5 ppm indicated the cyclisation. The reduction of this compound with Lithium aluminium hydride in tetrahydrofuran gave N-propylamino-2,5-dimethyl-3-phenyl indole. The disappearance of peak at 2250 cm^{-1} due to $-C \equiv N$ and appearance of doublet at 3300 cm^{-1} in IR spectrum of this compound indicated reduction of $-C \equiv N$ group to $-CN_2NH_2$ group. The different derivatives of N-cyanopropylamino-2,5 dimethyl-3-phenyl indole have been prepared. [SCHEME - 1]

Preparation of α-Benzoyl ethyl bromide[153] :

A solution of 33.5 g. (0.25 mole) of propiophenone in 50 C.C. of pure anhydrous ether is placed in a dry three necked flask fitted with a separating funnel, mechanical stirrer and reflux condenser. This is then cooled in an ice bath. Anhydrous aluminium chloride (0.5 g.) was introduced followed by the addition of 40 g. (13.5 ml. 0.25 mole) of bromine gradually from the separating funnel, with stirring, at the rate of 1 ml. per minute.

After the bromine has been added, the ether and dissolved HBr were removed at once under reduced pressure with a slight current of air. The α-Benzoyl ethyl bromide remain as a liquid. The black colour of the compound was removed by shaking it with a mixture of 10 ml. of water and 10 ml. of pt. ether. The viscous liquid is distilled under reduced pressure, yield 40.00 g. (75.4%), B.P. 245-250°C.

NMR (CCl_4) δ = 2,0 (3H,d-CH_3), 5.25(1H,q,-C-H), 7.2-8(5H,m, aromatic portions). Fig. 1.

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Synthesis of N-Cynoethyl p-toluidine (2).

In a round bottom flask fitted with reflux condenser a mixture of p-toluidine 53.5 g. (0.5 mole) and acrylonitrile 26.5 g. (0.5 mole) and cupric acetate monohydrate (2.5 g.) was heated under reflux for 0.5 hrs at 100°C and 140°C for 3 hrs. The dark reaction mixture was distilled under reduced pressure to remove unreacted p-toluidine. On cooling the separated solid which when recrystalised gave 2, 40 g. (53%). M.P. 102°C. (Found : C, 82.15; H, 8.13; N, 9.50. $C_{10}H_{12}N_2$ requires : C, 82.19; H, 8.21; N, 9.58%)

UV (ethanol) λ max - 265 nm and 300 nm; Fig.2

IR (Nujiol) : νmax; 3200-300 (-NH), 2250 ($-C \equiv N$), 1700($>C=O$), 1600 cm^{-1} ($>C=C<$); Fig.3

NMR (TFA), δ ppm : 2.1 (3H, s,Ar-CH_3), 2.8 (2H, t, -CH_2CN), 3.8(1H,s,-NH), 3.7 (2H,t, N-CH_2), 7.1 (5H,s,aromatic protons) Fig.4.

Synthesis of N-Cyanoethyl-2,5-dimethyl 3-phenyl indole (3)

In a two necked flask carrying reflux condenser and a dropping funnel a solution of 2, 30 g. (0.2 mole) in methyl alcohol (50 ml.) to which α-Benzoyl ethyl bromide 10 g. (0.05 mole) and few drops of triethyl amine were added through dropping funnel and the reaction mixture was heated on water bath for about 24 hrs., cooled and distilled under reduced pressure The residue was further heated under reflux in dry xylene for 8 hrs. The hot solution was filtered and the xylene was removed under reduced pressure. The solid obtained was recrystallised from alcohol to give 3, 20 g. (36%); M.P. 88°C.

(Found : C, 83.16; H, 6.50; N, 10.12. $C_{19}H_{18}N_2$ requires C, 83.21; H, 6.56; N, 10.21%);

UV (ethanol) λ max : 265 nm and 285 nm Fig.5.

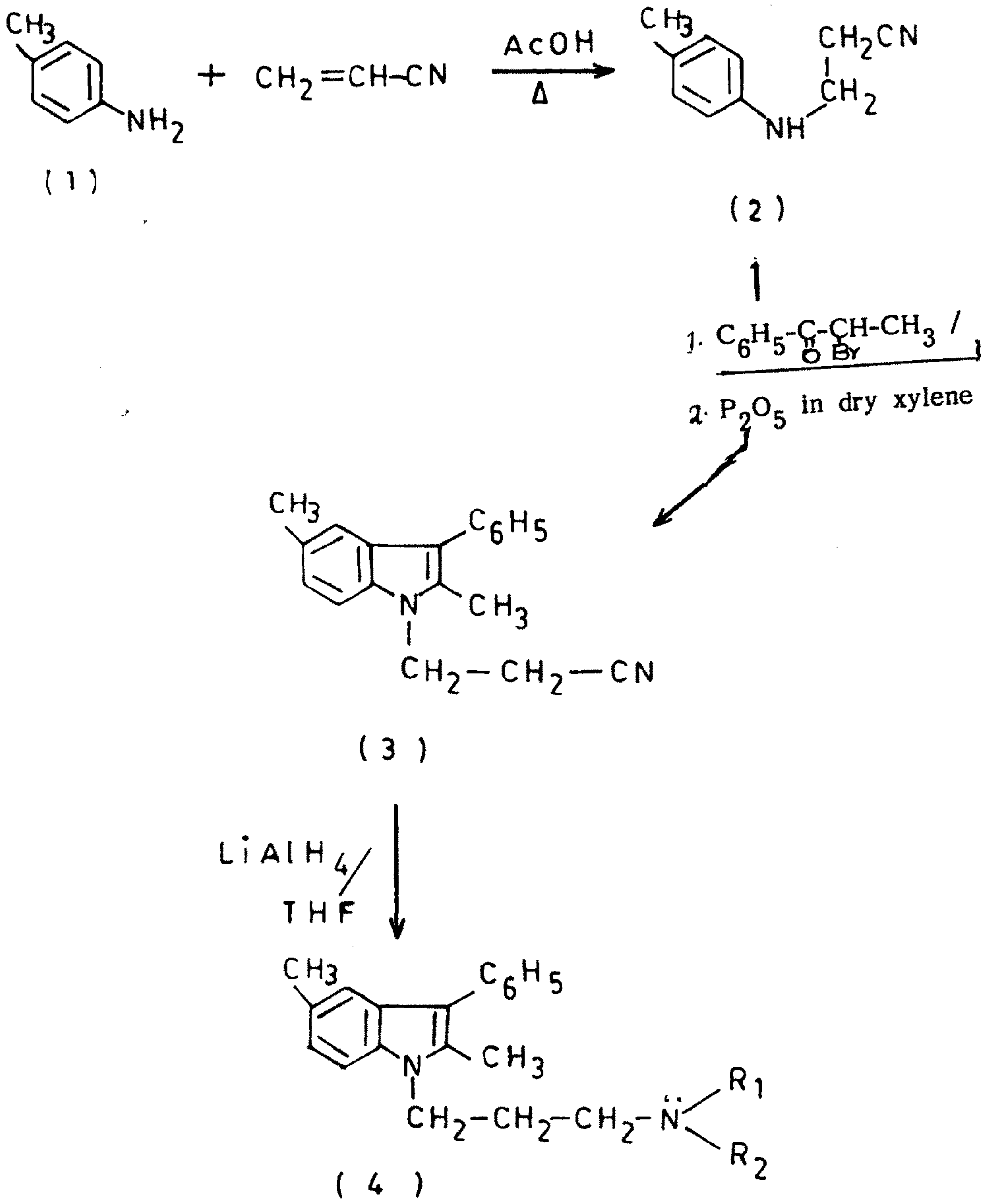
IR (Nujol) ν max : 2250 ($-C \equiv N$); 1600 ($>C = C<$)

NMR (TFA) δ ppm : 2.1 (3H, s, $ArCH_3$); 2.15 (3H, s, C_2-CH_3), 2.8 (2H, t, $-CH_2CN$), 3.75 (2H, t, $-N-CH_2$), 7.15-7.8 (8H, m, aromatic protons). Fig.6.

Synthesis of N-Propylamino-2,5-dimethyl-3-phenyl indole (4) :

To a solution of 7.6 g. (0.2 mole) of $LiAlH_4$ in 30 ml of dry ether in two necked flask, a solution of 23.5 g. (0.2 mole) of compound (3) in 30 ml of dry ether was added through dropping funnel over the period of 30 min. and stirred magnetically for 1.5 hrs. When the reaction had subsided ice was added to decompose excess of $LiAlH_4$ and the ether layer was washed with 50 ml sodium tartarate solution. Ether on evaporation gave solid which when recrystallised from alcohol gave 4. 12 g. (51%), M.P. 75°C.

SCHEME-1


CH3
NH2
(1)
+ CH2=CH-CN
AcOH
Δ
CH3
CH2CN
CH2
NH
(2)
1. C6H5-C-CH-CH3 / O Br
2. P2O5 in dry xylene
CH3
C6H5
N
CH3
CH2-CH2-CN
(3)
LiAlH4/THF
CH3
C6H5
N
CH3
CH2-CH2-CH2-N
R1
R2
(4)

(Found : C, 81.75; H, 7.86; N, 10.01. $C_{19}H_{22}N_2$ requires : C, 81.01; H, 7.91; N, 10.07 %);

IR (Nujol) : ν max 3300 (NH_2), 1600 ($>C = C<$), 1580 cm^{-1} ($-C = N$) Fig. 7.

NMR (TFA) : δ ppm 1.3 (2H,s br NH), 2.1 (3H,s,Ar-CH_3), 2.15 (3H,s, -C_2-CH_3), 2.6 (2H, t, -CH_2NH_2), 3.7(2H, t, N-CH_2), 7.05-7.7(8H,m,aromatic protons) Fig.8.

MASS : M^+,m/e 278 (0.2%), 187 (50%), 160 (25%), 120 (100%), 105 (15%), 91 (33%), 77 (17%), 65 (10%). Fig.9.

N-propylamino-2,5-dimethyl-3-phenyl indole Derivatives

Experimental Procedure :

N-(N-Acetylamino propyl)-2,5-dimethyl-3-phenyl indole (4_a) :

In round bottom flask fitted with reflux condenser and a guard tube, a solution of compound 4, 0.139 g.(0.0005 mole) in methanol (10 ml) 0.0392 g. (0.0005 mole) of acetyl chloride was added and stirred magnetically and heated on water bath for 6 hrs, then cooled. The separated solid was filtered and recrystallised from ethanol which gave 4a, 0.084 g.,(53%), M.P. above 300°C.

PMR (TFA); δ ppm : 1.1(2H,m,-CH_2-), 2.1(3H, s, -ArCH_3), 2.15(3H, s, C_2-CH_3), 3.55 (3H, s, -NHCOCH_3), 2.65 (2H, t, CH_2N), 3.7 (2H, t, N-CH_2), 7-7.8 (8H, m, aromatic protons), 7.6 (1H, s, br, -NHCO).

N-(N-Dimethylamino propyl)-2,5-dimethyl-3-phenyl indole (4_b) :

A mixture of compound 4, 0.139 g. (0.0005 mole), methyl iodide 0.071 g. (0.0005 mole) in THF (10 ml.) and 0.2 ml. (5% KOH) was refluxed for 5 hrs, cooled. The solvent was removed under reduced pressure. The solid obtained was recrystallised from ethanol to give 4 b, 0.084 g., (55%) M.P. above 280°C.

PMR (TFA), δppm : 1.1 (2H, m, -CH_2-), 2.15 (3H, s, ArCH_3), 2.2 (3H, s, C_2 - CH_3), 2.5 (2H, t, -CH_2N), 2.78 (6H, s, 2×N - CH_3), 3.7 (2H, t, N-CH_2), 7-7.8 (8H, m, aromatic protons).

N-(N-Phenyl carbamylamino propyl)-2,5-dimethyl-3-phenyl indole (4_c) :

In a two necked round bottom flask fitted with reflux condenser and dropping funnel a solution of compd. 4, (0.0005 mole) in THF (10 ml) to which 0.0595 g. (0.0005 mole) of phenyl isocyanate was added through the dropping funnel and stirred magnetically for 24 hrs. and kept over night. The separated solid was filtered and recrystallised from ethanol which gave 4 c, 0.158 g., (80%), M.P. 175°C.

PMR (TFA), δppm : 1.12 (2H, m, CH_2-), 2.1 (3H, s, Ar - CH_3), 2.15 (3H, s, C_2 - CH_3), 2.7 (2H, t, - CH_2N), 3.65 (2H, t, N - CH_2), 7-8 (13H, m, aromatic protons), 8.2 - 8.4 (2H, s, br, NHCO) Fig. 10

N-(N-Acetamidylamino propyl)-2,5-dimethyl-3-phenyl indole (4_d) :

In a flask fitted with reflux condenser the compound 4, 0.139 g. (0.0005 mole), chloroacetamide 0.04567 g. (0.0005 mole) in 10 ml. methanol and K_2CO_3 1.5 gms was refluxed for 6 hrs then filtered while hot and cooled. The filtrate was concentrated, the separated solid which when recrystallised from ethanol gave 4 d, 0.093 g. (56%), M.P. above 280°C.

PMR (TFA), δ ppm : 1.13 (2H, m, CH_3), 2.12 (3H, s, Ar-CH_3), 2.7 (1H, br s, NH), 2.17 (3H, s, -C_2) - CH_3), 2.6 (4H, m, -CH_2N), 3.65 (2H, t, NCH_2), 5.2 (2H, s, br, NHCO), 7.1 - 7.85(8H, m, aromatic protons).

N-(N-Benzoylamino propyl)-2,5-dimethyl-3-phenyl indole (4_e) :

To a solution of compd. 4, 0.139 g (0.0005 mole) in THF (10 ml) 0.070 g. (0.0005 mole) of benzoyl chloride was added dropwise with constant stirring. The mixture was refluxed for 8 hrs on water bath and cooled. The solid formed was filtered and recrystallised from ethanol to give 4 e, 0.124 g. (65%), M.P. 85°C.

PMR (TFA), δ ppm : 1.11 (2H, m, - CH_2), 2.11 (3H, s, Ar-CH_3), 2.15 (3H, s, C_2 - CH_3), 2.65 (2H, t, CH_2N), 3.65 (2H, t, N-CH_2), 7.1 - 8.1 (3H, m, aromatic protons), 8.4 (1H, s br, NH CO)

N-(N-4-Hydroxybenzilideneamino propyl)-2,5-dimethyl-3-phenyl indole (4_f) :

In a flat bottom flask, the mixture of compound 4, 0.139 g. (0.0005 mole) and p-hydroxy benzaldehyde 0.062 g. (0.0005 mole) in 20 ml of methanol was refluxed on water bath for about 8 hrs then cooled. The solvent was removed under reduced pressure, the solid obtained was recrystalized from ethanol to furnish 4_f. 0.131 g. (69%), M.P. 105°C.

PMR (TFA), δ ppm : 1.1 (2H, m, -CH_2), 2.12 (3H, s, Ar - CH_3), 2.15 (3H, s, C_2 - CH_3), 2.65 (2H, t, -CH_2 N-), 3.7 (2H, t, N-CH_2), 7 - 7.8 (12H, m, aromatic protons), 8.4 (1H, s, - C = CH), 9.5 (1H, s, OH).

N-(N-4-Dimethylaminobenzilideneamino propyl)-2,5-dimethyl-3-phenyl indole (4_g) :

The compound 4, 0.139 g. (0.0005 mole) in THF (15 ml.) to which p-dimethylaminobenzaldehyde was added and the mixture was stirred magnetically for 8 hrs. The solvent was removed under reduced pressure and cooled. The solid obtained was recrystallised from ethanol to give 4_g 0.141 g. (69%), M.P. 80°C.

PMR (TFA), δ ppm : 1.13 (2H, m, $-CH_2$), 2.10 (3H, s, Ar - CH_3), 2.15 (3H, s, C_2 - CH_3), 2.60 (2H, t, - CH_2N-), 3.1 (6H, s, $-N(CH_3)_2$), 3.72 (2H, t, $N-CH_2$-), 7.8 (12H, m, aromatic protons),8.3 (1H,s,-C = CH-). Fig. 11.

N-(N-p-Chlorophenoxy-1,3,4-oxadiazolo meth-2-ylamino propyl)-2,5-dimethyl-3-phenyl indole (4_h) :

A mixture of compd. 4, 0.139 g. (0.0005 mole) and 5-(p-chlorophenoxy)-2-chloromethyl-1,3,4-oxadiazole 0.129 g. (0.0005 mole) in THF (20 ml) was refluxed in the presence of 0.5 ml. of triethylamine for about 8 hrs, cooled. The solvent was removed under reduced pressure. The solid obtained was filtered and recrystallised from ethanol to give 4_h 0.137 g., (5%) M.P. 120°C.

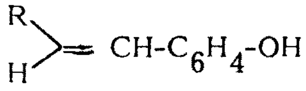
PMR (TFA), δ ppm : 1.1 (2H, m, $-CH_2$), 2.15 (3H, s, Ar - CH_3), 2.2 (3H, s, C_2 - CH_3), 2.6 (2H, t, $-CH_2N$), 3.65 (2H, t, $-CH_2N$), 3.8 (2H, s, $-CH_2$), 4.55 (2H, s, - OCH_2), 7-7.8 (12H, m, aromatic protons).

N-(N-Phenylthiocarbamylamino propyl)-2,5-dimethyl-3-phenyl indole (4_i) :

To a solution of compd. 4, 0.139 g. (0.0005 mole) to which 0.068 g. phenyl thiocyanate was added and stirred magnetically for 4 hrs and kept over night. The separated solid was filtered and recrystallised from ethanol to give 4_i, 0.103 g. (50%), M.P. 205°C.

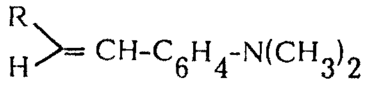
NMR (TFA), δ ppm : 1.11 (2H, m, $-CH_2$), 2.15 (3H, s, Ar - CH_3), 2.22 (3H, s, C_2 - CH_3), 2.62 (2H, t, $-CH_2N$), 3.6 (2H, t, - CH_2N), 5.2 (1H, s. br, $N\underline{H}$), 7-7.8 (13H, m, aromatic protons), 8.2 (1H, s br, $N\underline{H}$-ph).

Table - 1 : SUBSTITUTED N-PROPYLAMINO-2,5-DIMETHYL-3-PHENYL INDOLES

Compound (4)	R	R'	Molecular formula	Yield %	M.P. °C	Elemental Analysis Found % / Calcd. % C	H	N
a	H	$COCH_3$	$C_{21}H_{24}N_2O$	53	above 300	78.60 (78.75)	7.48 (7.50)	8.70 (8.75)
b	CH_3	CH_3	$C_{21}H_{26}N_2$	55	above 280	82.40 (82.35)	8.45 (8.49)	9.05 (9.15)
c	H	-CONHPh	$C_{26}H_{27}N_3O$	60	175	78.53 (78.58)	6.75 (6.80)	10.55 (10.57)
d	H	$-CH_2CONH_2$	$C_{21}H_{25}N_3O$	56	above 280	75.20 (75.22)	7.36 (7.46)	12.51 (12.53)
e	H	-COPh	$C_{26}H_{26}N_2O$	65	85	81.65 (81.67)	6.75 (6.80)	7.34 (7.32)
f			$C_{26}H_{26}N_2O$	69	105	81.60 (81.76)	6.76 (6.80)	7.30 (7.32)

contd.....

Table - 1 (contd..)

Compound (4)	R	R'	Molecular formula	Yield %	M.P. °C	Elemental Anlysis Found % / Calcd. % C	H	N
g			$C_{28}H_{31}N_3$	69	80	82.10 (82.15)	7.55 (7.57)	10.23 (10.26)
h	H		$C_{31}H_{31}N_2O_2Cl$	55	120	74.60 (74.62)	6.19 (6.21)	5.60 (5.61)
i	H	-CSNHPh	$C_{26}H_{27}N_3S$	50	205	75.57 (75.54)	6.54 (6.53)	10.17 (10.16)

Part-II

SYNTHESIS OF N-PROPYLAMINO-2,3-DIHYDRO-5-METHYL INDOLE

The synthesis of N-propylamino-2,3-dihydro-5-methyl Indole involved the reaction of p-toludine with acrylonitrile to give N-cynoethyl p-toluidine the formation of which was explained by the observation of two triplets centred at δ,3.6 ($-N-CH_2$) and 2.8 ($-CH_2-CN$) ppm in the PMR spectrum. This was further condensed with chloroacetyl chloride in the presence of triethylamine in benzene followed by the reaction with anhydrous $AlCl_3$ formed N-cyanoethyl-2-oxo-5-methyl indole III. The formation of III was acertained by the appearance of additional PMR signal at δ , 2.15 ppm in (III) due to $-COCH_2$ group. The compound (III) when reduced with $LiAlH_4$ in THF afforded IV. The reduction of $- C \equiv N$ into NH_2 was indicated by the disappearance of singlet at 2250 cm^{-1} ($-C \equiv N$) and appearance of doublet at 3200 - 3300 cm^{-1} in the IR spectrum of these compounds. Various derivatives of (IV) were prepared.

[SCHEME - 2]

Synthesis of N-Cyanoethyl-2-oxo-5-methyl indole III :

A mixture of N-cyanoethyl p-toluidine (40 g., 0.5 mole) and chloroacetyl chloride (24 g., 0.5 mole) in benzene (40 ml.) was refluxed on a water bath for 5 hrs, in the presence of triethyl amine (0.5 ml) and cooled The solvent was removed under reduced pressure. To the solid mass anhydrous. $AlCl_3$ (30 g.) was added small lot at a time and the content was heated on oil bath at 120°C for 1.5 hrs. and the Lewis acid complex was decomposed by dil. HCl. The product was extracted with ether and distilled under reduced pressure to furnish III, 30 g. (60%), B.P. 230°C (at 10 mm).

(Found : C, 71.50; H, 5.89; N, 13.05, $C_{12}H_2ON_2$ requires C, 72.00; H, 6.00; N, 14.00%).

UV (ethanol) λ max : 270 nm. fig. 12.

IR (Nujol), ν max : 2250 ($-C \equiv N$), 1700 ($>C = O$), 1600 (phenyl) cm^{-1} Fig.13.

NMR (TFA) δ ppm : 2.15 (2H, s, $-CH_2CO$), 2.35 (3H, s, $ArCH_3$),
3H | 2.6 (2H, t, $-CH_2CN$), 3.8 (2H, t, $-NCH_2$), 6.8 (4H, m, aromatic protons)
Fig. 14.

Synthesis of N-propylamino-2,3-dihydro-5-methyl indole (IV) :

The compound III (40 g., 0.2 mole) in THF (20 ml) to which $LiAlH_4$ (7.69 g., 0.2 mole) in THF (15 ml) was added slowly and stirred for about 1.5 hr. When the reduction was complete the mixture was poured in ice cold water and extracted with ether. Ether layer on evaporation gave solid which was recrystallised from ethanol 22.8 g.,(50%) M.P. 110°C. (Found C, 75.5; H, 9.2; N, 14.2, $C_{12}H_{15}N_2$ requires C, 75.7; H, 9.4; N, 14.7%).

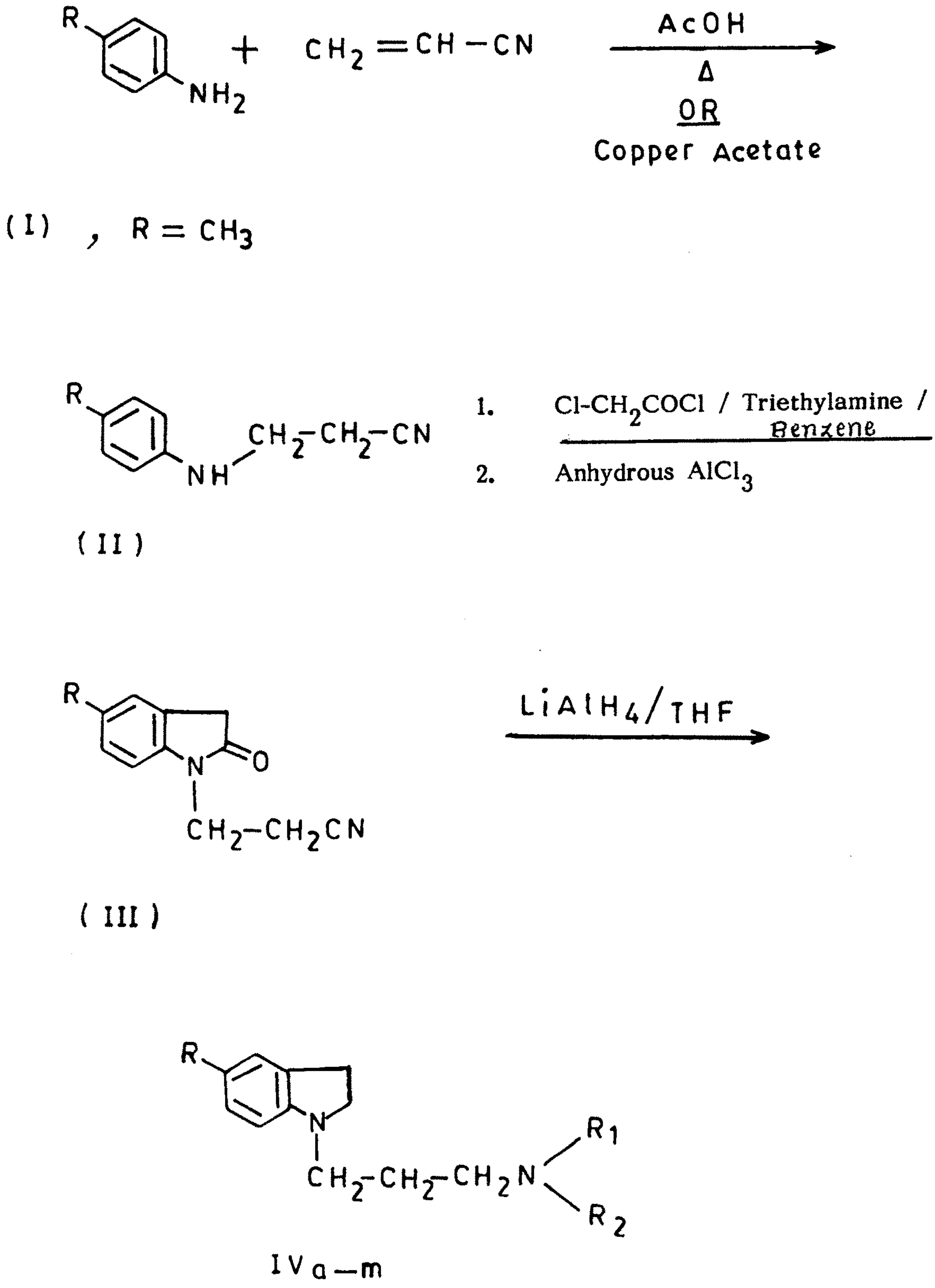
UV (ethanol) λ max : 280 nm

IR (Nujol) ν max : 3300 (NH_2), 1600 ($>C = C<$) cm^{-1}

NMR (CCl_4) δ ppm : 1.3-1.7 (4H, m, $2xCH_2$), 2.16(2H, d, $N\underline{H}_2$),
2.32 (3H, s, $Ar-CH_3$), 2.4-2.6 (2H, m, $C\underline{H}_2N$), 3.6-3.8(4H, m, $2xNCH_2$),
3H 6.9 - 7.8 (4H, m, aromatic protons); Fig. 15.

MASS : M^+ (M/e), 190 (1%), 173 (100%), 160 (12%); 146 (10%), 132 (20%), 105 (55%), 91 (55%). Fig. 16.

SCHEME-2


R
NH2
CH2=CH-CN
AcOH
Δ
OR
Copper Acetate
(I) , R = CH3
R
CH2-CH2-CN
NH
(II)
1. Cl-CH2COCl / Triethylamine / Benzene
2. Anhydrous AlCl3
R
N
O
CH2-CH2CN
(III)
LiAlH4/THF
R
N
CH2-CH2-CH2N
R1
R2
IVa-m

N-PROPYLAMINO-2,3-DIHYDRO-5-METHYL INDOLE DERIVATIVES.

Experimental Procedure :

N-(N-Dimethylamino propyl)-2,3-dihydro-5-methyl indole (IVa)

A mixture of compound IV, 0.095 g. (0.0005 mole), methyl iodide 0.071 g. (0.0005 mole) in THF (5 ml) and 0.2 ml (3% KOH) was refluxed for 4 hrs, cooled, the solvent was removed under reduced pressure. The solid obtained was recrystallised from ethanol to furnish IVa 0.054 g. (50%), M.P. 85°C.

N-(N-Propylamino propyl)-2,3-dihydro-5-methyl indole (IVb) :

In a round bottom flask fitted with reflux condenser a mixture of compound IV, 0.095 g. (0.0005 mole) and propyl bromide 0.061 g. (0.0005 mole) and 0.5 ml of triethyl amine was refluxed for about 5 hrs, cooled and the solvent was removed under reduced pressure. The solid obtained was recrystallised from ethanol to give IVb 0.069 g. (60%). M.P. 220°C.

N-(N-Acetylamino pyropyl)-2,3-dihydro-5-methyl indole (IVc) :

The mixture of IV, 0.095 g. (0.0005 mole) and 0.0392 g. (0.0005 mole) of acetyl chloride was stirred magnetically for 6 hrs. and cooled. The separated solid was filtered and recrystallised from ethanol to form IVc 0.078 g. (68%), M.P. 99°C.

N-(N-Benzoylamino propyl)-2,3-dihydro-5-methyl indole (IVd) :

To a solution of IV, 0.095 g. (0.0005 mole) in THF (5 ml), 0.070 g. (0.0005 mole) of Benzoyl chloride was added dropwise with constant stirring. The mixture was refluxed for 8 hrs and cooled. The separated solid was recrystallised from ethanol to give IVd, 0.102 g., (70%), M.P. 115°C.

N-(N-Phenylcarbomylamino propyl)-2,3-dihydro-5-methyl indole (IVe) :

To a solution of IV, 0.095 g. (0.0005 mole) in THF (10 ml), 0.0595 g. (0.0005 mole) of phenyl isocyanate was added over the period of 30 min. with stirring and kept overnight. The separated solid was filtered and recrystallised from ethanol to give IVe 0.110 g. (75%), M.P. 52°C.

N-(N-Phenylthiocarbamylamino propyl)-2,3-dihydro-5-methyl indole (IVf) :

To a solution of IV, 0.095 g. (0.0005 mole) in THF (10 ml), 0.0685 g. (0.0005 mole) of phenyl thiocyanate was added and stirred magnetically for 24 hrs. and kept overnight. The separated solid was filtered and recrystallised from ethanol to give IVf 0.093 g. (60%), M.P. above 320°C.

(N-(N-p-Dimethylaminobenzilideneamino propyl)-2,3-dihydro-5-methyl indole (IVg)

A mixture of compound IV, 0.095 g. (0.0005 mole), p-dimethyl aminobenzaldehyde 0.0745 g. (0.0005 mole) in THF (10 ml) was stirred and refluxed for 6 hrs. on water bath, then the solvent was removed under reduced pressure and cooled. The solid formed was recrystallised from ethanol to give IVg 0.115 g. (75%), M.P. 65^{o}C.

N-(N-p-Hydroxybenzilideneamino propyl)-2,3-dihydro-5-methyl indole (IVh) :

The mixture of compound IV, 0.095 g. (0.0005 mole) and p-hydroxy benzaldehyde 0.062 g. (0.0005 mole) in 20 ml of ethanol in a flat bottom flask fitted with reflux condenser was heated on water bath for about 8 hrs. at 80^{o}C, cooled, the solvent was removed under reduced pressure. The separated solid was recrystallised from ethanol to give IVh 0.105 g. (72%) M.P. 105^{o}C.

N-(N-p-Methoxybenzilideneamino propyl)-2,3-dihydro-5-methyl indole (IVi) :

In two necked flask fitted with reflux condenser the compound IV 0.095 g. (0.0005 mole) and 0.068 g. (0.0005 mole) of p-methoxy benzaldehyde in 10 ml of methanol was stirred magnetically and heated on water bath for 6 hrs and cooled. The solid formed was recrystallised from ethanol to give IVi 0.100 g., (65%) M.P. 95^{o}C.

N-(N-Cinnamilideneamino propyl)-2,3-dihydro-5-methyl indole (IVj) :

The mixture of IV 0.095 g. (0.0005 mole) and 0.066 g. (0.0005 mole) cinnamaldehyde in 10 ml methanol was refluxed for 5 hrs in the presence of few drops of acetic acid. On cooling the solid obtained was recrystallised from ethanol to give IVj 0.083 g. (55%) M.P. above 320^{o}C.

N-(N-2-Methylcyclohexilideneamino propyl)-2,3-dihydro-5-methyl indole (IVk):

The mixture of IV 0.095 g. (0.0005 mole) and 2-methyl cyclohexanone 0.0555 g. (0.0005 mole) in 15 ml methanol was refluxed for 8 hrs. in the presence of few drops of acetic acid. On ice cooling the solid formed was filtered and recrystallised from ethanol to give IVk 0.085 g. (60%), M.P. 140°C.

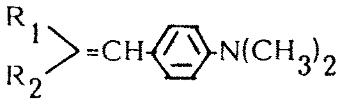
N-(N-Carboethoxymethylami no propyl)-2,3-dihydro-5-methyl indole (IVl) :

In a three necked flask fitted weith reflux condenser the mixture of IV 0.095 g. (0.0005 mole), ethyl bromoacetate 0.0835 g. (0.0005 mole) and 1.5 g. an hydrous K_2CO_3 was refluxed for 6 hrs and filtered while hot to remove K_2CO_3. The hot liquid on cooling gave solid which when recrystallised gave IV' 0.096 g. (70%), M.P. 125°C.

N(N-Cyclohexelideneamino propyl)-2,3-dihydro-5-methyl indole (IVm) :

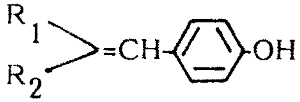
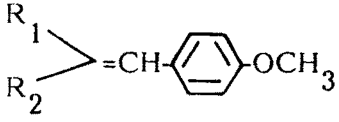
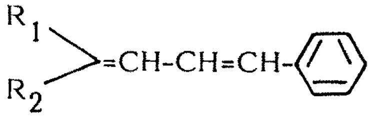
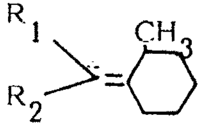
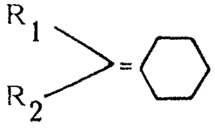
The mixture of IV, 0.095 g, (0.0005 mole) and cyclohexanone 0.049 g (0.0005 mole) in 10 ml methanol was refluxed for 8 hrs. in the presence of few drops of acetic acid. On cooling the solid obtained was recrystallised from ethanol to yield IVm 0.067 g. (50%), M.P. 90°C.

Table - 2 : CHARACTERISATION DATA OF N-PROPYLAMINO-2,3-DIHYDRO-5-METHYL INDOLE DERIVATIVES

Compd.	R_1	R_2	Yield	M.P. °C	Molecular formula	Elementa Analysis found (%) / (calcd.) % C	H	N
IV	H	H	50	111	$C_{12}H_{18}N_2$	75.5 (75.7)	9.2 (9.4)	14.2 (14.7)
IV_a	$-CH_3$	$-CH_3$	50	55	$C_{14}H_{22}N_2$	77.16 (77.06)	10.19 (10.09)	12.79 (12.84)
IV_b	H	$-CH_2-CH_2-CH_3$	60	220	$C_{15}H_{24}N_2$	77.52 (77.58)	10.30 (10.34)	12.01 (12.07)
IV_c	H	$-COCH_3$	68	99	$C_{14}H_{20}ON_2$	72.35 (72.41)	8.60 (8.62)	12.00 (12.07)
IV_d	H	-COPh	70	115	$C_{19}H_{22}ON_2$	77.50 (77.55)	7.45 (7.48)	9.37 (9.52)
IV_e	H	-CONHPh	75	52	$C_{19}H_{23}ON_2$	77.29 (77.28)	7.80 (7.79(	9.40 (9.48)
IV_f	H	-CSNHPh	60	above 320	$C_{19}H_{23}SN_2$	73.28 (73.31)	7.35 (7.39)	9.10 (9.00)
IV_g			75	65	$C_{21}H_{27}N_2$	82.05 (82.08)	8.75 (8.79)	9.10 (9.12)

contd......

Table - 2 (contd..)

Compd.	R_1	R_2	Yield	M.P. °C	Molecular formula	Elementa Analysis found (%) / (calcd.) % C	H	N
IV_h			72	80	$C_{19}H_{22}N_2O$	77.50 (77.57)	7.43 (7.48)	9.49 (9.52)
IV_i			65	95	$C_{20}H_{24}ON_2$	77.89 (77.92)	7.80 (7.79)	9.01 (9.09)
IV_j			55	above 320	$C_{21}H_{24}N_2$	82.90 (82.89)	7.91 (7.89)	9.16 (9.21)
IV_k			60	140	$C_{19}H_{28}N_2$	80.24 (80.28)	9.87 (9.85)	9.80 (9.85)
IV_l	H	$-CH_2COOC_2H_5$	70	125	$C_{16}H_{24}N_2O_2$	69.57 (69.56)	8.64 (8.69)	10.16 (10.15)
IV_m			50	90	$C_{18}H_{26}N_2$	79.56 (80.00)	9.60 (9.62)	10.35 (10.37)

The structures of these compounds were confirmed by IR and PMR spectral studies in addition to elemental analysis.

Part-III

SYNTHESIS OF N-PROPYLAMINO-2-METHYL-3-PHENYL INDOLE

The synthesis of some new indole derivatives has been reported. The strategy employed for the synthesis of desired compounds involved the reaction of aniline with acrylonitrile in acetic acid to form corresponding N-Cyanoethyl aniline (II') followed by the reaction with substituted phenacyl bromide to give N-cyanoethylamino-2-methyl-3-phenyl indole(III'). This when reduced by lithium aluminium hydride formed N-propylamino-2-methyl-3-phenyl indole (IV'). Some derivatives of this compound were prepared.

[SCHEME - 3]

Synthesis of N-Cyanoethyl aniline (II') :

A mixture of aniline 46.5 g. (0.5 mol) and acrylonitrile 26.5 g. (0.5 mole) and acetic acid (2.5 ml) was heated under reflux on water bath for 4 hrs., cooled. The dark reaction mixture obtained was distilled under reduced pressure to remove unreacted aniline. On cooling the separated solid which when recrystallised gave(II') 50 g. (67.57%), M.P. 50°C.

Found : C, 72.90; H, 6.712; N, 18.89 ; $C_9H_{10}N_2$ requires : C, 72.96; H, 6.756; N, 18.92 %).

UV (ethanol) λmax : 310 nm Fig. 17.

IR (Nujol) νmax : 3360 cm^{-1} (NH), 2250 (-C $\equiv$ N), 1620 cm^{-1} ($>C = C<$);

NMR (CCl_4) δ ppm : 2.5 (2H, s, $-CH_2CN$), 3.64 (2H, t, $-NCH_2$), 3.8 (1H, s, -N<u>H</u>-), 6.6-7.3 (5H, m, aromatic protons) Fig. 18.

Synthesis of N-Cyanoethyl-2-methyl-3-phenyl indole (III') :

To a solution of (II) 29.6 g. (0.2 mole) in 50 ml of alcohol and α-Benzoyl ethyl bromide 10 g. (0.09 mole) few drops of triethylamine were added and the reaction mixture was heated on water bath for 24 hrs., cooled and distilled under reduced pressure to remove excess of alcohol. The residue was further heated under reflux with P_2O_5 in dry xylene for 8 hrs. The hot solution was filtered and the xylene was removed under reduced pressure The solid obtained was recrystallised from alcohol to give III', 20 g. (40%), M.P. 250°C.

Found C, 65.92; H, 6.101; N, 10.73, $C_{18}H_{16}N_2$ requires : C, 66.00; H, 6.153; N, 10.76 %)

UV (ethanol) λmax : 280 nm;

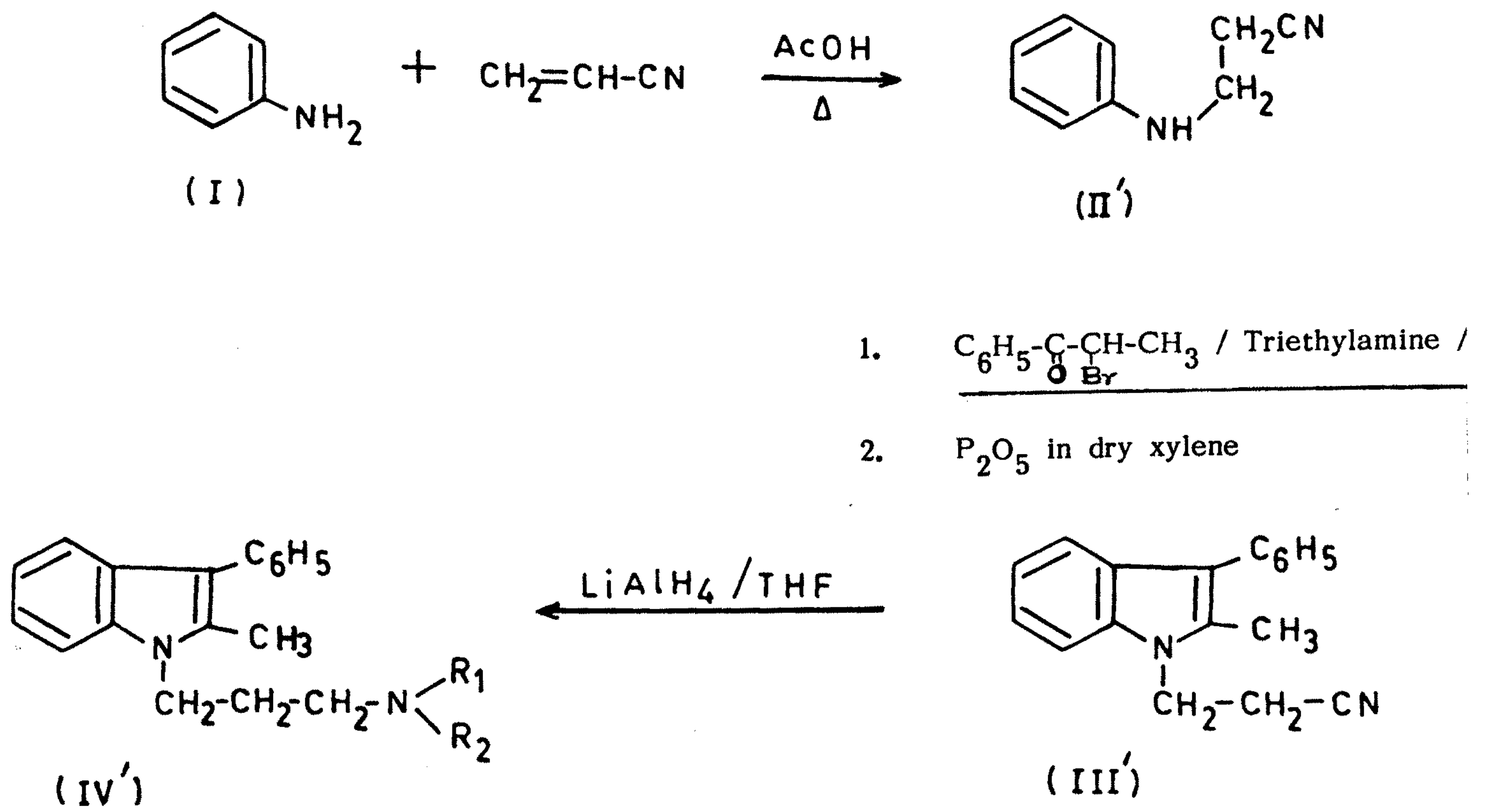
IR (Nujol) νmax : 3000 (C-H); 2250 ($C \equiv N$); 1600-1620 cm^{-1} ($>C = C<$)

NMR (TFA) δ ppm : 2.5 (2H, t, unresolved, $-CH_2CN$), 3.1 (2H, t, unresolved, $-N-CH_2$), 7.3 - 7.8 (4H, m, aromatic protons).

Synthesis of N-propylamino-2-methyl-3-phenyl indole (IV') :

To a solution of 7.0 g. (0.2 mole) of $LiAlH_4$ in 30 ml of THF, a solution of 52 g. (0.2 mole) of compound(III') in 30 ml of THF was added, and stirred magnetically for 1.5 hrs. When the reaction was complete the ice was added to decompose excess of $LiAlH_4$ and ether layer was washed with 50 ml sodium tartarate solution. Ether on evaporation gave solid which when recrystallised from alcohol gave (IV'), 26.5 g. (50%), M.P.40°C (Found : C, 81.79; H, 7.570; N, 10.58. $C_{18}H_{20}N_2$, requires : C, 81.86; H, 7.525; N, 10.60 %).

SCHEME - 3



(V′) $R_1 = H$, $R_2 = -CONHPh$

(VI′) $R_1 = R_2 = CH_3$

(VII′) $R_1 = H$, $R_2 = -CH_2-CH_2-CH_3$

UV (ethanol) λ max : 280 nm;

IR (Nujol) ν max : 3200-3300 ($-NH_2$); 1600 cm^{-1} (>C = C<);

(NMR (TFA) δ ppm : 0.85 (2H, s br, N$\underline{H}$), 1.3 (2H, m, $-C\underline{H}_2-$); 1.75 (2H, t, $-CH_2C\underline{H}_2-CN$), 2.3 (3H, s, C_2-CH_3), 3.6 (2H, t, $-NCH_2-$); 7 - 7.5 (4H, m, aromatic protons) Fig. 19.

Synthesis of urethane derivative of N-propylamino-2-methyl-3-phenyl Indole (V') :

To a solution of (IV') 0.132 g. (0.0005 mole) in THF (10 ml.); 0.059 g. (0.005 mole.) of phenyl isocyanate was added and stirred magnetically for 30 minutes and kept overnight. The separated solid was filtered and recrystallized to give (V'), 0.100 g. (75.75%), M.P. 214°C.

(Found : C, 84.90; H, 7.042; N, 7.925, $C_{25}H_{25}N_2O$ Requires C, 84.98; H, 7.081; N, 7.932).

Synthesis of N-(dimethylaminopropyl)-2-methyl-3-phenyl indole (VI') :

A mixture of compound (IV') 0.132 g. (0.0005 mole), methyl iodide 0.0171 g. (0.0005 mole) in THF (10 ml) and 0.2 ml KOH (5%) was refluxed for 4 hrs, cooled, the solvent was removed under reduced pressure, the solid obtained was crystallised from ethanol to furnish VI' 0.090 g. (68.17%), M.P. 120°C.

(Found : C, 82.14; H, 8.19; N, 9.57; $C_{20}H_{24}N_2$ requires : C, 82.19; H, 8.21; N, 9.59 %).

propyl

Synthesis of N-monoethylaminopropyl-2-methyl-3-phenyl indole (VII') :

A mixture of (IV') 0.132 g. (0.0005 mole) and propyl bromide 0.061 g. (0.0005 mole) in THF was refluxed in the presence of 0.5 ml of triethylamine for about 5 hrs, cooled and the solvent was removed under reduced pressure. The solid obtained was recrystallised from ethanol to yield (VII') 0.110 g. (83.33%), M.P. 80°C.

(Found : C, 82.20; H, 8.423; N, 9.134. $C_{21}H_{26}N_2$ requires : C, 82.35; H, 8.498; N, 9.152 %).

Part - IV

SYNTHESIS OF N-PROPYLAMINO-2,3-DIHYDRO INDOLE

Condensation of aromatic amines with acrylonitrile has resulted in the formation of N-Cyanoethylaniline (II'). Reaction of II' with chloroacetyl chloride in benzene in the presence of triethylamine gave N-cyanoethyl-2-oxo-indole (III"), which when reduced by $LiAlH_4$ in THF gave N-propylamino indole (IV"). SCHEME - 4

The structures of these compounds have been confirmed by IR and NMR sdpectral studies.

Experimental procedure

Synthesis of N-cyanoethyl aniline (II)

The procedure is described in Chapter-III.

Synthesis of N-cyanoethyl-2-oxo-indole (III") :

A mixture of N-cynoethylaniline 10.22 g. (0.07 mole)and chloroacetyl chloride, 7.84 g. (0.07 mole) in benzene (40 ml) was refluxed on water bath for 5 hrs in the presence of triethylamine (0.5 ml), cooled, the solvent was removed under reduced pressure. To this solid mass anhydrous $AlCl_3$ (20 g.) was added small lot at a time and the content was heated on oil bath at 120°C for 1.5 hrs., cooled and Lewis acid complex was decomposed by dil. HCl. The solid obtained was then extracted with ether and recrystallised from ethanol to yield. IV", 10 g. (76.8%), M.P. 50°C (found : C, 70.86, H, 5.30, N, 15.11; $C_{11}H_{10}N_2O$ requires, C, 70.96; H, 5.37; N, 15.05%).

UV (ethanol) λmax : 280 nm. Fig. 20.

IR (KBr) ν max : 2200-2250 (-C ≡ N), 1700 (>C = O), 1580-1600 (>C = C<), 1250-1300 cm^{-1} (-C-N). Fig. 21.

NMR (TFA) δ ppm : 2.65 (2H, t -$C\underline{H}_2$CN), 3.65 (2H,s, -CH_2CO-), 3.85 - 4 (2H, t, N-CH_2-) 7.2 - 7.6 (4H, m unresolved, aromatic protons). Fig. 22.

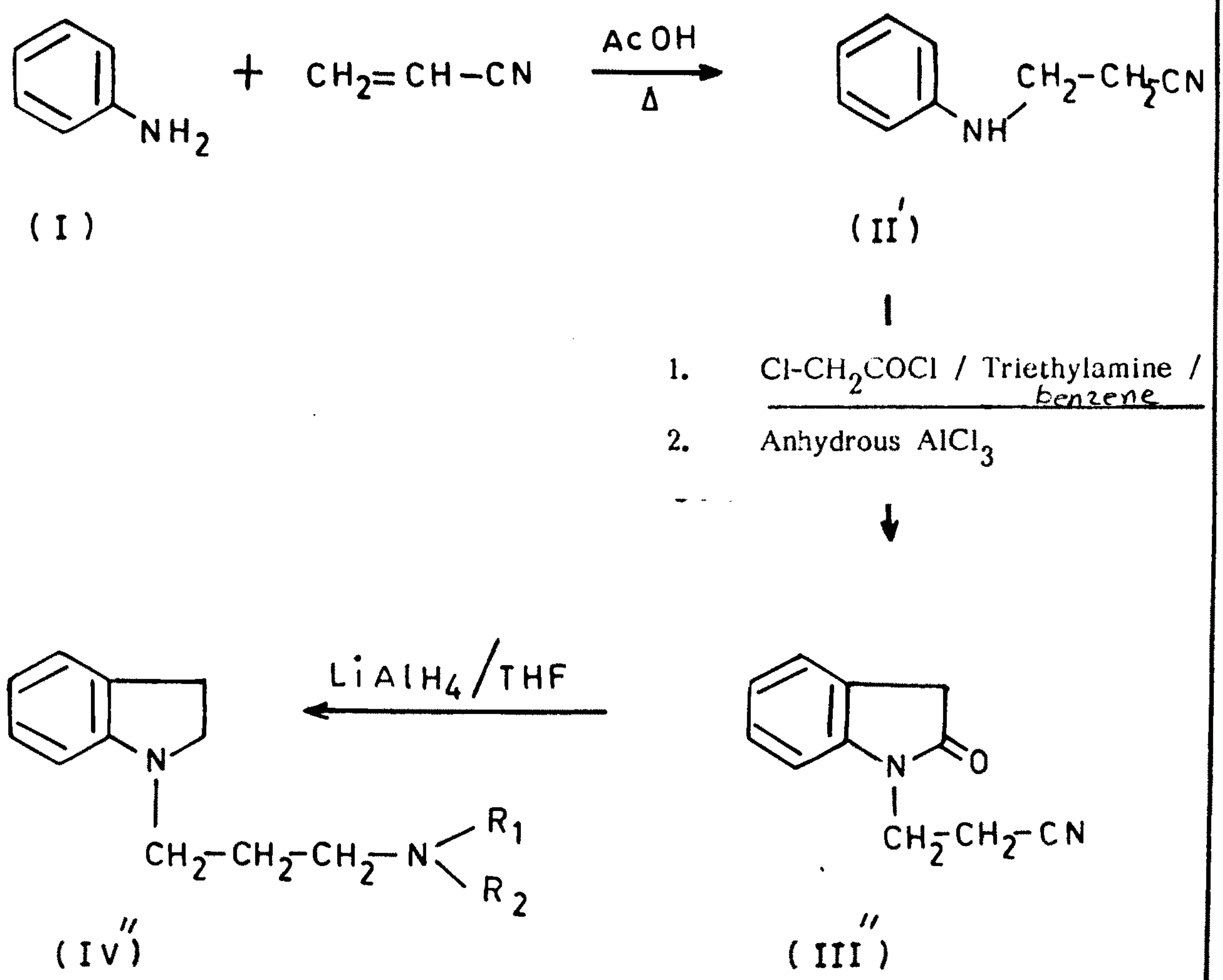
Synthesis of N-Propylamino-2,3-dihydro indole (IV") :

To a solution of 0.388 g. (0.05 mole) of $LiAlH_4$ in 30 ml of dry ether in two necked flask 9.3 g. (0.05 mole) of compound (III") in 30 ml of dry ether was added through dropping funnel over the period of 30 min. and stirred magnetically for 1.5 hrs. When the reaction had subsided ice was added to decompose excess of $LiAlH_4$ and the ether layer was washed with 40 ml of sodium tartarate solution. Ether on evaporation gave solid which when recrystallised from alcohol gave IV", 6.5 g. (73.86%) M.P. 35°C.

(Found : C, 74.80; H, 9.12; N, 15.85; $C_{11}H_{16}N_2$ requires C, 75.0; H, 9.09; N, 15.90%).

PMR (CCl_4), δ ppm : 0.85 (2H, s br, N$\underline{H}$), 1.1 - 1.3 (4H,m,CH_2), 2.2 - 2.4 (2H,m,$C\underline{H}_2$N), 3.8 - 4 (4H,t, 2xN-CH_2), 6.6 - 7 (4H,m, aromatic protons). Fig. 23.

SCHEME-4


NH$_2$
+
CH$_2$=CH−CN
AcOH
Δ
NH
CH$_2$−CH$_2$CN
(I)
(II′)
1. Cl-CH$_2$COCl / Triethylamine / benzene
2. Anhydrous AlCl$_3$
LiAlH$_4$/THF
N
O
CH$_2$−CH$_2$−CN
N
CH$_2$−CH$_2$−CH$_2$−N
R$_1$
R$_2$
(IV″)
(III″)

Synthesis of N-(N:N-Dimethylamino propyl)-2,3-dihydro indole (IV"$_a$)

A mixture of compound IV", 0.176 g. (0.001 mole) methyl iodide 0.0352 g. (0.001 mole) in THF (5 ml) and 0.2 ml (3% KOH) was refluxed for 4 hrs, cooled, the solvent was removed under reduced pressure. The solid obtained was recrystallised from ethanol to furnish IV"$_a$, 0.150 g. (73.52%). M.P. 280°C.

(Found : C, 76.24; H, 9.72; N, 13.24). $C_{13}H_{20}N_2$ requires : C, 76.47; H, 9.80; N, 13.72%).

Synthesis of N- (N-Phenylcarbamylamino propyl)-2,3-dihydro indole(IV"$_b$)

To a solution of IV" 0.176 g. (0.001 mole) in THF (10 ml), 0.0287 g. (0.001 mole) of phenyl isocyanate was added over the period of 30 min. with stirring and kept overnight. The separated solid was filtered and recrystallised from ethanol to give IV"$_b$ 0.200 g. (69.93%).

M.P. 180°C.

(Found : C, 76.80; H, 7.42; N, 9.91; $C_{18}H_{21}N_2O$ requires : C, 76.86; H, 7.47; N, 9.96%).

SPECTRAL STUDY OF INDOLE DERIVATIVES

1) UV Study[162]: UV spectrum of indole derivatives absorbs at 250-280 nm in a broad band with λmax at about 280 and has shown an outlying peak at 288 nm.

2) IR Study[163]: Indole show N-H group streching absorption in the region of 3500-3200 cm^{-1}. Indole in non-polar solvent and in dilute solution shows a sharp band at about 3495 cm^{-1} and in concentrated solution near 3400 cm^{-1}.

The amino derivatives of indoles absorb at 3400-3330 cm^{-1} and at 3330-3250 cm^{-1}. The secondary amines shows a single peak band at the 3350-3320 cm^{-1} region. The N-H bending of the primary amines is observed in the 1650-1580 cm^{-1} region of the spectrum. The $-C \equiv N$, $C = N$ and $C - N$ streching bands are observed in the 2250, 1580-1620, 1250-1360 cm^{-1} region of the spectrum.

3) NMR Study[164] : In the indole N-H absorbs from δ , 8.5 (τ = 1.5) to δ , 5.0 (τ = 5.0). The effect on the absorption position of concentration, solvent and temperature is generally small than in the case of amines. In indole the coupling of the -NH proton to the adjacent proton is observed like amides and pyrroles. C_2 and C_3 protons are observed at δ , 6.5(τ-3.5) and δ, 6.3 (τ = 3.7) while aromatic protons in between δ , 7-8 ppm in the NMR spectrum.

4) Mass spectral study : Earlier studies[165-167] of various indole derivatives under electron impact of mass spectrometry invariably lead to the fragmentation of the side chain initially followed by the fragmentation of heterocyclic ring.

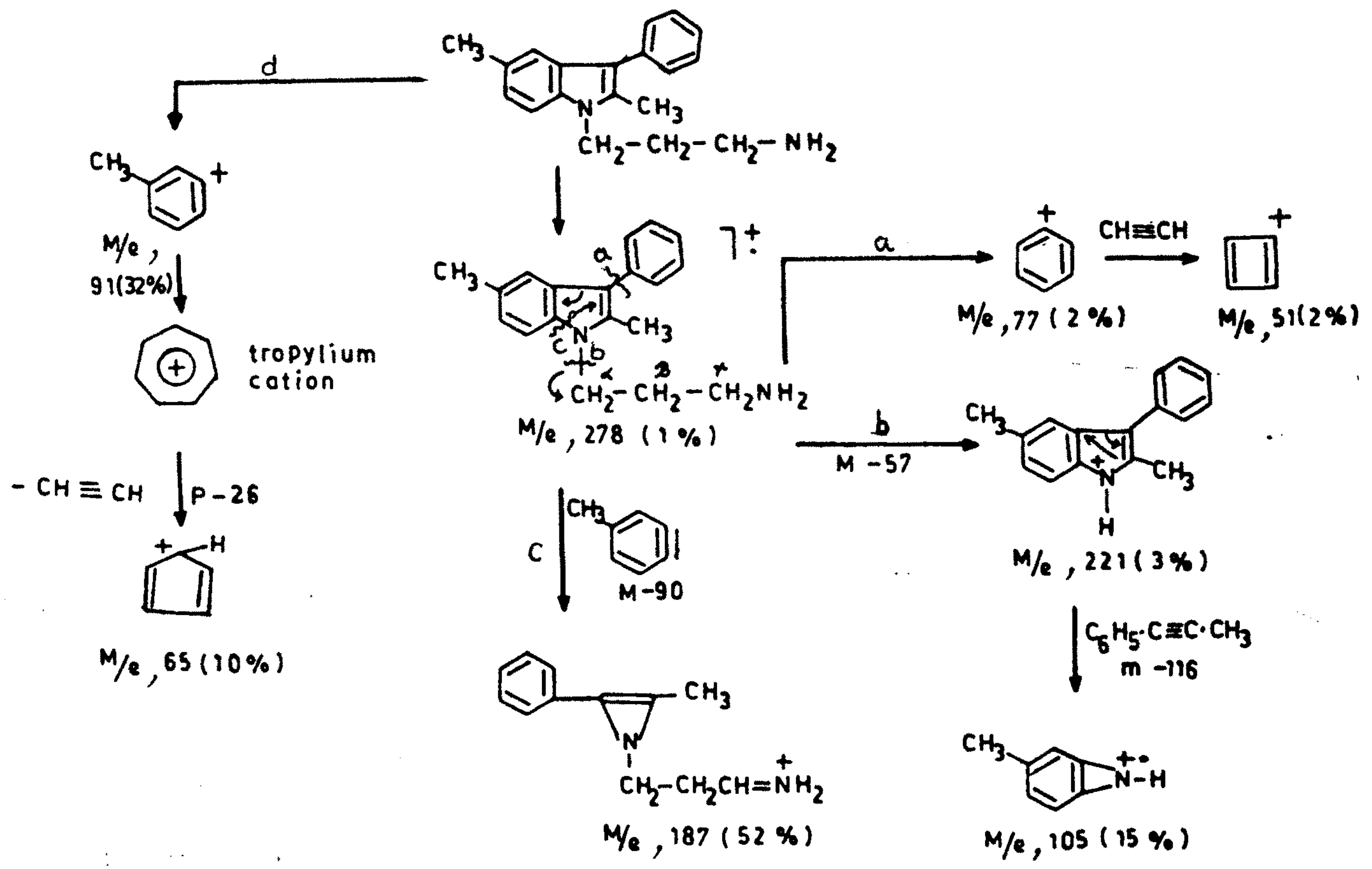
Mass spectrum discussion :

The behaviour of N-propyl amino-2,5 dimethyl 3-phenyl indole (4) and N-propylamino-2,3-dihydro- indole (IV) under electron impact was studied. On this basis the structure of these compounds were confirmed.

The mass spectra of the compound 4 & IV (70 eV, intet temp. 200^{o}C) with the E_1-MS computor system, the results obtained are depicted in Fig.9 and Fig. 16 respectively. The probable fragmentation pattern of the compound 4 & IV are given in the Scheme 5 & 6 accordingly.

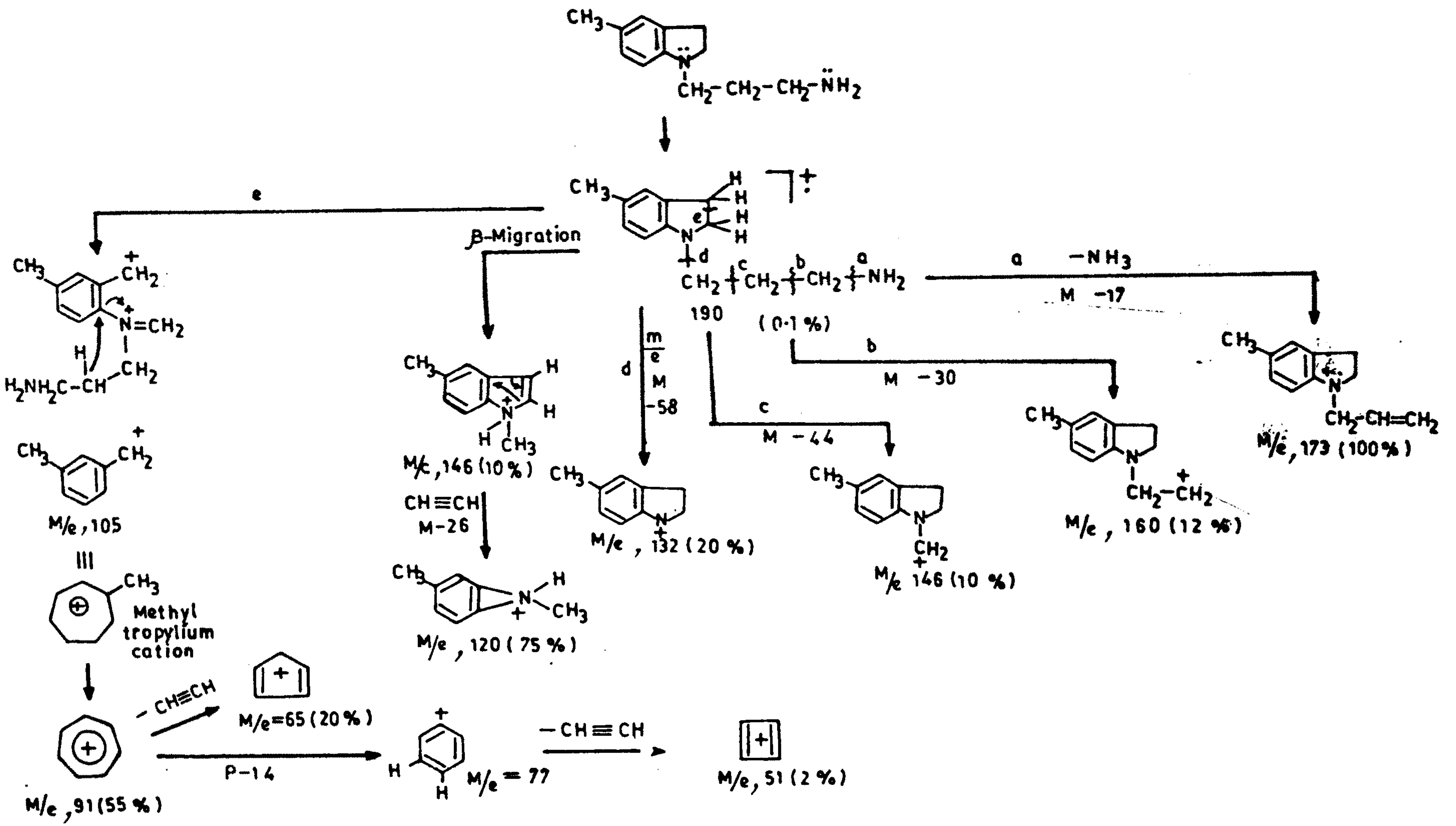
SCHEME – 5 (For Fig.9)

PROBABLE FRAGAMENTATION PATTERN OF N-PROPYLAMINO, 2,5-DIMETHYL, 3-PHENYL INDOLE .



SCHEME–6 (For Fig.16)

PROBABLE FRAGMENTATION PATTERN OF 2,3–DIHYDRO, N–PROPYLAMINO INDOLE.



PMR SPECTRUM OF α — BENZOYL ETHYLBROMIDE .

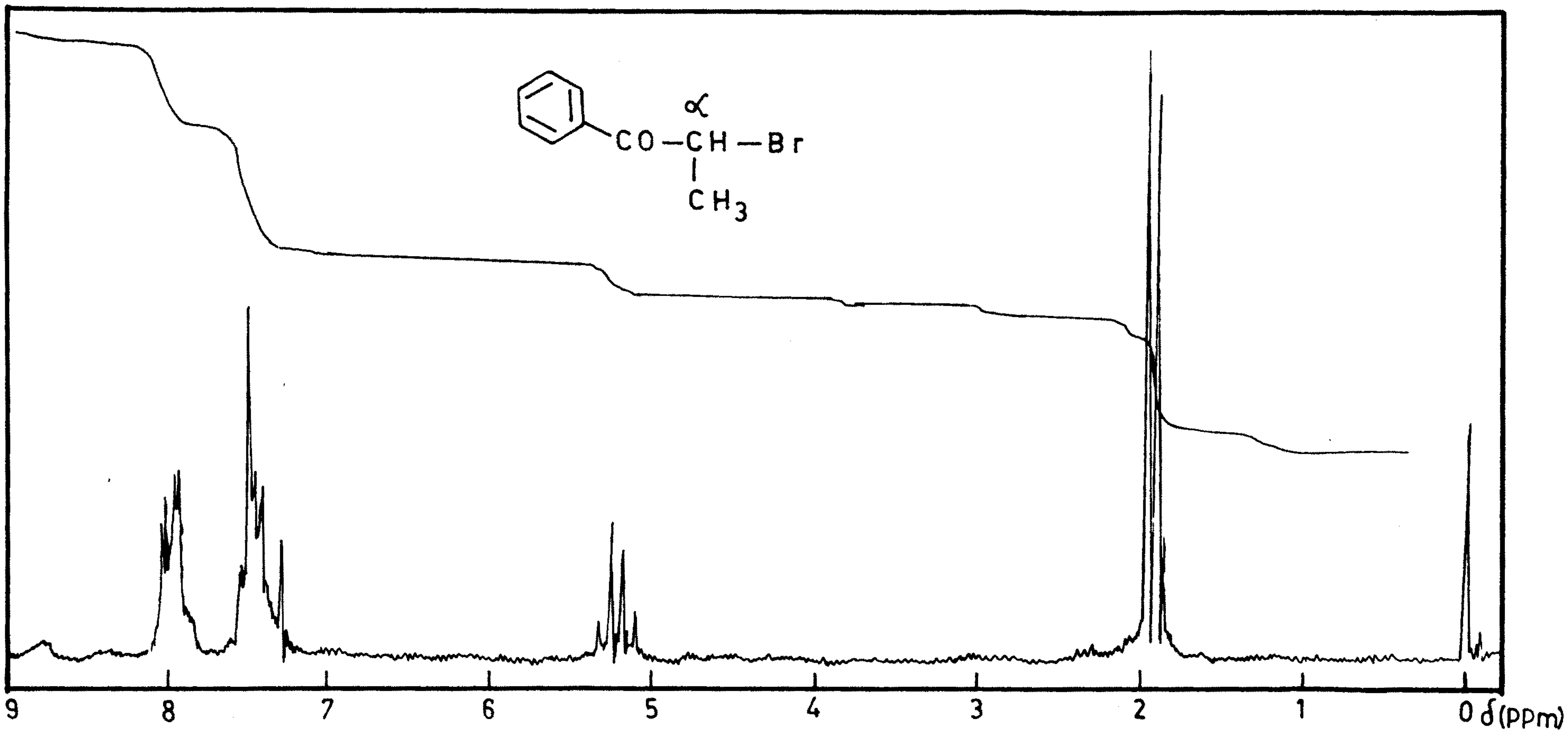


FIG. 1

U V SPECTRUM OF N-CYNOETHYL P-TOLUIDINE.

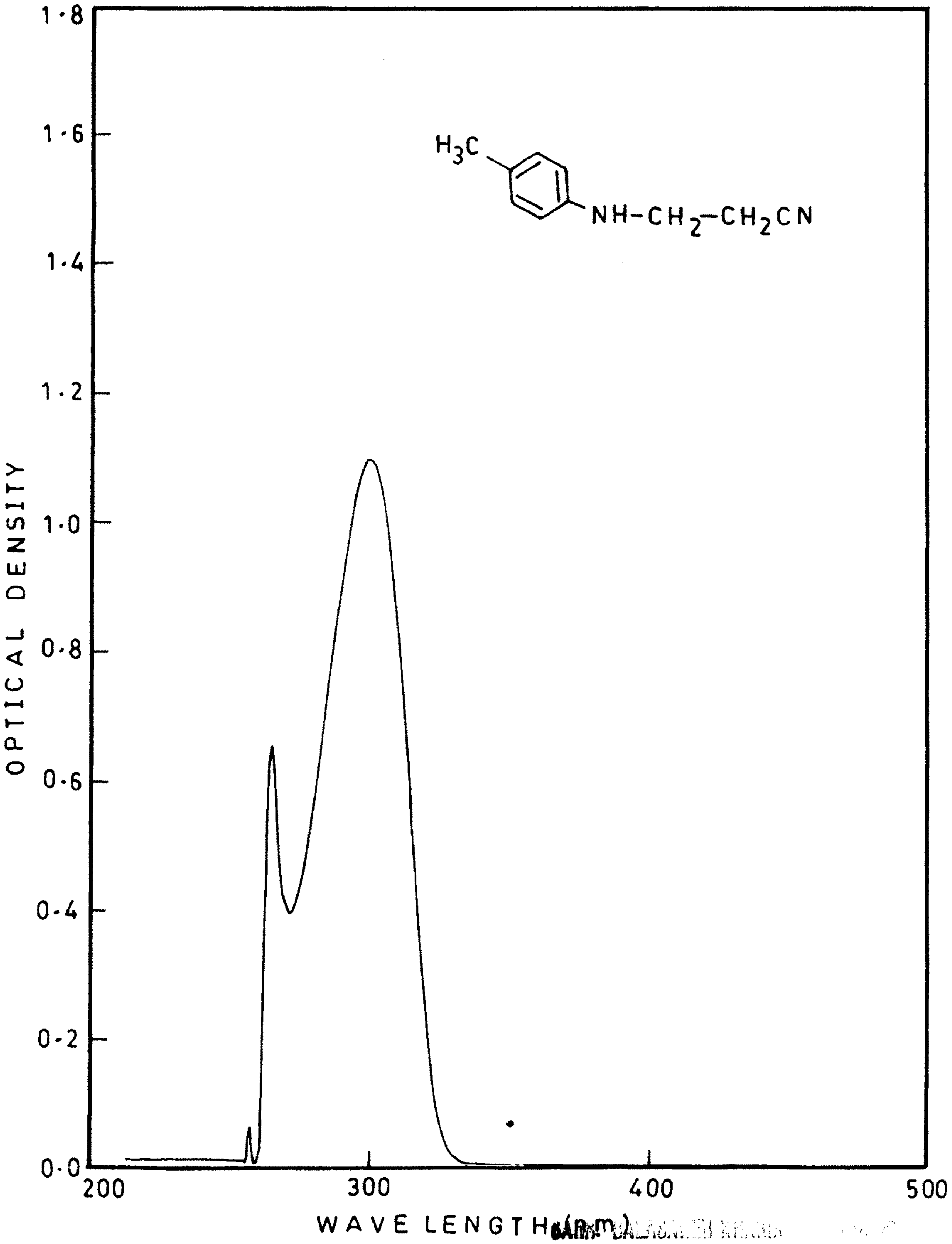


FIG. 2

I R SPECTRUM OF N-CYNOETHYL, P-TOLUIDINE.

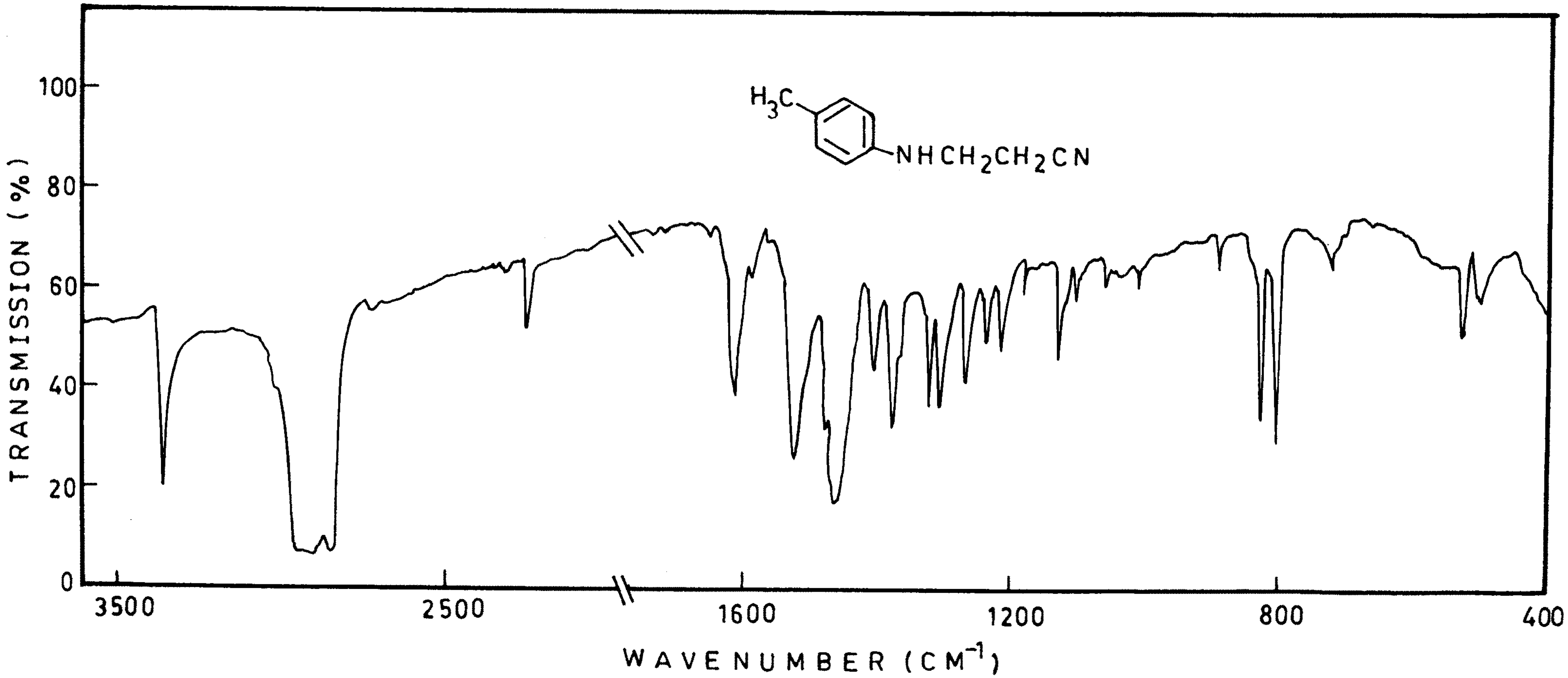


FIG. 3

PMR SPECTRUM OF N—CYANOETHYL P-TOLUIDINE .

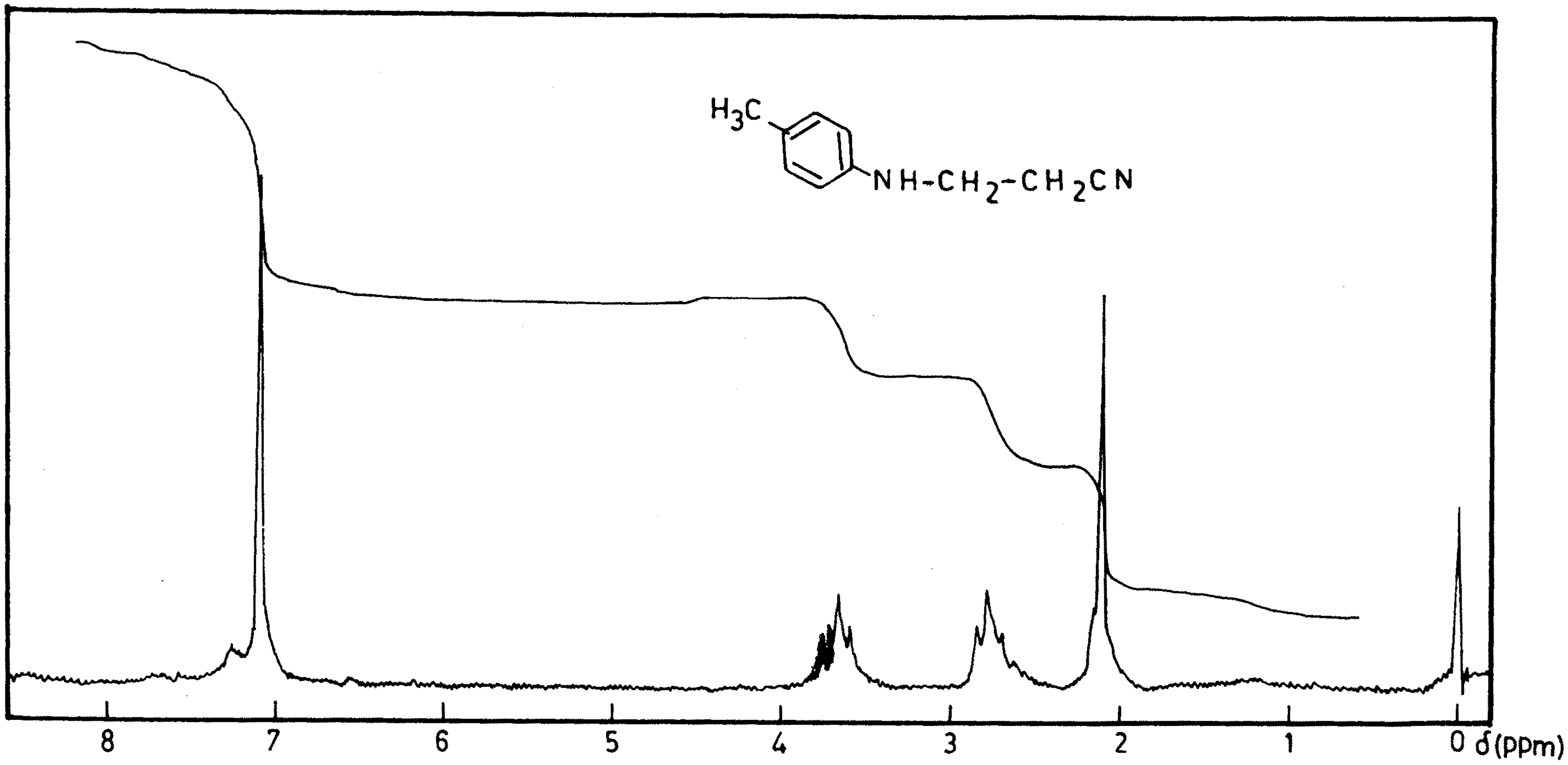


FIG. 4

U V SPECTRUM OF N-CYNOETHYL, 2,5-DIMETHYL ,- 3—PHENYL INDOLE .

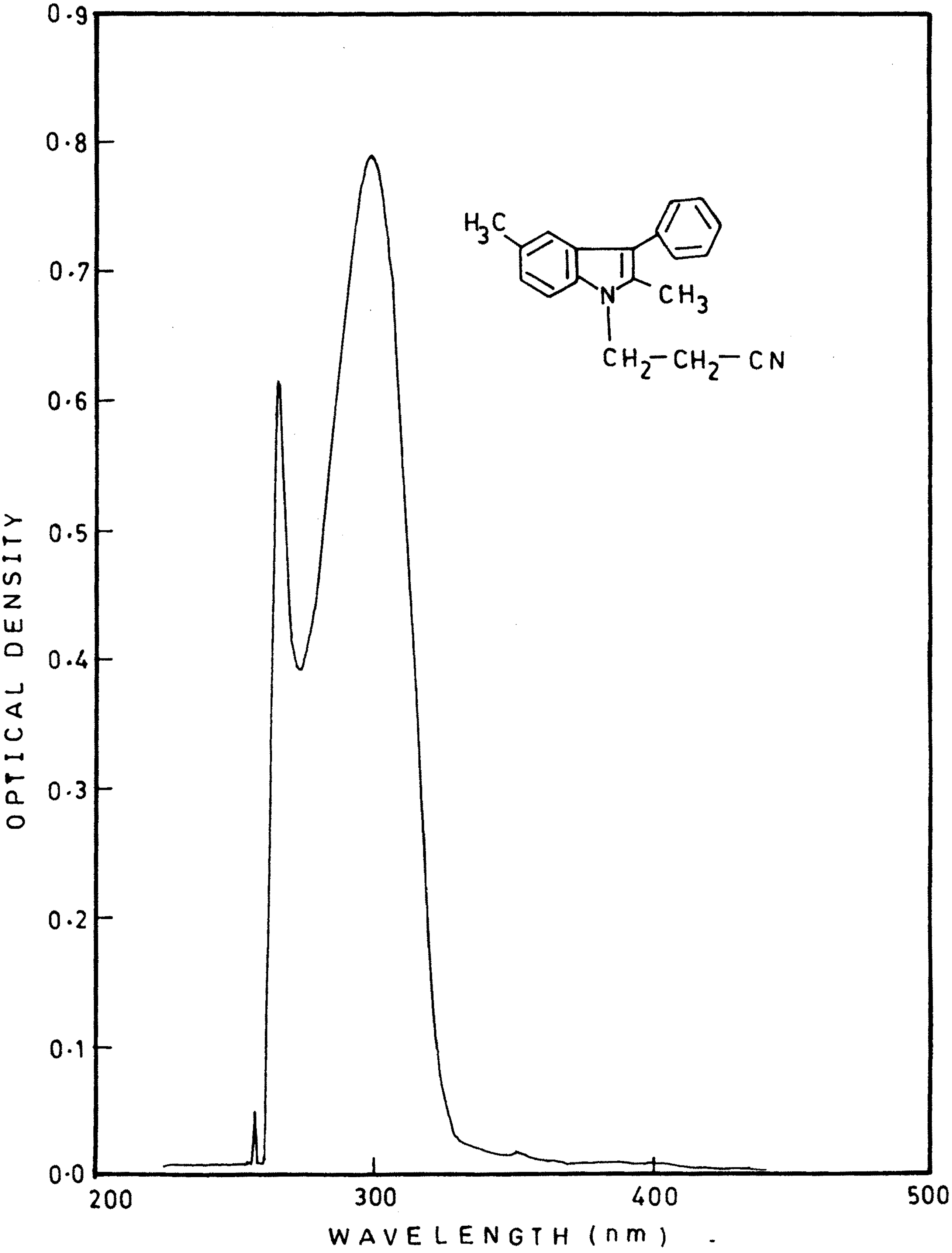


FIG. 5

PMR SPECTRUM OF N-CYNOETHYL, 2,5-DIMETHYL , 2 PHENYL INDOLE .

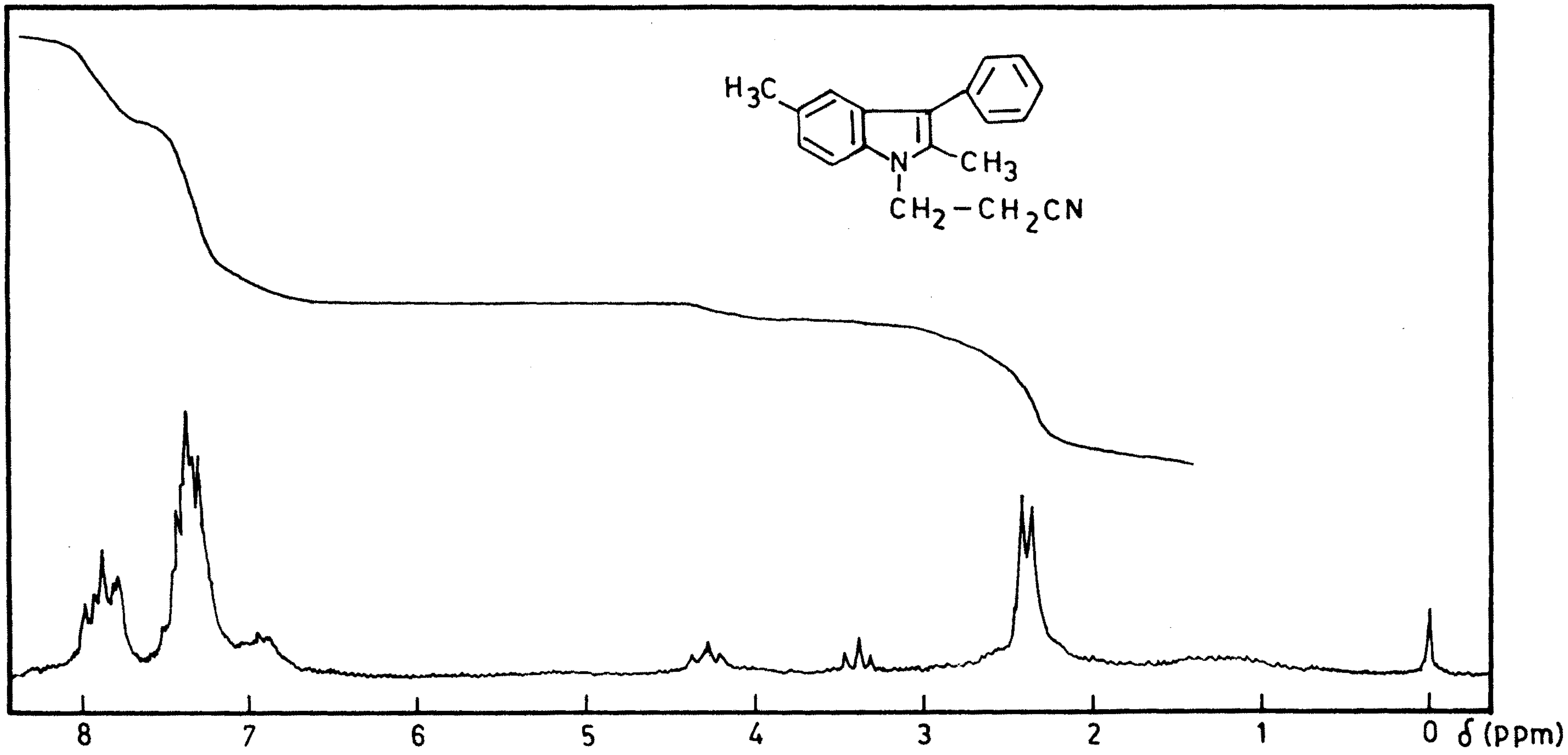


FIG. 6

IR SPECTRUM OF N-CYNOPROPYLAMINO, 2,5-DIMETHYL, 3-PHENYL INDOLE.

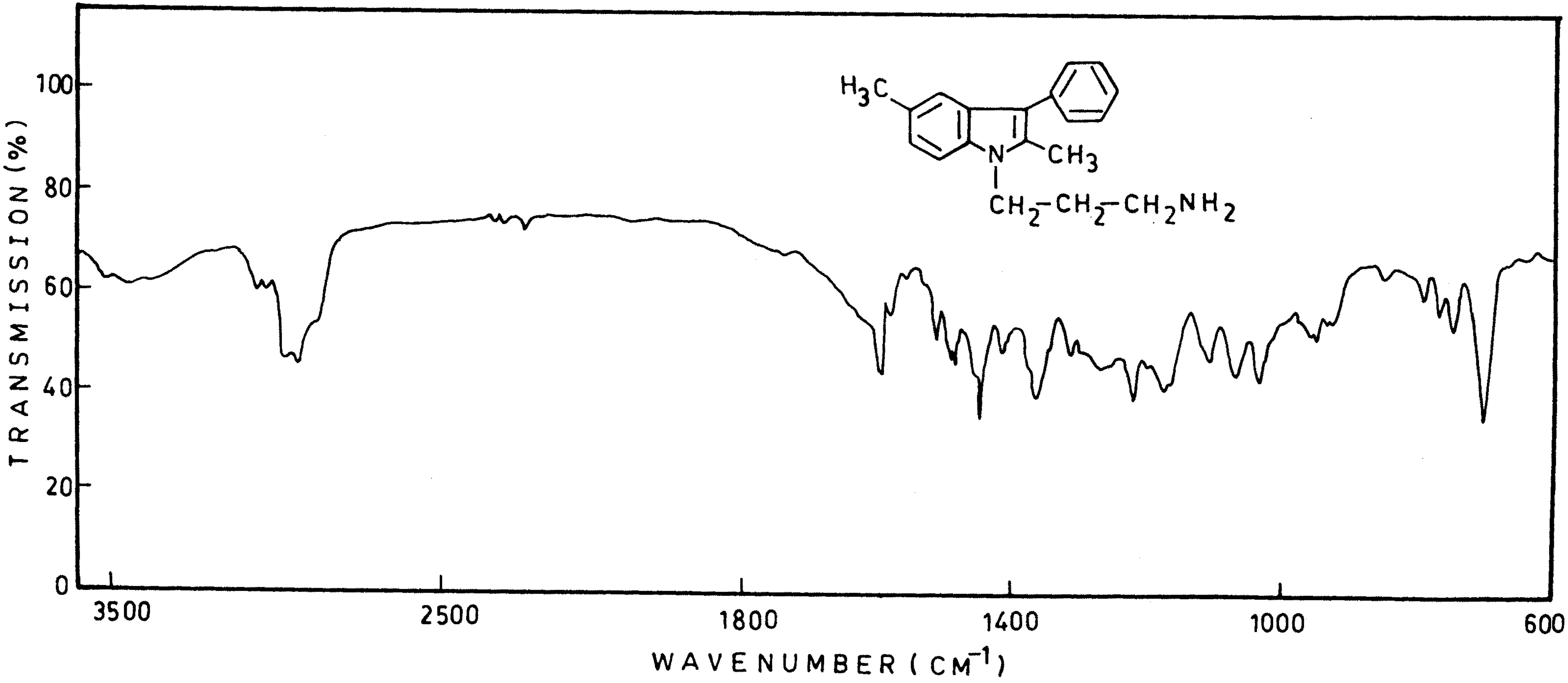


FIG. 7

PMR SPECTRUM OF N-PROPYLAMINO, 2,5-DIMETHYL, 3-PHENYL INDOLE .

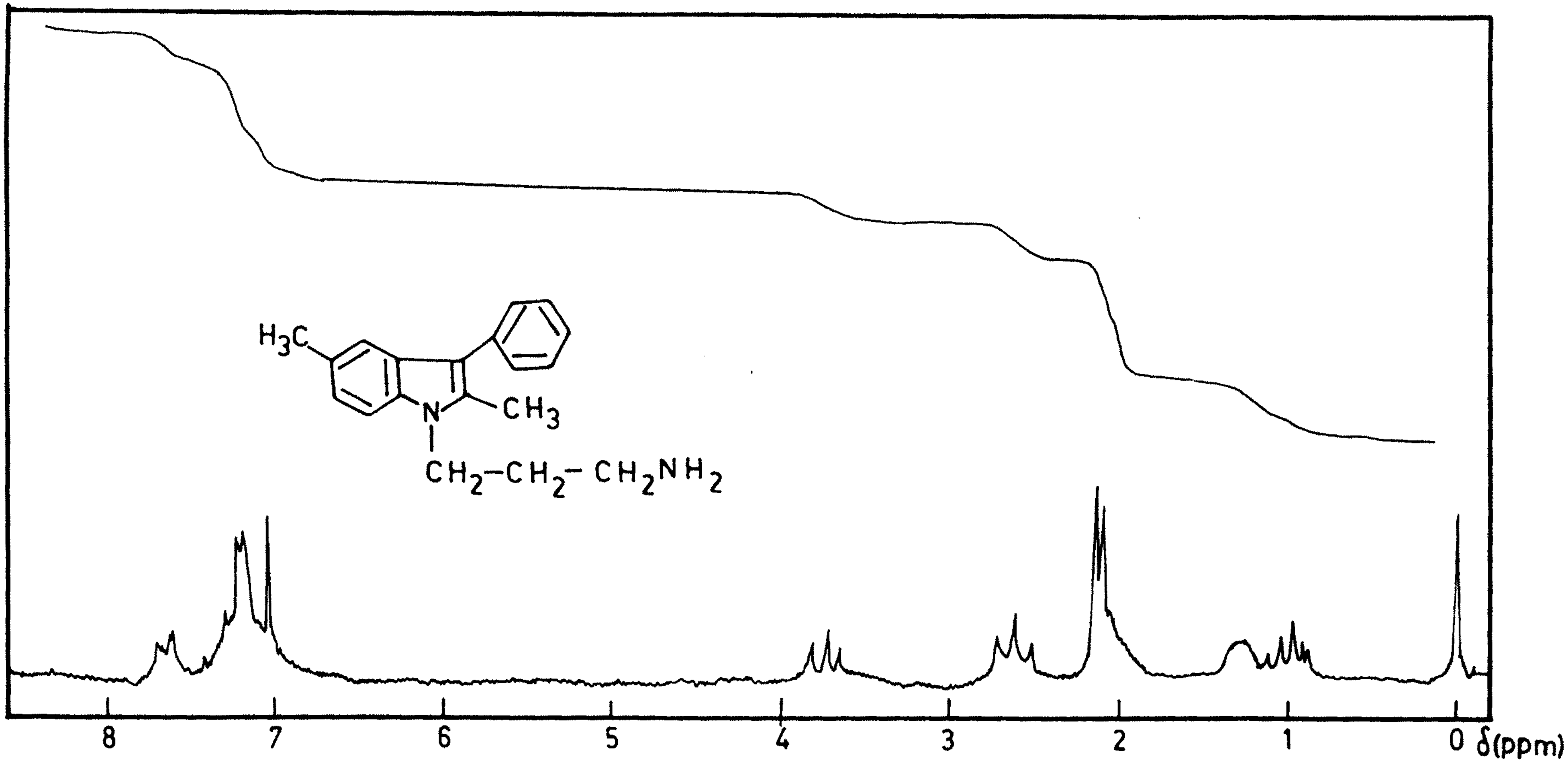


FIG. 8

MASS SPECTRUM OF N-PROPYLAMINO, 2,5-DIMETHYL, 3-PHENYL INDOLE.

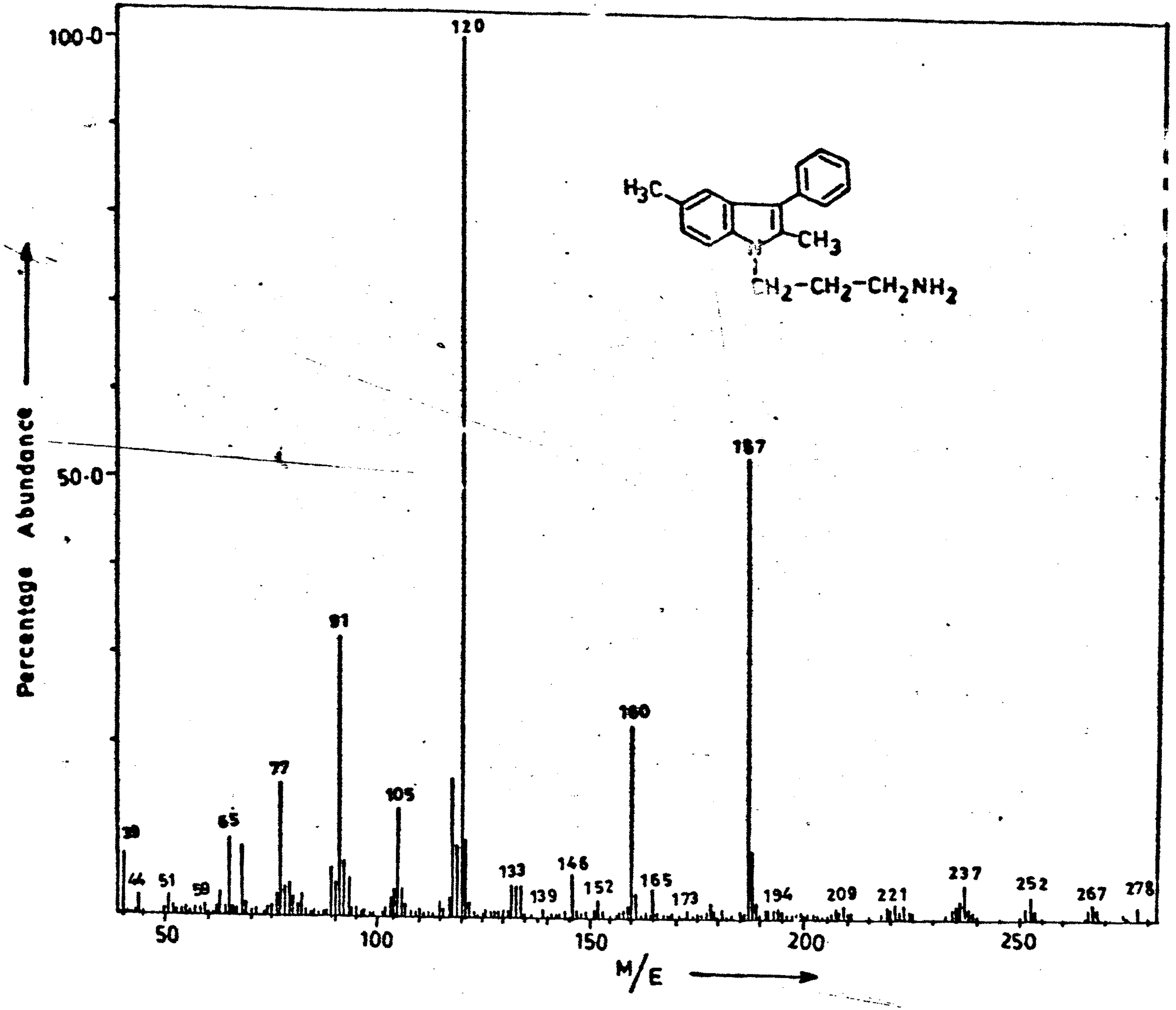


FIG. 9

PMR SPECTRUM OF URETHANE DERIVATIVE OF N-PROPYLAMINO, 2,5-DIMETHYL, 3-PHENYL INDOLE .(4c)

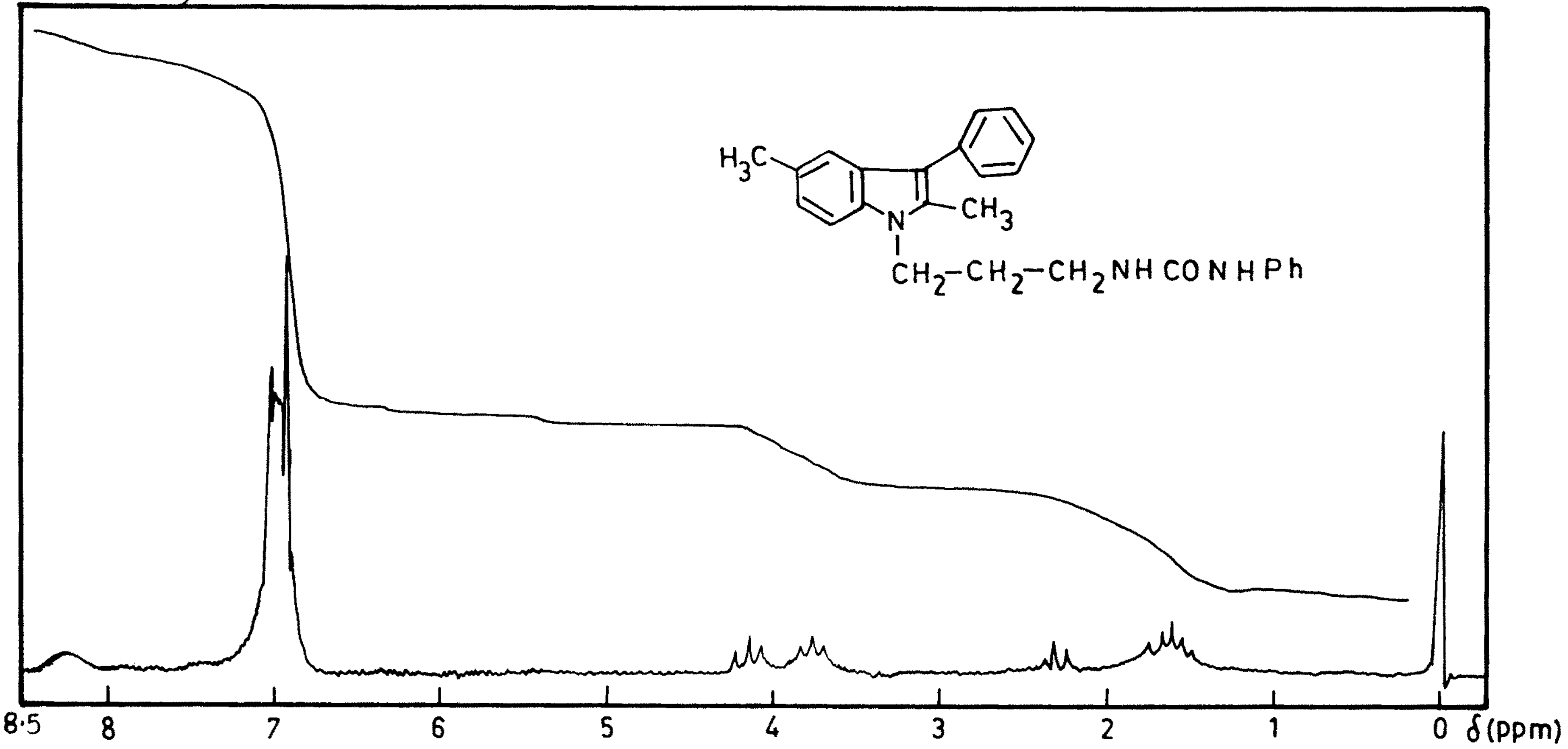


FIG. 10

PMR SPECTRUM OF SCHIFF'S BASE OF N-PROPYL AMINO 2,5 DIMETHYL, 3-PHENYL INDOLE WITH P-DIMETHYLAMINO BENZALDEHYDE · (4g)

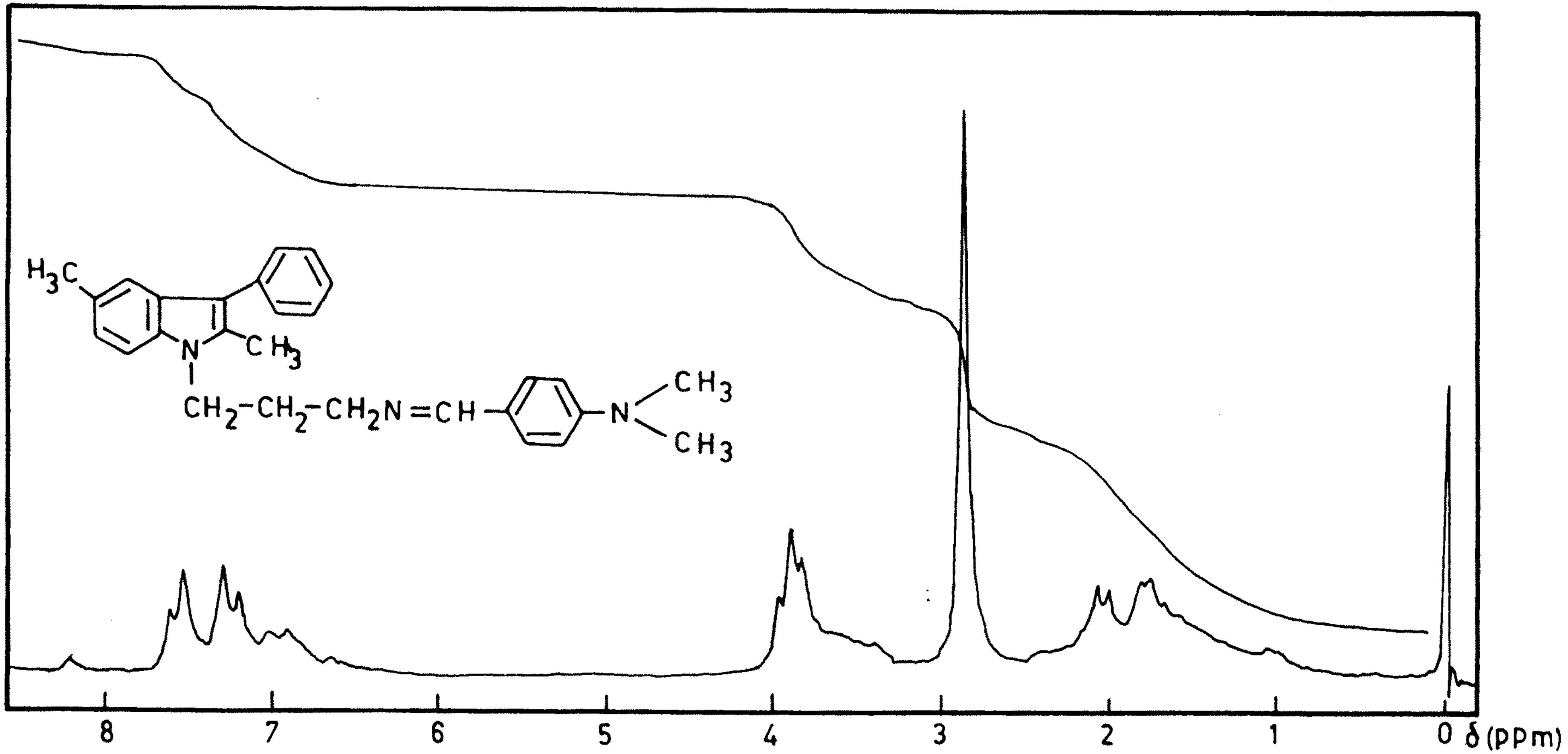


FIG. 11

U V SPECTRUM OF N-CYNOETHYL, 2-OXO, 5-METHYL INDOLE.

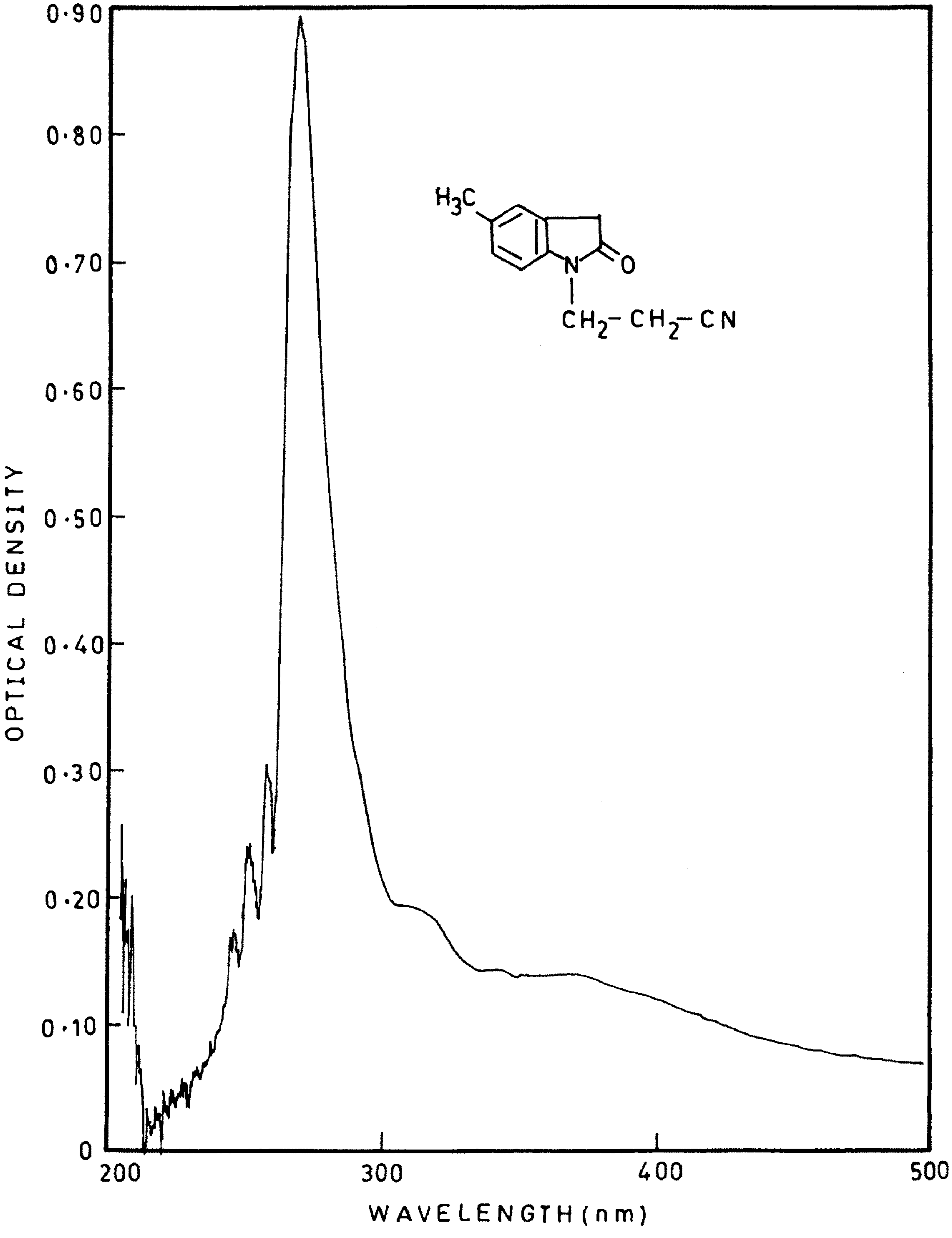
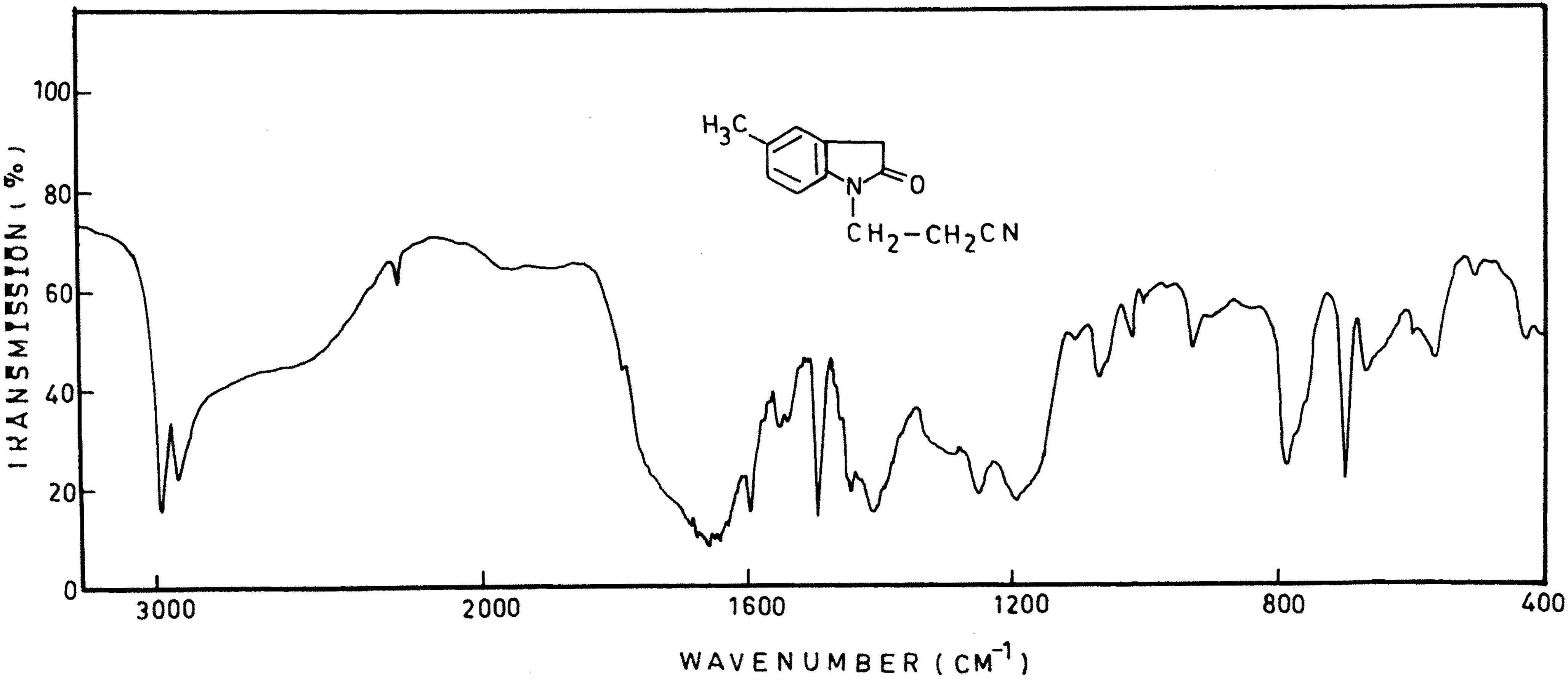


FIG. 12



IR SPECTRUM OF N-CYNOETHYL, 2-OXO-5-METHYL INDOLE .

FIG. 13

PMR SPECTRUM OF N-CYNOETHYL, 2-OXO-5-METHYL INDOLE

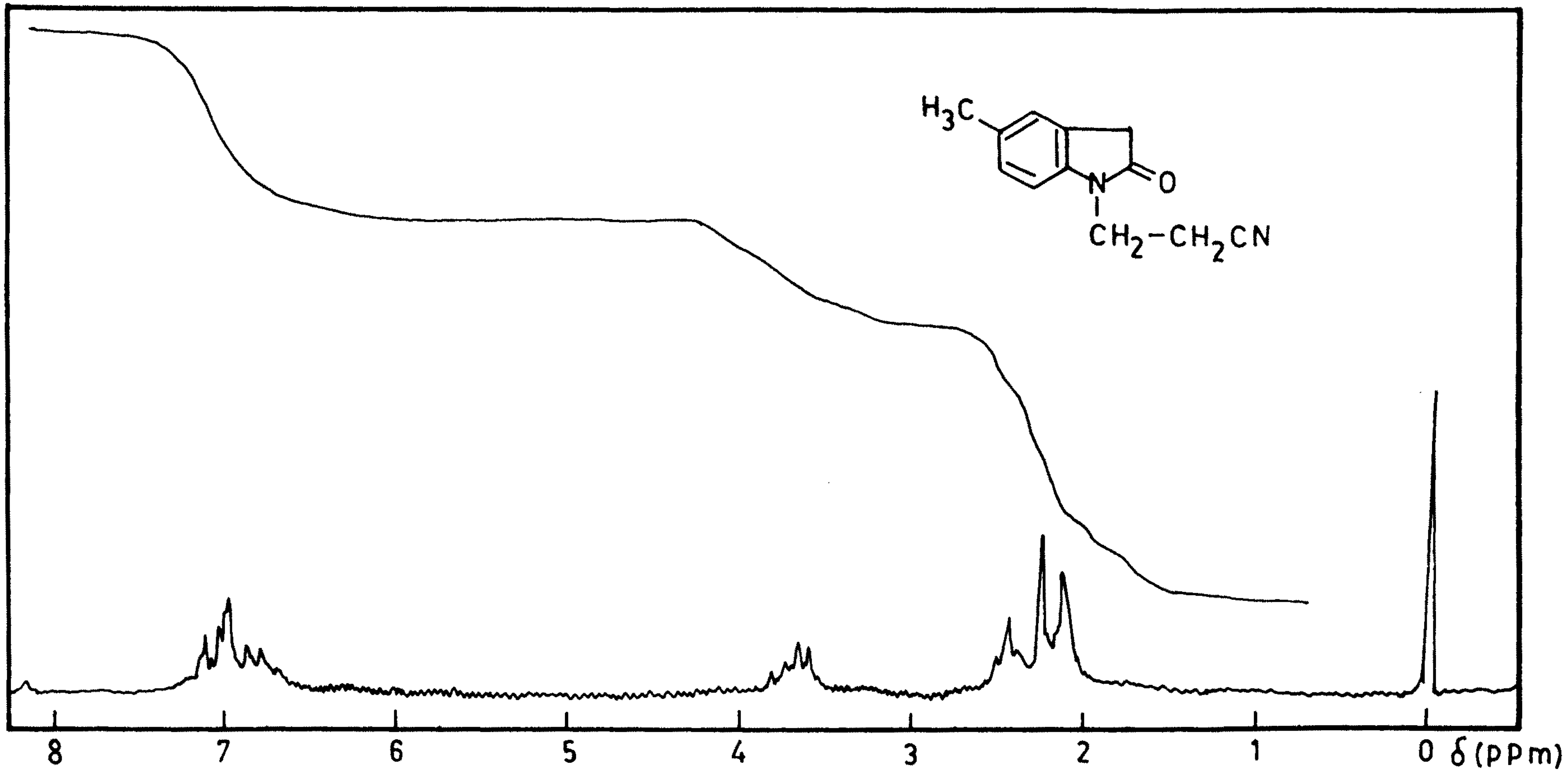


FIG. 14

PMR SPECTRUM OF N-PROPYLAMINO, 2,3-DIHYDRO, 5-METHYL INDOLE.

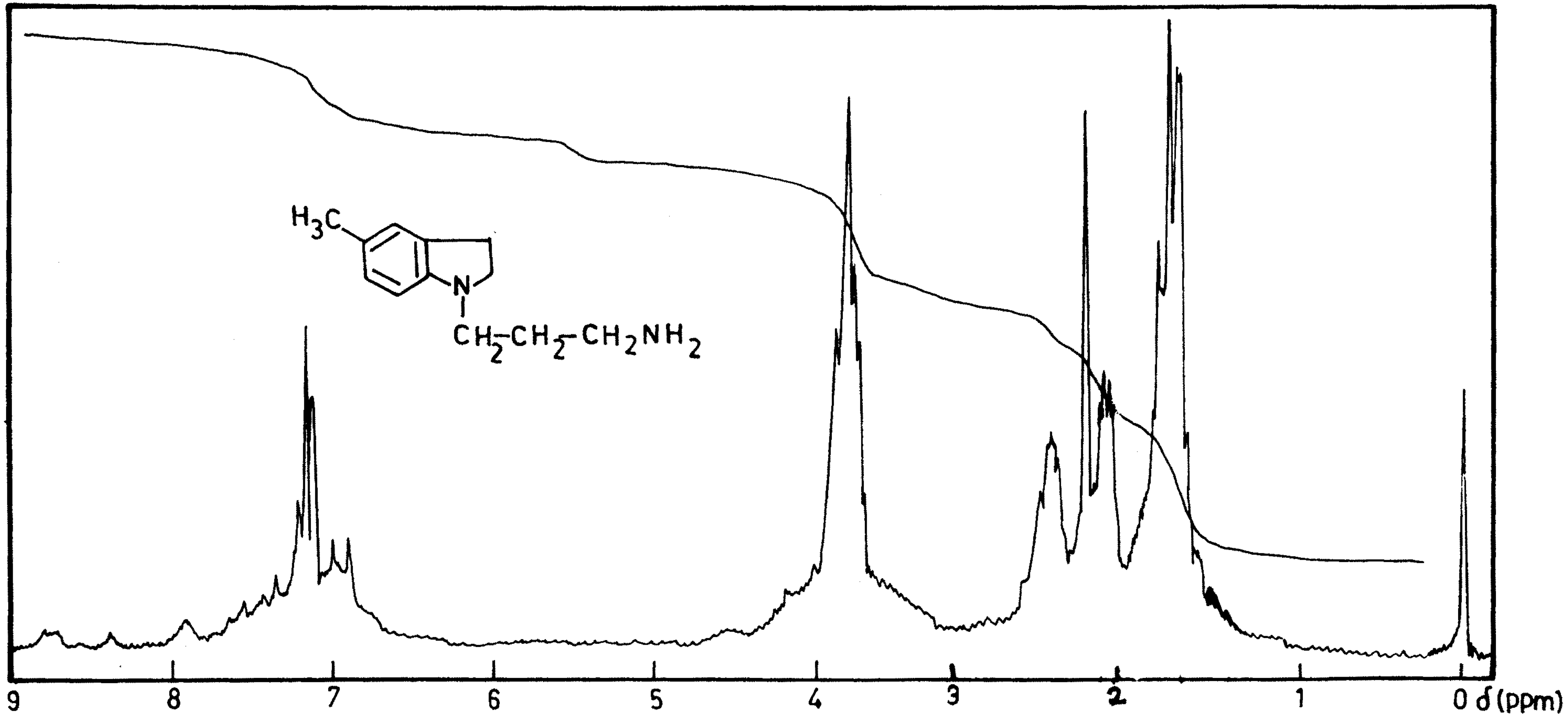


FIG. 15

MASS SPECTRUM OF 2,3-DIHYDRO, N-PROPYLAMINO INDOLE .

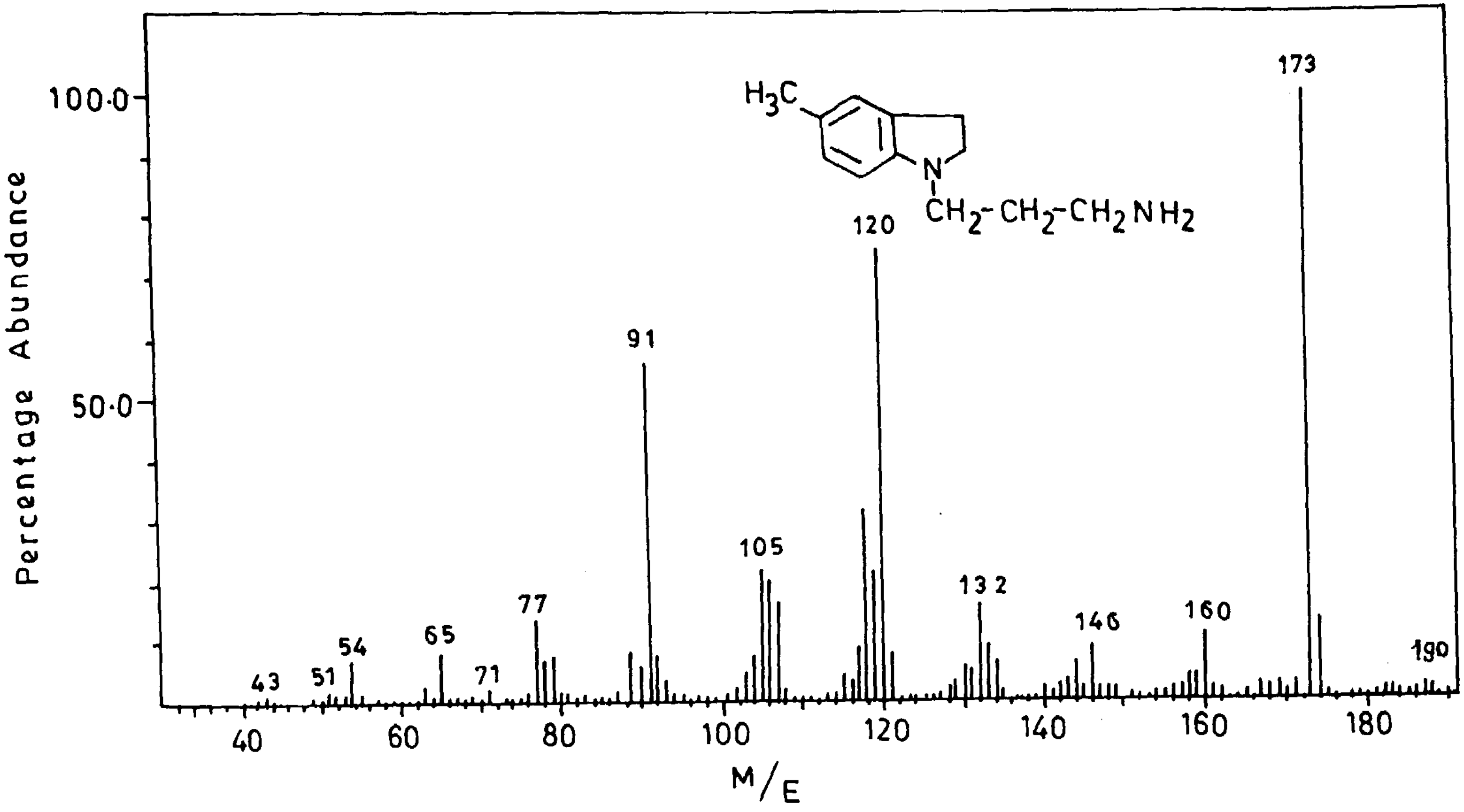


FIG. 16

U V SPECTRUM OF N—CYNOETHYL ANILINE .

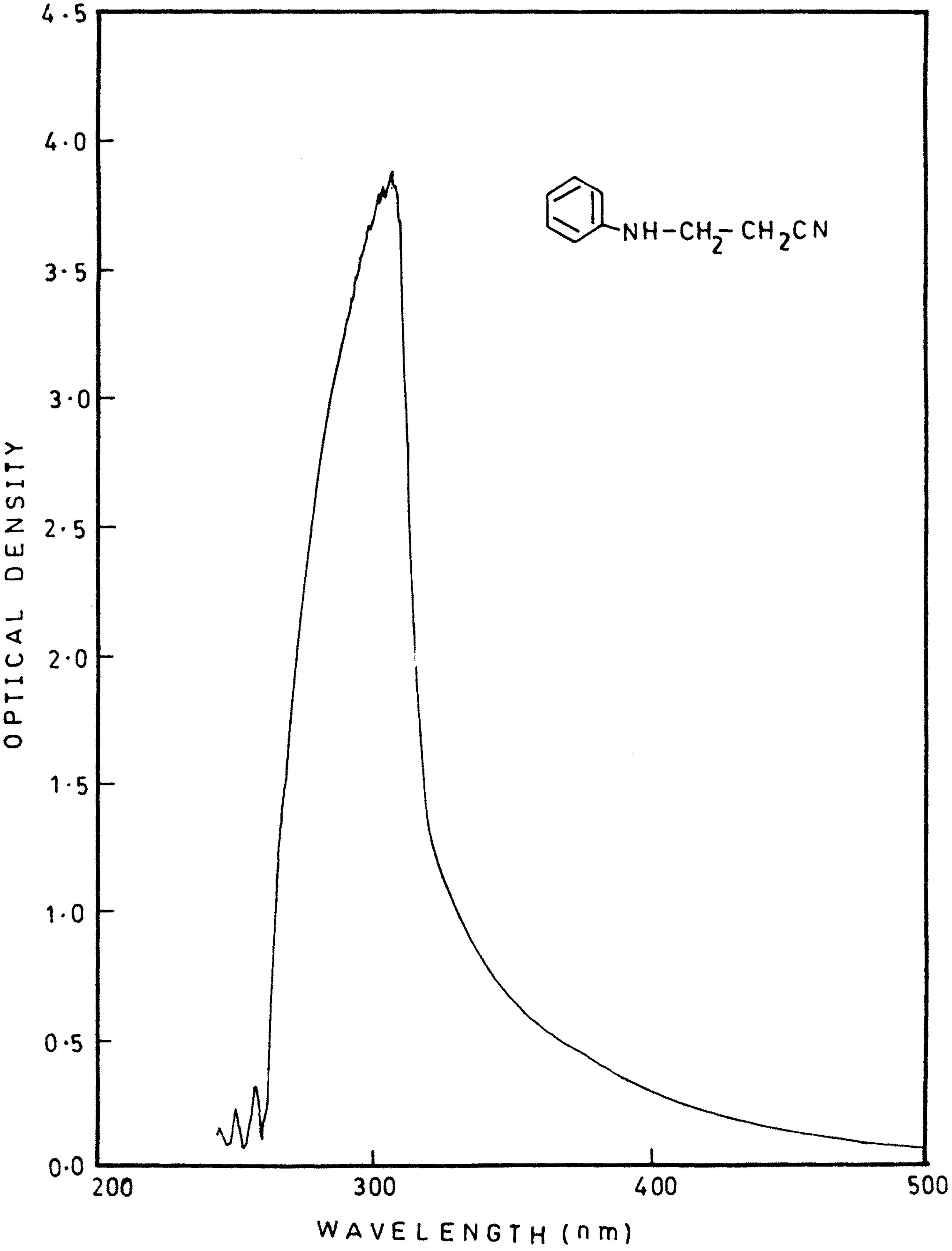


FIG. 17

PMR SPECTRUM OF N-CYNOETHYLANILINE .

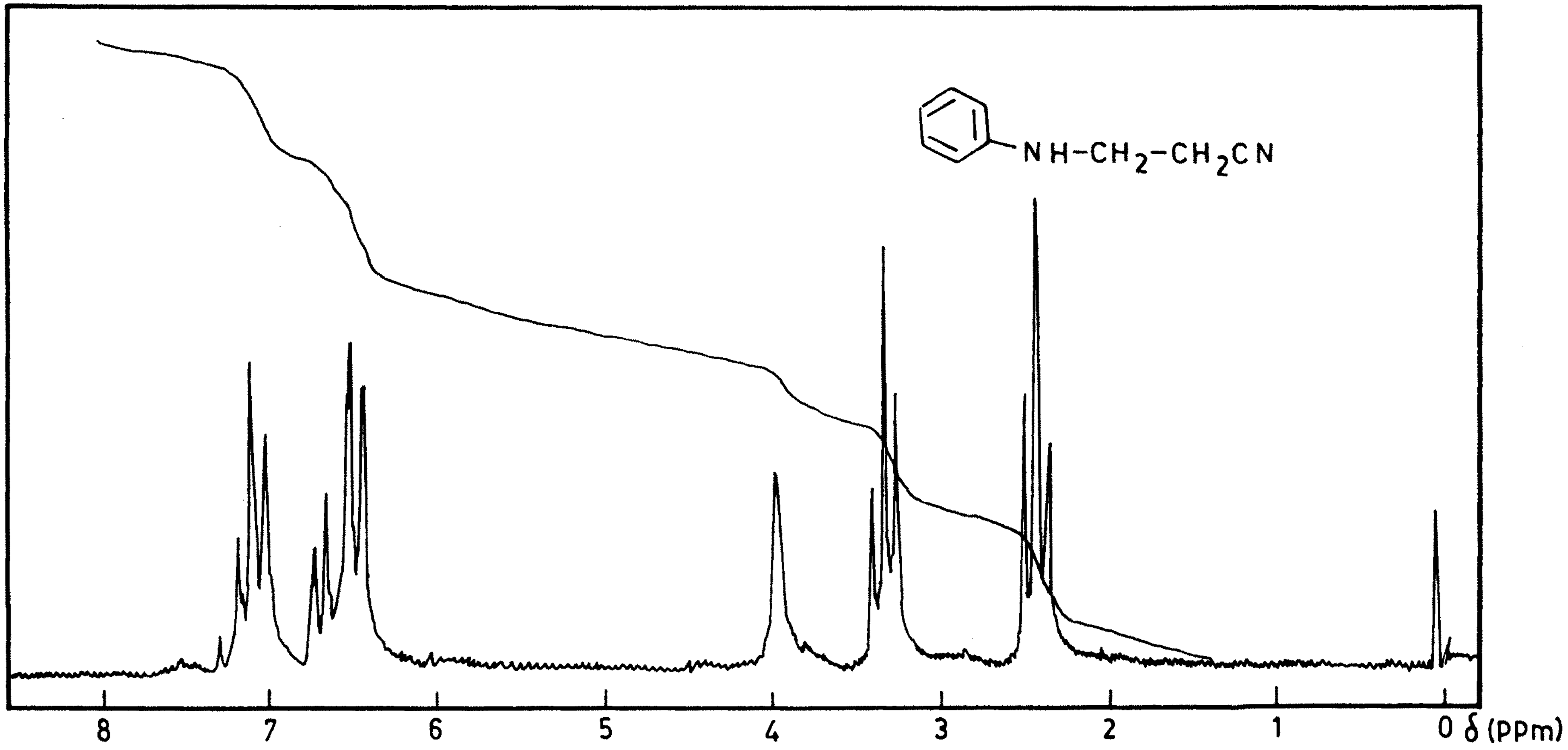


FIG . 18

PMR SPECTRUM OF N-PROPYLAMINO , 2-METHYL , 3-PHENYL INDOLE .

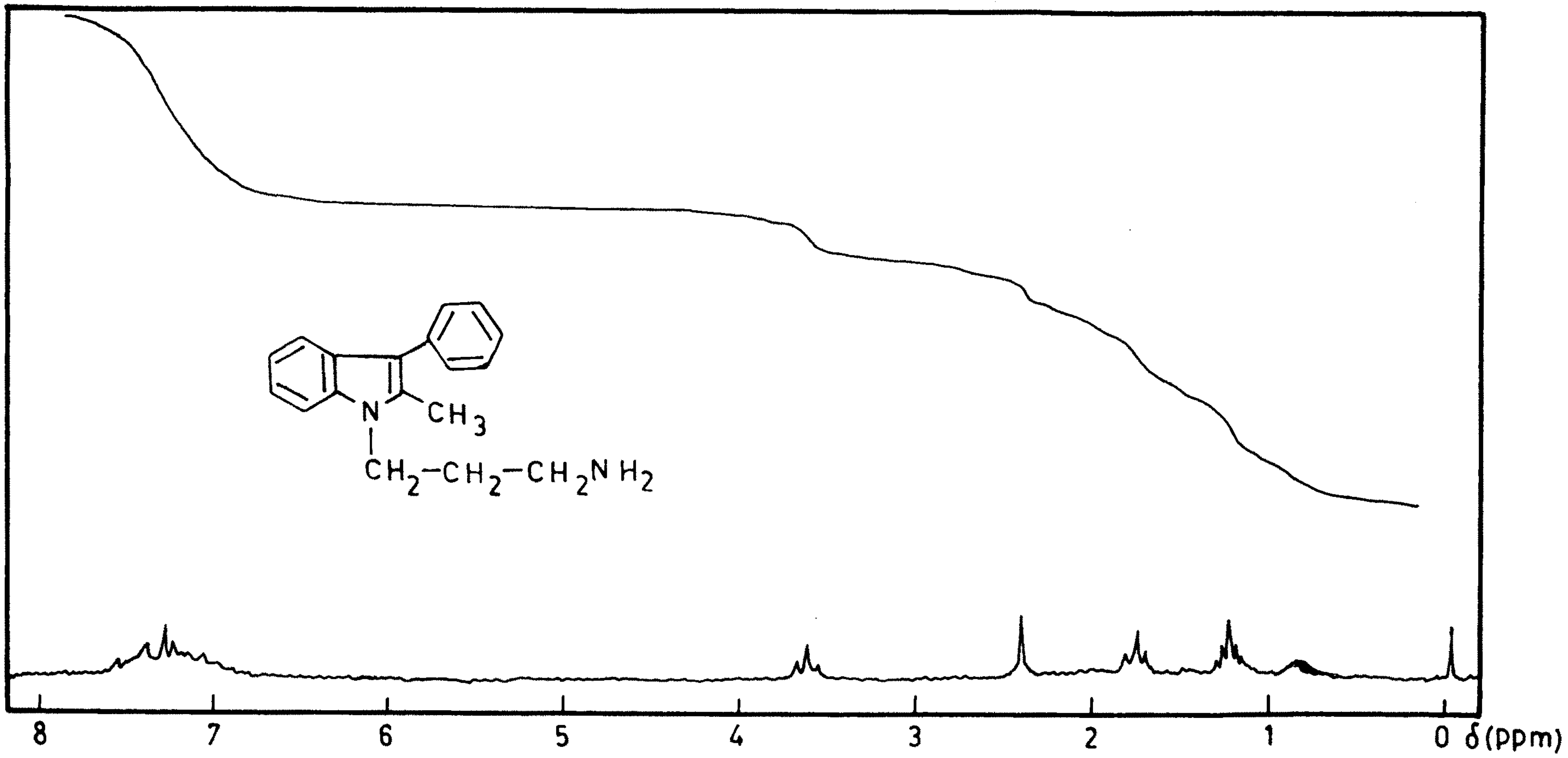
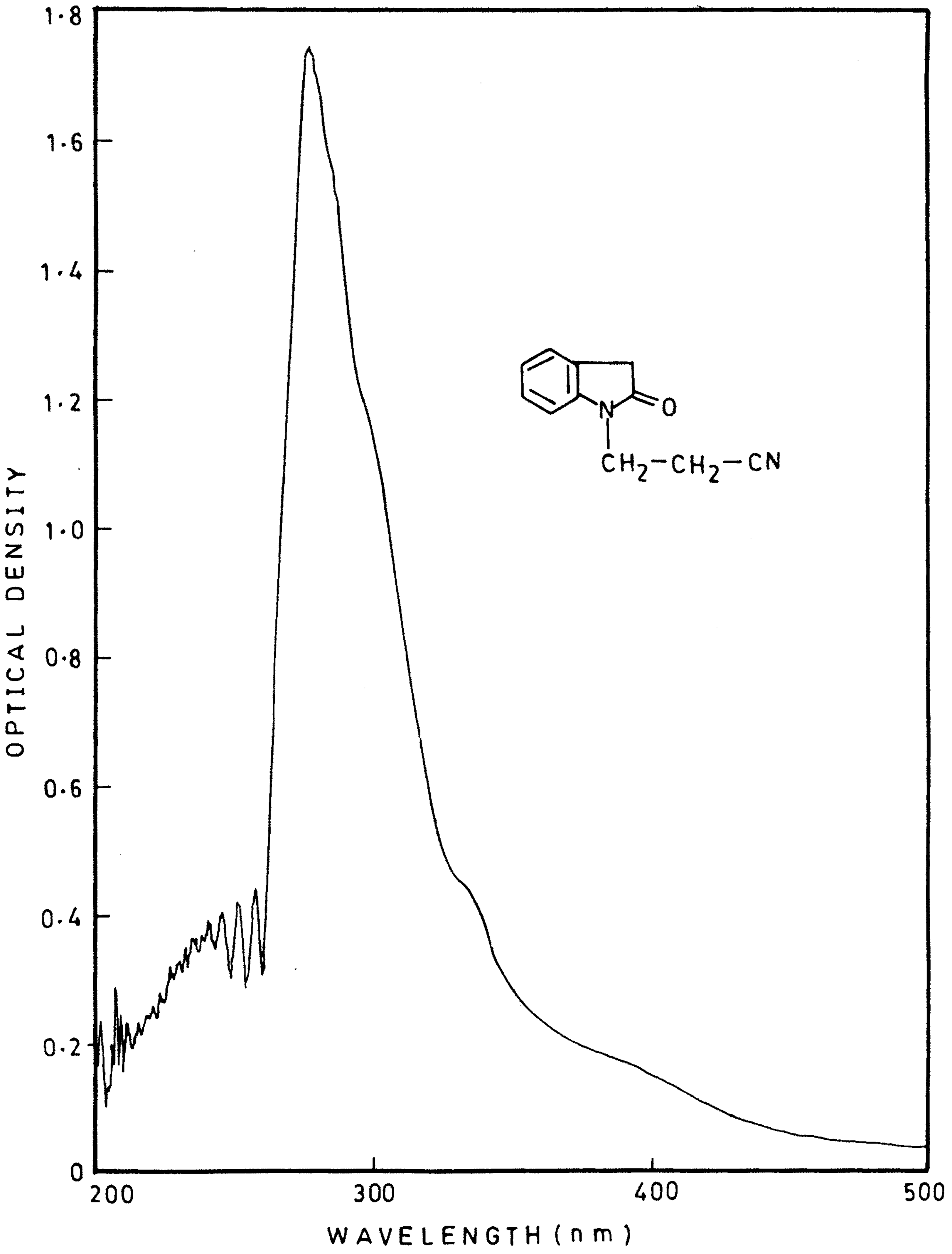


FIG. 19



UV SPECTRUM OF N-CYNOETHYL 2-OXO-INDOLE ·

FIG. 20

IR SPECTRUM OF N-CYNOETHYL, 2-OXO-INDOLE .

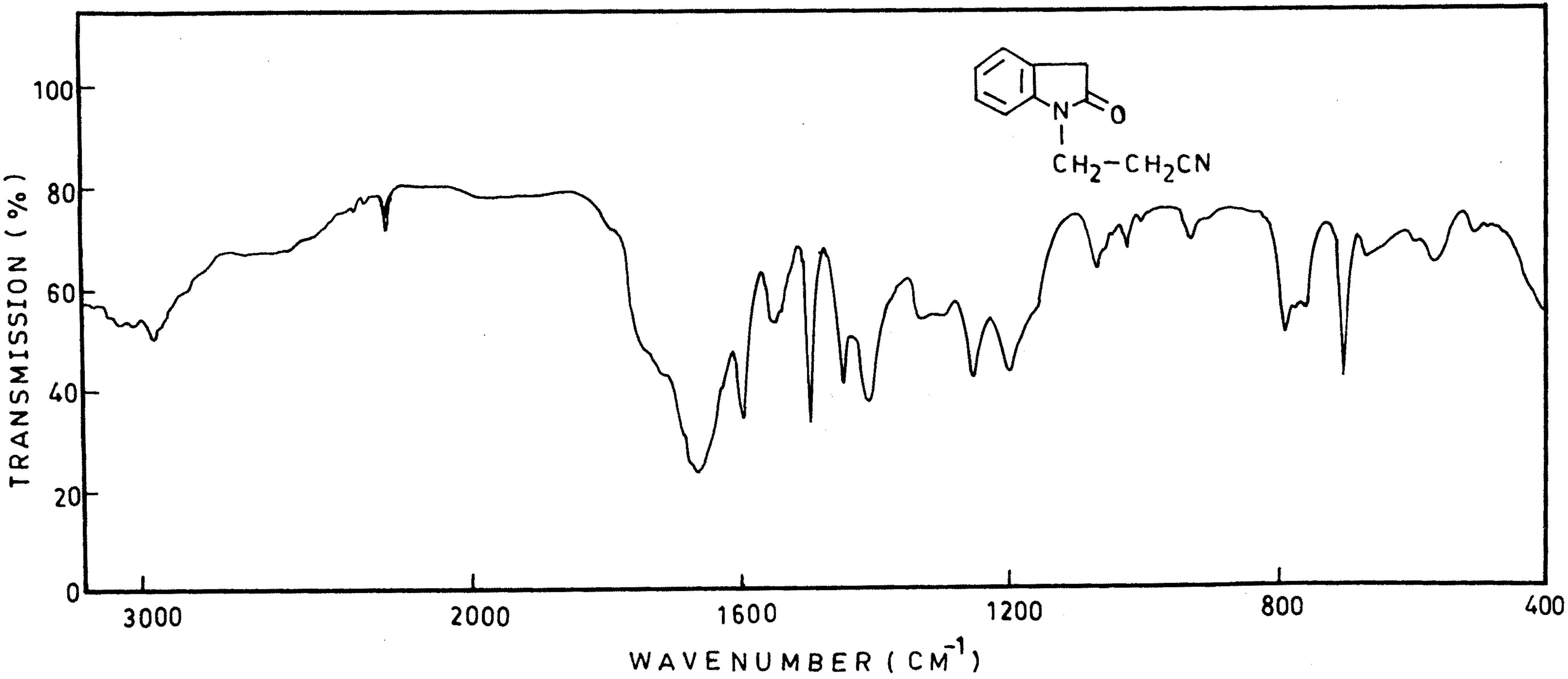


FIG. 21

PMR SPECTRUM OF N-CYNOETHYL, 2-OXO-INDOLE .

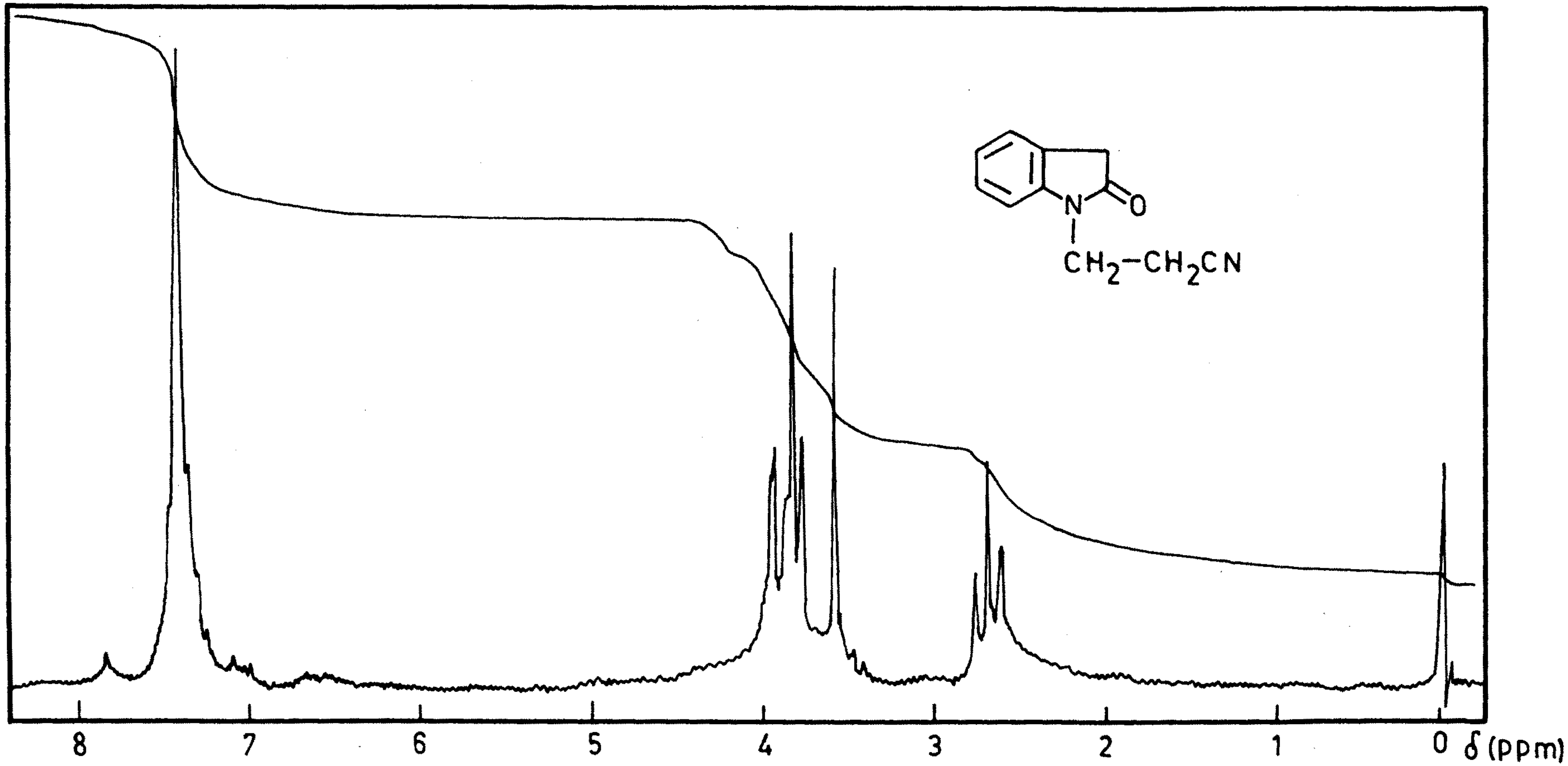


FIG. 22

PMR SPECTRUM OF N-PROPYLAMINO-, 2,3-DIHYDRO INDOLE .

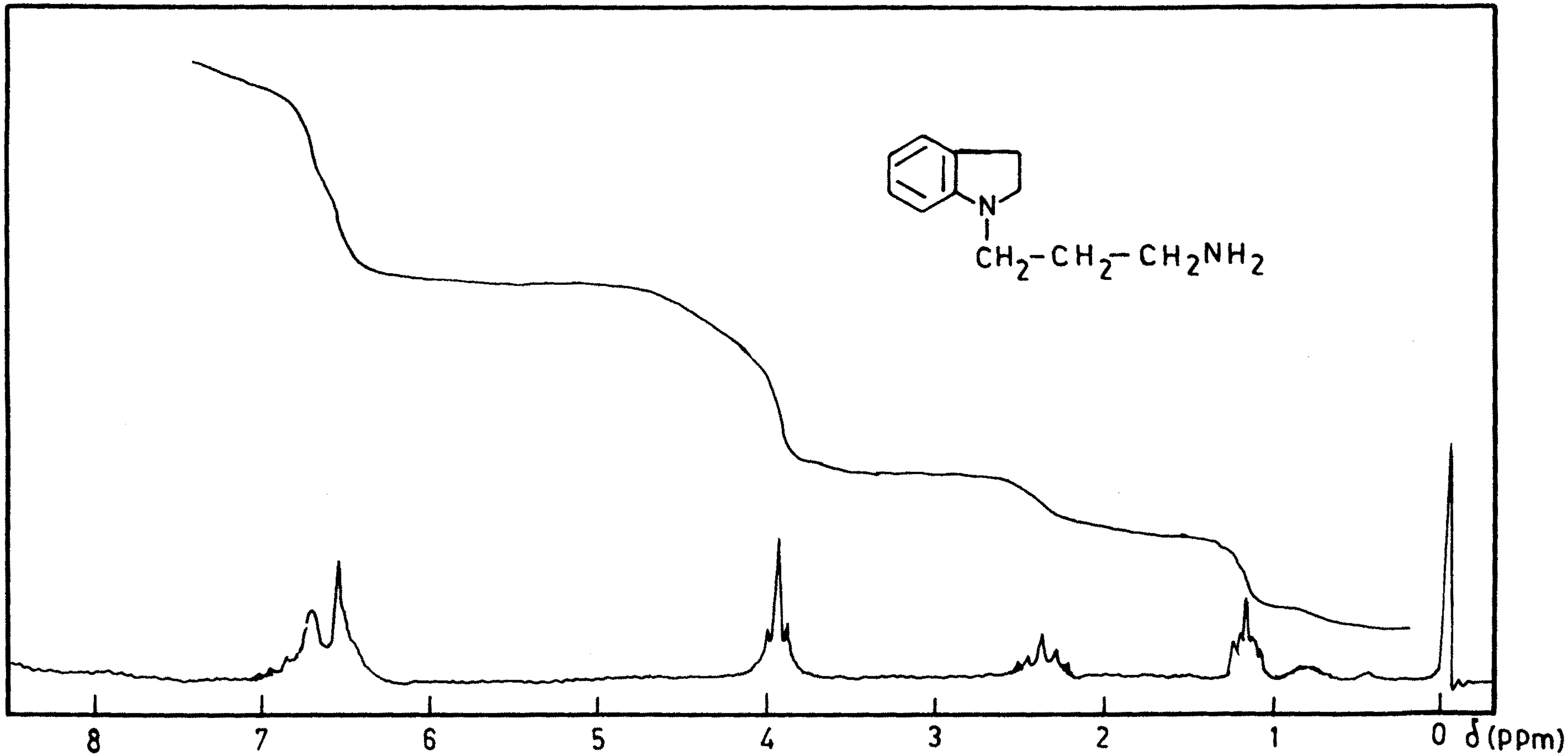


FIG. 23