PROTON MAGNETIC RESONANCE SPECTRA OF PHENOTHIAZINE DERIVATIVES

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Abstract: Proton magnetic resonance spectra of nuclear substituted, N-alkylated- and aza-phenothiazines with particular reference to structural elucidation has been discussed.

Although the literature is fully provided with studies of phenothiazine[1], there are few data dealing with the nmr spectra of nuclear substituted phenothiazines[2]. The use of nmr spectroscopy has been recommended for the identification of phenothiazine drugs and in the detection of impurities in samples of drugs[3-5], in as much as the substituents and particularly the side chain gave rise to characteristic signals.

The widespread use of phenothiazine tranquilisers has given rise to extensive investigations into the structure of their metabolites[6], variously thought to be hydroxylated in the 3-, 7-[7], or 8- positions[8]. Since the infra- red spectrum will not readily distinguish a 2, 7- disubstituted phenothiazine from its 2, 8- isomer[9] (both being 1,2,4-trisubstituted benzenes), the use of nmr spectroscopy offered an attractive solution to the problem of unambiguous structure assignment of the metabolites of the phenothiazine drugs, if individual substitution sites in the molecule could be distinguished.

Comparison of the nmr spectra of phenothiazine and 2-chlorophenothiazine on one hand, and those of the corresponding 10-(3-dimethylaminopropyl)-substituted phenothiazines on the other, showed clearly that the only difference between the spectra of each N-unsubstituted and N-substituted pair was the bulk chemical shifts of each aromatic hydrogen atom, and the coupling constants, were the same.

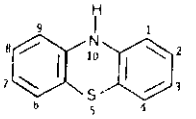
Analysis of the chemical shift data for phenothiazine and chloro-substituted phenothiazines (in which the hydrogen frequencies are not altered by shielding)[10] gave the values summerised in Table I. The strong interaction between neighbouring hydrogens (spin-spin coupling) which exists between neighbouring hydrogens (J = 5 to 10 c.p.s.), and the weaker couplings by meta hydrogens (J = 1 to 5 c.p.s.), are very sensitive to substitution. When substitution takes place in the 3-position, the 3,4-ortho coupling disappears and only the large 1,2-, 6,7-, and 8,9-

ortho couplings remain. Disubstitution at the 2,8-positions leaves only the 3,4-and 6,7-ortho couplings and weak meta coupling of H-1 and H-9. Disubstitution at 3,7-leaves only 1,2- and 8,9-ortho couplings and weak meta coupling of H-4 and H-6. A combination of chemical shift, spin-spin couplings and integration data permits the identification of individual hydrogens at each site in the aromatic rings[11].

Table I

Chemical Shifts of Aromatic Hydrogens

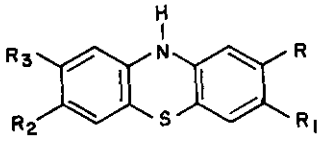
in Chloro-substituted Phenothiazines.



Hydrogen	Chemical Shifts[a], c.p.s.	Coupling Constants, c.p.s.
1	395(m)-401(0)	$J_{1',8} = 9$
2	423(0)	
3	404(0)	
4	414(m)-418(0)	
6	419(m)-420(0)	$J_{6,8} = 2$
7	405(0)	
8	422(0)	
9	396(m)-401(0)	$J_{8,9} = 8$

a. Shifts are listed for hydrogens substituted either ortho (0) or meta (m) to a chlorine atom.

Nmr spectrum of 2,7-dichlorophenothiazine (1, Fig. I) shows two peaks centered about 396 c.p.s. which are due to part of the AB coupling between hydrogens at C-8 and C-9 and are assigned to the C-9 hydrogen ($J_{8,9} = 8$ c.p.s.). The adjacent line at 402 c.p.s. is caused by the hydrogen on C-1. The low field doublet at 421 c.p.s. is the other half of the AB system, arising from the C-8 hydrogen ($J_{6,8} = 2$ c.p.s.). The line at 419 c.p.s. is assigned to the hydrogen pn C-6, while the multiplet centered about 412 c.p.s. is part of an AB system involving the C-3 and C-4 hydrogens, the remaining half of which lies under the peaks assigned to hydrogens at C-6 and C-1.



1, $R_1 = R_3 = H$; $R = R_2 = Cl$

2, $R = R_3 = H$; $R_1 = R_2 = Cl$

3, $R_1 = R_2 = H$; $R = R_3 = Cl$

4, $R_1 = OCH_3$; $R = R_2 = R_3 = H$

5, $R_1 = R_2 = OCH_3$; $R = R_3 = H$

6, $R = Cl$; $R_2 = OCH_3$; $R_1 = R_3 = H$

In 3,7-dichlorophenothiazine (2, Fig. 2) the doublet centered at 395 c.p.s. is one-half of an AB system belonging to the C-1 hydrogen with $J_{1,2} = 9$ c.p.s. The other half of the AB due to the C-2 hydrogen at 423 c.p.s. is further split by the meta hydrogen on C-4 with $J_{2,4} = 2.5$ c.p.s. The tall sharp line at 418 c.p.s. is a superposition of the C-4 hydrogen

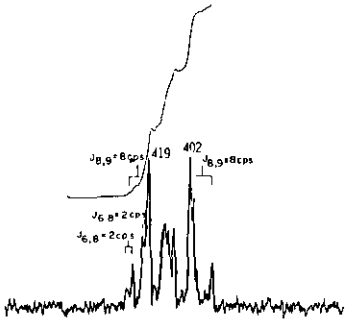


Fig. 1. N.m.r. spectrum (60 Mc.) of 3,7-dichlorophenothiazine in perdeuteriodimethyl sulfoxide. Field increases from left to right. Chemical shifts are in c.p.s. downfield from an internal tetramethylsilane reference.

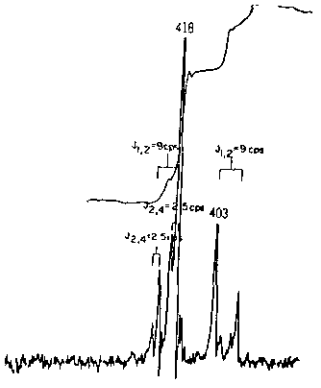


Fig. 2. N.m.r. spectrum (60 Mc.) of 2,7-dichlorophenothiazine in perdeuteriodimethyl sulfoxide. Field increases from left to right. Chemical shifts are in c.p.s. downfield from an internal tetramethylsilane reference.

and part of the AB coupling from the C-3 hydrogen.

In 2,8-dichlorophenothiazine (3, Fig. 3) both aromatic rings are identical. The doublet centered about 418 c.p.s. is part of an AB system due to the C-3 and C-4 hydrogens and is assigned to the hydrogen at C-4, since no meta splitting is observed. The multiplet at 400 c.p.s. is assigned to the C-1 hydrogen with a small meta coupling due to the C-3 hydrogen. This group also includes part of the AB system of the hydrogen at C-3. The signal at 408 c.p.s. contains part of the AB coupling of hydrogens at C-3 and C-4.

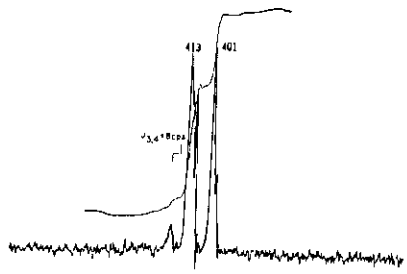


Fig. 3. N.m.r. spectrum (60 Mc.) of 2,8-dichlorophenothiazine in perdeuteriodimethyl sulfoxide. Field increases from left to right. Chemical shifts are in c.p.s. downfield from an internal tetramethylsilane reference.

The spectrum of 3-methoxyphenothiazine (4, Fig. 4) demonstrates the strong shielding caused by the methoxy group. There, the C-1, C-2, and C-4 hydrogens are clustered together at 396 c.p.s. There appears to be an ABX pattern for the hydrogens at C-6 and C-7 and C-8 and C-9, in which the two sets are equivalent, one portion of the AB (at 415 c.p.s.) being due to the hydrogens at C-7 and C-8 and the other (407 c.p.s.) attributed to those at C-6 and C-9.

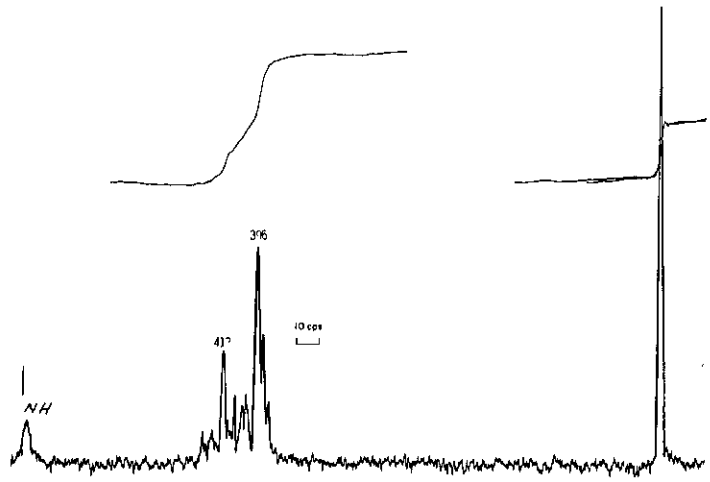


Fig. 4. N.m.r. spectrum (60 Mc.) of 3-methoxyphenothiazine in perdeuteriodimethyl sulfoxide. Field increases from left to right. Chemical shifts are in c.p.s. downfield from an internal tetramethylsilane reference.

Both 3,7-dimethoxy-(5) and 2-chloro-7-methoxyphenothiazine (6) showed the same effect (Fig. 5 and 6) reducing the chemical shift between hydrogens at position 6, 8 and 9, and resulting in an incompletely resolved multiplet at 396 c.p.s.

Fig. 5. N.m.r. spectrum (60 Mc.) of 3, 7-dimethoxyphenothiazine in perdeuteriodimethyl sulfoxide. Field increases from left to right. Chemical shifts are in c.p.s. downfield from an internal tetramethylsilane reference.

In 2-chloro-7-methoxyphenothiazine(6), the doublet centered at 415 c.p.s. is part of the AB system of the C-3 and C-4 hydrogens, and is assigned to that at C-4. A small doublet

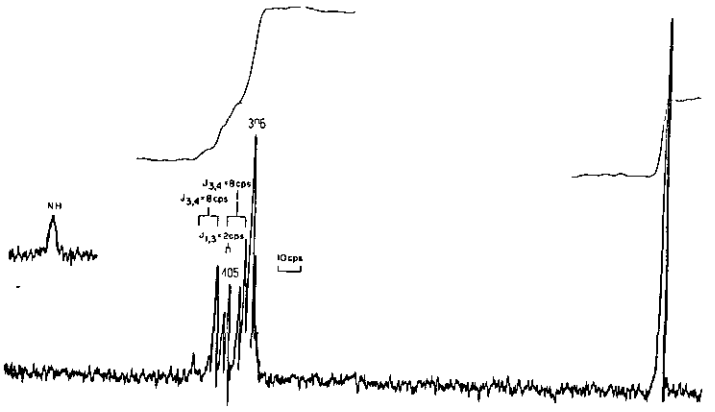
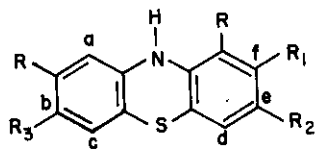


Fig. 6. N.m.r. spectrum (60 Mc.) of 2-chloro-7-methoxyphenothiazine in perdeuteriodimethyl sulfoxide. Field increases from left to right. Chemical shifts are in c.p.s. downfield from an internal tetramethylsilane reference.

at 405 c.p.s. represents the remaining half of the AB coupling due to hydrogen at C-3 and also shows meta coupling by the C-1 hydrogen, which is present in the multiplet at 396 c.p.s. Integrated intensities were in agreement with the predicted ratio of 1:1:8.[11]

In 8-ethoxy-1-nitrophenothiazine (7) there is a triplet for CH_3, at δ = 1.36 (J = 6 c.p.s.), whereas for $-CH_2-$, a quartet at δ = 3.95 (J = 6 c.p.s.). The most downfield aromatic proton (H_d) appeared at δ = 7.81 (J_o = 8; J_m = 2) owing to the electron sink caused by a nitro group in the para position, and secondly, to the peri-effect of the adjacent sulphide linkage. The proton H_f appears as a doublet (J_o = 8; J_m = 2) at δ 7.10, and H_e at δ = 6.70 (J_o = 8) as a triplet.[12]



7, R = NO_2; R_4 = OC_2H_5 = R_2 = R_3 = R_1 = H

8, R = NO_2; R_4 = OCH_3; R_2 = R_3 = R_1 = H

9, R_3 = NO_2; R_1 = OCH_3; R = R_2 = R_4 = H

10, R_1 = R_3 = CH_3; R = R_2 = R_4 = H

11, R_3 = NO_2; R_1 = OC_2H_5; R = R_2 = R_4 = H

12, R_1 = CH_3; R_3 = NO_2; R = R_2 = R_4 = H

13, R_1 = CH_3; R_3 = OCH_3; R = R_2 = R_4 = H

14, R = R_2 = NO_2; R_4 = OC_2H_5; R_1 = R_3 = H

The comparative downfield shift of H_f to H_e may be ascribed to the large (-I effect) of the nitro group at its ortho position. The proton H_e appeared as a doublet at δ = 6.91 and protons H_a and H_b appeared as a singlet and a doublet (J_o = 8) at δ = 6.33 and δ = 6.41, respectively. The comparative shielding of H_a to H_b may be attributed to the electronic effects of the ring substituents. The proton at nitrogen appeared as a broad hump at δ = 9.73, which was confirmed by D_2O exchange.

In 8-methoxy-1-nitrophenothiazine (8) the three protons of the methoxyl group ($-O-CH_3$) appeared as a singlet at δ = 3.73. The proton at nitrogen (-N-H) appeared at δ = 9.75, confirmed by D_2O exchange. The aromatic proton H_a appeared at δ = 6.33, and H_b, H_c, H_d, H_e and H_f at δ = 6.43, δ = 6.95, δ = 7.80, δ = 6.71 and δ = 7.06 respectively with J_o = 8 and J_m = 2 c.p.s.

In 3-nitro-8-methoxyphenothiazine(9), a singlet at δ = 3.70 for three protons of the methoxyl group is consistent with the one reported above. The most downfield proton H_e appeared as a doublet (J_o = 8; J_m =2) at δ = 7.90, which has been accributed to the electron sink caused by the o-nitro group. The proton H_d showed a singlet at δ = 7.71. The comparative downfield shift of H_e to H_d, however, could not be explained. The proton H_f appeared as a

sharp doublet (J_o = 8) at δ = 6.73. The protons H_b and H_c appeared as two doublets (J_o = 8) at δ = 6.50 and δ = 6.86 respectively. The proton H_a showed a singlet at δ = 6.36 (J_m = 2).

In 3,8-dimethylphenothiazine(10), the protons of the two methyl groups appeared as a sharp singlet at δ = 2.30. The most downfield aromatic proton H_d appeared as a broad singlet at δ = 7.91 (J_m =2). The protons H_e and H_f appeared as doublets at δ = 7.18 and δ = 7.41 (J_o = 8). The protons H_b and H_c showed two doublets (J_o = 8; J_m = 2 c.p.s.) at δ = 6.88 and δ = 6.76, and proton H_a appeared as a singlet (J_m = 2) at δ = 6.76. The protons at nitrogen appeared at δ = 9.33, confirmed by D_2O exchange.[12]

In 3-nitro-8-ethoxyphenothiazine(11), a triplet appeared at δ = 1.3, (J = 6 c.p.s.) for $-CH_3$ and a quartet at δ = 4.05 (J = 6 c.p.s.) for $-CH_2-$ protons. The aromatic protons appeared in the range δ = 6.16 to δ = 8.0 and could not be distinguished due to the low solubility of the sample in the deuterated solvent used.

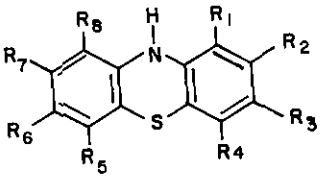
In 3-nitro-8-methylphenothiazine(12), a sharp singlet appeared at δ = 2.0 for $-CH_3$ protons and aromatic protons appeared in between δ = 6.33 to δ = 8.0 region.

3-Methoxy-8-methylphenothiazine(13) gave a sharp singlet at δ = 2.11 for the three protons of the methoxyl group. The -N-H- proton was found at δ = 8.21, and the aromatic protons appeared between δ = 6.38 to δ = 6.90 and could not be resolved.

1,3-Dinitro-8-ethoxyphenothiazine(14) gave a triplet at δ = 1.38 (J = 7) and a quartet at δ = 4.05 (J = 2) for three and two protons of $-CH_3$ and $-CH_2-$ groups respectively. The aromatic protons H_a, H_d and H_e appeared as singlets at δ = 6.41, δ = 8.80 and δ = 9.13, respectively. The protons H_b and H_c showed two doublets at δ = 6.70 (J_o = 6) and δ = 7.30 (J_o = 9; J_m = 3), respectively. The proton at 10-N appeared as a broad singlet at δ = 10.45.

A combination of the chemical shifts, spin-spin couplings, and integration data for these phenothiazines(7-14) permits the identification of an individual proton in the aromatic ring.[12] The results are summerised in Table II and Table III.

TABLE II



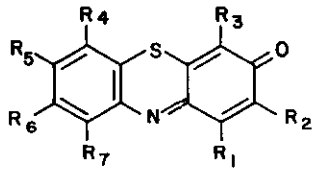
Compound	Solv.	Chemical Shift (δ), (Multiplicity) (Coupling Constant), (J) Assignment	(δ for aromatic protons); (multiplicity); (Coupling Constant) (J)	Ref.
8-Ethoxy-1-nitro-	$CDCl_3$	9.73(s), -NH-	R_2, 7.10 (d), (J_m^* = 2, J_o^* = 8)	12
phenothiazine(7)		3.95(q), (J-6),-O-CH_2-	R_3, 6.70 (t), (J_m - 2, J_o = 8)	
		1.36(t), J=6, -CH_3	R_4, 7.81 (d), (J_m = 2, J_o = 8)	
			R_5, 6.91 (d), (J_m = 2, J_o = 8)	
			R_6, 6.41 (d), (J_m = 2, J_o = 8)	
			R_8, 6.33 (s), (J_m = 2)	
8-Methoxy-1-Nitro-	$CDCl_3$	9.75(s), -NH-	R_2, 7.06 (d), (J_m = 2, J_o = 8)	12
phenothiazine(8)		3.73(s), -O-CH_3	R_3, 6.71 (t), (J_m = 2, J_o = 8)	
			R_4, 7.80 (d), (J_m = 2, J_o = 8)	
			R_5, 6.95 (d), (J_m = 2, J_o = 8)	
			R_6, 6.43 (d), (J_m = 2, J_o = 8)	
			R_8, 6.33 (s), (J_m = 2)	
8-Methoxy-3-nitro-	$DMSO-d_6$	3.70(s), -O-CH_3	R_1, 6.73 (d), (J_o = 8)	12
phenothiazine(9)			R_2, 7.90 (d), (J_m = 2, J_o = 8	
			R_4, 7.71 (s), (J_m = 2)	
			R_5, 6.86 (d), (J_o = 8)	
			R_6, 6.50 (d), (J_m = 2, J_o = 8)	
			R_8, 6.36 (s), (J_m=2)	
3, 8-Dimethyl-	$CDCl_3$	9.33(s), -NH-	R_1, 7.41 (d), J_o = 8	12
phenothiazine(10)		2.30(s), -CH_3	R_2, 6.76 (d), J_m = 2, J_o = 8	
			R_4, 7.91 (s), J_m = 2	
			R_5, 7.18 (d), J_o = 8	
			R_6, 6.88 (d), J_m = 2, J_o = 8	
			R_8, 6.76 (s), J_m = 2	

Compound	Solv.	Chemical Shift (δ), (Multiplicity) (Coupling Constant), (J) Assignment	(δ for aromatic protons); (Multiplicity), (Coupling Constant) (J)	Ref.
8-Ethoxy-3-nitro-phenothiazine(11)	DMSO-d_6	4.05(q), (J=6), $-O-CH_2-$ 1.30(t), (J=6), $-CH_3$	R_1 - R_8, 6.16 - 6.80, m.	12
8-Methyl-3-Nitro-phenothiazine(12)	Acetone-d_6	2.0 (s), $-CH_3$	R_1 - R_8, 6.33 - 8.00, m	12
3-Methoxy-8-methyl-phenothiazine(13)	DMSO-d_6	8.21(s), -NH- 2.11(s), $-CH_3$ 3.63(s), $-O-CH_3$	R_1 - R_8, 6.38 - 6.90, m.	12
1,3-Dinitro-8-ethoxy-phenothiazine(14)	$CDCl_3$	10.45(s), -NH- 4.05 (q), (J=2), $-O-CH_2-$ 1.38(t), (J=7), $-CH_3$	R_2, 9.13 (s) R_4, 8.80 (s) R_5, 7.30 (d), J_m=3, J_o=9 R_6, 6.70 (d), J_o = 6 R_8, 6.41 (s)	12

* J_m, meta coupling, J_o, multiplicity owing to ortho coupling

s, singlet; d, doublet; t, triplet; q, quartet.

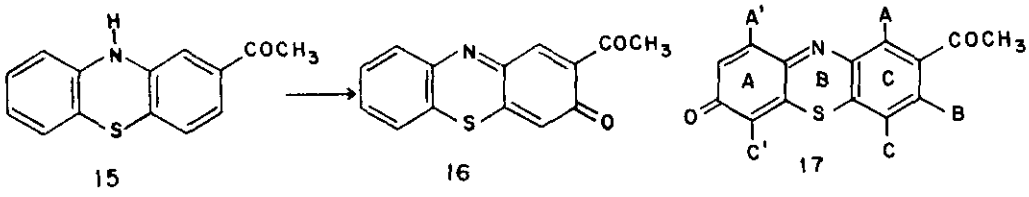
TABLE III



Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), assignment.	Ref.
R_1 - R_7 = H	$CDCl_3$	7.62 (d), $J_{1,2}$ = 10, R_1 6.87 (q), $J_{2,3}$ = 2, R_2 6.74 (d), $J_{3,2}$ = 2, R_3 7.5 - 8.1 (m), R_4 - R_7	35
R_5 = Cl R_1 - R_7 = H	$CDCl_3$	7.56 (d), $J_{1,2}$ = 10, R_1 6.92 (q), $J_{2,3}$ = 2, R_2 6.73 (d), $J_{3,2}$ = 2, R_3 7.45 (s), R_4	35

Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), Assignment	Ref.
		7.42 (d), $J_{6,7}$ = 9, R_6	
		7.80 (d), $J_{7,6}$ = 9, R_7	
$R_5 = NO_2$	$CDCl_3$	7.62 (d), $J_{1,2}$ = 10, R_1	35
$R_1 - R_7 = H$		6.97 (q), $J_{2,3}$ = 2.5, R_2	
		6.78 (d), $J_{3,2}$ = 2.5, R_3	
		7.8 - 8.4 (m), R_4, R_6, R_7	
$R_3 = I$	$CDCl_3$	7.62 (d), $J_{1,2}$ = 10, R_1	35
$R_5 = Cl$		7.11 (d), $J_{2,1}$ = 10, R_2	
		7.56 (d), R_4	
		7.47 (q), $J_{6,7}$ = 9, R_6	
		7.88 (d), $J_{7,6}$ = 9, R_7	
$R_2 = R_5 = Cl$	$CDCl_3$	7.85 (s), R_1	35
		6.86 (s), R_3	
		7.50 (s), R_4	
		7.62 (d), $J_{6,7}$ = 9, R_6	
		7.85 (d), $J_{7,6}$ = 9, R_7	
$R_5 = R_6 = Cl$	$CDCl_3$	7.56 (d), $J_{1,2}$ = 10, R_1	35
		6.92 (q), $J_{2,3}$ = 2, R_2	
		6.73 (d), $J_{3,2}$ R_3	
		7.50 (s), R_4	
		7.96 (s), R_7	
$R_3 = R_5 = Cl$	$CDCl_3$	7.64 (d), $J_{1,2}$ = 10, R_1	35
		7.09 (d), $J_{2,1}$ = 10, R_2	
		7.58 (s), R_4	
		7.50 (d), $J_{6,7}$ = 9, R_6	
		7.90 (d), $J_{7,6}$ = 9, R_7	
$R_4 = R_5 = H$	$CDCl_3$	7.60 (d), $J_{1,2}$ = 10, R_1	35
		6.93 (q), $J_{2,3}$ = 2, R_2	
		6.85 (d), $J_{3,2}$ = 2, R_3	
		7.56 (d), $J_{6,7}$ = 9, R_6	
		7.75 (d), $J_{7,6}$ = 9, R_7	

Oxidation of 2-acetylphenothiazine(15) with potassium dichromate in acetic acid could result in the formation of 16 or 17. Nmr analysis leadsto the conclusion that the oxidation product is 2-acetylphenothiazone-7(17). Indeed, the coupling of the proton AB;BC (J_{AB} = ' c.p.s.; J_{BC}=8 c.p.s.) emphasizes the presence of proton B, and the coupling of the protons A'B'; B'C'



($J_{A'B'}$ = 2 cps; $J_{B'C'}$ = 9.5 cps) points out that in the ring A, there are only three protons. As expected, the resonance signals produced by the protons ABC are at lower fields than those of the protons A'B'C'.[13]

In N-acetylated phenothiazines or analogues of phenothiazine, the carbonyl group representsstrong anisotropic centres and the relative effect of the carbonyl (C=O) on the α - protons (1 and 9) of the phenothiazine or analogue molecule would be expected to show a shielding or deschielding effect on the chemical shift of α -protons depending on the orientation of the carbonyl group either in H-intra or H-extra positions. Nmr spectrum of N-acetylphenothiazine gave a multiplet signal at 7.35 ppm for the aromatic protons (Fig. 7) and the signals of the α-protons remained in the general peak group. This type of spectrum is possible only with an H-extra configuration. It is only with an H-extra configuration, that the steric position of the carbonyl group makesit impossible for the α-protons to land under its anisotropic influence. The opposite effect is observed, when N-acetylphenothiazine is oxidised to the respective dioxide. In that case regardless of the configuration transitions, one S = O bond will always be directed

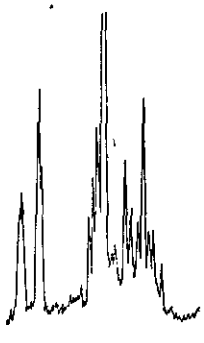


Fig. 7

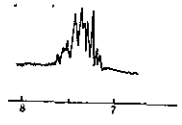
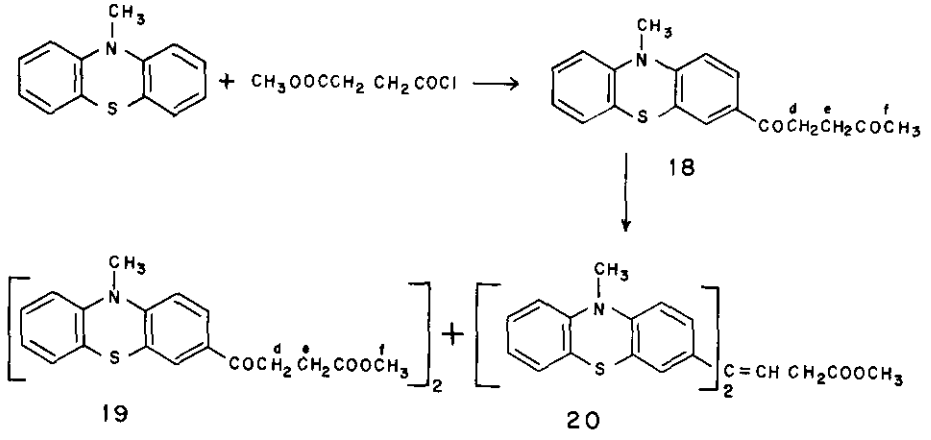


Fig. 8

between the benzene nuclei and its position will correspond to the carbonyl group in the H-intra configuration.[14]

Since the sulphoxide group produces strong anisotropic effect, the 4H and 6H protons appear magnetically unshielded with a weaker field shift of their signals. This is shown by a well separated two proton doublet (J=8 c.p.s., additional cleavage 2 c.p.s.), displaced by the general signal of the aromatic protons of 0.75 p.p.m. (Fig.8).[14]

Acylation of 10-methylphenothiazine with β-carbomethoxypropionyl chloride resulted in the formation of 3 products (18, 19, 20), the structures of which were established by their Nmr spectra. Product 18 showed a chemical shift of the aromatic protons (δ 7.82, 7.73, 6.86 for a_1 a_2 and b) which agree well with those calculated for a 3-alkyl, 5-alkylthio, 6-alkyldiamino-substituted benzene (δ 7.81, 7.78, 6.66), using a table of aromatic chemical shifts.[15] Comparing these results with other related [16-18] cases, the product was assigned to be the 3-substituted derivative.[19]

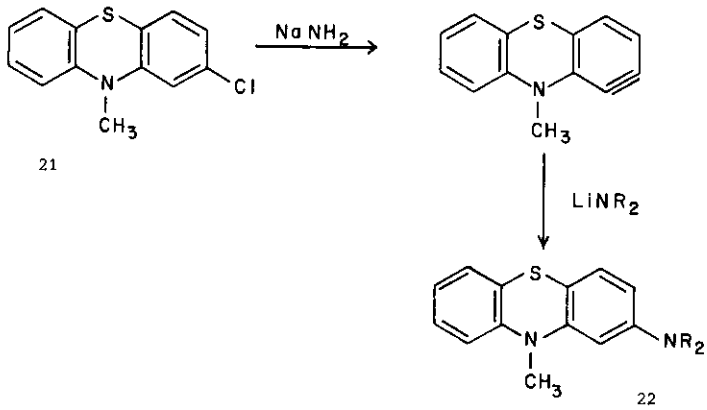


Nmr results are given in Table IV.

TABLE IV

Compound	Chemical Shift (δ), (Multiplicity), (Coupling Constant (J) assignment.	Chemical Shift (δ) for aromatic protons, (Multiplicity), (Coupling constant (J).
Methyl-4-(10-methyl-3-phenothiazinyl)-4-oxobutanoate (18)	3.71 (s), $-OCH_3$ 3.40 (s), $-CH_3$ 2.75 (t), (J = 6), $-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-O-$ 3.22 (t), (J = 6), $-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-O-$	H-3, 7.81 (d), (J = 8.5), H-4, 7.72 (s) H-1, (H-6)-(H-9) 6.70-7.40, m
Dimethyl-4, 4-(10-methyl-3,7-phenothiazinylene)-di-(4-oxobutanoate (19)	3.72 (s), $-OCH_3$ 3.44, (s), $-CH_3$ 3.24, (t), (J = 6) $-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-O-$ 2.75, (t), (J = 6), $-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-O-$	H-2, H-8, 7.82, (d), (J = 9) H-4, H-5, 7.73 (s) H-1, H-9, 6.86 (d), (J = 8.5)
Methyl-4, 4-Bis(10-methyl-3-phenothiazinyl) butene-3-oate (20)	3.70 (s), $-OCH_3$ 3.33 (s), $-CH_3$ 3.12 (d), (J = 7.5), $>C=CH-CH_2-$ 6.10 (t), (J = 7.5), $>C=CH-CH_2$	6.58 - 7.34, m

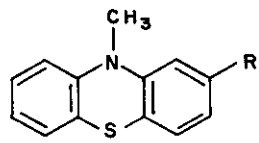
Behl et al.[20] have demonstrated that lithium dialkylamide/dialkylamino converted halophenothiazine (21) into the corresponding dialkylaminophenothiazine (22) without any significant reduction to 10-methylphenothiazine. The assignment of location of the N,N-dialkylamino group was based on the nmr spectrum, which gave a multiplet at 3.2 τ (5H), a doublet (1H, J= 2 (Hz) at 3.82 τ and a partially resolved quartet (1H) at 3.92 τ indicating that the nucleophilic addition of the amine to 10-methyl-1,2-phenothiazine occurs at the 2-position.[20] Nmr



21 22

data of the compounds are given in Table V.

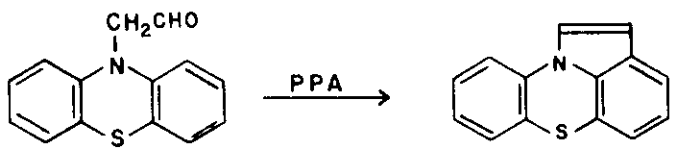
TABLE V



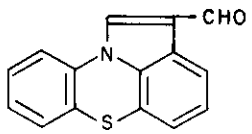
R	Chemical Shift (δ), (Multiplicity)	Chemical Shift (δ) of aromatic protons, (Multiplicity).
$N\ (\overset{a}{CH_2}\ \overset{b}{CH_3})_2$	3.28 (s), $-CH_3$ 3.25 (q), R - a 1.1 (t), R - b	6.15 - 6.85, m
$N\ (\overset{a}{CH_2}\ \overset{b}{CH_2}\ \overset{c}{CH_3})_2$	3.24 (s), $-CH_3$ 3.15 (t), R - a 1.55 (m), R - b 0.85 (t), R - c	6.15 - 6.80, m
$N\ (\overset{a}{CH_2}-\overset{b}{CH}-\overset{c}{CH_3})_2$ CH_3	3.38 (s), $-CH_3$ 3.06 (d), R - a 1.95 (m), R - b 0.88 (d), R - c	6.12 - 6.82, m

R	Chemical Shift (δ), (Multiplicity)	Chemical Shift (δ) of aromatic protons, (Multiplicity).
$NH\text{-}CH_2\ CH_2\ CH_3$ a b c d	3.5 (s), R - a 3.12 (s), $-CH_3$ 3.0 (q), R - b 1.55 (m), R - c 0.95 (t), R - d	5.95 - 6.8, m
$NH\text{-}CH(CH_3)\text{-}CH_3$ a b c	3.57 (m), R - b 3.35 (s), R - a 3.23 (s), $-CH_3$ 1.23 (d), R - c	6.05 - 6.9, m
$NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\ CH_3$ a b c d e	3.39 (s), R - a 3.12 (s), $-CH_3$ 2.98 (t), R - b 1.45 (m), R - c, d 0.95 (m), R - e	5.95 - 6.75, m
$NH\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_3$ a b c d	3.3 (m), R - a, b 3.11 (s), $-CH_3$ 1.1 (m), R - c, d, e.	5.95 - 6.77, m

Synthesis of Pyrrolo[3,2,1-kl]phenotheiazine (23) was achieved by cyclising a chloroform solution of 10-formylphenothiazine (24) with polyphosphoric acid at room temperature. Its structure was established by NMR spectrum, which gave a complex multiplet from δ 6.40 to 7.15 and a pair of doublets (Ax pattern) at δ 7.3 (J = $3H_z$) and δ 6.35 (J = $3H_z$) corresponding to the two protons of the pyrrole ring, positions 1 and 2 respectively.[21]



Formylation of 23 with phosphorous oxychloride and dimethylformamide resulted in the formation of the 2-carboxaldehyde (25), the nmr of which gave a singlet (1-Proton) at δ. 8.28 due to proton confirming that the substitution occurred in the 2-position.[21]



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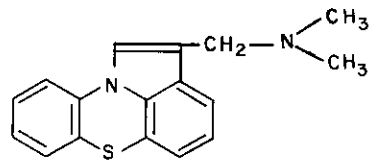

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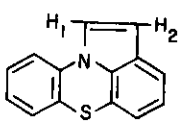
The Mannich condensation of 23 with formaldehyde and dimethylamine afforded 26 in 78% yield. Substitution at position 2 was again confirmed by nmr, which gave a singlet at δ 7.14 due to proton at C-1.[21] The results are summarised in Tables VI and VII.

TABLE VI

Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), assignment.	Chemical Shift (δ) of aromatic protons, (Multiplicity), Coupling Constant (J).	Ref.
R =-CH_2-$CONH_2$ a b	DMSO-d_6	4.39 (s), -CH_2- 6.60-7.30 (m), NH_2	6.60 - 7.30 (m).	21
R = CH_2-CHO a b	$CDCl_3$	9.75 (t), J=1, -CHO 4.45 (d), -CH_2-	6.50 - 7.26 (m)	21
R =-CH_2-CN	$CDCl_3$	4.48 (s), -CH_2-	6.72 - 7.30 (m)	21
R =-CH_2-CH=NOH a b c	$CDCl_3$ -DMSO-d_6	11.3 (s), = N-OH 6.62-7.30 (m), -CH= 4.69 (d), J=4, -CH_2-	6.62 - 7.30 (m)	21
	$CDCl_3$	7.30 (d), J=3.0, H_1 6.35 (d), J=3.0, H_2	6.40 - 7.15 (m)	21

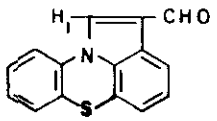
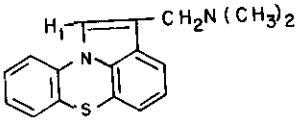
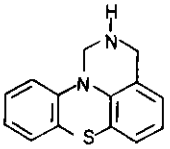
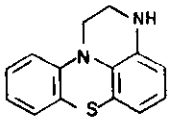
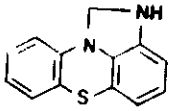
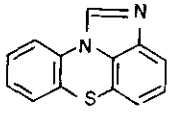
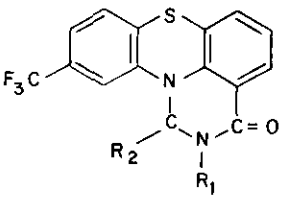
Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), assignment.	Chemical Shift (δ) of aromatic protons (Multiplicity), Coupling Constant (J).	Ref.
	DMSO-d_6	10.05 (s), CHO 8.28 (s), H_1	6.75 - 7.82 (m)	21
	$CDCl_3$	7.14 (s9, H_1 3.35 (s), $-CH_2-$ 2.16 (s), $N-CH_3$	6.3 - 7.1 (m)	21
	$CDCl_3$	4.58 (s), CH_2-3 3.90 (s), CH_2-2 8.0 (s), N-H	6.57 - 7.28 (m)	30
	$CDCl_3$	3.80 (t), CH_2-1 3.55 (t), CH_2-2 3.47 (s), N-H	6.29 - 7.35 (m)	30
	$CDCl_3$	3.92 (s), N-H 5.12 (s), $-CH_2-$	6.30 - 7.52 (m)	30
	$CDCl_3$	8.32 (s), -CH=N-	6.60 - 7.37 (m)	30

TABLE VII

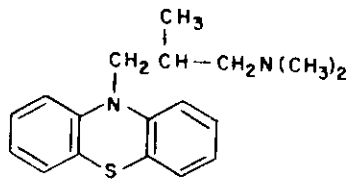


Compound	Solv.	(δ), (Multiplicity), Coupling Constant (J), assignment	(δ) aromatic protons, (Multiplicity), Coupling Constant (J)	Ref.
R_2 = S =	DMSO-d_6	13.00 (s), -NH	5H, 7.20 - 8.15 (m)	31
R_1 = H	$CDCl_3$		H-11 8.49 (s)	
R_2 = -S-CH_3	$CDCl_3$	2.75 (s), -S-CH_3	4H, 7.44 (m)	31
			2H, 8.00 (m)	
R_2 = OXO	$CDCl_3$	11.80 (s), -NH	5H, 7.60 - 8.00 (m)	31
R_1 = H	DMSO-d_6		11-H, 8.10 (s)	
R_1 = -CH_2 CH_3	$CDCl_3$	4.21 (q), -CH_2-	6H, 7.10 - 7.70 (m)	31
R_2 = OXO		1.40 (t), -CH_3	2H, 7.85 - 8.2 (m)	
R_1 = -CH_2-CH_2-OH	$CDCl_3$	2.75 (s), -OH	5H, 7.00 - 7.80 (m)	31
R_1 = OXO	$CDCl_3$	3.92 & 4.40 (2t), -CH_2-CH_2-	H-11, 7.90 (s)	
R_1 = -CH_2-CH(OH)CH_2-OH	$CDCl_3$	3.60 & 3.66 (2s), 2-OH	4H, 7.00 - 7.60 (m)	31
R_2 = OXO	DMSO-d_6	3.8 - 4.68 (m), -CH_2-CH-CH_2-	2H, 7.70 - 8.10 (m)	31
R_1 = -CONCS	$CDCl_3$	10.6 (s), -NH	5H, 6.55 - 7.39 (m)	31
R_7 = -CF_3		7.60 (d), R_2		
R_2 = R_3 = R_4 = R_5 = R_6 = R_8 = H				
R_1 = -CO-$OCO_2CH_2CH_3$	$CDCl_3$	9.81 (s), -NH	5H, 6.60 - 7.29 (m)	31
R_7 = CF_3		4.40 (q), R_1-CH_2		
R_2 = R_3 = R_4 = R_5 = R_6 = R_8 = H		1.40 (t), R_1-CH_3		
		7.50 - 7.60 (d), R_2		
R_7 = CF_3	$CDCl_3$	9.80 (s), -NH	5H, 6.60 - 7.20 (m)	31
Dimer of Type		7.55 - 7.69 (d), R_2		
R_1 - COC - R_1 (O O)				

For nmr study and correlations the commercially available phenothiazines have been separated into 5 groups: 4 groups according to the type of side chain on the nitrogen in the 10-position, a fifth group consisting of the oxidation products (sulphone and sulphoxides).[5]

The first group comprises compounds having an aliphatic side chain with no heterocyclic ring. All contain an N,N-dimethyl group, all have a CH_2 group attached to the 10-position of the phenothiazine ring. Their nmr spectra are similar in many respects and have characteristic absorbance bands unique to their general group. The N,N-dimethyl group is found at 131 c.p.s. for the compounds with straight chain amines and at 138 c.p.s. in the case of branched chain amines. The position of the branched chain amine is influenced by its proximity to the ring N. The CH_2 group on the nitrogen atom in the 10-position is found to be a triplet at 232 ± 3 p.c.s. for straight chain amines and in the same area but with more splitting in the case of branched chain amines due to the increased number of adjacent protons. All of the phenothiazine spectra show a complex pattern for the aromatic protons in the area 400-440 c.p.s.[11]

It is known that the chemical shifts of the protons of a radical linked with a nitrogen atom depend on the basicity of the latter.[22] If there are two nitrogen atoms of different basicity in the molecule as in 27, the signal from the protons of the methylene group linked to the more acidic cyclic nitrogen atom is located at 235 Hz, while that of the CH_2- group



27

linked to a dimethylamine group is found at 128 Hz.[23] This has been attributed to the development of positive charge on the ring nitrogen atom due to the participation of its unshared electron pair in the aromatic system; this leads to a shift of the proton signals of a substituent to the weak field side. One should therefore expect that the nitrogen substituent in phenothiazines should absorb at stronger field than the substituent in the corresponding aliphatic amines. (Table VIII).[24]

TABLE VIII

Amines	Chemical shift (PPm)
Allylamine	3.30
N-Allylphenothiazine	4.15
N-Butylamine	2.70
N-Butylphenothiazine	3.60

The proton signal from the methylene group attached to the nitrogen atom is shifted by 0.85 and 0.90 PPm, respectively, to the strong field side on passing from N-butylphenothiazine to butylamine and from N-allylphenothiazine to allylamine. Thus the participation of the unshared electron pair of the nitrogen atom leads to a change in the chemical shift of the directly attached substituent.

Oxidation of sulphur to sulphoxide also leads to a shift in the signals of all the protons of the substituent on the nitrogen atom to the weak field side, during which the shift of the proton signals of the methylene group attached to the nitrogen atom is the greatest (0.3 - 0.7 p.p.m.).[24]

Further oxidation of the sulphur to sulphone does not result in such a sharp change in the chemical shift as observed in the first oxidation. This effect of the degree of oxidation of sulphur is due to the formation of an electron accepting group (S=o or So_2) which decreases the electron density on the nitrogen atom through the aromatic π system, and the proton signals of the substituent are shifted to weaker field. The inductive effect of the nitrogen atom apparently makes a major contribution to the chemical shift of the protons of the methylene group directly attached to it.

In examining the aromatic protons of the spectra of N-alkylated phenothiazines, a doublet (J = 6-9 Hz) with an additional splitting ($\sim$ 2 Hz) and an intensity of two proton units can be seen on passing from the general aromatic group to compounds with oxidised sulphur. This is explained by the fact that H_4 and H_6 protons fall into the deshielding region of the anisotropic S=O bond, which causes a shift of the proton signals to weaker field (0.6 - 1.0 PPm). The addition of a second oxygen atom to the sulphur atom causes an additional shift of H_4 and H_6 by 0.15 - 0.2 PPm. A bromine atom has an appreciable effect on the chemical shift of the protons only in the vicinal position. Its effect is slight when it is located farther away.[24]

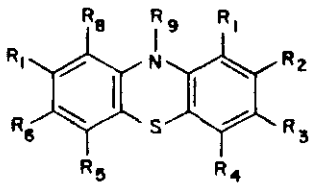
In case of chlorpromazine sulphoxide and sulphone, an increase in chemical shift has also been observed. The $N(CH_3)_2$ is shifted 4-6 c.p.s. to 135-137 c.p.s. The CH_2 in position 10 is shifted to 254-256 c.p.s. and the aromatic protons show additional splitting and shift to 490 c.p.s.

The phenothiazines containing a piperidine group in the side chain have chemical shifts due to the piperidine ring in the range 90-130 c.p.s., depending on the position and nature of the substituent. The CH_2 attached to the N at the 10-position is again found at 235 c.p.s. with one exception, where the CH_2 is the only link between the N and the piperidine ring. In this case the CH_2 is a doublet located at 220 and 227 c.p.s. The aromatic pattern is found at 400-450 c.p.s.

The group containing a pyrrolidine ring shows a chemical shift in the range of 100-180 c.p.s. due to the substitution on the ring. The CH_2 which links the N at 10-position and the pyrrolidine ring is a doublet at 224 and 231 c.p.s.

Phenothiazines having a piperazine ring in their side chain have common features attributable to their specific group which distinguish them from other phenothiazines. The 8 protons *in the piperazine ring being equivalent are found as a single peak* at 146 ± 2 c.p.s. This is the strongest peak and the dominant feature of a phenothiazine in this group. The CH_2 attached to the N in the 10-position is found at 234 ± 4 c.p.s. In those piperazine derivatives where the piperazine ring is attached directly to a CH_2 in the chain, the CH_2 adjacent to the piperazine is located at 215 c.p.s. The complex aromatic pattern is located at 400-450 c.p.s.[5] The results are summerised in Table IX.

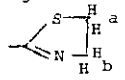
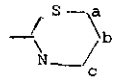
TABLE IX

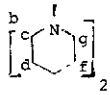
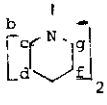


Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) of aromatic protons	Ref.
R_2= CF_3 R_9 = $-CH_2CH_2CH_2N$ (a a c) $[CH_2]$ d $[CH_2]$ e $[OH]_2$ f	$CDCl_3$	1.90 (t), R_9 - b 2.53 (t), R_9 - c, d 2.71 (s), R_9 - f 3.50 (t), R_9 - e 3.95 (t), R_9 - a	6.8 - 7.2 (m)	25
R_2= Cl R_9 = CH_2-CH_2-CH_2 (a b c) Cl [N-H] d [CH_2] e [CH_2] f [Cl]$_2$ R_1 - R_8 = H.	$CDCl_3$	2.35 (broad), R_9-b 3.33 (t), R_9 - c, e 3.85 (t), R_9 - f 4.06 (t), R_9 - a	6.80 - 7.2 (m)	25
R_1 - R_8 = H R_9 = CH_2-$CH(CH_3)$-$N(CH_3)_2$ (a b c d)	$DMSO-d_6$	3.71 (dd), R_9 - a 2.95 (nc), R_9 - b 0.97 (d), R_9 - c 2.12 (s), R_9 - d		26

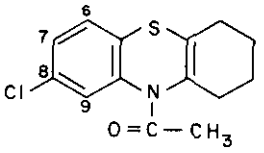
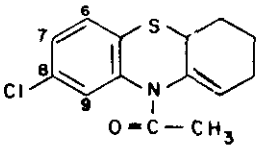
Compound	Solv.	Chemical Shift (δ) (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) of aromatic protons	Ref.
$R_1 - R_8 = H$ $R_9 = -CH_2-CH=CH_2$ a b c (sulphoxide)	$CDCl_3$	4.89, R_9 - a 5.80 - 6.30, R_9 - b 5.18 - 5.40, R_9 - c	R_4, R_6, 7.94 (q), J_o=7.2, J_m=1.5-1-8 (R_1-R_3, R_5-R_8) 7.38 (m)	24
$R_1 - R_8 = H$ $R_9 = -CH_2-C(CH_3)=CH_2$ a c b (sulphoxide)	$CDCl_3$	4.53, R_9 - a 4.94, R_9 - c 1.87, R_9 - b	R_4, R_6, 7.97 (q), J_o=8.4, J_m=2-2.5 (R_1-R_3, R_5-R_8) 7.14 (m)	24
$R_1 - R_8 = H$ $R_9 = -CH_2-CH=CH_2$ a b c (sulphone)	$CDCl_3$	4.73; R_9 - a 5.60 - 6.00, R_9 - b 5.20 - 5.40, R_9 - c	R_4, R_6, 7.98 (q), J_o=6.6, J_m=1.2-1.8 (R_1-R_3, R_5-R_8), 7.14 (m)	24
$R_1 - R_8 = H$ $R_9 = -CH_2-C(CH_3)=CH_2$ a c b (sulphone)	$CDCl_3$	4.50, R_9 - a 5.00, R_9 - c 1.88, R_9 - b	R_4, R_6, 8.16 (q), J_o=7.12, J_m=1.5-18 (R_1-R_3, R_5-R_8), 7.11 (m)	24
$R_1 - R_8 = H$ $R_9 = CH_2-C\equiv CH$ a b	$CDCl_3$	4.74 (d), Ja,b= 2.9, R_9 - a 2.53 (d), Jb,a= 2.4, R_9 - b	R_4, R_6, 8.23 (q), J_o=7.8, J_m=1-1.2 (R_1-R_3, R_5-R_8), 7.48 (m)	24
$R_1 - R_8 = H$ $R_9 = CH_2-C(Br)=CH_2$ a n	$CDCl_3$	4.82, R_9 - a	R_4, R_6, 8.19 (q), J_o=6.0, J_m=1.5-1.8	24
$R_1 - R_8 = H$ $R_9 = -CH_2-C(CH_3)=CHBr$ a c b	$CDCl_3$	1.90, R_9 - b	R_4, R_6, 7.94 (q), J_o=7.2, J_m=1-1.2 (R_1-R_3, R_5-R_8),7.20 (m)	24
$R_1 - R_8 = H$ $R_9 = -CH_2-CBr(CH_3)-CH_2Br$ a b c	$CDCl_3$	1.66, R_9 - b	R_6, R_4, 8.08 (q), J_o=7.8, J_m=1.2-1.5 (R_1-R_3, R_5-R_8),7.49,(m)	24

Compound	Solv.	Chemical Shift (δ) (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) of aromatic protons	Ref.
R_9= CH_2-CH[$N(CH_3)_2$]- a b c $CH_2N(CH_3)_2$ d e $R_1 - R_8$ = H	DMSO-d_6	3.78 (dd), R_9 - a 2.96 (mc), R_9 - b 2.31 (d), R_9 - d 2.23 (s), R_9 - c 2.14 (s), R_9 - e		26
R_2 = Cl R_9 = CH_2 CH_2 CH_2 CH_2- a b c d $(CH_3)_2$ e R_1 = R_3 - R_8 = H	DMSO-d_6	3.91 (t), R_9 - a 1.78 (q), R_9 - b 2.31 (t), R_9 - d 2.09 (s), R_9 - e		26
R_2 = - OCH_3 R_9 = -CH_2 $CH(CH_3)$-CH_2- a b c d $N(CH_3)_2$ e R_1 = R_3 - R_8 = H	DMSO-d_6	3.63 (dd), R_9 - a 2.30 (mc), R_9 - b 0.91 (d), R_9 - c 2.10, R_9 - d 2.12 (s), R_9 - e		26
R_1 - R_8 = H R_9 = CH_2-$CH(CH_3)$-N- a b c $(CH_3)_2$ d	DMSO-d_6	4.18 (dd), R_9 - a 2.21 (mc), R_9 - b 0.78 (d), R_9 - c 2.05, R_9 - d 2.10 (s), R_9 - e		26
R_1 - R_8 = H R_9 = -CH_2-CH = CH_2 a b c	$CDCl_3$	4.15, R_9 - a 5.40 - 6.05, R_9 - b 4.88 - 5.10. R_9 - c		24
R_1 - R_8 = H R_9 = -CH_2-C = CH_2 a CH_3 c b	$CDCl_3$	4.16, R_9 - a 4.48. R_9 - c 1.70, R_9 - b		24
R_1 - R_8 = H R_9 = -CH_2 - C≡CH a b	$CDCl_3$	4.40 (d), Jab=2.2, R_9-a 2.36 (d), Jba=2.5, R_9-b		

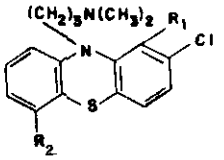
Compound	Solv.	Chemical Shift (δ) (Multiplicity), Coupling Constant (J) Assignment	Chemical Shift (δ) of aromatic protons	Ref.
R_2 = Cl R_9 = -CH_2-CH-CH a \ / e CH_2- CH_2 d N $(CH_3)_2$ f R_1 - R_8 = H	$CDCl_3$	0.8 (m), R_9 - b, c, d 2.5 (d), R_9 - e 2.25 (s), R_9 - f 3.75 (d), J=5, R_9 - a	R_1 - R_8, 7.0 (m)	27
R_3 = NO_2 R_7 = CF_3 R_9=  R_1 = R_2 = R_4 - R_6 = R_8 = H	$CDCl_3$	3.43 (t), J = 7HZ, R_9-a	R_1-R_8, 7.23-8.20 (m)	28
R_1 - R_8 = H R_9= 	$CDCl_3$	1.76 (m), R_9 - b 3.08 (t), J = 6, R_9-c 3.96 (t), J = 6, R_9-a	R_1-R_8, 7.10-7.55 (m)	28
R_9 = -CH_2-CHO a b R_1 = R_8 = H	$CDCl_3$	4.45 (d), R_9 - a 9.9 (t), R_9 - b	R_1 - R_8, 6.8-7.3 (m)	29
R = Cl R_9 = -CH_2-CHO a b R_3 - R_8 = R_1 = H	$CDCl_3$	4.55 (d), R_9 - a 9.95 (t), R_9 - b	R_1, R_3 - R_8, 6.7-7.3 (m)	29
R_9 = -CH_2-CH=N-N$(CH_3)_2$ a b c d R_1 - R_8 = H	$CDCl_3$	2.3 (s), R_9 - d 4.6-4.7 (d), R_9 - a 6.6-6.8 (t), R_9 - b	R_1 - R_8, 6.9-7.3 (m)	29
R_1 = R_8 = H R_9 = -CH_2-CH_2-N- N a b c | d N h e g f	$CDCl_3$	1.4-1.7 (m), R_9-e,f,g 2.45 (s), R_9 - c 2.50-2.60 (m), R_9-d,h 3.05-3.25 (t), R_9 - b 3.95-4.15 (t), R_9 - a	R_1, R_3 - R_8, 6.9-7.3 (m)	29

Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), Assignment	Chemical Shift (δ) of aromatic protons (Multiplicity)	Ref.
R_9 = CH_2-CH=N-N a b  R_1 - R_8 = H	$CDCl_3$	1.5-1.8 (m), R_9-d,e,f 2.9-3.1 (m), R_9-c, g 4.6-4.7 (d), R_9 - a 6.75-7.30 (m), R_9 - b	R_1 - R_8, 6.75-7.30 (m)	29
R_9 = -CH_2-CH=N-N(X)$_2$ a b X = 4-Methylpiperazine R_1 - R_8 = H	$CDCl_3$	2.3 (s), CH_3 2.4-2.6 (m), H-3,H-5, c 2.95-3.15 (m), H-2,H-6 c 4.6-4.7 (d), R_9 - a 6.75-7.30 (m), R_9 - b	R_1 - R_8, 6.75-7.30 (m)	29
R_2 = Cl R_9 = -CH_2-CH=N-N(CH$_3$)$_2$ a b c R_1 = R_3 - R_8 = H	$CDCl_3$	2.81 (s), R_9 - c 4.55 - 4.65 (d), R_9 - a 6.45 - 6.65 (t), R_9 - b	R_1, R_3 - R_8, 6.95-7.30 (m)	29
R_2 = Cl R_9 = -CH_2-CH=N-N a b  R_1=R_3-R_8=H	$CDCl_3$	1.5-1.8 (m), R_9-d, e, f 2.9-3.1 (m), R_9 - c, g 4.65-4.75 (d), R_9 - a 6.8-7.3 (m), R_9 - b	R_1, R_3 - R_8 6.8-7.3 (m)	29
R_2 = Cl R_9 = -CH_2-CH=N-N(X)$_2$ a b c X = 4-Methylpiperazine R_1 = R_3 - R_8 = H	$CDCl_3$	2.3 (s), CH_3 - c 2.4-2.6 (m), H-3, H-5 4.55-4.65 (d), R_9 - a 6.8-7.3 (m), R_9 - b	R_1, R_3 - R_8, 6.8-7.3 (m)	29
R_9 = -CH_2-CH_2-N(H)-N(CH$_3$)$_2$ a b c R_1 = R_8 - R_8 = H	DMSO-d_6	2.85 (s), R_9 - d 3.2-3.4 (t), R_9 - b 3.9-4.3 (t), R_9 - a	R_1 - R_8, 6.9-7.3 (m)	29

Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), assignment	Chemical Shift (δ), of aromatic protons (Multiplicity), Coupling Constant (J)	Ref.
R_2 = Cl R_9 = $-CH_2CH_2-\overset{H}{N}-N(CH_3)_2$ a b c d R_1 = R_3 - R_8 = H	$CDCl_3$	2.4 (s), R_9 - c 2.45 (s), R_9 - d 3.0-3.2 (t), R_9 - b 3.95-4.15 (t), R_9 - a	R_1, R_3 - R_8, 6.9-7.3 (m)	29
R_9 = $-CH_2CH_2-\overset{H}{N}-N$ a b c (d, e, f, g, h = pyridine ring)$_2$ R_1 - R_8 = H	$CDCl_3$	1.4 - 1.7(m), R_9-e,f,g 2.30 (m), R_9 - c 2.40-2.65 (m), R_9-d,h 3.05-3.25 (t), R_9 - b 3.95-4.20 (t), R_9 - a	R_1 - R_8, 6.9-7.3 (m)	29
R_9 = $-CH_2CH_2-\overset{H}{N}-N(X)_2$ a b c d X = 4-Methylpiperazine R_1 - R_8 = H	$CDCl_3$	2.3 (s), R_9 - d 2.50 (m), R_9 - c 2.4-2.9 (m), R_9-d (ring protons) 3.05-3.25 (t), R_9 - b 3.90-4.15 (t), R_9 - a	R_1 - R_8, 6.9-7.3 (m)	29
R_2 = Cl R_9 = $CH_2CH_2\ \overset{H}{N}-N(X)_2$ a b c d X = 4-Methylpiperazine R_1 = R_3 - R_8 = H	$CDCl_3$	2.3 (s), R_9 - d 2.65 (m), R_9 - c 2.4-2.9 (m), R_9 - d (ring protons) 3.0-3.25 (t), R_9 - b 3.9-4.15 (t), R_9 - a	R_1, R_3 - R_8, 6.9-7.3 (m)	29
R_9 = $-CH_2-CH(O-CH_2CH_3)_2$ a b c d R_1 - R_8 = H	$CDCl_3$	1.0-1.25 (t), R_9 - d 3.3-3.7 (q), R_9 - c 4.0-4.1 (d), R_9 - a 4.80-4.95 (t), R_9 - b	R_1 - R_8, 6.9-7.3 (m)	29
R_2 = Cl R_9 = $-CH_2-CH(O-CH_2-CH_3)_2$ a b c d R_3 - R_8 = R_1 = H	$CDCl_3$	1.05-1.30 (t), R_9 - d 3.4-3.8 (q), R_9 - c 3.95-4.05 (d), R_9 - a 4.75-4.90 (t), R_9 - b	R_1 - R_8, 6.9-7.3 (m)	29

Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J), assignment	Chemical Shift (δ), of aromatic protons (Multiplicity), Coupling Constant (J)	Ref.
	$CDCl_3$	1.75 (broad)-CH_2-CH_2 2.07 (sharp), - CH_3 2.35 (broad), CH_2~,-CH_2 (1 4)	6, 7, 9-H, 7.24 (m)	34
	$CDCl_3$	1.82 (broad), - CH_2-CH_2 (3 4) 2.16 (sharp), $-CH_3$ 2.44 (broad), $-CH_2$-2 4.20 (m), -CH -6 5.98 (sharp), -CH-1	6, 7, 9-H, 7.30 (m)	34

Nmr spectra were helpful in elucidating the structure of 1- and 6-hydroxychloropromazines (28, 29), the two metabelites of chloropromazine.[33]

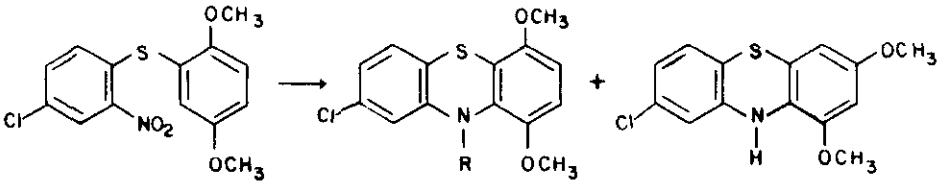


28, R_1 = OH; R_2 = H

29, R_2 = OH; R_1 = H

An AB quartet with J=8.4 c.p.s.arising from spin coupling of the protons at C-3 and C-4 was present at 6.62 and 7.04p.p.m. respectively. No other hydroxy isomer would have such a quartet. On the other hand nmr spectrum of 29 showed the remaining protons at C-7 and C-9 as one half of AB quartets due to coupling with the proton at C-8. Chemical shifts of H-7 and H-9 resonances were further split due to spin coupling with each other. $J_{7,8}$, $J_{7,9}$ and $J_{8,9}$ were measured to be 7.25, 1.4 and 7.03 c.p.s. respectively.[33]

Cyclisation of 4'-chloro-2,5-dimethoxy-2'-nitrophenyl sulfide (30) resulted in the formation 2-chloro-6,9-dimethoxyphenothiazine (31) as the major product alongwith 2-chloro-7,9-dimethoxyphenothiazine (30) as the minor product.[32]



30, 31; R = H 32; R = H

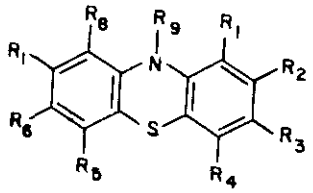
33; R = $(CH_2)_3 N(CH_3)_2$ 34; R = $(CH_2)_3 N(CH_3)_2$

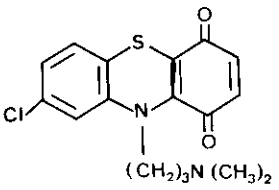
Nmr analysis of 31 displayed a complex pattern at δ 6.3-6.8 containing a quartet having ortho-coupling, $J_{7,8}$ = 10 Hz. According to the author, the nmr of the mixture (31, 32; 1:19) gave a distinguishable quartet showing that 32 had a meta coupling, $J_{6,8}$ = 3 Hz. Corresponding samples of 33 and 34 had similar coupling constants.

The 6,9-dioxochlorpromazine (33) gave a lowest field signal, δ 7.24, and appeared as a singlet and was assigned to H_4, which is expected to be most affected by substantial partial positive charge on the ring nitrogen atom. No ortho- or meta-coupling is observed. Protons, H_3, H_4 and H_7, H_8 appear as 2-proton singlets, and have thus become essentially equivalent.[32]

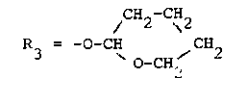
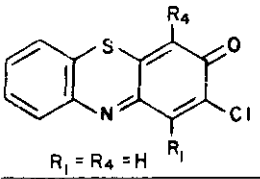
The assignment of methoxy group was based primarily on the effect of the N-substituted side chain. In 30, two resolved 3-proton singlets were observed at δ 3.78 and 3.79. In 33, the two signals coincide and appear at δ 3.79 as a 6-proton singlet. Thus the higher field signal was assigned to the C_9-methoxy group. Similarly, the high field methoxy signals in 21 and 24 were assigned to the C_9-methoxy group, which exhibits a small but perceptible downfield shift with the addition of the side chain.[32] The resultsare summarised in Tables X and XI.

TABLE X

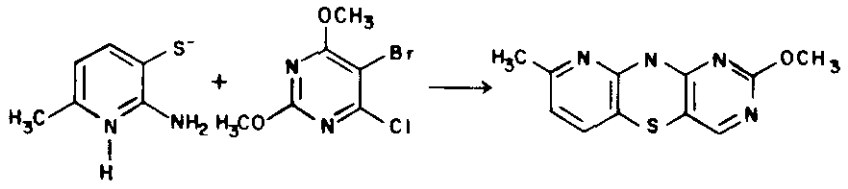


Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) of aromatic protons (Multiplicity), Coupling Constant (J).	Ref.
$R_1 = R_4 = -OCH_3$ $R_7 = Cl$ $R_2=R_3=R_5=R_6=R_8=H$	CD_3-OD	3.78 (s), R_4 q 3.72 (s), R_1	R_2, 6.35 (d), J_o=10 R_3, 6.59 (d), J_o=10 R_5, R_6, R_8, 6.64-6.79, m	32
$R_1 = R_3 = -OCH_3$ $R_7 = Cl$ $R_2=R_4=R_5=R_6=R_8=H$	CH_3-OD	3.84 (s), $-R_3$ 3.69 (s), $-R_1$	R_2, 6.10 (d), J_m=3 R_4, 6.32 (d), J_m=3 R_5, 7.07 (d), J_o=10 R_6, 6.89 (dd), J_m=3, J_o=10 R_8, 7.02 (d), J_m=2.5	32
 	DMSO-d_6		H_1, 7.24 (s) H_3, 7.12 (s) H_4, 7.12 (s) H_7, H_8, 6.79 (s)	32
$R_1 = R_3 = -OCH_3$ $R_9 = -(CH_2)_3-N(CH_3)_2$ HCl	CD_3-OD	3.84 (s), R_4 3.72 (s), R_1	R_2, 6.39 (d), J_m=3 R_4, 6.46 (d), J_m=3 R_5, 7.25 (d), J_o=8 R_6, 6.91 (dd), J_m=3, J_o=8 R_8, 7.05 (d), J_m=3	32
$R_9 = -(CH_2)_3-N(CH_3)_2$ $R_1 = R_4 = -OH$ $R_7 = Cl$ $R_2=R_3=R_5=R_6=R_8=H$	DMSO-d_6		R_2, 6.40 (d), J_o=10 R_3, 6.52 (d), J_o=10 R_5, 7.08 (d), J_o=8 R_6, 6.92 (dd), J_m= J_m=2.5, J_o=8 R_8, 7.01 (d), J_m=2.5	32
$R_9 = -(CH_2)_3-N<(CH_3)_2$ $R_1 = R_4 = -OCH_3$ $R_7 = Cl$ $R_2=R_3=R_5=R_6=R_8=H$	CD_3-OD	3.72 (s), R_1 3.79 (s), R_4	R_2, 6.65 (d), J_o=10 R_3, 6.76 (d), J_o=10 R_5, 7.08 (d), J_o=8 R_6, 6.92 (dd), J_m=2.5, J_o=8 R_8, 7.01 (d), J_m=2.5	32

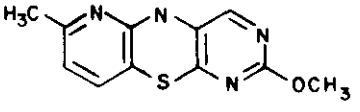
Compound	Solv.	Chemical Shift (δ), (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) of aromatic protons (Multiplicity), Coupling Constant (J)	Ref.
R_9=-$(CH_2)_2$-N$(CH_3)_2$ R_1 = R_3 = -OH R_7 = Cl R_2=R_4=R_5=R_6=R_8=H	DMSO-d_6		R_2, 6.04 (d), J_m=3 R_4, 6.22 (d), J_m=3 R_5, 7.07 (d), J_o=10 R_6,6.89(dd),J_m=2.5,J_o=10 R_8, 7.02 (d), J_m=2.5	32
R_9=$CH_2CH_2CH_2N(CH_3)_2$ a b c d R_5 = -OCH$(CH_3)_2$ R_2 = Cl R_1=R_3=R_4=R_6=R_7=R_8=H	CD_3-OD	2.08 (s), R_9 - d 3.60 (t), (J=6.2),R_9-a 1.78 (m), R_9 - b 2.36 (m), R_9 - c		33
R_9=$CH_2CH_2CH_2$-CN a b c R_2 = Cl R_3 = -O-CH(-CH_2-CH_2-)-CH_2-O-CH_2	DMSO-d_6	2.89 (t), J = 6.4,		33
R_1 = -OH R_2 = Cl R_9=-$CH_2CH_2CH_2$-N$(CH_3)_2$ a b c d	$CDCl_3$	3.50 (t), J=6.0,R_9-a 2.71 (t), J=6.5,R_9-c 2.36 (s), R_9 - d 1.69 (q), J=6.25,R_9-b	R_1, 9.54 (s) R_3, 7.04(dq), J=8.4 R_4, 6.62(dq), J=8.4 R_5-R_8, 7.15, m	33
R_2 = Cl R_5 = OH R_9=$CH_2CH_2CH_2N(CH_3)_2$ a b c d	DMSO-d_6	3.81(t), J=6.6, R_9-a 2.28(t), J=6.6, R_9-c 2.09 (s), R_9 - d 1.75(q), J= 6.4,R_9-b	R_1, R_3, R_4, 6.97 (m) R_5, 6.3-7.2 (bs) R_6, 6.53 (1), J_o=7.25, J_m=1.4 R_7, 6.97 (m) R_8, 6.59 (1),J_o=7.03, J_m=1.4	33
R_2 = Cl R_3 = OH R_9=-$CH_2CH_2CH_2$-NH_2 a b c d R_1=R_4=R_5=R_6=R_7=R_8=H	DMSO-d_6	3.76 (t), J=6.6,R_9-a 2.62 (t), J=6.5,R_9-c,d 1.72 (q), J=6.6,R_9-b	R_1, 6.96 (s) R_3, 4.22 (s) R_4, 6.74 (s) R_5-R_8, 7.00 (m)	33

Compound	Solv.	Chemical Shift (δ) (PPm) (Multiplicity), Coupling Constant (J). assignment	Chemical Shift (δ) (PPm) of aromatic protons, (Multiplicity), Coupling Constant (J)	Ref.
$R_9 = CH_3$ $R_{11} = CH_3$ $R_{10} = -CH_2-C_6H_5$ (a b) $X = NO_3$ $R_1 - R_8 = H$ $R_2 = Cl$ $R_3 = OH$	CD_3CN	4.15 (s), R_{10} - a 3.85 (s), R_9 2.25 (s), R_{11}	(R_1-R_8, R_{10}-b), 6.91-8.18 (m)	36
$R_1=R_4=R_5=R_6=R_7=R_8=H$	CD_3-OD	4.7 (bs), R_3, -NH	R_4, 6.66 (s) R_1, 6.54 (s)	33
$R_2 = Cl$ R_3 = 	DMSO-d_6	8.50 (s), -NH 5.41 (m), 2' 3.60 (m), 6' 1.75 (m), 3', 4', 5'		33
 $R_1 = R_4 = H$	$CDCl_3$		R_1, 6.86 (s) R_4, 7.88 (s)	21

In the synthesis of triazaphenothiazine derivatives, reaction of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (35) with 36 could lead to the formation of either 37 or 38. Nmr spectra



36 35 37



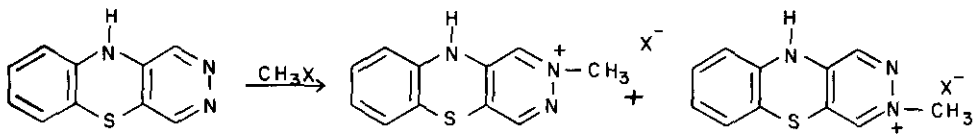
38

TABLE XI

Compound	Solv.	Chemical Shift (δ) (PPm) (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) (PPm) of aromatic protons, (Multiplicity), Coupling Constant (J).	Ref.
$R_9 = C_6H_5$ R_{11}=H, R_{10}=-CH_2-C_6H_5 a b $X = \bar{I}$ $R_1 - R_8 = H$	$CDCl_3$	3.45 (s), R_{10} - a	R_9, R_{10}-b, R_1-R_8, 6.3-8.5 (m)	36
$R_9 = C_6H_5$ $R_{11} = CH_3$ $R_{10} = CH_2$-C_6H_5 a b X = I $R_1 - R_8 = H$	$CDCl_3$	2.45 (s), R_{11} 4.4 (s), R_{10} - a	(2H), 6.6-6.83 (m) (14H), 7.0-7,9 (m) (2H), 8.16-8.4 (m)	36
$R_9 = CH_3$ $R_{11} = CH_3$ X = $\bar{I}$ R_{10} = -CH_2-C_6H_5 a b $R_1 - R_8 = H$	$CDCl_3$	4.27 (s), R_{10} - a 3.94 (s), R_9 2.31 (s), R_{11}	(R_{10}-b, R_1-R_8), 7.16-8.32 (m)	36
$R_9 = CH_3$ R_{10}-$(CH_2)_5$ - R_{11} X = $\bar{I}$ $R_1 - R_8 = H$	$CDCl_3$	3.95 (s), R_9 2.8 (s), -$(CH_2)_2$- 1.43 (s), -$(CH_2)_3$-	$R_1 - R_8$, 7-8.4 (m)	36
$R_9 = CH_3$ $R_{11} = CH_3$ R_{10} = -CH_2-C_6H_5 a b X = ClO_4 $R_1 - R_8 = H$	CD_3CN	4.08 (s), R_{10} - a 3.78 (s), R_9 2.22 (s), R_{11}	(R_1-R_8, R_{10}-b), 7.12-8.12 (m)	36

showed absorption at δ 2.33 (8-CH_3) 3.63 (4-O CH_3), and 3.68 (2-O CH_3). Absense of a more diffuse nmr signal and a stronger intramolecular hydrogen bonding ruled out the possibility for the alternative structure 39.[37]

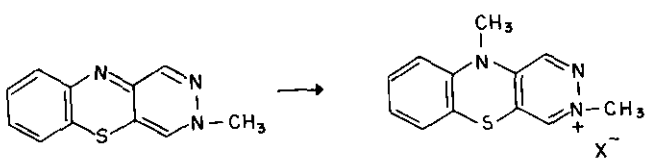
Methylation of 2,3-diazaphenothiazine (39) resulted in the formation of two isomers 40 41). Nmr spectroscopy showed that the two isomers are present in roughly equal percentage; 58% of 41 and 42% of 40. This demonstrated, that there is no substantial difference in nucleophilic



39 40 41

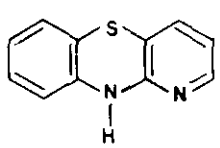
reactivity between nitrogens in position 2 and 3. The structure 40 was confirmed by nmr spectra, which showed an inversion in shielding for the proton on C-1 and C-4 on passing from 40 (δ 8.43 and 8.13) to 41 (δ 8.05 and 8.82).[38]

Addition of dimethyl sulphate to 42 gave 43, the nmr spectrum of which gave the signals of

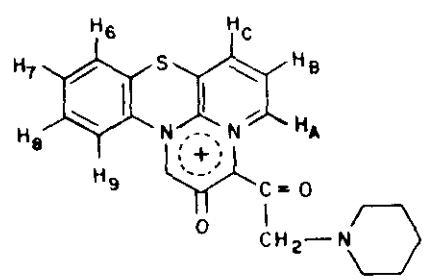


the C-1 and C-4 protons at δ 9.03 and δ 8.70.[38]

Chloroacetylation of 1-azaphenothiazine (44) followed by reaction with piperidine afforded 45, the structure of which was based on nmr spectrum.[39] Analysis of the nmr spectrum showed that



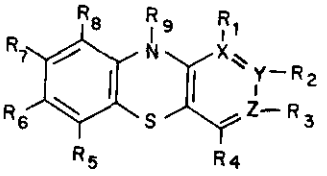
44



45

the piperidine derivative (45) contained 4 adjacent protons in an aromatic system in which one (H_9, quartet at 9.23 PPm) is experiencing a strong deshielding effect. The remaining three low-field protons are accounted for by an ABX system[40] with three adjacent protons (H_A, H_B, H_C) in an aromatic ring, with one of the three again experiencing a strong deshielding effect (H_A, quartet at 9.36 PPm).[39] The results are summarised in Table XI.

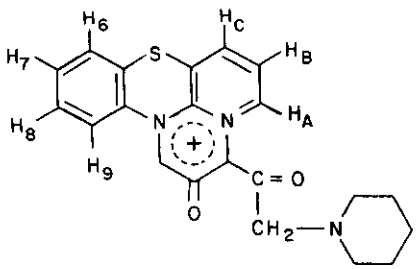
TABLE XI



Compound	Solv.	Chemical Shift (δ)(PPm) (Multiplicity), Coupling Constant (J) assignment	Chemical Shift (δ) of aromatic protons (PPm) (Multiplicity), Coupling Constant (J)	Ref.
X = Z = A = N	DMSO-d_6	2.33 (s), R_7	R_5, 7.40 (d), J = 8.2	37
B = Y = C		3.63 (s), R_4	R_6, 6.37 (d), J = 8.2	
R_2 = R_4 = -O CH_3		3.68 (s), R_2		
R_7 = CH_3		6.30 (b), R_9		
R_5 = R_6 = R_9 = H				
X = Z = A = N	DMSO-d_6	8.20 (b), R_4	R_2, 7.58 (s)	37
B = Y = C		7.63 (s), R_7	R_5, 7.60 (d) J = 9.0	
R_4 = NH_2, R_7 = CH_3			R_6, 6.69 (d), J = 9.0	
R_5=R_6=R_2=R_9=H				
X = Z = A = N	CF_3CO_2D	2.36 (s), R_7	R_5, 7.43 (d), J = 8.1	41
B = Y = C		5.07 (s), R_9	R_6, 6.20 (m)	
R_2 = R_4 = NH_2		6.20 (m), R_2, R_4		
R_7 = CH_3				
R_5 = R_6 = R_9 = H				
X = Z = A = N	DMSO-d_6	2.33 (s), R_7	R_5, 7.87 (d), J = 8.7	41
B = Y = C		2.52 (s), R_4	R_6, 6.87 (d), J = 9.2	
R_2 = NH_2		6.80 (b), R_2		
R_4 = R_7 = CH_3		7.48 (b), R_9		
R_5 = R_6 = R_9 = H				

Compound	Solv.	Chemical Shift (δ) (PPm) (Multiplicity), Coupling Constant (J) Assignment	Chemical Shift (δ) of aromatic protons (PPm) (Multiplicity) Coupling Constant (J)	Ref.
X = Z = A = N B = Y = C $R_2 = NH_2$, $R_4 = Cl$ $R_7 = CH_3$ $R_5 = R_6 = R_9 = H$	DMSO-d_6	2.46 (s), R_7 5.90 (b), R_2, R_9	R_7, 7.88(d), J = 9.2 R_6, 6.87(d), J = 9.2	41
X = Z = A = N B = Y = C $R_2 = -SCH_3$ $R_4 = NH_2$, R_7, = CH_3 $R_5 = R_6 = R_9 = H$	DMSO-d_6	2.18 (s), R_7 2.74 (s), R_2 7.20 (b), R_4	R_5, 7.43(d), J = 8.5 R_6, 6.47(d), J = 8.5	41
X = Z = B = N A = Y = C $R_4 = NH_2$, $R_6 = OCH_3$ $R_2 = R_7 = R_8 = R_9 = H$	DMSO-d_6	3.33 (s), R_6 8.07 (b), R_4 10.50 (b), R_9	R_8, 6.92(d), J = 8.6 R_7, 7.60(d), J = 8.6 R_2, 7.80(s)	41
X = Z = B = N A = Y = C $R_2 = NH_2$, $R_4 = OH$ $R_6 = Cl$ $R_7 = R_8 = R_9 = H$	DMSO-d_6	6.54 (b), R_2 8.83 (b), R_9	R_7, R_8, 6.88 (s)	41
X = Z = B = N A = Y = C $R_7 = R_8 = R_9 = H$ $R_2 = R_4 = Cl$ $R_6 = OCH_3$	CF_3CO_2D	3.73 (s), R_6 7.98 (bs), R_9	R_8, 7.32(d), J = 8.6 R_7, 8.14(d), J = 8.6	41
X = Z = B = N A = Y = C $R_2 = NH_2$, $R_4 = OH$ $R_6 = OCH_3$ $R_7 = R_8 = R_9 = H$	CF_3CO_2D	3.83 (s), R_6	R_8, 6.90(d), J = 9.2 R_7, 7.91(d), J = 9.2	41
X = Z = B = N A = Y = C $R_2 = R_4 = R_6 = Cl$ $R_7 = R_8 = R_9 = H$	CF_3CO_2D	6.80 (s), R_9	R_8, 7.60(d), J = 8.2 R_7, 8.07(d), J = 8.2	41

Compound	Solv.	Chemical Shift (δ) (PPm) (Multiplicity), Coupling Constant (J), Assignment	Chemical Shift (δ) of aromatic protons (PPm) (Multiplicity) Coupling Constant (J)	Ref.
X = Z = B = N A = Y = C $R_2 = NH_2$, R_4 = Cl $R_6 = OCH_3$ $R_7 = R_8 = R_9$ = H	DMSO-d_6	3.37 (s), R_6 7.58 (m), R_9	R_8, R_7, 7.58 (m)	41
X = Z = B = N A = Y = C $R_2 = R_4 = -NH_2$ $R_6 = -OCH_3$	*DMSO-d_6*	4.00 (s), -R 6.22 (b), 4-NH_2 6.50 (b), 2-NH_2 9.28 (b), 10-NH	R_8, 6.88(d), J = 8.4 R_7, 7.60(d), J = 8.4	42
X = Z = B = N A = Y = C $R_2 = R_4 = -NH_2$ R_6 = Cl	DMSO-d_6	6.37 (b), R_4 6.68 (b), R_2 9.60 (b), R_9	7.52 (s)	42
Y = Z = N X = A = B = C $R_2 = CH_3$ (salt) $R_1 = R_4 = R_9$ = H	DMSO-d_6	4.15 (s), R_2 10.35 (s), R_9	R_1, R_4, 8.13 (s), 8.43 (s) R_5-R_8, 6.40-7.11 (m)	38
Y = Z = N X = A = B = C $R_3 = CH_3$ (salt) $R_9 = CH_3$ $R_1 = R_5 = R_8$ = H	*DMSO-d_6*	3.47 (s), R_9 4.15 (s), R_3	R_1, R_4, 8.63 (s), 8.93 (s) R_5-R_8, 7.0-7.3 (m)	38
Y = Z = N X = A = B = C $R_2 = CH_3$ (salt) $R_9 = CH_3$ $R_5 = R_8 = R_1$ = H	DMSO-d_6	3.31 (s), R_9 4.30 (s), R_3	R_1, R_4, 8.80 (s), 9.05 (s) R_5-R_8, 7.0-7.3 (m)	38
$R_9 = CH_3$ Y = Z = N X = A = B = C $R_1 = R_4$-R_8 = H	DMSO-d_6	3.34 (s), R_9	R_1, R_4, 8.66 (s), 8.73 R_5-R_8, 6.80-7.40 (m)	38

Compound	Solv.	Chemical Shift (δ) (PPm) (Multiplicity) Coupling Constant (J) Assignment	Chemical Shift (δ) of aromatic protons (PPm) (Multiplicity) Coupling Constant (J)	Ref.
Y = Z = N X = A = B = C R_1=Cl, R_3=CH_3(salt) R_4 - R_9 = H	DMSO-d_6	4.02 (s), R_3	R_4, 8.73 (s) R_5-R_8, 6.75-7.30 (m)	38
Y = Z = N X = A = B = C R_1=Cl, R_3 = CH_3 R_4 - R_9 = H	DMSO-d_6	3.42 (s), R_9	R_4, 7.10 (s), R_4 R_5-R_8, 6.38-7.00 (m)	38
Y = Z = N X = A = B = C R_2 = CH_3 (salt) = (>$\overset{+}{N}$ CH_3) R_4 = Cl R_1 = R_5 - R_9 = H	DMSO-d_6	4.12 (s), R_2	R_1, 8.16 (s) R_5-R_8, 6.40-7.20 (m)	38
Y = Z = N X = A = B = C R_1 = Cl R_3 = >$\overset{+}{N}$-CH_3 (salt) R_9 = CH_3	DMSO-d_6	3.72 (s), R_9 4.25 (s), R_3	R_4, 9.25 (s) R_5-R_8, 6.90-7.50 (m)	38
	C_6H_6-d_6	1.41 (m), H-$_3$, 1.70 (m), H-$_{2'}$, H-$_4$, 2.84 (t), H-$_{1'}$, H-$_5$, 4.02 (s), H-14	H_2, H_3, 5.85 (ABX) J_{AB}=8.0 J_{AX}=7.0 J_{BX}=0.8 H_6, 6.4 (q), $J_{6,7}$ = 7.7, $J_{6,8}$ = 7.7 H_4, 9.36(ABX), J_{AB} = 8.0 J_{AX} = 7.0 J_{BX} = 0.8 R_6-R_9, 6.40, 6.51, 6.71 and 9.23	39

* The coupling constant (J) throughout in the tables is given in Hertz (HZ), unless otherwise stated.

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