Proton Magnetic Resonance Spectra of Some Nuclear-Substituted Phenothiazines

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The pmr spectra of a number of nuclear-substituted phenothiazines are recorded and discussed. Significant characteristic chemical shifts and coupling constant data for various substituents (viz., methyl, methoxy, and ethoxy groups) are taken into account for structural elucidation. The proton at 10-N (NH) is identified by deuterium exchange. The effects of substitution patterns and heteroatoms on the chemical shift values of different aromatic protons are also studied.

Although the literature is replete with studies of phenothiazines (*2*), there are few data dealing with the pmr spectra of nuclear-substituted phenothiazines (*3*). Although the application of this technique to this class of compounds is still in its infancy, the use of pmr has been recommended for the identification of phenothiazine drugs and the detection of impurities in samples of such drugs (*1, 5*), in as much as the substituents and particularly the side chain give rise to characteristic signals.

In the present investigation, the pmr spectra of a number of nuclear-substituted phenothiazines are recorded and discussed (Table I). The effects of substitution patterns and heteroatoms on the chemical shift values of different aromatic protons are also studied.

The compounds were prepared by the Smiles rearrangement by condensing thiophenol with reactive halogenonitrobenzene, formylation followed by cyclization.

The pmr spectra were recorded on a Varian A-60D spectrometer at 60 Mc/sec using TMS as an internal standard and DMSO-d_6, $CDCl_3$, and acetone-d_6 as solvents.

The protons of the unsubstituted phenothiazine (used as the reference compound) appear in the form of a complex multiplet between $\delta = 6.58 - \delta = 7.20$, in which it is not possible to isolate the signals of any one of the aromatic protons.

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

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_c appeared as a doublet at $\delta = 6.91$, and protons H_a and H_b appeared as a singlet and a doublet ($J_o = 8$) at $\delta = 6.33$ and $\delta = 6.41$, 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 $\delta = 9.73$, which was confirmed by D_2O exchange.

In compound II, 8-methoxy-1-nitrophenothiazine, the three protons of the methoxyl group ($—OCH_3$) appeared as a singlet at $\delta = 3.73$. The proton at nitrogen (—NH) appeared at $\delta = 9.75$, confirmed by D_2O exchange. The aromatic proton H_a appeared at $\delta = 6.33$, and H_b, H_c, H_d, H_e, and H_f at $\delta = 6.43$, $\delta = 6.95$, $\delta = 7.80$, $\delta = 6.71$, and $\delta = 7.06$ with $J_o = 8$ and $J_m = 2$ cps.

In compound III, 2-methoxy-7-nitrophenothiazine, a singlet at $\delta = 3.70$ 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 $\delta = 7.90$, which is attributed to the electron sink caused by the *O*-nitrogroup. The proton H_d showed a singlet at $\delta = 7.71$. 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 $\delta = 6.73$. The protons H_b and H_c appeared as two doublets ($J_o = 8$) at $\delta = 6.50$ and $\delta = 6.86$, respectively. The proton H_a showed a singlet at $\delta = 6.36$ ($J_m = 2$). The observed values for chemical shift and coupling constants agree well with the theoretically predicted values (*4*).

In compound IV, 2,7-dimethyl phenothiazine, the protons of the two methyl groups appeared as a sharp singlet at $\delta = 2.30$. The most downfield aromatic proton H_d appeared as a broad singlet at $\delta = 7.91$ ($J_m = 2$). The protons H_c and H_f appeared as doublets at $\delta = 7.18$ and $\delta = 7.41$ ($J_o = 8$). The protons H_b and H_e showed two doublets ($J_o = 8$; $J_m = 2$ cps) at $\delta = 6.88$ and $\delta = 6.76$, and proton H_a appeared as a singlet ($J_m = 2$) at $\delta = 6.76$. The protons at nitrogen appeared at $\delta = 9.33$, confirmed by D_2O exchange.

In compound V, 2-ethoxy-7-nitrophenothiazine, a triplet appeared at $\delta = 1.3$ ($J = 6$ cps) for $—CH_3$ and a quartet at $\delta = 4.05$ ($J = 6$ cps) for $—CH_2—$ protons. The aromatic protons appeared in the range $\delta = 6.16$ to $\delta = 8.0$ and could not be distinguished separately because of the low solubility of the sample in the deuterated solvent used.

In compound VI, 2-methyl-7-nitrophenothiazine, a sharp singlet appeared at $\delta = 2.0$ for $—CH_3$ protons, and aromatic protons appeared in between $\delta = 6.33$ to $\delta = 8.0$ region.

Compound VII, 2-methyl-7-methoxy phenothiazine, gave a sharp singlet at $\delta = 2.11$ for the three protons of the methyl group and a singlet at $\delta = 3.63$ for the three protons of the methoxyl group. The —NH— proton was found at $\delta = 8.21$, and the aromatic protons appeared between $\delta = 6.38$ to $\delta = 6.90$ and could not be resolved.

For trisubstituted phenothiazines, compound VIII, 1,3-dinitro-8-ethoxy phenothiazine, gave a triplet at $\delta = 1.38$ ($J = 7$) and a quartet at $\delta = 4.05$ ($J = 2$) 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

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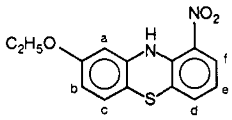
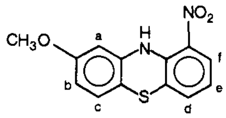
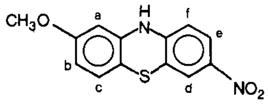
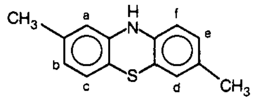
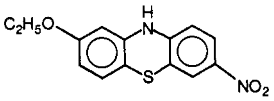
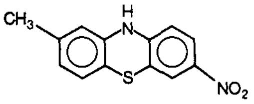
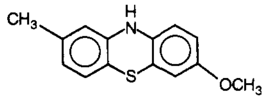
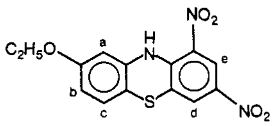
Table I. Pmr Spectral Data of Nuclear-Substituted Phenothiazines[a]

Compounds		Solvent	δ, ppm	Assignment	Aromatic protons	J_m	J_o*	
I		$CDCl_3$	9.73 (s)	—NH—	a 6.33	2		s
			1.36 (t) (J = 6)	$—CH_3$	b 6.41	2	8	d
			3.95 (q) (J = 6)	$—OCH_2—$	c 6.91	2	8	d
					d 7.81	2	8	d
					e 6.70	1	8	t
					f 7.10	2	8	d
II		$CDCl_3$	9.75 (s)	—NH—	a 6.33	2		s
			3.73 (s)	$—OCH_3$	b 6.43	2	8	d
					c 6.95	2	8	d
					d 7.80	2	8	d
					e 6.71	2	8	t
					f 7.06	2	8	d
III		DMSO-d_6	3.70 (s)	$—OCH_3$	a 6.36	2		s
					b 6.50	2	8	d
					c 6.86		8	d
					d 7.71	2		s
					e 7.90	2	8	d
					f 6.73		8	d
IV		$CDCl_3$	9.33 (s)	—NH—	a 6.76	2		s
			2.30 (s)	$—CH_3$	b 6.88	2	8	d
					c 7.18		8	d
					d 7.91	2		s
					e 6.76	2	8	d
					f 7.41		8	d
V		DMSO-d_6	1.30 (t) (J = 6)	$—CH_3$	6.16–6.80			
			4.05 (q) (J = 6)	$—OCH_2—$	(Not resolvable)			
VI		Acetone-d_6	2.0 (s)	$—CH_3$	6.33–8.00			
					(Not distinguishable)			
VII		DMSO-d_6	8.21 (s)	—NH—	6.38–6.90			
			2.11 (s)	$—CH_3$	(Not distinguishable)			
			3.63 (s)	$—OCH_3$				
VIII		$CDCl_3$	10.45 (s)	—NH—	a 6.41			s
			1.38 (t) (J = 7)	$—CH_3$	b 6.70		6	d
			4.05 (q) (J = 2)	$—OCH_2—$	c 7.30	3	9	d
					d 8.80			s
					e 9.13			s

[a] J_m, meta coupling. J_o, multiplicity owing to ortho coupling. s, singlet; d, doublet; t, triplet; q, quartet.

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 permits the identification of an individual proton in the aromatic rings of these compounds.

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Literature Cited

(1) Alexander, T. G., Koch, S. A., *J. Ass. Offic. Agr. Chem.*, **48**, 618 (1965).
(2) Bodea, C., Silberg, I., in "Advances in Heterocyclic Chemistry," A. R. Katritzky, A. J. Boulton, Eds., Vol 9, p 322, Academic Press, London, England, 1968.
(3) Cymerman-Craig, J., Green, D. E., Roy, S. K., Piette, L. H., Loeffler, K. O., *J. Med. Chem.*, **8**, 392 (1965).
(4) Jackman, L. M., Sternheil, S., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," p 179, Pergamon Press, New York, N.Y., 1969.
(5) Warren, R. J., Eisdorfer, I. B., Thomson, W. E., Zarembo, J. E., *J. Pharm. Sci.*, **55**, 144 (1966).

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