CHAPTER - II

SYNTHESIS OF 2-LEPIDINE SULFONAMIDES

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2.1 INTRODUCTION :

Certain amines exhibit a noticeable antiplasmodial action and this effect is increased considerably by attaching the amino group to an aromatic heterocyclic nucleus.[1] A systematic search for potential chemotherapeutic agents is based on newer and easily available starting materials.

An excellent antimalerial activity towards S. aureus and E. coli have been exhibited by heterocyclic Sulfonamides[2] and the activity was attributed to the sulfonamide group in the drug.[3] Pharmacological properties of quinoxaline sulfonamides are reported.[4]

2.2 PREVIOUS WORK :

Quinonaline Sulfonamides have been reported as pharmaceuticals.[5-7] Ciba Ltd.[8] have also patented heterocyclic sulfonamides, that show antimalerial and disinfectant properties.

The antibacterial activity and uses of quinoxaline have been reported.[9-11] Quinoxaline compounds have been also used in the treatment of tuberculosis.[12]

Quinoline derivatives possess a wide therapeutic activity viz. antiseptic[13], analgesics[14], tryphocidal[15], germicidal[16], antitubercular[17], anthelimintics[18] and antiserotonin[19], chalcones also possess anthelmintic[20] and antimicrobial activity.[21]

Sulfur containing compounds are perticularly known for their effectiveness against bacteria. Thiazolidine and thiazole compounds possess fungicidal and other biological activities.[22]

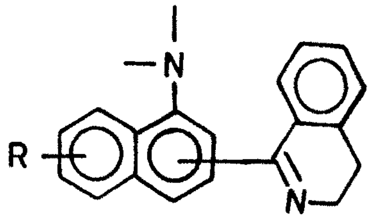
8-Hydroxy quinoline derivatives and 4-substitued-7-chloroquinoline have been extensively used as powerful antiamoebic drugs.[23,24]

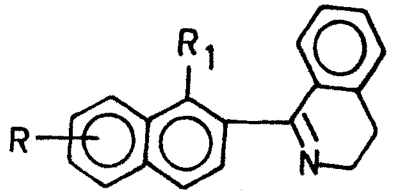
The quinoline and isoquinoline derivatives,[25-27] besides having antifilarial properties,[28,29] these were also efficaceous against many worm infections.[30-32]

Isoquinolyl quinoline of general structures (1 and 2) have been synthesized and these compounds are shown as antifitarial agent.

Recently, 2 and 8 substituted quinolines (3 and 4) containing 1, 3, 4 thiadiazole residue have been found to possess antimalerial and schistomicidal activities.[33,34]

STRUCTURES

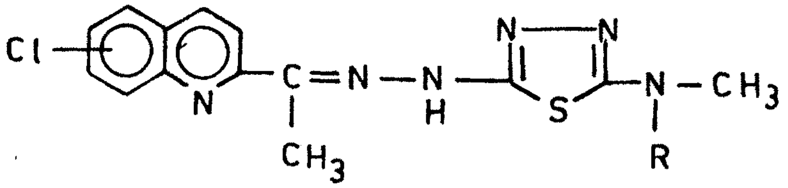




R=R'= OCH_3, H, OH, Cl, etc.

(I)

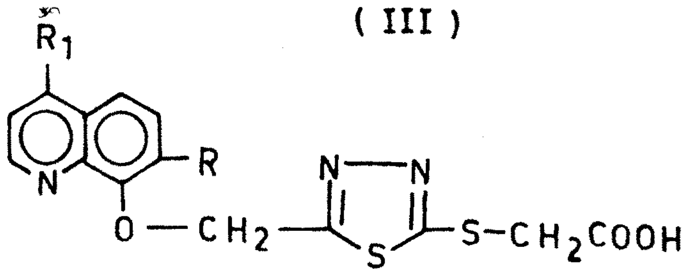
(II)



R = OCH_3, H, OH, etc.

2—Substituted quinoline

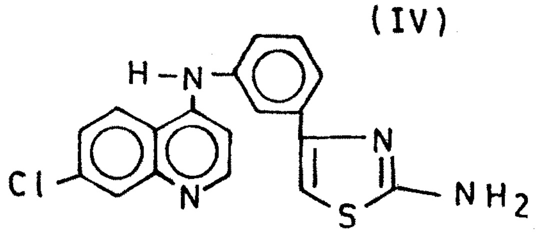
(III)



R = OCH_3, H, OH, etc.

8—Substituted quinoline

(IV)



[4-amino-7-chloro-quinoline-Phenyl thiazole]

(V)

The 4-amino-7-chloroquinolines[35] (5) with phenyl thiazole and phenyldiathiazole are known to exhibit antibacterial and antiviral efficacy.

All the compounds of 4-amino-7-chloro quinolines were evaluated for their antimalerial activity against plasmodium berghei in mice, and antifilarial activity against lifomosoides cornii, in cotton rat and found to be inactive. Some of the compounds were tested for their in vitro growth, inhibitory activity against different strain of bacteria and fungi.

a) Haloquinoline :

Haloderivatives of quinoline are known as antimalerial drugs.[36,37] These are made by using a large variety of synthesis. Particularly 2 and 4 halo-quinolines have been synthesised by using Skraup quinoline synthesis.[38]

Alkyl groups at 2-and 4-position of the quinoline nucleus are found to be active.

More recently[39,40] quinoline is successfully chlorinated by Derbyshire and water method.[41] In this method, by passing dry chlorine at room temperature through a solution of quinoline in concentrated sulfuric acid containing silver sulfate gives a mixture of 5-chloroquinoline, 8-chloroquinoline and 5,8 dichloroquinoline, is used as antiamoebic activity in man.[42,43]

2-chloroquinoline[44] is prepared by heating 2-quinolone with a mixture of phosphorus pentachloride and phosphorus oxychloride at 140°C formed 2-chloroquinoline.

2-chloro-4-methylquinoline by simply heating with phosphorus pentachloride and phosphorus oxychloride[45-47] formed 2-chloro-4-methyl quinoline.

b) Nitrogen Analogs :

The thirty nitrogen mustard derivatives in the quinoline and acridine series of antimaterial drugs have been synthesised for studies of their antitumor[48] potentialities. The nitrogen mustard group has been incorporated into many organic molecules possessing varying types of physiological activity.[49,50] Several of the antimalerials themselves show bone marrow depressant activity.[51]

c) Heterocyclic sulfonamides :

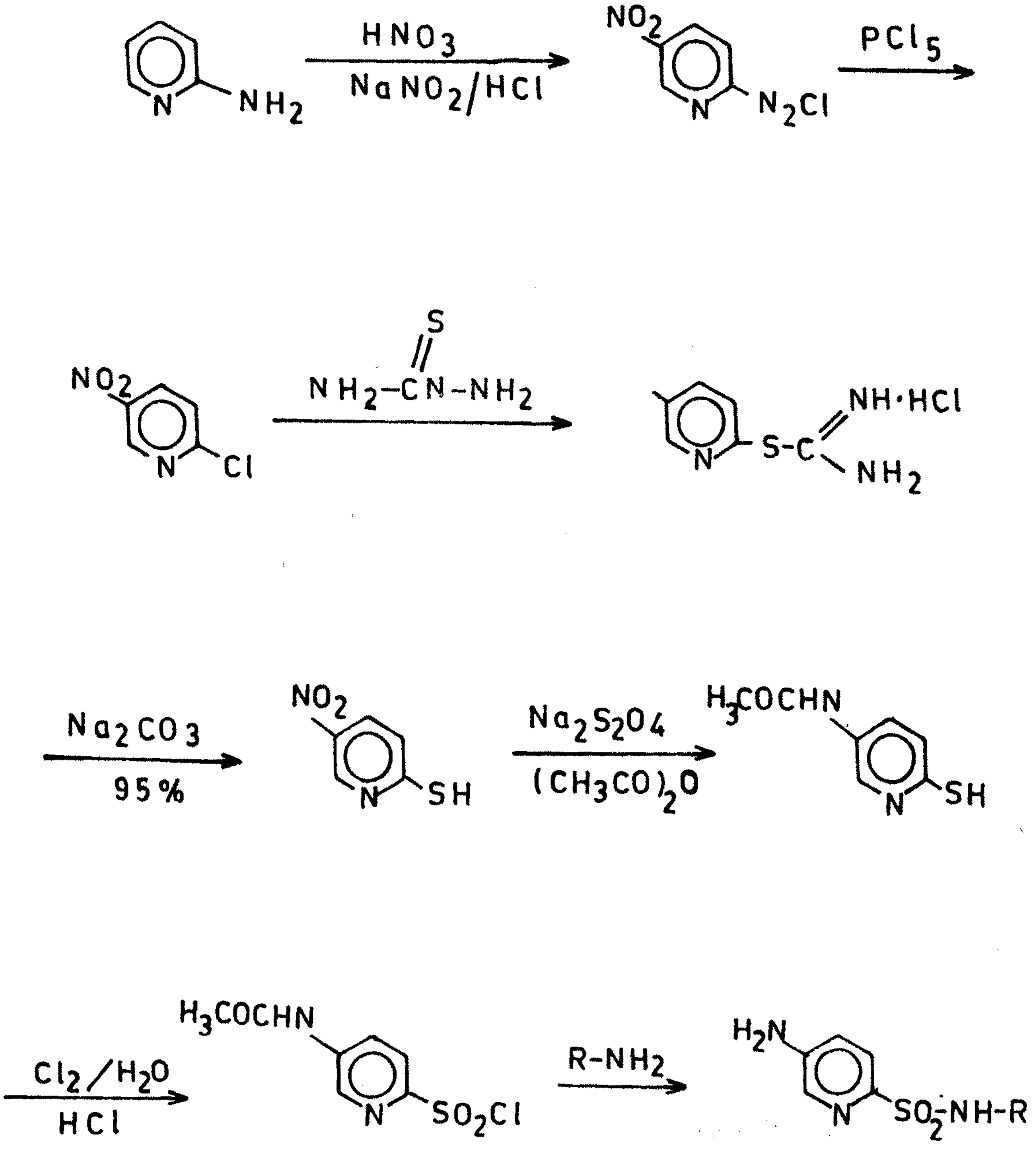
A number of heterocyclic sulfonamides have been reported as follows :

5-Aminopyridine-2-sulfonamides -

Showed a promising antibacterial activity against streptococci infections. These compounds were synthesised from 2-aminopyridine first by nitration, diazotisation and further conversion to 5-nitropyridine. Further treated with PCl_5 to give 2-chloro-5-nitropyridine. This was made to

CHART – 1

Synthesis of 5-Aminopyridine-2-Sulfonamide



react with thiourea which gave 5-nitro-2-pyridylpseudothiourea hydrochloride. Then it was hydrolysed by sodium hydroxide to 2-mercapto-5-nitropyridine. Then reduced to the amino with sodium dithionite and acetylated to give 2-mercapto-5-acetamidopyridine which was oxidised with chlorine in ice water to 5-acetamide-2-pyridine sulfonyl chloride. This then underwent reaction similar to acetylsulfanilyl chloride in preparing the desired sulfonamide[52] as shown in Chart-I.

The another important heterocyclic sulfonamides reported are :

<u>2-aminopyridine-5-sulfonamides</u> :

In which 2-Aminopyridines can be directly sulfonated to 2-aminopyridine-5-sulfonic acids. Then on diszotisation and heating in water it was converted to 2-pyridone-5-sulfonic acid. Further it was converted in to its 2-chloroderivative by the reaction of phosphorus pentachloride. Then by treating with ammonia the 2-chlorine was substituted by amino group to give 2-aminopyridine-5-sulfonamide.[53]

These compounds have been claimed to be active in the petent literature but pharmalogical reports are not available.

Recently heterocyclic sulfonamides are prepared by sulfonation followed by reduction and cyclisation[54] (Chart-III).

N-halosulfonamides are formed when sodium salt is reacted with halogen[55] (Chart-III).

p-Toluene sulfonyl iso-cynate on condensation with benzene, Napthalene, or anisole etc. using aluminium chloride at 25°C gives sulfonamides in excellent yield while at higher temperature mainly sulfone is formed.[56]

Quinoline Sulfonamide :

The disodium salt of 2-methyl-6-sulfamylcinchonic acid was found active against streptococci and less active against phenumococci. The disodium salt of 2-methyl-6-sulfamylcinchonamide was inactive against streptococci.

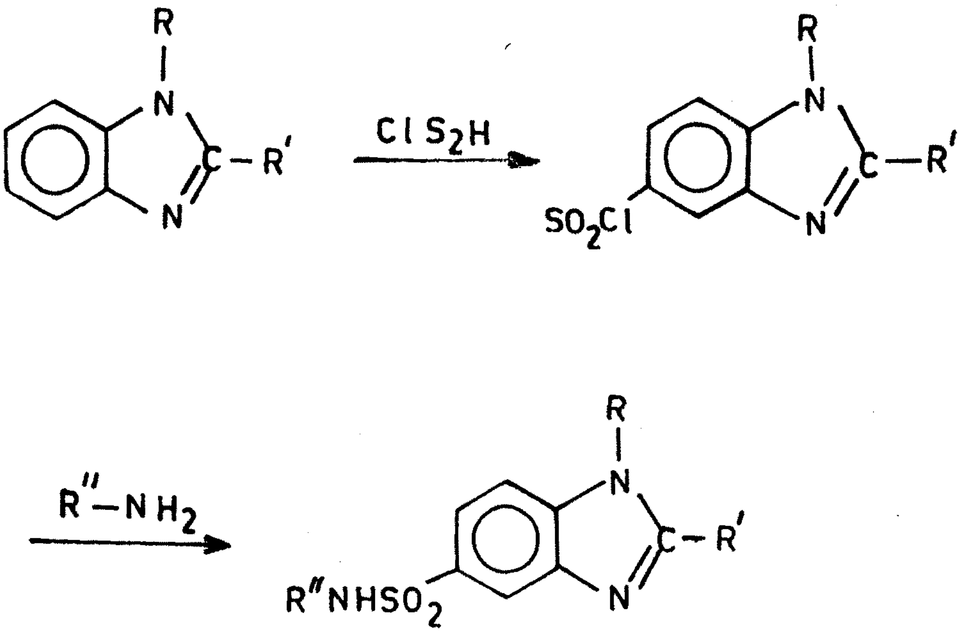
2.3 PRESENT WORK :

Discussion :

As heterocyclic sulfonamides exhibit an excellent antibacterial activity against *S. auris* and *E. coli* and this activity was attributed to the sulfonamide group. Also quinoxaline sulfonamides are reported to posses a good antibacterial activity[9-11] and used in the treatment of

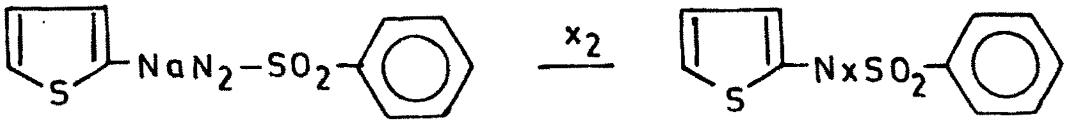
CHART–II

Synthesis of hetero–sulfonamide



CHART–III

Synthesis of-N-halo-sulfonamide



tuberculosis. So it was considered that sulfonamides when condensed with 2-chloro-4-methyl quinoline would form an useful and good variety of antibacterial drugs. With this view, we have made a series of compounds by reacting 2-chloro-4-methyl quinoline with substituted sulfonamide derivatives.

Following the procedure of Knorr Ann. and Mikhalove[57] ________________________________ for the conversion of 2-chlorolepidine, from its precrussor carbostyrol (Scheme I), the yields obtained were unsatisfactory and improved by modifying this procedure as reported in the experimental section of this chapter.

In all ten 2-lepidine sulfonamides were prepared by reacting 2-chlorolepidine with a variety of substituted sulfonamide derivatives using the method of C. Pellarino.[58] Scheme II depicts the general outline of the synthesis of substituted sulfonamides. Using this scheme we have prepared p-amino-benzene sulfonamide (IIa) p-amino-otoludine sulfonamide (IIb) and p-amino-m-toludine sulfonamide (IIc).

Scheme III and IV have been used for the condensation between 2-chlorolepidine and - SO_2NH_2 end of the substituted sulfonamides. This was done by reacting the 2-chlorolepidine and the aminobenzene sulfonamides at about 250° using paraffin bath in the presence of copper powder and potassium carbonate as a catalyst.

The progress of the reaction was monitored by thin layer chromatography at different intervals of time. All these reactions were completed within about one and half hour time. Powdered product boiled with sodium hydroxide, salty material was obtained. This was dissolved in water and on acidification solid compound obtained was recrystallised from ethanol.

The following sulfonamide derivatives were prepared by using Scheme - III and IV.

IIIa 2-Lepidyl-p-amino benzene sulfonamide M.P. 230°
IIIb 2-Lepidyl-p-amino-o-toludine sulfonamide M.P. 226°
IIIc 2-Lepidyl-p-amino-m-toludine sulfonamide M.P. 228°

IVa 2-Lepidyl-p-acetamido benzene sulfonamide M.P. 258°
IVb 2-Lepidyl-p-acetamido-o-toludine sulfonamide M.P. 254°
IVc 2-Lepidyl-p-acetamido-m-toludine sulfonamide M.P. 245°
IVd 2-Lepidyl-p-toluene sulfonamide M.P. 248°

Weh have used scheme V for the substituted sulfonamides.

This was done by treating the 2-chlorolepidine and the aminobenzene sulfonamides at temperatures about 190°-200° in oil bath. No catalyst was used in this case. After extraction with 15 % hot hydrochloric acid, the hydrochloride obtained was purified by recrystallisation from water.

Using this procedure following sulfonamides were prepared -

Va 2-Lepidyl benzene-p-sulfonamide M.P. 255°

Vb 2-Lepidyl-o-toludine-p-sulfonamide M.P. 262°

Vc 2-Lepidyl-m-toludine-p-sulfonamide M.P. 257°

All the sulfonamides derivatives prepared were soluble in high polar solvents, such as alcohol, acetone and water and insoluble in a less polar solvents.

They were having high melting points. Nuclear magnetic resonance spectra have been taken in $CDCl_3$. However, their poor solubility in $CDCl_3$ caused turbidity, to make it a clear solution few drops of trifluroacetate were added.

These compounds were tested for their antibacterial activity against Bacillus-Megaterium, E. coil etc. The cup plate method was used for testing their antibacterial activity.

2.4 GENERAL REMARKS :

(1) The structures and reactions are indicated by a double number, the first part of which indicates the chart in which it occurs and the second part indicates the serial number of the structures or reaction e.g. (1.1) means structure 1 in chart 1.

(2) Yield percentage, physical constant (M.P.) and elemental analysis (found and required) of the compounds have been reported.

(3) M.P. were determined by open capillary method and are uncorrected.

(4) PMR Spectra were recorded in CCl_4 and $CDCl_3$, T.F.A. with tetramethyl Silane (TMS) as an internal reference. The chemical shifts are in ppm.

(5) The purity of the compounds was checked by T.L.C. using silca gel as absorbent.

(6) I.R. spectra are recorded. The values of stretching frequencies are in Cm^{-1}.

2.5 EXPERIMENTAL WORK :

Synthesis of 2-chlorolepidine[57]

The mixture of aniline (9 ml) and ethyl aceto-acetate (17 ml) refluxed for one and half hour. Then 10 % sodium hydroxide (100 ml) was added and the mixture heated for 5 minutes which gave acetoacetanilide. After extraction of aqueous layer with ether excess of acetic acid was added and precipitate obtained was filtered and recrystallised from petrolium ether m.p. (60 - 80°).

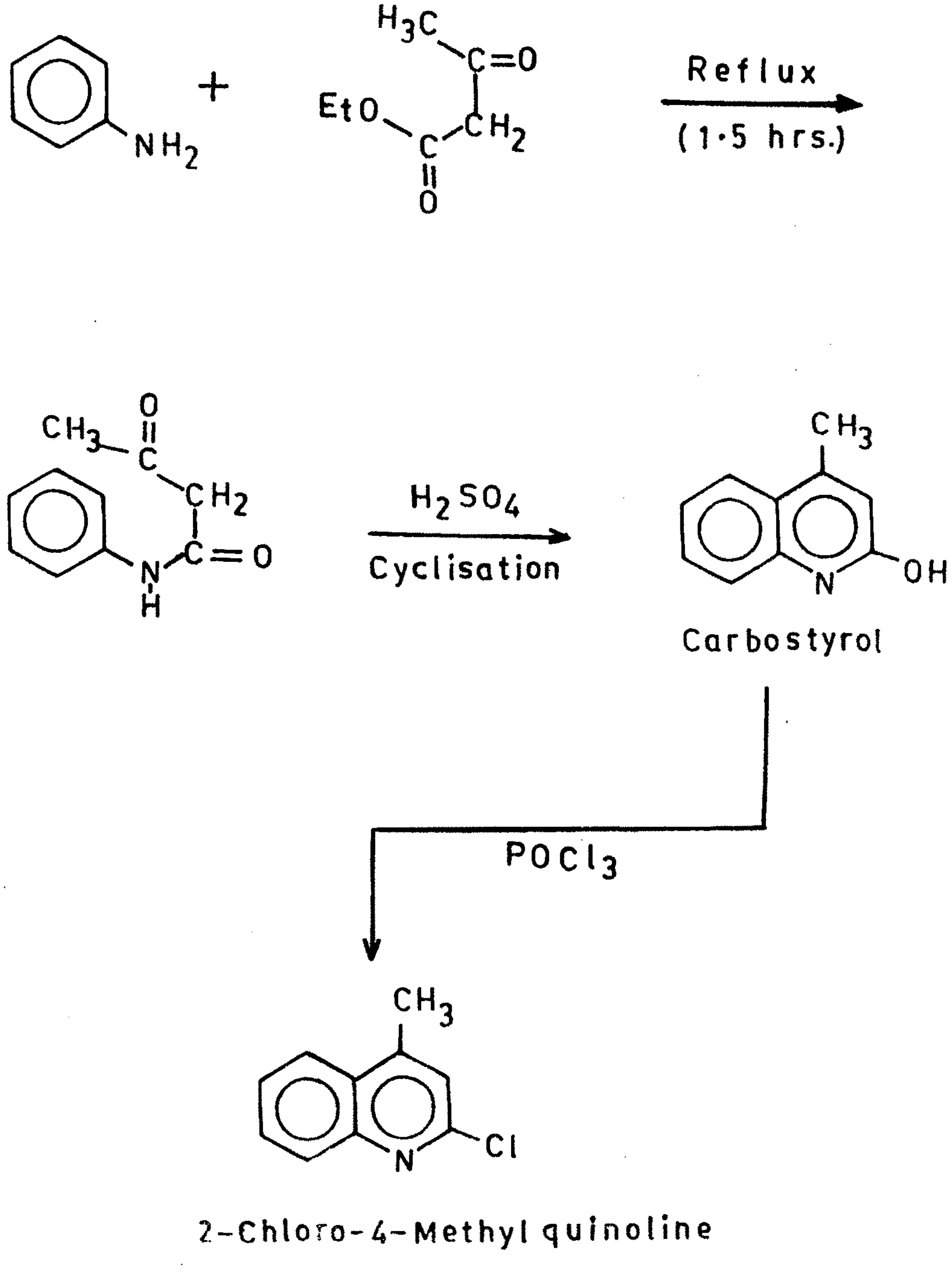
The above purified product under goes cyclisation with concentrated sulfuric acid gives 4-methyl carbostyrol. It is filtered, further recrystallised from 95 % ethanol m.p. (219 - 221°).

The purified above product further treated with phosphorus oxychloride and heated at 70-80° until liquified completely. Then anhydrous sodium carbonate was added which gave precipitate. It was filtered and recrystallised from aqueous ethanol m.p. 58°.

The above experimental work has been represented by Scheme I.

SCHEME-1

Synthesis of 2-chloro-4-methyl quinoline



2-Chloro-4-Methyl quinoline

(2-Chloro-Lepidine)

General Procedure for the Preparation of Substituted P-aminobenzene sulfonamides[59]:

Acetanilide was prepared by heating the mixture of aniline (20 ml) acetic anhydride (21 gm) glacial acetic acid (20 ml) and 0.1 gm Zn dust. It was poured into ice-cold water when precipitate was obtained. It was obtained. It was filtered and recrystallised from boiling water.

Yield - (22 gm) m.p. 112° (lit. 114°)

To the above product (20 gm) chlorosulfonic acid (90 gm) was added in to small quantity and heated for one hour. Finally the oily solution was added in to ice-cold water. The p-aminobenzyl sulfonyl chloride was precipitated. It was filtered.

Yield (18 gm) m.p. 148° (lit 146°)

The above crude product was then treated with concentrated ammenia (70 ml) and water (70 ml). It was heated just below its boiling point for 15 minutes. The sulfuric acid (dil) was added till the mixture was acidic to cango-red paper. P-Acetamidobenzene sulfonamide was precipitated, filtered and dried.

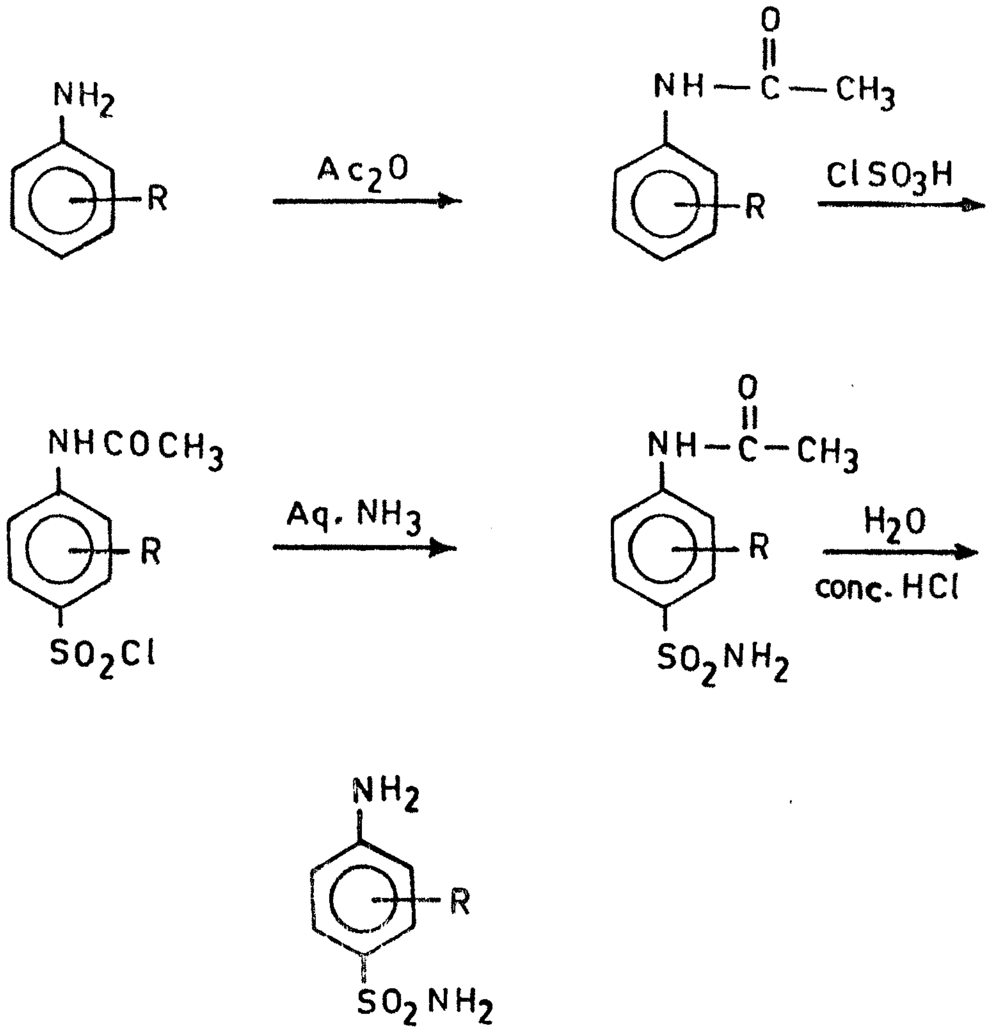
Yield about (16 gm) m.p. 216° (lit 218°)

The above crude product and concentrated hydrochloric acid (10 ml) water (30 ml) boiled for 30-45 minutes. It was cooled and filtered. Charcoal (2 gm) added boiled for few minutes then solid sodium-bicarbonate (16 gm) was added till neutral. The precipitate of p-aminobenzene sulfonamide obtained was filtered and recrystallised from ethanol yield (13 gm). m.p. 160° (lit. 163°).

Synthesis of the above compounds is shown in the Scheme II.

SCHEME-2

Preparation of p-aminobenzene sulfonamide



Compound —

IIa R = H

IIb R = CH_3 , o-NH_2

IIc R = CH_3 , m-NH_2

Synthesis of 2-Lepidyl-p-aminobenzene Sulfonamides :

General Procedure[58] :

2-chlorolepidine (3 gm) and the substituted p-aminobenzene sulfonamide (2.85 gm) and anhydrous potassium carbonate (2.4 gm) and copper powder (0.05 gm) was heated at about 250° on the paraffin bath for about 1.5 hrs. powdered product was boiled with 0.2 N sodium-hydroxide (40 ml) for about 10 minutes. Then acidified with dilute acetic acid. Gummy solid obtained was dissolved in 2 N sodium hydroxide and boiled for few minutes, cooled and salty material dissolved in water and treated with 50 % acetic acid. It gave a solid compound which was recrystallised from ethanol.

General outline for the synthesis of these compounds is shown in schemes III and IV.

Using this procedure the sulfonamides compounds prepared are IIIa, IIIb, IIIc; IVa, IVb, IVc, IVd.

The physical constant (m.p.), percentage yield, elemental analysis (found calculated) have been reported in Table 1 & 2.

Table 1

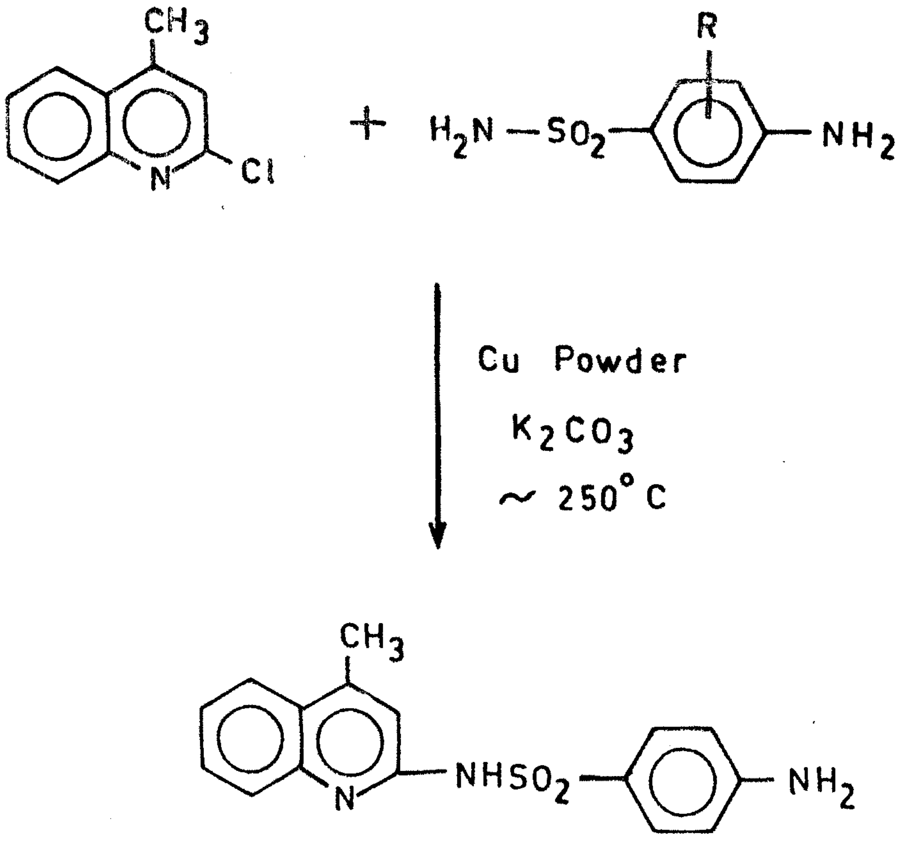
Compound	M.P. °C	% Yield	Molecular formula	Elemental analysis					
				Found			Required		
				C	H	N	C	H	N
IIIa	230	52.94	$C_{16}H_{15}N_3SO_2$	61.29	4.66	13.23	61.35	4.71	13.43
IIIb	236	52.47	$C_{17}H_{17}N_3SO_2$	62.39	5.12	12.80	62.38	5.19	12.84
IIIc	228	51.33	$C_{17}H_{17}N_3SO_2$	62.36	5.20	12.80	62.38	5.19	12.84

Table 2

IVa	258	46.312	$C_{18}H_{17}N_3SO_3$	62.60	4.50	12.15	62.62	4.92	12.17
IVb	254	46.499	$C_{19}H_{19}N_3SO_3$	61.70	5.13	11.40	61.79	5.15	11.39
IVc	245	45.689	$C_{19}H_{19}N_3SO_3$	63.78	5.14	11.38	63.79	5.15	11.30
IVd	248	53.110	$C_{17}H_{16}N_2SO_2$	63.40	5.10	8.9	63.43	5.12	8.97

SCHEME-3

Synthesis of 2-Lepidyl-p-aminobenzene sulfonamide



Compound —

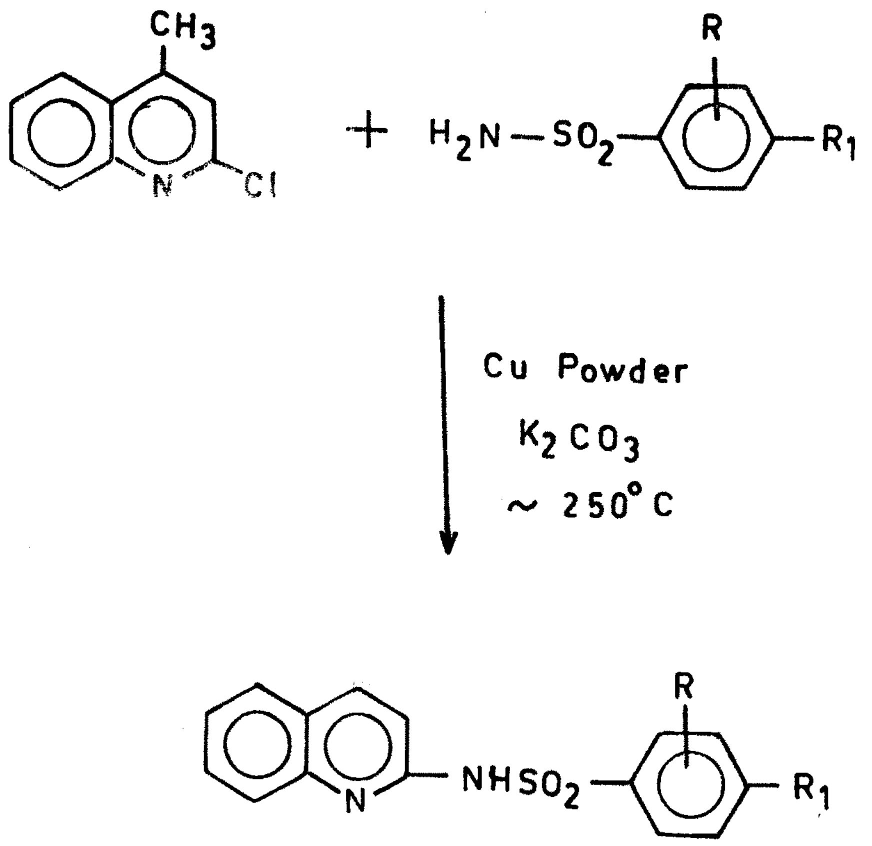
III a $R = H$

III b $R = CH_3$ (o-NH_2)

III c $R = CH_3$ (m-NH_2)

SCHEME-4

Synthesis of 2-Lepidyl sulfonamide



Compound —	R	R$_1$
IV$_a$	H	$\mathrm{NH-\overset{O}{\overset{\|}{C}}-CH_3}$
IV$_b$	CH_3 (o-NH_2)	$\mathrm{NH-\overset{O}{\overset{\|}{C}}-CH_3}$
IV$_c$	CH_3(m-NH_2)	$\mathrm{NH-\overset{O}{\overset{\|}{C}}-CH_3}$
IV$_d$	H	CH_3

Synthesis for 2 - Lepidyl - p - aminobenzene Sulfonamide :

General Procedure[58]:

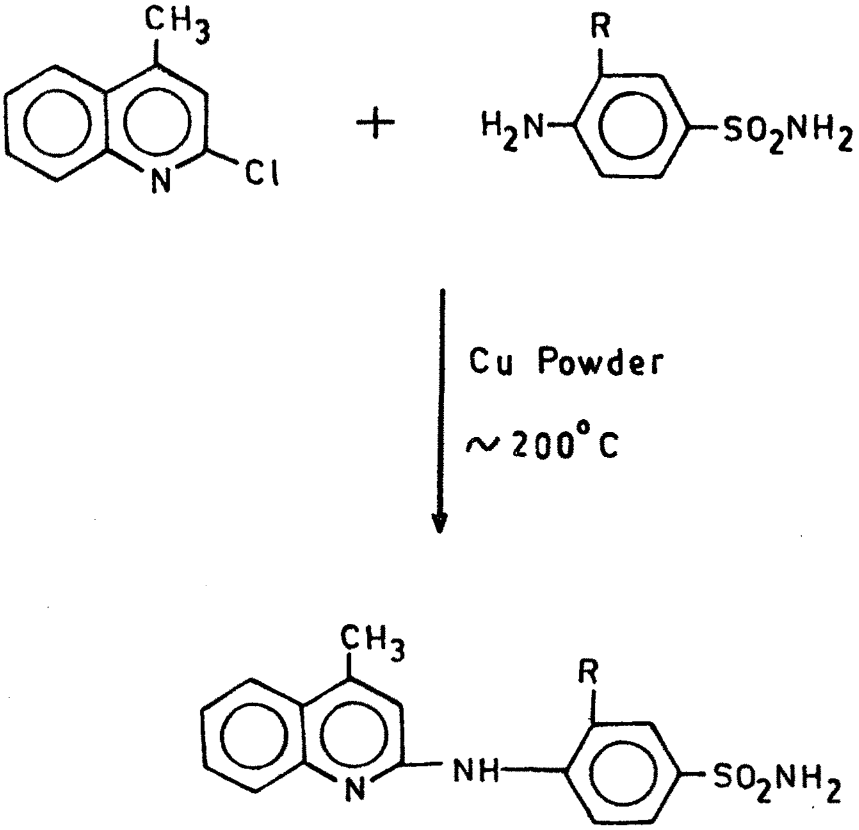
Equimolecular quantities of 2-chlorolepidine (3.55 gm 0.02 mole) and substituted P-aminobenzene sulfonamide (3.2 gm 0.02 mole) were heated. An exothermic reaction occured at 195-200°. After three minutes the mixture was cooled and extracted with hot 15 % Hydrochloric acid. The residue obtained was recrystallised from water. This gave the hydrochloride of the substituted p-aminobenzene sulfonamide derivatives of 2 - chlorolepidine. It was purified by recrystallisation from water.

The general outline for the synthesis of these components is given in Scheme V. Using this procedure, the compounds prepared are Va and Vb, Vc.

The physical constant (m.p.), percentage yield, elemental analysis (found and calculated) have been reported in Table No. 3.

SCHEME-5

Synthesis of 2-Lepidyl p-amino benzene sulfanilamide



Compound —

V_a — R = H

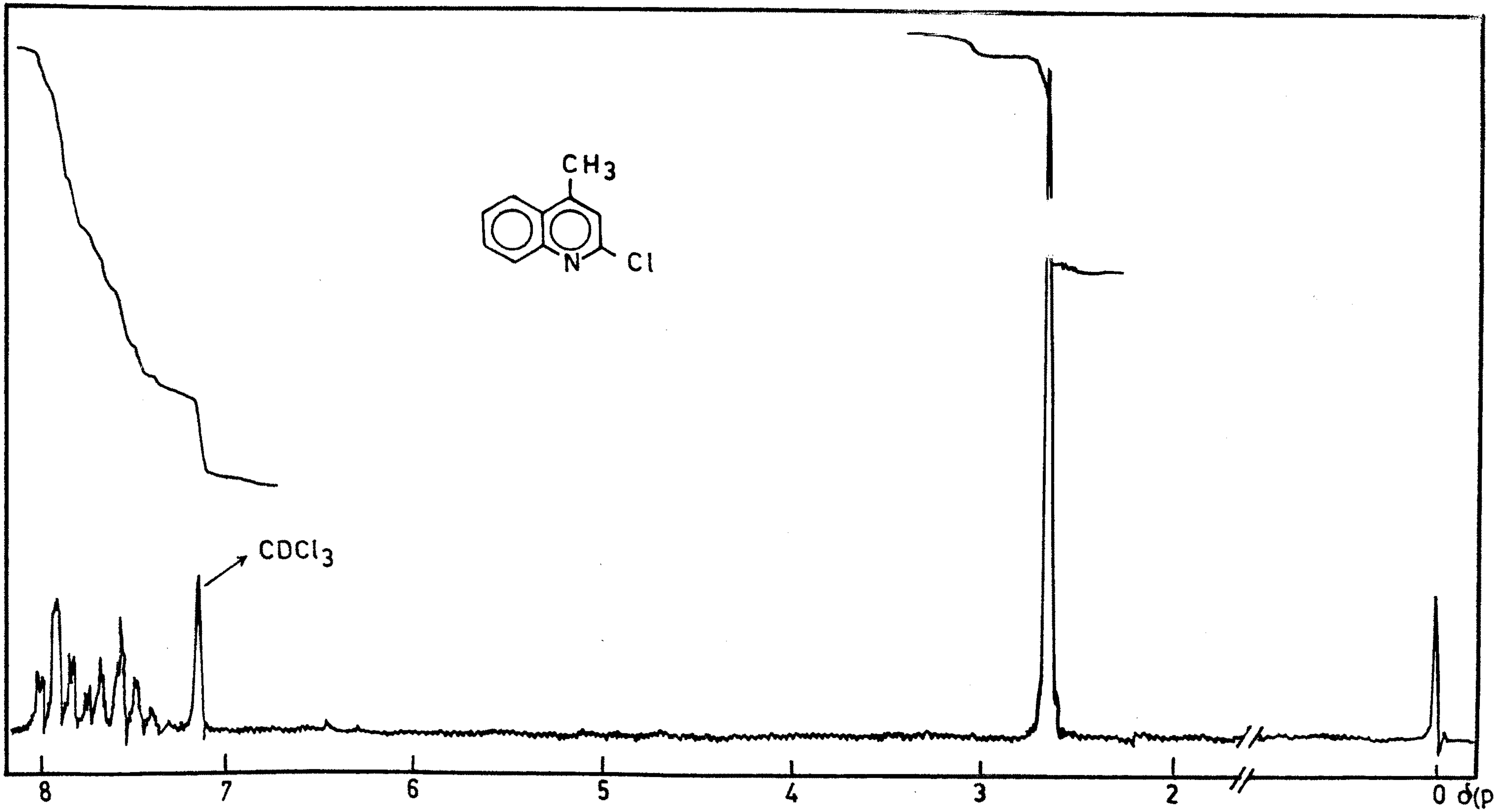
V_b — R = CH_3 (o-NH_2)

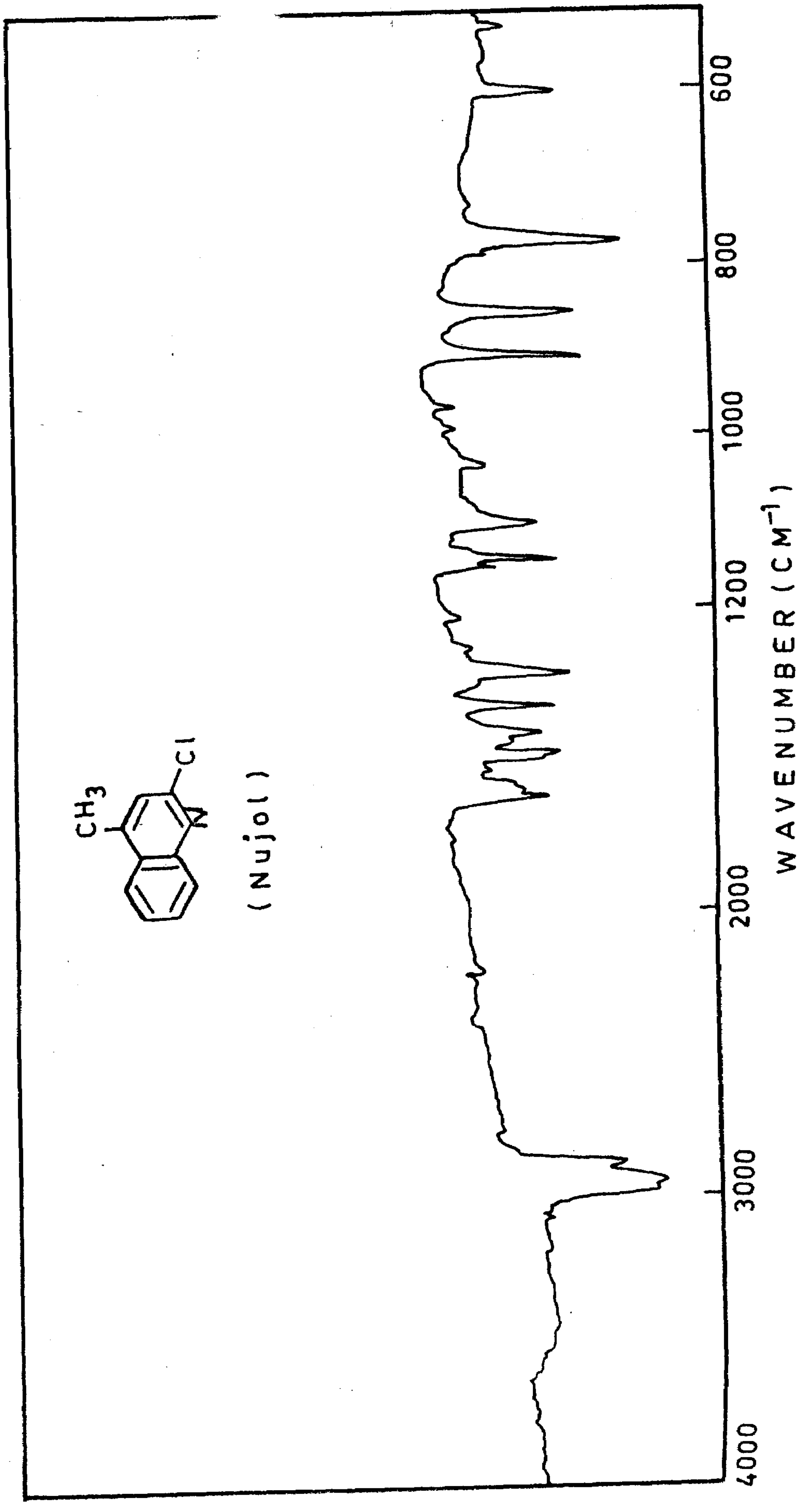
V_c — R = CH_3 (m-NH_2)

Table 3

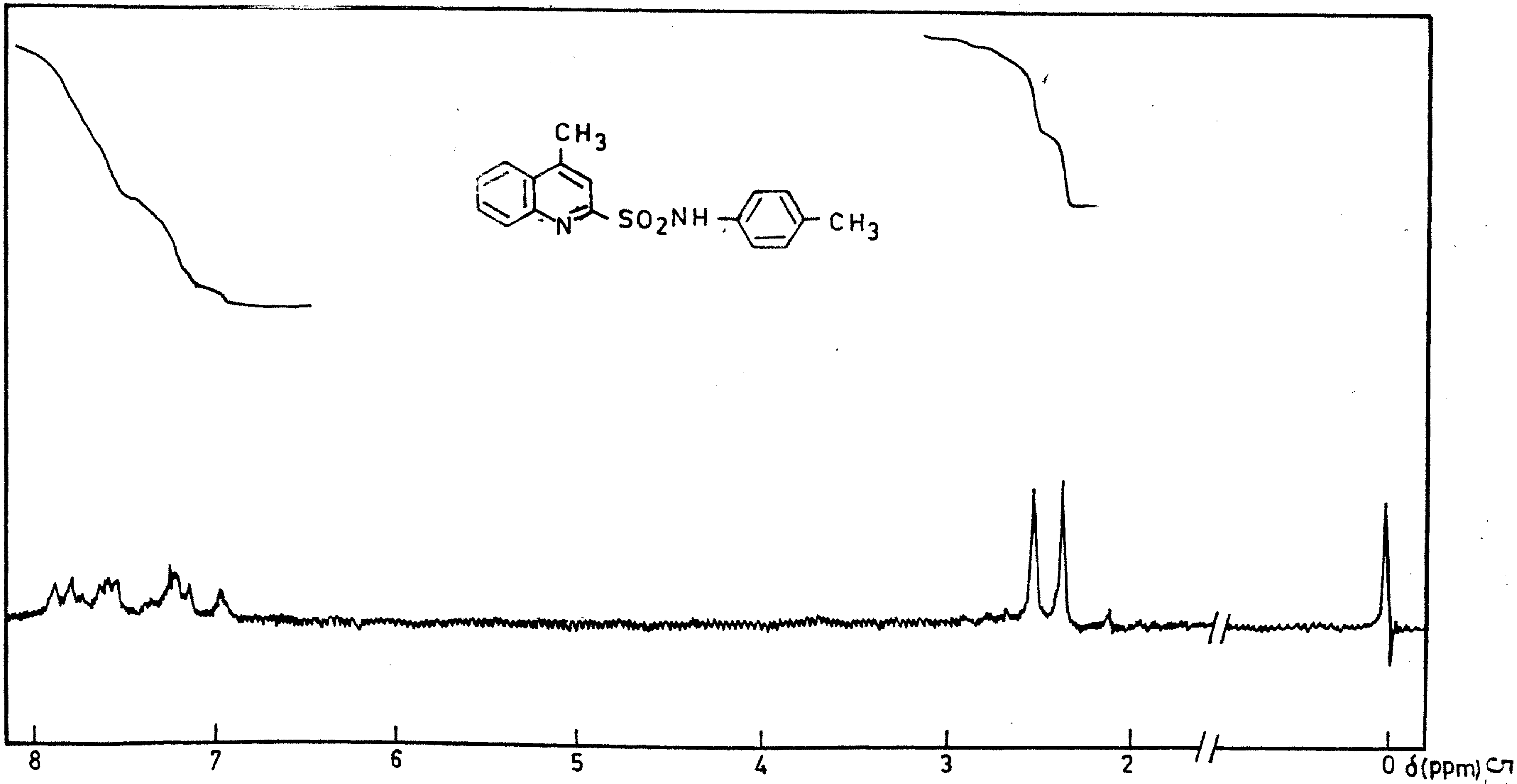
Compound	M.P. °C	% Yield	Molecular formula	Elemental analysis					
				Found			Required		
				C	H	N	C	H	N
Va	255	52.47	$C_{16}H_{15}N_3SO_2$	61.30	4.70	13.40	61.35	4.71	13.42
Vb	262	50.66	$C_{17}H_{17}N_3SO_2$	62.32	5.20	12.80	62.38	5.19	12.84
Vc	258	53.60	$C_{17}H_{17}N_3SO_2$	62.30	5.18	12.79	62.38	5.19	12.84

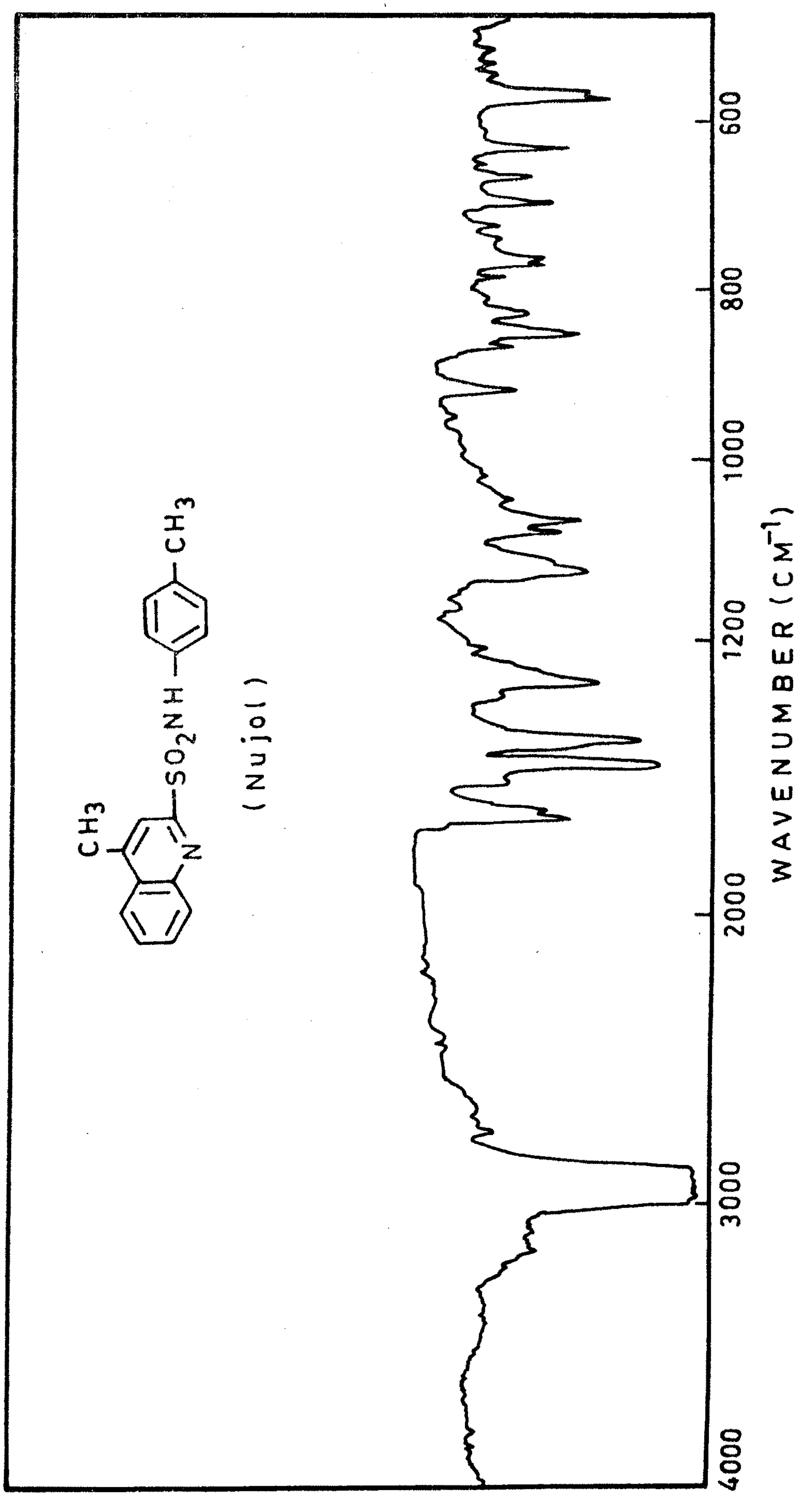
PMR Spectrum of 2-chloro-4-methyl quinoline .



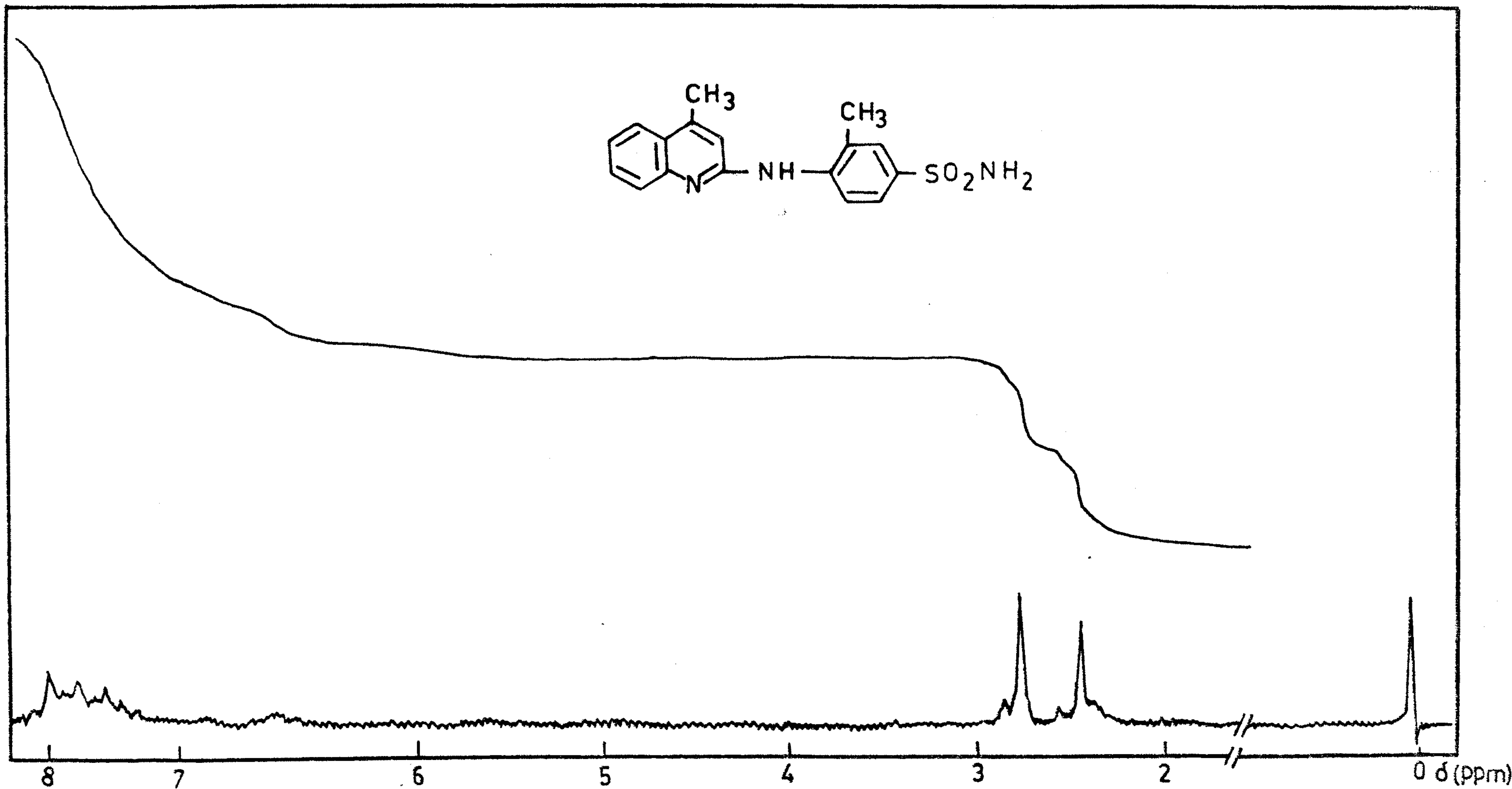

CH₃
Cl
N
(Nujol)
600
800
1000
1200
2000
3000
4000
WAVENUMBER (CM⁻¹)

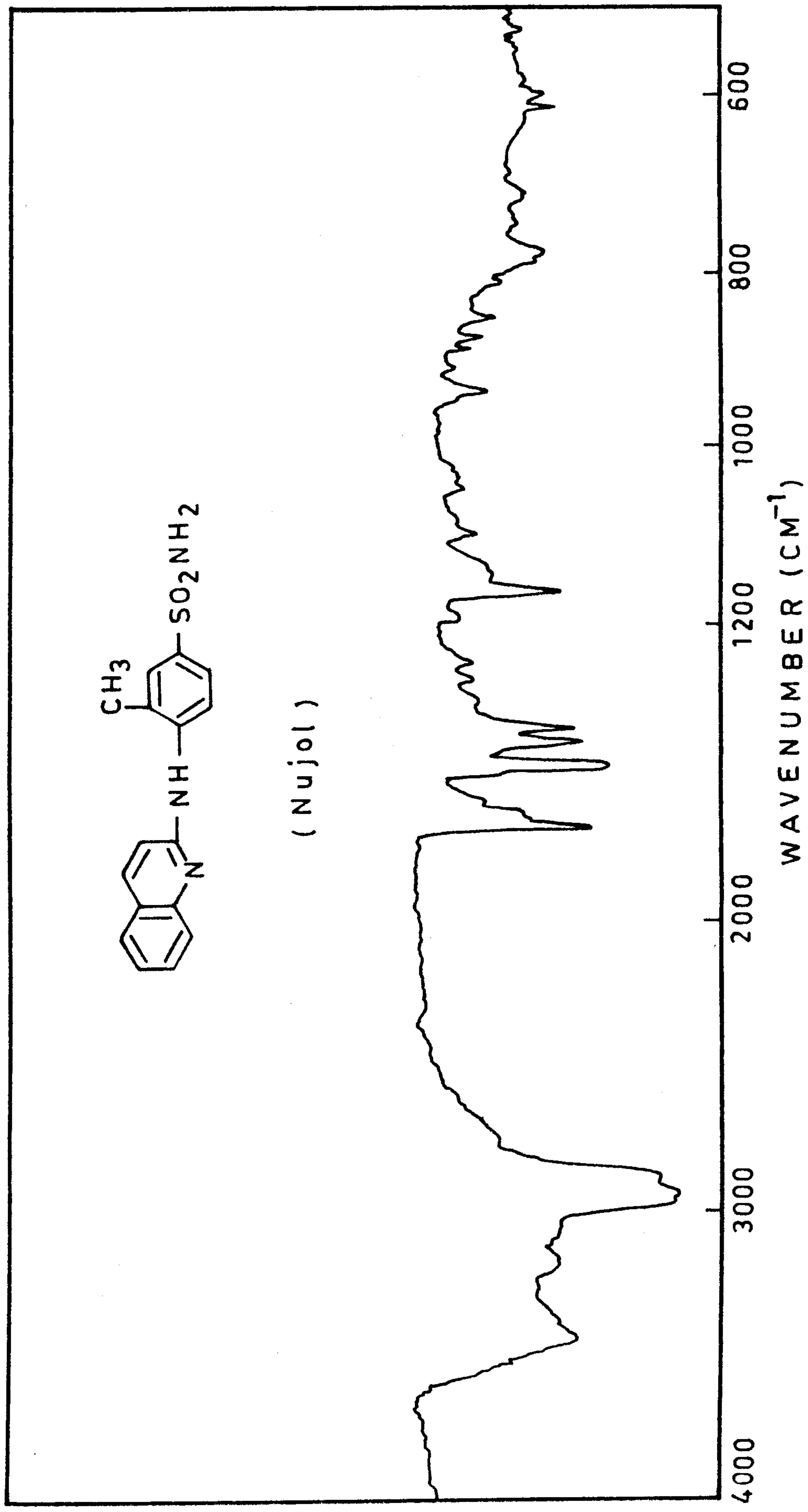
PMR Spectrum of 2-Lepidyl-p-toluene sulfonamide.



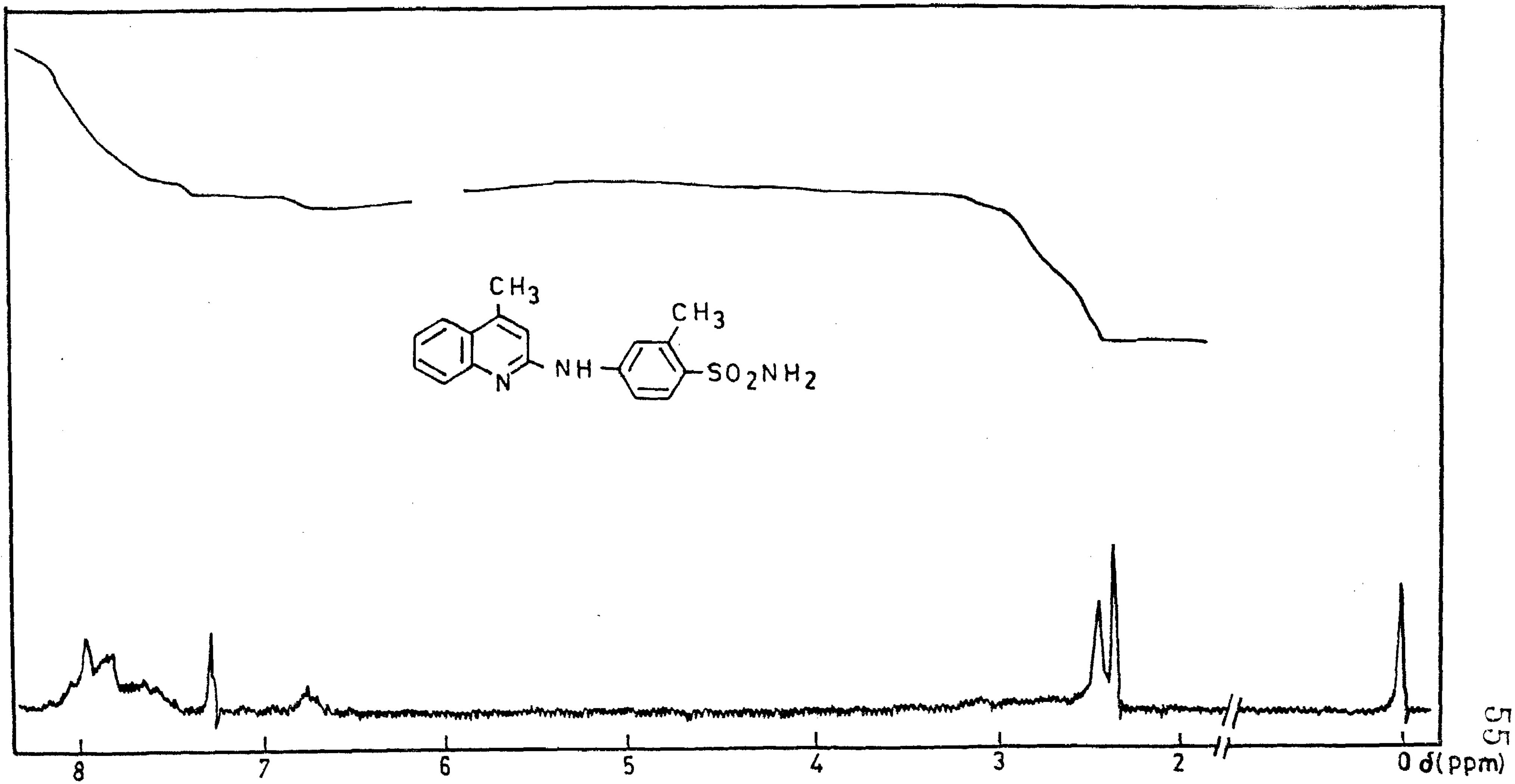

CH3
CH3
N
SO2NH
(Nujol)
4000
3000
2000
1200
1000
800
600
WAVENUMBER (CM-1)

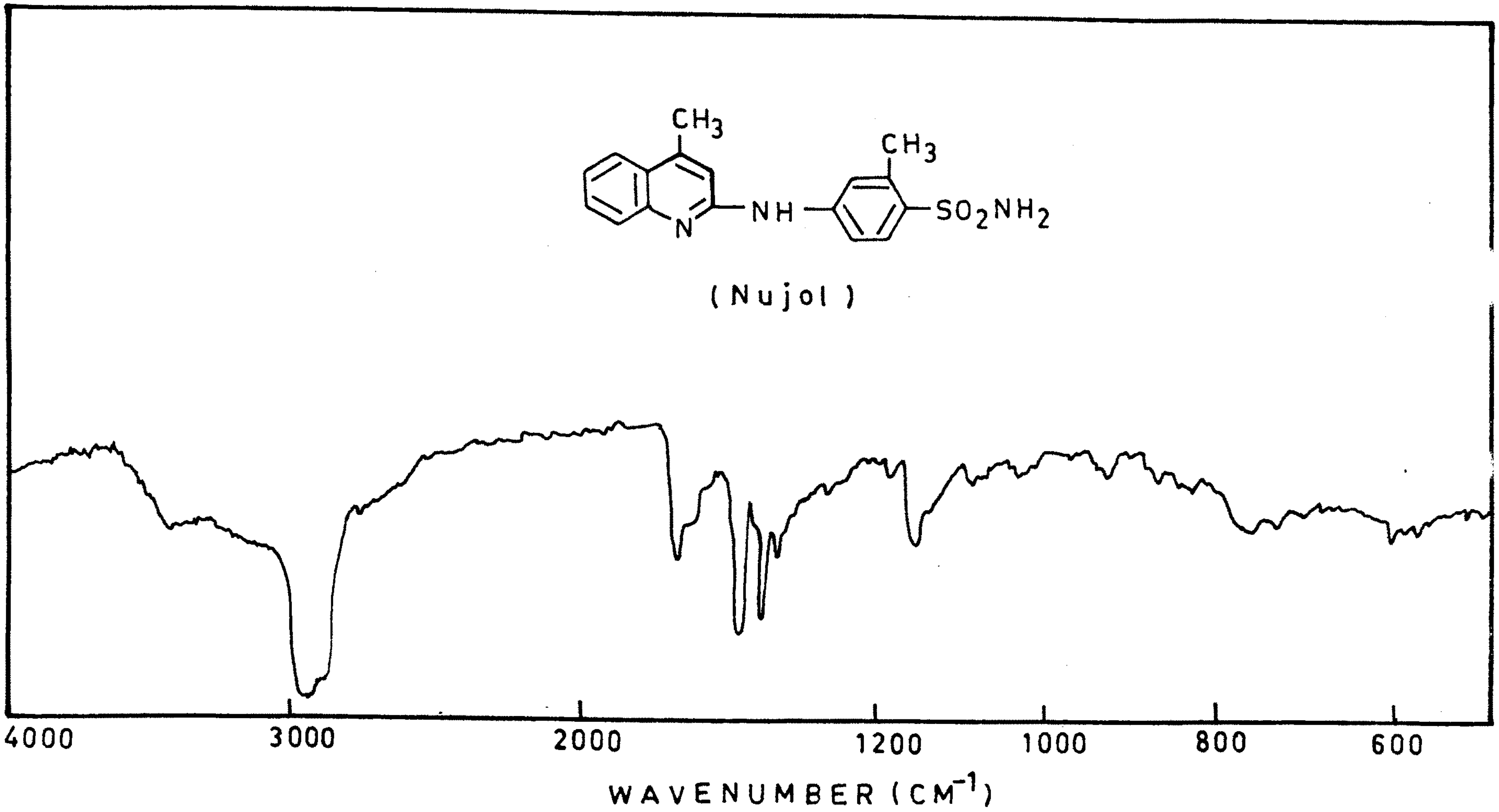
PMR Spectrum of 2-Lepidyl-o-toludine-p-sulfonamide .

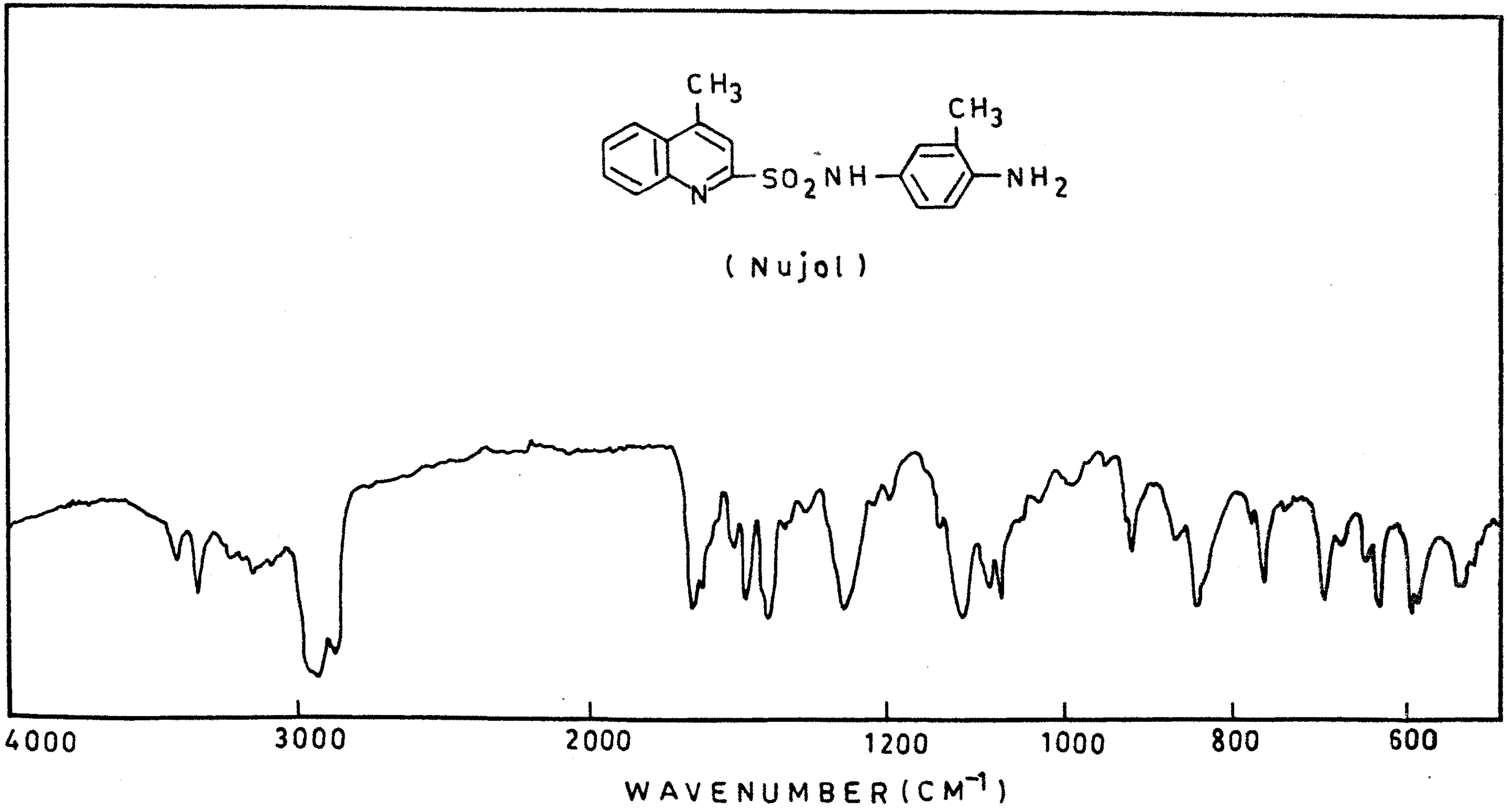


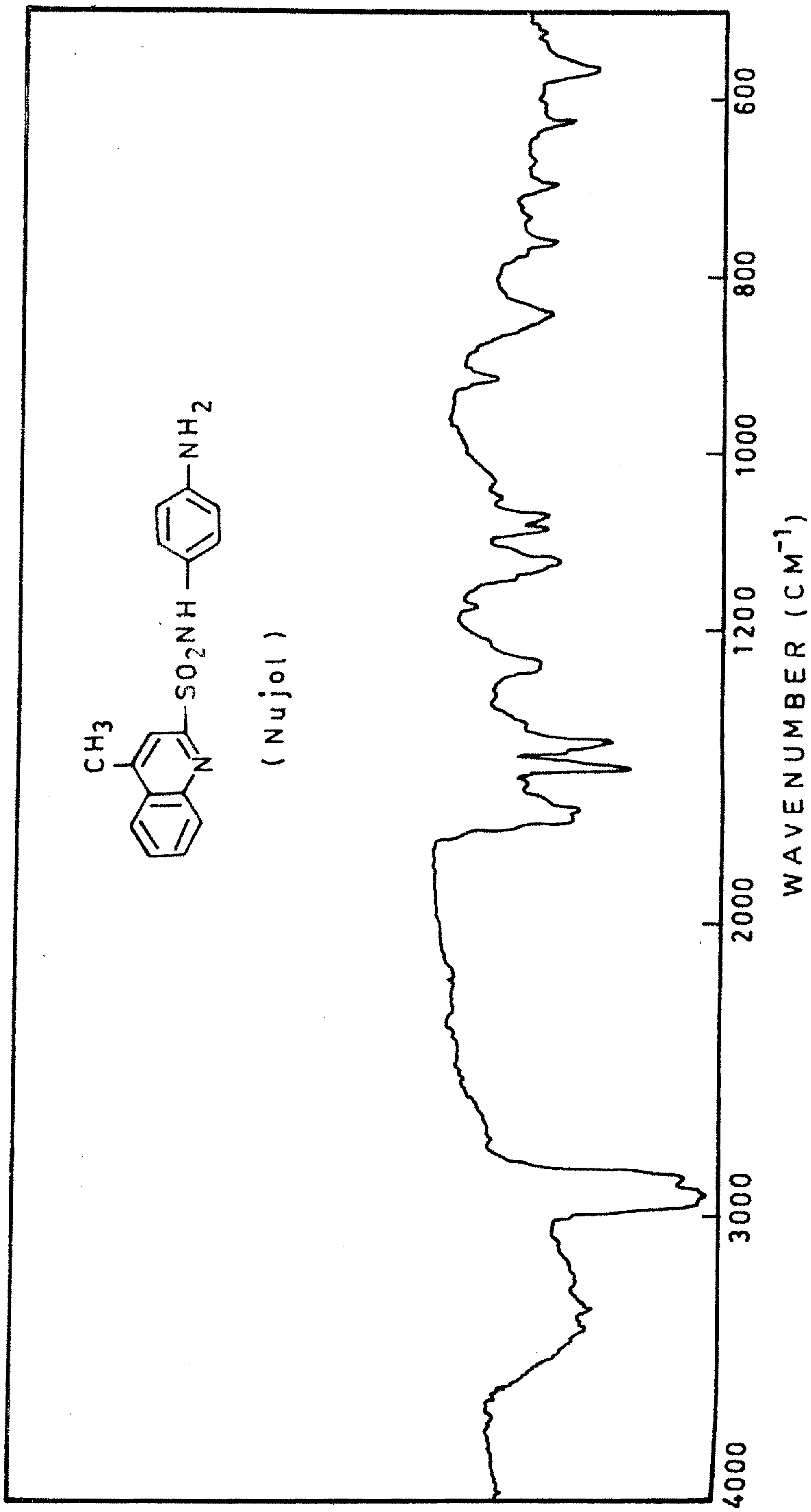

CH3
SO2NH2
NH
N
(Nujol)
4000
3000
2000
1200
1000
800
600
WAVENUMBER (CM-1)

PMR Spectrum of 2-Lepidyl-m-toludine sulfonamide . 2




CH3
CH3
N
NH
SO2NH2
(Nujol)
4000
3000
2000
1200
1000
800
600
WAVENUMBER (CM-1)


CH3
CH3
N
SO2NH
NH2
(Nujol)
4000
3000
2000
1200
1000
800
600
WAVENUMBER (CM-1)



CH3
SO2NH
NH2
N
(Nujol)
4000
3000
2000
1200
1000
800
600
WAVENUMBER (CM-1)

2 ·7 REFERENCES

1 Barger and Modlin, J. Am. Chem. Soc. <u>62</u> 1079 (1940).

2 Jeney, E. and Zsolani, T., Baktsriol, Parasitank Abst. I Orgig., 537 (1964).

3 Burger A. Medicinal Chemistry, 3rd Ed. Part I Wiley Interscience, N.Y., p. 69 (1970).

4 Dandegaonkar, S.H. and Mesta C.K.J. Med. Chem., <u>8</u> 884 (1963).

5 Acheson, J. Chem. Soc., 4731 (1956).

6 Gawnon and Sporri, J. Am. Chem. Soc., <u>67</u> 514 (1945).

7 Mizzank and Spoerri, J. Am. Chem. Soc. <u>67</u> 1652(1945).

8a Ciba Ltd. Brit. Patent 866838 May 3, 1961.

8b Chem. Abst. <u>56</u> 3490 (1962).

9 Berry, Belton, Conalty, and Towomey. Nature <u>162</u>, 622 (1948).

10 Kind and Beer. J. Chem. Soc., 791 (1961).

11 Schales and Fridman Arch. Biochem., <u>6</u> 329 (1945).

12 Deliwala and Rajgopalan, Proc. Ind. Acad. Sci., 31 A, 107 (1950).

13 C.H. Browning, J. Path. Bact., 27 121 (1924).

14 E. Hesse Arch. Exptl. Path. Pharmacol., 249 (1930).

15 C.H. Browning Proc. R. Soc. London, 372 (1932).

16 K. Matsamura Bull, Agric. Chem. Soc., (Japan) 2 159 (1926),

17 B.L. Freedlandev, Proc. Soc. Exptl., Biol. Med., 81 66, (1952).

18 H. Coline S. African, Pat. 68 03, 636 (1968).

19 Miroslav Czech. Pat., 110, 180 (1954).

20 O.H. Iversen, Nature, (London) 219, 5149 (1968).

21 S.H. Dandegaonkar and G.R. Revanker, Arch. Pharm., 300 897 (1967).

22 A.R. Surry, J. Am. Chem. Soc., 71 3354 (1949).

23 G.P. Dutta, Ind. J. Microbiol., 6 83 (1956).

24a J.N.S. Yadava, and G.P. Datta Indian J. Med. Res., 61 971 (1973).

24b S.S. Chakravorthi, Pranab, K. Sen Gupta, Subhankar Chaudhuri Michael Das Ind. Jr. of Chemistry Vol. 24 B 737 - 746 July, (1985).

25 Bueding, E. Ann. N.Y. Acad. Sci., 50 115 (1948).

26a Robinson, R. Nature., 162 524 (1948).

26b Barash, M. and Osbond, J.M. Chemy Ind., 490 (1958).

27 Taylor A.E.R. and Terry, R.J.J. Pharm. Pharmacol. 11 94 (1959).

28 Austin W.C., Lunts L.H.C. Potter M.D. and E.P.J. Pharm. Pharmacol., 11 80 (1959).

29 Hawking, F. and Terry, R.J.J. Pharm. Pharmacol. 11 94 (1959).

30 Mohr W. Berka W., Knutgen H. and Ohr. A.Med. Mschr. N.Y. 5 676 (1951).

31 Grote K. Wschr Kinderheik., 103 462 (1955).

32 Reese G. Bornemann. V. and Mander E. Klin Wschr., 34 1131 (1956).

33 Soliman R. and Hammouda N.A. J. Pharm. Sci., 68 1377 (1979).

34 Pathak B.R., Pathak B., Dattas and Lahiri S. : C.J. Ind. Chem. Soc., 61 151 (1984).

35a Rashmi Dury Syed Abüzar and Satyavan Sharma - Ind. J. of Chemistry Vol., 24B 408-413, April (1985).

35b Peter W. Exptl. Parasitology., 45 231 (1955).

36 Lutz Ashburn Freek, Jordon leak martin, Rowlett and Wilson J. Am. Chem. Soc., 68 1285 (1946).

37 Rowlett and Lutz, J. Am. Chem. Soc., 68 1288 (1946).

38 H. Gilman and D. Blume J. Am. Chem. Soc., 65 2467 (1943).

39 M. Kiamud Din and A.K. Choudhary Chem. Ind. (London) 1840 (1963).

40 M. Kiamud-din, and A.K. Choudhary Pakistan J. Sc. Ind. Res., 9 326 (1966).

41 M. Grodon and D.E. Pearson. J. Org. Chem., 29 329 (1964).

42 A.L. Palo-Coll and G. Palomo Coll. Afinidad., 28 101 (1951).

43 J.P. Phillips Chem. Rev., 56 271 (1956).

44 L. Knorr Annalene. 69 236 (1886).

45 A.D. Ainley, and H. King Proc. Roy Soc., 60 B 125 (1938).

46 Y. Mizuno, Yakugaku Zasshi, 69, 126 (1949).

47 C.E. Kaslow and W.M. Lauer Org. Synth. Collective Vol.3. J.Wiley and Sons Inc. New York 194 (1955).

48 H.J. Creech Proc. Am. Assoc. Cancer Research., 2 195 (1957) Ann. N.Y. Acad Sci.,68 868 (1958).

49 F. Bergel V.C.E. Burnop and J.A. Stock J. Chem. Soc. 1223 (1955).

50 F. Bergel and G.E. Lewis J. Chem. Soc. 1816 (1957).

51 L.H. Schimidt National Research Council Pub. 81 206 (1951).

52 Cadwell W.T. and Kornfeld E.C.J. Am. Chem. Soc. 64 1965 (1942).

53 Naegeli C. Kundig W. and Brandenburger H. Helv. Chem. Acta 21 1746-56 (1938).

54 Chemetron S. a. r. l Fr. patent 1450625 (1966).

55 Chrzaszczewska, A. and Szalecki W. Acta Chim. 12 129-32 (1967).

56 Mcfarland J.W. and Lucilac Yao J. Org. Chem.35 (1) 1235 (1970).

57a Knorr Anne. (69 236 (1886).

57b Mikhailov J. Gen. Chem. (U.S.S.R.) 6 511 (1936).

58 C. Pellerano, Ann. Chim. 53 1850-9 (1963).

59 Text-Book of Practical Organic Chemistry including Qualitative and quantitative by Vogel 4th Ed. 684.

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