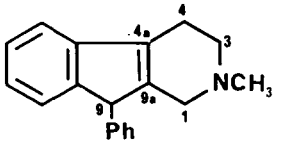
J. Pharm. Pharmacol. 1988, 40: 83–84
Communicated June 12, 1987

The structure of phenindamine base and salts in the solute state

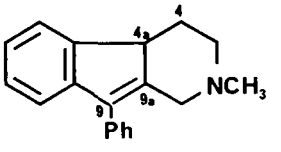
S. K. BRANCH, A. F. CASY, R. HUSSAIN, C. UPTON, *School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK*

Abstract—High-field NMR (^{13}C and ^{1}H) studies of phenindamine are reported which establish structures of the free base and some of its salts in the solute condition. The base exists as a mixture of two isomers which differ in double bond position (9–9a or 4a–9a) while most salts are 9–9a isomers. The clinically employed tartrate (Thephorin) is exceptional in being a 4a–9a ene. Salts of both double bond type exist in solution as mixtures of protonated epimers of variable epimeric ratio, that of the tartrate in D_2O being approximately 1 : 1.

The complexity of a 400 MHz ^{1}H NMR spectrum of the antihistaminic agent phenindamine tartrate (Thephorin) in terms of its generally accepted 4a–9a ene structure (**1**) has prompted the present report. Since phenindamine is obtained by reduction of the corresponding 4–4a, 9–9a diene hydrobromide (Plati & Wenner 1955), the 9–9a ene formula (**2**) is also possible (NMR evidence—absence of a vinylic C_4-H resonance—clearly precludes the 4–4a ene isomer).



1



2

The 67·8 MHz proton-decoupled ^{13}C NMR spectrum of the base (derived from the commercial tartrate and recrystallized from ethanol) displayed about twice the number of signals required for a single structure and was consistent with that of a mixture of similar amounts of isomers **1** and **2** (Table 1). The ^{1}H NMR spectrum of the base also displayed features charateristic of both isomers (see below). While most isomeric resonances differed little in chemical shift, the two methine carbon signals (55·7, 45·2 ppm) and the high field methylene carbons (26·5, 19·4 ppm) were well separated. The latter were assigned to C-4 (β- to electronegative nitrogen), and the fact that the 26·5 ppm signal displayed more long-range couplings to protons than that at higher field (as revealed in a proton-coupled spectrum, Fig. 1) allowed its assignment to structure **2** in which C-4 is subject to three $^{2}J_{(C,H)}$ couplings (C-4 of **1** has one less ^{2}J coupling and gives rise to the narrower 19·4 ppm resonance). The appearance of the two C–H resonances in the coupled spectrum likewise allowed assignment of that at 55·7 ppm to C-9 of **1** and 45·2 ppm to C-4a of **2**; a model chemical shift value for the former resonance was provided by a C-9 chemical shift of 53·4 ppm recorded for a dihydro analogue of phenindamine base.

According to Plati & Wenner (1955), addition of alkali metal salts of various acids to the aqueous hydrogenation liquor containing the hydrobromide of phenindamine yields salts of either **1** or **2** dependent upon the nature of the added anion. The salts were characterized structurally by small differences in their UV spectra and by vigorous degradations of derived bases. In our hands most salts had ^{13}C NMR spectra consistent with the 9-9a ene **2**, e.g. HBr and HNO_3 (Table 1). Often a duplication of signals was observed (e.g. HCl, Table 1) which could be attributed to the presence of significant populations of the two protonated epimers of **2** rather than an equilibrium mixture of isomeric alkenes **1** and **2**. Thus chemical shift differences between duplicate signals were mostly small, while corresponding ^{1}H NMR spectra recorded in $CDCl_3$ or DMSO-d_6 displayed duplicate $^{+}$N-H, N-Me

Correspondence to: A. F. Casy, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK.

Table 1. ^{13}C NMR chemical shifts of phenindamine base and some of its salts.[a]

Sample and solvent	Low field Cq[b]	Low field CH	High field CH	CH_2	NMe
Base (crystallized from ethanol)[c] in $CDCl_3$	147·4, 144·9 143·4, 142·7 141·3, 137·0 134·9, 134·4 132·2, 132·0	129·0, 128·7 128·6, 128·2 127·7, 127·3 127·1, 126·9 126·1, 126·0 123·7, 122·9 121·0, 118·6	55·7 45·2	52·7, 52·1 51·5, 50·4 26·5, 19·4	42·1 41·6
HBr salt in $CDCl_3$	144·8, 143·4 141·7, 132·7 132·1	128·6, 128·5 128·0, 127·0 125·8, 122·7 120·9	44·9	53·1 52·3 27·2	42·6
HNO_3 salt in DMSO-d_6	145·7, 143·4 139·8, 135·7 132·5	129·0, 128·8 128·3, 127·3 125·9, 123·5 120·5	45·3	52·5 51·7 27·2	42·2
HCl salt[d] in $CDCl_3$	145·7, 145·1 144·9, 143·7 142·9, 142·2 132·7, 132·2 131·6	129·7, 129·1 128·9, 128·8 128·4, 128·2 127·6, 127·2 126·6, 126·0 123·1, 122·9 121·3, 121·2	45·8, 45·2	53·4, 52·5 51·3, 51·0 27·4, 23·9	43·0 37·4
Salicylate salt in DMSO-d_6	complex[e]	complex[e]	55·0 45·8	52·4, 51·8 51·1, 49·8 27·4, 20·0	42·0
Tartrate salt[f] in D_2O	174·4, 174·3[g] 148·0, 147·6 141·9, 141·8 137·8, 137·5 135·6, 135·5 134·7, 134·2	129·1, 127·8 127·7, 127·4 127·1, 125·8 123·4, 119·2	71·7[g] 55·5, 55·1	51·9, 51·6 50·9, 50·6 19·65, 19·41	42·2 41·8

[a] In ppm from TMS, recorded at 67·8 MHz using a Jeol GX270 FT NMR spectrophotometer. The number of protons attached to carbons was established from DEPT experiments.

[b] Quaternary carbons.

[c] For a single structure a maximum of 5 low field Cq and 7 low field CH signals and, at high field one CH and two CH_2 signals, are required.

[d] In the corresponding 270 MHz ^{1}H spectrum NH (broad singlets 11·8, 10·7 ppm) and NMe (doublets 279, 2·47 ppm separation 5·1 Hz and intensity ratio 67 : 28) signals were resolved. The former signals were absent and the latter collapsed to singlets after addition of D_2O.

[e] Many lines including those due to salicylate carbons.

[f] ^{1}H NMR features from 400 MHz spectrum (chemical shifts in ppm from DSS, separations in parentheses) (br broad, s singlet, d doublet, dt doublet of triplets, m multiplet). See also 2D COSY plot, Fig. 2.

4·71, 4·68	brs	epimeric H-9
4·25}	brd (16·8 Hz)	
3·69}	narrow dt (16·4 Hz)	}epimeric H-1
4·00}	brd (16·8 Hz)	methylene protons
3·85}	brd (16·4 Hz)	
3·8–3·75	m	overlapping signals of
3·5–3·4	m}	epimeric H-3 and H-4
3·1–3·0	m	methylene protons
2·97	s	epimeric NMe
2·96	s	signals

All resolved epimeric signals had similar intensities.

[g] Carbonyl and CH resonances of tartaric acid.

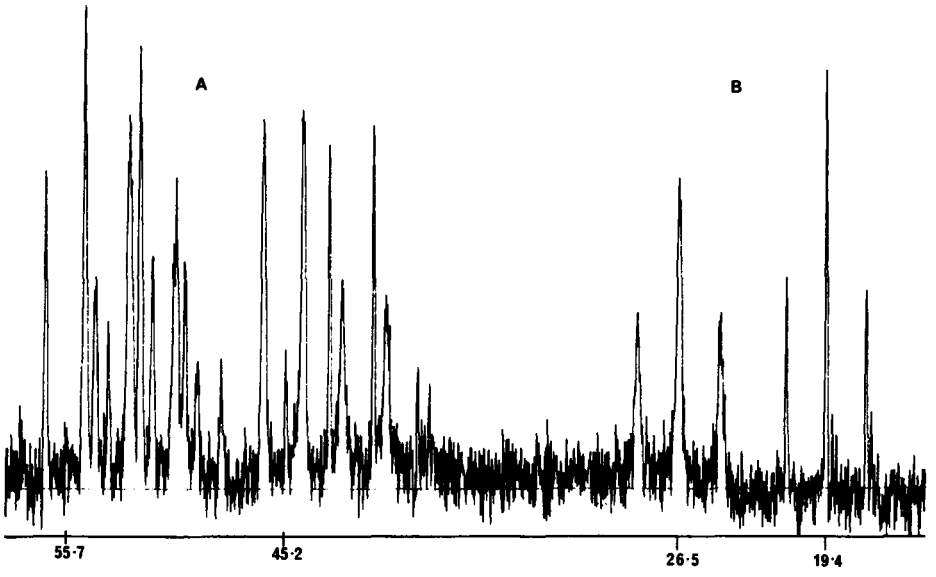


FIG. 1. Part of the proton-coupled 67·8 MHZ ^{13}C NMR spectrum of phenindamine base in $CDCl_3$: (A) shows the two CH resonances (55·7, 45·2 ppm) as doublets (^1J 129 Hz) with additional small splittings (<10 Hz) evident on lines of the higher field signal; (B) shows the C-4 methylene resonances (26·5, 19·4 ppm) as triplets (^1J 133 Hz)—both show additional small coupling effects (<10 Hz) which are more extensive for the lower field signal.

(coupling of N-Me to N-H was seen in some cases, e.g. HCl Table 1) and other signals. The epimer ratio, dependent upon solute and solvent purity and nature of the counter ion, varied considerably. Some salts, notably the salicylate (Table 1) gave ^{13}C NMR evidence of being a mixture of **1** and **2** in that resonances characteristic of C-9 (**1**) and C-4a (**2**), and C-4 (**1** and **2**) were recorded.

The clinically employed tartrate salt also had a ^{13}C NMR spectrum of the multiple-signal type (Table 1) but in this case duplicate CH and high field CH_2 resonances differed little and were close in chemical shift to signals characteristic of C-9 and C-4 of **1**, respectively. As in salts of **2**, signal duplication reveals that **1** tartrate is composed of a mixture (1 : 1) of protonated epimers as solute in D_2O. With this evidence in hand, the ^1H NMR spectrum of phenindamine tartrate could be interpreted in terms of protonated epimers of **1** (Table 1), an operation aided by a 2D proton-correlation (COSY-45) plot (Fig. 2). Thus both epimeric H-9 protons are resolved— these are long range coupled to one of the C-1 methylene protons (probably the one that may adopt a W-linked pathway with H-9) (Sternhell 1969). The C-1 proton resonances form duplicate AB doublet pairs with doublets 3/7 (see Fig. 2) due to one epimer and 4/5 to the other. Epimeric signals due to the four C-3 and C-4 protons overlap forming unresolved multiplets (6,8,9) and the 2D plot shows all to be coupled. Proton resonances near 4·7 ppm (broad singlets due to H-9) are thus characteristic of salts of structure **1**, while those near 1–2 ppm (doublet of quartets attributed to the pseudo axial proton of C-4 which is strongly coupled to H-4a, axial H-3 and its geminal H-4 partner, and weakly to equatorial H-3) are diagnostic of salts of structure **2**; the latter signal (as is the former) is clearly duplicated in epimers. The fact that spectra of salts of either kind in D_2O or organic solvents were little changed after solutions had been stored for four days (at 20 °C) demonstrates that the rates of isomerization of **1** and **2** are slow under these conditions. In view of the marked difference in antihistaminic potency of **1** and **2** (Plati & Wenner 1955) (which may be related to pronounced differences in their molecular shape), the present demonstration of an unequivocal means of their structural characterization should be of value in the interpretation of the structure-activity relationships of phenindamine and related antagonists of H-1 receptors of histamine.

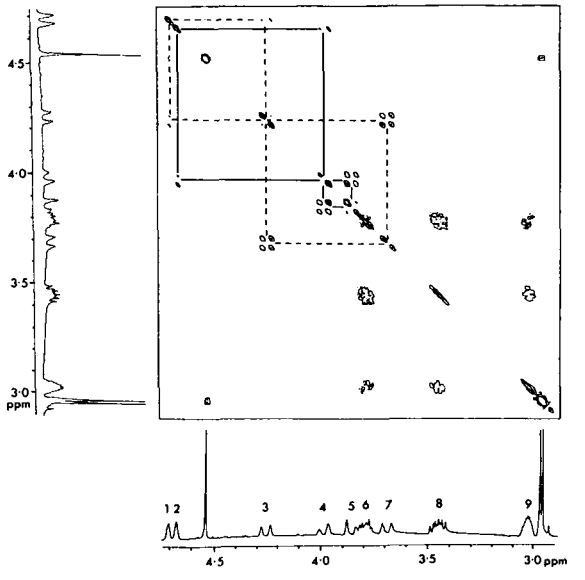


FIG. 2. 400 MHz ^1H COSY-45 spectrum of phenindamine tartrate in D_2O, with the conventional spectrum on the axes. Experimental details are as follows: 96 transients acquired for 256 t_1 values with a complex data set of 1024 × 256 points; zero-filled once in f_1 dimension and transformed with a sinebell window function in both dimensions: spectral width 879 Hz in both dimensions giving a resolution of 1·7 Hz per point. Chemical shifts of signal 1–9 of lower spectrum are given in footnote [f] of Fig. 1. The solid and dotted lines show the connectivity pathways for H-9 and the methylene protons at C-1 in each epimer.

We thank Roche Laboratories UK for a generous supply of phenindamine tartrate, and R. H. thanks the Mendaki and Muis Foundation (Singapore) for sponsorship.

References

Plati, J. T., Wenner, W. (1955) J. Org. Chem. 20: 1412–1423
Sternhell, S. (1969) Q. Rev. Chem. Soc. 23: 236–270