Phenindamine and its Analogues and Precursors: NMR Evidence of Structure and Configuration

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The ¹H and ¹³C NMR spectra of analogues of the antihistaminic agent phenindamine and its precursors are interpreted in terms of structure and geometry. Points of interest are the conformations of 4-piperidinol and dihydro-1-pyrindene(diene) intermediates, and the configuration of the hexahydro analogue of phenindamine and its corresponding product of equilibration. Results of an antihistamine evaluation test are presented.

KEY WORDS Phenindamine Antihistamines Di, tetra- and hexahydro-1-pyrindenes ¹H and ¹³C NMR

INTRODUCTION

The popular antihistaminic agent phenindamine tartrate (Thephorin) presents several points of NMR interest relating to structural and stereochemical detail, as also do its precursors and analogues. The synthesis of phenindamine (4a) via the bis-Mannich base 1 and 4-piperidinol 2 or diene 3 (Scheme 1) leads to a binary mixture of 4a,9a- and 9,9a-ene tetrahydro-1-pyrindenes 4. According to Plati and Wenner,¹ addition of alkali metal salts of various acids to the aqueous hydrogenation liquor derived from the diene 3 (R = H)hydrobromide yields salts of either the 4a,9a- or 9,9aene depending on the nature of the added anion. The salts were characterized by small differences in their UV spectra and by vigorous degradations of corresponding bases. Because of the importance of a precise structural knowledge to the inclusion of phenindamine into

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structure–activity relationship correlations amongst ligands which block H-1 receptors of histamine,² the structure of the phenindamine group has been addressed by NMR spectroscopy, a technique which carries no risk of isomerization. Some of the results in regard to phenindamine itself have been reported previously.³

RESULTS AND DISCUSSION

The first point of NMR interest in Scheme 1 relates to the configuration of the 4-piperidinols 2, obtained by an intramolecular aldol condensation of the *bis*-Mannich bases 1. Details of the ¹³C and ¹H NMR features of 2 (R = H) and its analogues are given in Tables 1 and 2 respectively.

Evidence of the cis 4-OH/3-COAr configuration and eq-4-Ar chair conformation (I) of these products is provided by the ${}^{3}J$ magnitudes of the H-3 signal (one large, ca. 12 Hz, and one small, ca. 3.5 Hz), and the demonstration of a coupling of ca. 3 Hz between the ax-H-5



Scheme 1. (a) R = H; (b) R = Me; (c) R = Et; (d) R = Br; (e) R = Cl.

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Compound ^b	C-2	C-3	C-4	C-5	C-6	N–Me	со	Ar	Others
2a (R = H)	54.6	50.5	72.5	39.9	51.35	45.9	204.2	124.5–133.9 (5 × CH) 135.8 (Cq) 147.0 (Cq)	
2b (R = Me)	54.6	50.1	72.3	40.0	51.3	45.8	203.6	124.27–129.3 (4 × CH) 133.2–144.8 (4 × Cq)	Ar–CH ₃ 20.7, 21.5
2c (R = Et)	54.7	50.25	72.4	40.1	51.4	45.9	203.7	124.4–128.5 (4 × CH) 133.5–151.0 (4 × Cq)	Ar–CH ₂ CH ₃ 14.9,° 15.2
2d · HCl (R = Br)	52.3	46.1	71.1	36.5	50.8	43.4	200.9	126.2–132.5 (4 × CH) 121.7–142.7 (4 × Cq)	
2e (R = CI)	54.3	50.7	72.3	39.7	51.1	45.8	202.6	125.9–129.6 (4 × CH) 132.6–145.5 (4 × Cq)	



and the OH (the intervening bonds between these two protons assume a near planar W-system in I conducive to long-range coupling).⁴ Conformation I is stabilized by an intramolecular hydrogen bond. The diene intermediates 3 could be obtained either by acid treatment of the piperidinols 2 or directly from the *bis*-Mannich bases 1. The NMR spectra of the products, isolated as HBr salts (Tables 3 and 4), were consistent with a flexible diene structure but in certain cases (notably in the spectra of products obtained from a piperidinol) they gave evidence of high degrees of conformational preference. Thus the N-Me(s), H-1(br s), H-3(nd) and H-4(nt) (n = narrow) resonances of $3a \cdot HBr$ (form of signal under rapid equilibrium conditions in parentheses) appeared as multiplets characteristics of pseudo-axial and pseudo-equatorial protons and displayed coupling to the N⁺-H proton, evidence of a slow interconversion rate (see II). The fact that the magnitudes of the coupling between N⁺-H and the C-1 and C-3 protons all fell below 5 Hz is evidence that the pseudo-axial N-methyl protonated epimer is favoured (from models the nonbonded interactions of the methyl group are judged to be greater in the axially protonated epimer).

Compound	H-2	H-3	H-5	H-6	N–Me	O-H	Ar~H	Others
2a	ax: 2.74 m ^b eq: 2.92 ddd (11, 4, 1)	ax: 4.40 dd (12, 4)	ax: 2.07 m ^c eq: 1.81 dt (12.7, two <4)	ax/eq∶ 2.74 m⁵	2.39 s	5.16 d (3)	7.40 m	_
2b	ax: 2.66 m ^b eq: 2:89 ddd (11, 3.4, 1)	ax: 4.38 dd (11.4, 3.7)	ax: 2.03 m eq: 1.79 dt	ax/eq: 2.66 m ^ь	2.20 s	5.24 d (2.6)	7.027.8 m ^d	ArCH ₃ 2.34, 2.37 s
2c	ax: 2.71 m ^b eq: 2.91 dd (11.4, 3.1)	ax: 4.37 dd (11.4, 3.1)	ax: 2.05 m eq: 1.81 dt	ax/eq: 2.71 m ^ь	2.38 s	5.22 d (2.6)	7.067.82 m ^d	ArCH ₂ CH ₃ 2.52, 2.71 q 1.18 t (7.5)
2d HCI	ax/eq: 3.48 m ^b	ax: 5.52 dd (11, 3.4)	ax: 2.02 m eq.: 1.95 bd (∼14)	ax/eq: 3.48 m ^ь	2.91 d (3.3)	3.48 m ^e	7.38–7.99 m	_
2e	ax: 2.76⁵ eq. 2.89 ddd (11.3, 3.4, 1)	ax: 4.29 dd (11.4, 3.7)	ax: 1.98 m eq: 1.78 dt	ax/eq: 2.76 ^ь	2.39 s	5.10 d (2.9)	7.41 m	_

^a Chemical shifts in ppm from TMS, coupling constants or line separations (Hz) follow signal descriptions. Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; ax, axial; eq, equatorial.

^b Overlap of ax H-2, ax H-6 and eq H-6 signals.

° Two large (\sim 12.7) and one small (\sim 4) couplings revealed when the OH signal was irradiated.

^d Four d (\sim 8) resolved.

^e Overlaps other resonances.

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Compound ^b	H ₂ -1	H ₂ -3	H-4	N-Me	Ar–H	Other
За	4.46 s	4.28 d (3.3)	6.66 t (∼3.5)	3.03 s	7.43 m	
3a°	4.26, 4.55 dd (15.5, 2.9)	4.07, 4.40 dt (13.4, 4.5, 4.5)	6.61 t (4)	2.90 d (4.95)	7.43 m	
3b	4.32 m ^d	4.32 m	6.51 t (3.6)	2.89 d (4.8)	7.06–7.48 m ^e	Ar–CH ₃ 2.35, 2.43 s
3с	4.29 m ^d	4.29 m ^a	6.53 bs t(3.9)°	2.89 d (4.9)	7.02–7.47 m	Ar–CH₂CH₃ 2.58, 2.69 q (7.2) 1.16, 1.28 t (7.2)
3d	4.60 s	4.33 bs	7.28 t (4)	3.10 s	7.68 m	_
3e	4.64 s	4.40 d (2.7)	7.27 t (2.7)	3.04 s	7.35–7 <i>.</i> 92 m	_

Table 3.	¹ H NMR	characteristics	of some di	hvdro-1-n	ovrindene ((3)	hvdrobromide	s in '	CDCL	а
			v						~~~~	

^a Footnote a in Table 2 applies.

^b Derived from corresponding bis-Mannich base 1 unless noted otherwise.

^c Derived from corresponding 4-piperidinol 2.

^d Overlaps H₂-3 signal.

e Three d (7.7) resolved.



II N-protonation equilibrium (partial formulae)

NMR spectral assignments of phenindamine base and some of its salts have been made previously and features characteristic of isomeric 4a,9a- and 9,9a-enes described.³ The spectra of the salt forms of each isomer are complicated by the presence of protonated epimers in slow equilibrium. The 4a,9a-ene structure of the clinically used D-tartrate salt of phenindamine was confirmed (Thephorin is a mixture of diastereoisomers in the ratio 60:40).⁵ Salts of the dimethyl and diethyl analogues of phenindamine could only be isolated in the 9,9a-ene form (4, R = Me or Et); their NMR spectra displayed signals characteristic of such isomers (Table 5). Dibromo and dichloro dienes (3, R = Br or Cl) could not be reduced to corresponding analogues of phenindamine because of concurrent dehalogenation reactions.

Hexahydro isomers

Catalytic hydrogenation of the diene 3 (R = H) under conditions more vigorous than those employed for reduction aimed at isolation of the tetrahydro products 4 gave the hexahydro derivative 5a. Its ¹³C NMR characteristics were indicative of a single isomeric form, as

Table 4. ¹³ C NMR chemical shifts of some dihydro-1-pyrindene (dienes 3) hydrobromides in CDCl ₃ ^a								
Compound	C-1 ^b	C-3	C-4	N–Me	Ar	Other		
За	50.4	51.3	116.1	41.46	120.2–141.9 (7 CH, 6 Cq resolved)			
3b	50.9	51.8	114.1	41.29	120.6–142.7 (5 CH, 5 Cq)	ArCH ₃ 21.4, 21.9		
3c	50.6	51.5	115.3	41.5	119.9–145.1 (5 CH, 8 Cq)	ArCH ₂ CH ₃ 15.0, 15.4 28.3, 28.7		
3d	49.9	51.6	122.8	42.0	123.0–143.4 (5 CH, 8 Cq)	-		
3e°	49.7	51.3	119.8	41.7	122.4–143.1 (5 CH, 8 Cq)			

^a Footnote a in Table 1 applies.

^bC-1 and C-3 signals assigned by the aid of a ¹³C-¹H correlation experiment.

^c Solvent DMSO-d₆.

Compound	CH (non-Ar)	CH2	N Me	Ar–Me (CH ₂ <i>Me</i>)	Ar–CH	ArCq
4b · HBr (R ≕ Me)	45.1, 45.6 ^ь	24.3, 27.7° 51.5, 54.0ª 51.2, 53.1	42.8	21.0, 21.2	122.1–130.0 (5 pairs)	131.8–146.4 (4 pairs)
4c · HCl (R = Et)	45.1, 45.5 ^ь	24.3, 27.6° 28.5, 28.9° 50.9, 51.3° 52.9, 53.8	37.3, 43.2	15.3, 16.0 ^r	120.8–128.9 (5 pairs)	129.1–145.5 (4 pairs)
5a base	40.2, 45.7 53.4 (C-9)°	24.4 (C-4),º 51.5 54.2	46.2	_	122.9–129.0 (7 signals)	143.1, 144.2, 144.3
5a · HBr	38.0, 42.4 52.0	21.1, 50.6 52.5	43.8	_	122.3–128.1 (6 signals)	135.3, 140,9, 141.7
Epimer of 5a · HCl	38.8, 48.0 49.8	26.5, 52.0 52.5	43.7	_	122.7–128.8 (6 signals)	141.0, 144.0, 144.4
5b · HCl R = Me)	38.0, 41.4 41.9	22.7, 55.1 55.6	44.3	20.8, 20.9	126.5–129.2 (5 signals)	129.3–137.8 (5 signals)
5c base (R = Et)	39.2, 44.5 52.8	23.1, 28.4° 28.8,° 51.2 53.7	45.0	15.4, 15.8 ^r	122.6–129.0 (5 signals)	134.3–143.9 (5 signals)

Table 5. ¹³C NMR chemical shifts of some tetrahydro (4) and hexahydro-1-pyrindenes (5) in CDCl₃^a

^a Footnote a in Table 1 applies; duplicate signals are evidence of pairs of protonated epimers.

^b Characteristic of C-4 of a 9,9a-ene,³ corresponding ¹H spectra showed H-4a resonances at 3.45/3.53 dd (12.4, 4.6) for **4b** HBr and 3.45/3.55 dd (12.4, 5.6) for **4c** HCl, signals which replace those of H-9 (br s near 4.5 ppm) in isomeric 4a,9a-enes.^{3,6}

^o Characteristic of C-4 of a 9,9a-ene.³

^d C-1 and C-3 resonances.

^e Ar-CH₂Me.

[†]Ar-CH₂*Me*.

⁹ Assignments based on comparisons with ¹³C NMR features of the tetrahydro 4a,9a-ene 4a.³



were those of the related dimethyl and diethyl analogues (Table 5), but provided no direct evidence of stereochemistry. Configurational deductions were possible, however, from the comparison of the ¹H NMR spectrum of a mixture of 5a (original isomer) and its product of isomerization which resulted after treatment with 40% KOH in *n*-butanol at reflux temperature.⁷ In this spectrum a pair of H-9 doublets and N-Me singlets were clearly resolved, to lower field and higher field, respectively, for the resonances of the original product. If it is assumed that the original isomer has an all-cis geometry (probable from its mode of formation) and, further, that the reduced pyridine moiety adopts a nearchair conformation, then a molecular arrangement of type III should result. When the presumed all-cis material is equilibrated, C-9 is the most probable isomerization site with formation of the epimer of III in



III all-cis

which the H and Ph substituents of C-9 are interchanged.

In conformation III, the N-Me protons fall within the shielding zone of the aromatic ring,⁸ whereas in the epimer the same protons are well removed from the aromatic influence. The notably higher field N-Me chemical shift of the original isomer (2.01 ppm), as compared with that of its epimer (2.25 ppm), is in agreement with this argument. Consideration of the magnitude of the dihedral angle between H-9 and H-9a (from models: $20-30^{\circ}$ in all-*cis*-III, near 180° in the C-9 epimer) predict a large ³J value for the C-9 epimer, as observed (5.6 Hz for original product, 9.0 Hz for its equilibration form).

Subsequent full analysis of the original hexahydro derivative **5a**, made possible by a ${}^{1}H^{-1}{}^{3}C$ correlation spectrum and ${}^{1}H^{-1}H$ COSY plots, allowed the coupling interactions of H-9a and H-4a protons to be determined. The absence of large couplings was consistent with a *cis* relationship as in III. The ${}^{1}H$ NMR spectrum of the product of vigorous reduction of the diethyl diene (3, R = Et) was similar to that of material derived from 3 (R = H), and the compound is likewise assigned an all-*cis* configuraton.

In evaluations of antihistamine activity in rats by the compound 48/80 lethality test,⁹ phenindamine itself (4a, 4a,9a-ene) provided the greatest protection whereas 9,9a-enes were less effective (4a) or inactive (4b and 4c). The precursor diene 3a gave no protection. Of the epimeric hexahydro derivatives, the all-*cis* isomers 5a and 5c were ineffective, whereas the epimer of 5a was partially effective. Dosage levels were 10 mg kg⁻¹ subcutaneous.

EXPERIMENTAL

Bis-Mannich bases (1), 4-piperidinols (2) and dienes (3) were prepared by methods similar to those described for analogues lacking aromatic substituents.¹ Novel products were bis[2-(4-ethylbenzoyl)ethyl]methylamine · HCl, (1c · HCl), m.p. 134-135 °C (found, C 69.7, H 7.6, N 3.4; $C_{23}H_{30}CINO_2 \cdot 0.5H_2O$ requires C 69.6, H 7.9, N 3.5%), 1d · HCl, m.p. 189–191 °C (found, C 45.45, H 4.2, N 2.65; $C_{19}H_{20}Br_2ClNO_2 \cdot 0.5H_2O$ requires C 45.8, H 4.2, N 2.8%), 3-(4-ethylbenzoyl)-4-hydroxy-1methyl-4-(4-ethylphenyl)piperidine (2c), m.p. 92-94 °C (found, C 78.5, H 8.2, N 4.1; C₂₃H₂₉NO₂ requires C 78.6, H 8.3, N 4.0%), 2d, m.p. 87 °C (found, C 45.7, H 4.2, N 2.8; $C_{19}H_{19}Br_2NO_2 \cdot 3H_2O$ requires C 45.0, H 4.9, N 2.8%), 7-ethyl-2-methyl-9-phenyl-2,3-dihydro-1H-indeno[2,1-c]pyridine HBr (3c HBr), m.p. 176-178 °C (found, C 69.3, H 6.6, N 3.7; C₂₃H₂₆BrN requires C 69.7, H 6.6, N 3.5%), 3d HBr, m.p. 232-234 °C (found, C 46.0, H 3.2, N 2.8; $C_{19}H_{16}Br_3N$ requires C 45.8, H 3.2, N 2.8%) and 3e · HBr, m.p. 213-215°C (found, C 54.9, H 3.9, N 3.6; C₁₉H₁₆BrCl₂N 0.5H₂O requires C 54.9, H 4.1, N 3.35%).

To prepare the tetrahydro-1-pyrindenes, 2-methyl-9phenyl-2,3,4,9-tetrahydro- or -2,3,4,4a-tetrahydro-1*H*indeno[2,1-c]pyridine(4), asolution of the diene $3 \cdot$ HBr(12 g)inethanol(300ml) washydrogenated at a pressure of 50 psi for 3 h at room temperature using platinum oxide (0.1 g) as catalyst. The mixture was filtered, the filtrate concentrated under reduced pressure and the residue recrystallized from ethanol to give $4 \cdot$ HBr. Products isolated were $4a \cdot$ HBr, m.p. 188–190 °C (found, C 66.7, H 5.9, N 4.1; C₁₉H₂₀BrN requires C 66.9, H 6.0, N 3.9%), $4b \cdot$ HBr, m.p. 210–212 °C (found, C67.9,H6.4,N3.7;C₂₁H₂₄BrNrequiresC68.1,H6.5, N 3.8%) and $4c \cdot$ HCl, m.p. 158–160 °C(found, C76.2,H7.7, N 3.9; C₂₃H₂₈Cl N.0.5H₂O requires C 76.1, H 8.05, N 3.9%). To prepare hexahydro-1-pyrindenes (5), a solution of the diene $3a \cdot HBr$ (16 g) in ethanol (150 ml) was hydrogenated at a pressure of 80–100 psi at *ca*. 75 °C for 20 h using 5% palladium on activated carbon (1 g) as catalyst. The product, isolated as usual, was recrystallized from ethanol to give $5a \cdot HBr$ (10.8 g), m.p. 252–254 °C (reported⁶ m.p. 254–256 °C). The corresponding dimethyl derivative $5b \cdot HC1$, m.p. 164–165 °C (found, C 72.5, H 8.5, N 3.9; C₂₁H₂₆ClN · H₂O requires C 72.9, H 8.2, N 4.05%) and diethyl derivative $5c \cdot HBr$, m.p. 136–138 °C (found, C 64.5, H 7.7, N 3.4; C₂₃H₃₀BrN · 1.5H₂O requires C 64.6, H 7.8, N 3.5%) were similarly prepared.

A mixture of the base from $5a \cdot HBr$ (1 g) and KOH in *n*-butanol [20 ml, 25% (w/v)] was heated under reflux for 17 h. The product was concentrated under reduced pressure at 50 °C, diluted with water (220 ml) and extracted with diethyl ether (3 × 10 ml). The dried (MgSO₄) extract was evaporated to give an oil which reacted with ethereal HCl to give an HCl salt (0.8 g), m.p. 265-267 °C from ethanol (reported⁶ m.p. 269-271 °C). The base from this salt was shown to be a binary mixture of the original material (5a) (10%) and its isomeric product (90%) by capillary gas chromatography (retention times 116s for 5a and 97s for its isomer; obtained using OV-1 as stationary phase, nitrogen as carrier gas, column temperature 250 °C, ethyl acetate as solvent and a flame ionization detector).

The ¹³C and ¹H NMR spectra were recorded on JEOL GX270 and 400 spectrometers as described previously.¹⁰

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