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STUDIES OF THE ELIMINATION OF 4-ARYL-3-METHYL-4-PIPERIDINOLS—I

THE CONFORMATION OF EPIMERIC 1-ALKYL (AND ARALKYL)-4-ARYL-5-METHYL-1,2,5,6-TETRAHYDRO-PYRIDINE HYDROCHLORIDES

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Abstract—A detailed study of the products of elimination of some 4-aryl-3-methyl-4-piperidinols has been made and the PMR spectra of derived 1-alkyl (and aralkyl)-4-aryl-5-methyl-1,2,5,6-tetrahydropyridines and the corresponding hydrochloric salts reported and discussed. The 5-methyltetrahydropyridine hydrochlorides are shown to exist in epimeric forms in deuterochloroform and their PMR spectra have been interpreted in terms of probable conformations.

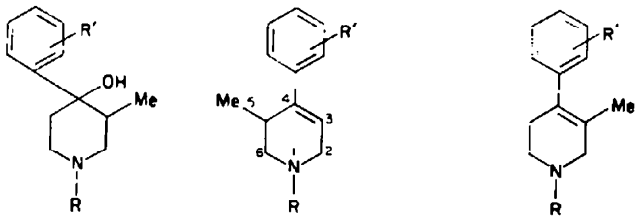
INTRODUCTION

ELIMINATION reactions have often been encountered during the investigation of structure-activity relationships in esters of 4-aryl-3-methyl-4-piperidinols (reversed esters of pethidine and allied compounds).[1,2] The more thorough study of such reactions, facilitated by use of NMR spectroscopy, has now been undertaken. In the present paper detailed examination of the products of elimination is reported.

Experimental procedures and spectroscopic data

4-Aryl-3-methyl-4-piperidinols (I) were obtained by treating 3-methyl-4-piperidones with lithium aryls. In one case (Ia, R′ = H) the configuration of an ester derivative of the alcohol has been established as *trans* Ar/Me;[3] in the other alcohols reported here the major reaction product (purified by crystallization) is assumed to have the same (*trans*) configuration from consideration of the stereochemistry of addition to cyclic ketones and from IR spectral data (Experimental).[4] Catalytic debenzylation of the piperidinol (Ic; R′ = H) gave the secondary base (Ie; R′ = H). The 4-piperidinols (I) of major yield were dehydrated by treatment with a mixture of acetic and hydrochloric acids at the reflux temperature and the binary mixtures of alkenes which resulted were analysed by means of NMR spectroscopy. In mixtures derived from 4-phenyl, *o*- and *m*-tolylpiperidinols (I, R′ = H, *o* and *m*- Me), the major component was a 5-methyl-1,2,5,6-tetrahydropyridine (II), characterized by signals due to vinylic hydrogen (a triplet) and 5-methyl (a doublet), and the minor component a 3-methyltetrahydropyridine (III), characterized by a 3-methyl signal (a singlet) and by the absence of a vinylic hydrogen signal. Under the conditions reported, the isomers

[1] A. H. Beckett, A. F. Casy and P. M. Phillips, *J. Med. pharm. Chem.* **2**, 245 (1960).
[2] A. F. Casy, A. H. Beckett and N. A. Armstrong, *Tetrahedron* **16**, 85 (1961).
[3] G. Kartha, F. R. Ahmed and W. H. Barnes, *Acta Crystallog.* **13**, 525 (1960).
[4] A. H. Beckett, A. F. Casy, G. Kirk and J. Walker, *J. Pharm. Pharmacol.* **9**, 939 (1957).



I II III

R = (a) Me, (b) Et, (c) CH_2Ph, (d) $(CH_2)_2Ph$, (e) H

were formed in the approximate ratio of 2:1, as assessed from integral curves. 3-Methyltetrahydropyridines (III) predominated in alkene mixtures derived from 4-*p*-tolylpiperidinols (I, R′ = *p*-Me). In all cases the mixtures of bases of type II and III were treated with excess of ethanolic hydrogen chloride and the resultant hydrochlorides fractionally crystallized to yield the major isomers which were isolated in a pure state. In addition, the isomers in minor amount were obtained in this manner from mixtures derived from the piperidinols (Ia, b, c and e; R′ = H; and Ib and c; R′ = *p*-Me). Attempts to separate isomeric alkenes by paper, thin-layer and gas chromatography were unsuccessful.[5] The NMR characteristics of the pure alkenes are given in Table 1 and the integral data for alkene mixtures in Table 2.

The NMR spectra of the alkene (II) hydrochlorides in deuterochloroform were also examined (Table 3). The 5-methyl signals of the hydrochlorides differ markedly from those in the corresponding free bases (e.g. Fig. 1). In the bases the 5-methyl signal is a doublet ($\tau \simeq 9{\cdot}0$ except for 4-*o*-tolyl examples) while in the hydrochlorides it is a pair of doublets ($\tau \simeq 8{\cdot}7$ and 9·1). In two cases (IIa and b; R′ = H) the 4-phenyl signal, a singlet in the base, appeared as a pair of singlets in the salt while the *m*- and *p*-tolyl aromatic signals of the alkenes (IIb; R′ = *m*-Me and IIc; R′ = *p*-Me) became more complex in the corresponding salts.

Discussion

These NMR spectral differences are interpreted in terms of the alkene (II) hydrochloride existing in deuterochloroform solution in *trans* and *cis* (1-R/5-Me) configurations (A and B, Fig. 2) which arise as a result of the two possible modes of proton addition to the basic centre.[6] Assuming half-chair conformations, A-1 is more likely than A-2 since in the former the group R attached to nitrogen is equatorial and the 5-methyl group is axial, a favoured position for bulky 6-substituents in 1-phenylcyclohexenes[7] (the aryl group and the double bond in conjugation with it may attain a greater degree of coplanarity when α-substituents are axial than when they are equatorial). In B, (2) is probably the more likely, despite the fact that an equatorial 5-methyl group will partially deflect the aryl group out of the plane of the 3-4 double bond, because B-1 contains two axial substituents. In conformations A-1 and B-2, the relative environments of both the 5-methyl and 4-aryl groups differ, hence the two

[5] H. Z. Youssef, Ph.D. Thesis University of London (1964).
[6] A. H. Beckett, A. F. Casy and H. Z. Youssef, *Tetrahedron Letters* No. 10, 537 (1965).
[7] E. W. Garbisch, Jr., *J. Org. Chem.* **27**, 4243, 4249 (1962).

TABLE 1. PROTON MAGNETIC RESONANCE CHARACTERISTICS OF 4-ARYL-5-METHYL-1,2,5,6-TETRAHYDROPYRIDINES (II) IN DEUTEROCHLOROFORM[a]

Compound (base)	N—R	4-Aryl	C-3-H(Vinylic)[c]	C-5-Me[d]	Miscellaneous
IIa(R′ = H)	7·62[b](N—Me)	2·68[b]	4·13 (J3·5)	9·00 (J6·5)	—
IIb(R′ = H)	8·85[c](J7·0) (N—CH_2Me)	2·68[b]	4·12 (J3·5)	9·00 (J6·5)	
(in CCl_4)	8·9[c](J7·5)	2·77[b]	4·21 (J4·0)	8·98 (J7·0)	
IIc(R′ = H)	6·37[b](N—CH_2Ph)	2·68[e]	4·12 (J3·5)	8·98 (J7·0)	—
IId(R′ = H)	2·73[b][N—$(CH_2)_2$Ph]	2·68[b]	4·13 (J3·5)	8·98 (J6·5)	—
IIe(R′ = H)	7·65[b](N—H)	2·67[b]	4·05 (J3·5)	9·00 (J7·0)	—
IIb(R′ = *o*-Me)	8·87[c](J7·0) (N—CH_2Me)	2·93[e]	4·53 (3·0)	9·13 (J6·5)	7·7[b](Ar—Me)
IIc(R′ = *o*-Me)	6·35[b](N—CH_2Ph)	2·83[e]	4·50 (J3·5)	9·13 (J7·0)	7·7[b](Ar—Me)
IIb(R′ = *m*-Me)	8·85[c](J7·0) (N—CH_2Me)	2·85[e]	4·15 (J3·5)	9·00 (J6·5)	7·67[b](Ar—Me)
IIc(R′ = *p*-Me) (in CCl_4 only)	6·43[b](N—CH_2Ph)	2·7[e]	4·23 (J3·5)	8·98 (J7·0)	7·68[b](Ar—Me)

[a] = chemical shifts in tau units, coupling constants in c/s.
[b] = singlet;
[c] = triplet;
[d] = doublet;
[e] = main peak of multiplet

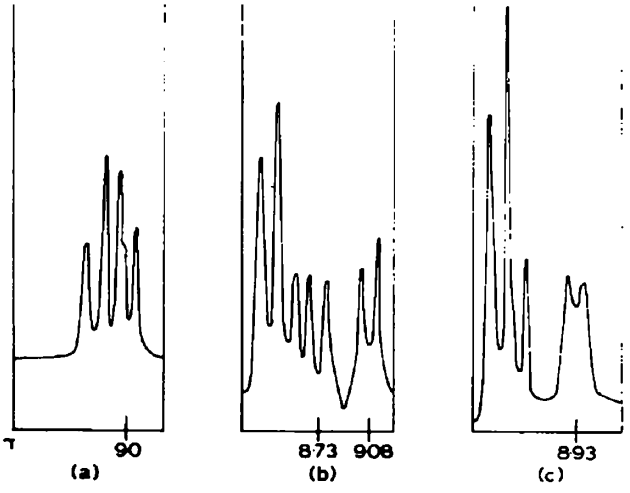


FIG. 1. Part of the NMR spectra of 1-ethyl-5-methyl-4-*m*-tolyl-1,2,5,6-tetrahydropyridine (IIb, R′ = *m*-Me): (a) base in $CDCl_3$; (b) base hydrochloride in $CDCl_3$; (c) base hydrochloride in $CDCl_3$–D_2O (low field triplet is the signal due to methyl of the 1-ethyl group).

TABLE 2. INTEGRAL DATA FOR MIXTURES OF TETRAHYDROPYRIDINES II AND III

Precursor alcohol	Tetrahydropyridine II (1) C-3-H(vinylic)	(2) C-5-Me	Tetrahydropyridine III (3) C-3-Me[a]	Ratio II From (1) and (3)	III From (2) and (3)	Notes
Ia(R′ = H)	6	17	17 (τ 8·45)	1:0·9	1:1	undistilled
Ib(R′ = H)	0·6	2·3	1·0 (τ 8·43)	2:1·1	2:0·9	distilled
Ib(R′ = H)	0·65	2·4	1·0	2:1	2:0·8	undistilled
Ic(R′ = H)	5	16	7·5 (τ 8·47)	2:1	2:0·9	undistilled
Id(R′ = H)	5·5	18	12 (τ 8·42)	2:1·5	2:1·3	undistilled
Ie(R′ = H)	6	19	18 (τ 8·45)	1:1	1:1	undistilled
Ib(R′ = *o*-Me)	7	24	10 (τ 8·62)	2:1	2:0·8	undistilled
Ib(R′ = *o*-Me)	8	26	10 (τ 8·62)	2:0·8	2:0·8	distilled
Ic(R′ = *o*-Me)	5	15	6 (τ 8·64)	1:0·4	1:0·4	undistilled
Ib(R′ = *m*-Me)	0·7	2	0·9 (τ 8·42)	2:0·9	2:1	distilled
Ib(R′ = *p*-Me)	v. small integral	9	27 (τ 8·45)	—	1:3	undistilled
Ic(R′ = *p*-Me)	v. small integral	5	23 (τ 8·48)	—	1:4·5	undistilled

[a] broad singlet showing evidence of long-range coupling

configurations of the salt in solution exhibit different signals for these two groups.* Since an axial methyl is close to the positively charged centre in the salt, its signal should be downfield relative to that of 5-methyl in the free base (τ8·98–9·00); hence the lower field doublet (τ8·79 ± 0·07) is attributed to the *trans* (1-R/5-Me) isomer with

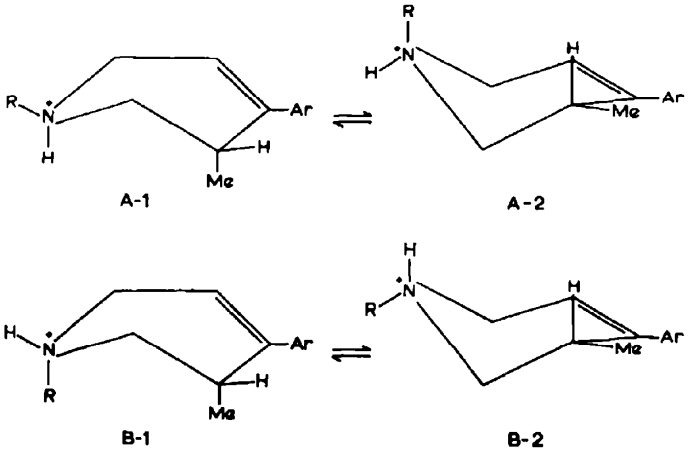


FIG. 2. Conformations of the *trans*-1-R/5-Me(A-1 and A-2) and *cis*-1-R/5-Me (B-1 and B-2) isomers of 1-substituted-4-aryl-5-methyl-1,2,5,6-tetrahydropyridine (II) hydrochlorides.

the population of conformation A-1 exceeding that of A-2. Assignment of the higher field doublet (τ9·12 ± 0·04) to 5-methyl in the *cis* (1-R/5-Me) isomer is in accord with this group's further removal from charged nitrogen in B-2, the predominant conformation (deshielding is assumed to operate largely across space rather than via σ-bonds), and with its possible receipt of a screening contribution from the phenyl group as a result of the latter's rotation out of the plane of the double bond. The significance of the last aspect is supported by the fact that the 5-Me doublet pair suffers a further upfield shift in the 4-*o*-tolyl analogue (IIb; R′ = *o*-Me; τ8·90/9·17 in the salt and IIc; R′ = *o*-Me; τ8·97/9·22 in the salt) in which the aryl group is even further rotated out of the plane of the double bond due to increasing steric inhibition of planarity,[8] while the chemical shifts of 5-Me in the 4-phenyl 4-*m*- and 4-*p*-tolyl tetrahydropyridine salts (IIb) are identical. Further support of the assignment of the doublet at τ9·12 ± 0·04 to equatorial methyl in the salts is provided by the value τ8·97 for the chemical shift of 5-methyl in the methiodide of IIb (R′ = H); the conformer with an equatorial 5-methyl group must predominate in this compound because the axial conformation (IV) is highly unfavoured on steric grounds.

* Isomeric alkene (II) salts could not be demonstrated so clearly when trifluoroacetates (formed in the probe tube by adding the acid to the base in $CDCl_3$) rather than hydrochlorides were employed (Table 3) and splitting of the 5-methyl doublet was then only observed in the cases of the N-methyl (IIa, R′ = H) and N-phenethyl (IId, R′ = H) derivatives. This result is most likely caused by a more rapid proton exchange in the presence of trifluoroacetic acid and its anion.

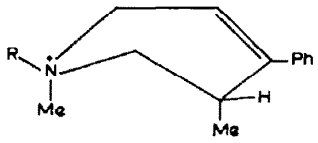
[8] R. B. Carlin and H. P. Landerl, *J. Amer. Chem. Soc.* **75**, 3969 (1953); E. W. Garbisch, Jr., *Ibid* **85**, 927 (1963).

TABLE 3. PROTON MAGNETIC RESONANCE CHARACTERISTICS OF 4-ARYL-5-METHYL-1,2,5,6-TETRAHYDROPYRIDINE (II) HYDROCHLORIDES[a]

Compound (hydrochloride)	Solvent	N—R	4-Aryl[m]	C-3-H(vinylic)	C-5-Me lower field (A)	C-5-Me upper field (B)	Integral Ratio A:B	+ N—H
IIa(R′ = H)	$CDCl_3$	6·94,[d] 7·03[d](J3 c/s)(N–Me)	2·67,[b] 2·72[b]	4·24[h](W_H12)	8·70[d](J7·5)	9·08[d](J7·5)	1·2:1·3	−2·0[h]
IIa(R′ = H)	$CDCl_3$–D_2O	7·0[b]	2·7[b]	4·25[h](W_H7·5)	8·87[d](J6)		—	—
Base-CF_3CO_2H	$CDCl_3$	7·03[f](W_H4)	2·64[g]	4·27[h](W_H10)	8·85[i](J7)	9·08[i](J6·5)	1·0:1·0	—
IIb(R′ = H)	$CDCl_3$	8·5[j](J7)(N–CH_2Me)	2·63[b], 2·68[b]	4·25[h](W_H11)	8·72[d](J7·5)	9·08[d](J6·5)	1·3:1·7	−1·8[h]
IIb(R′ = H)	$CDCl_3$–D_2O	8·48[c](J7)	2·68[b]	4·25[h](W_H8)	8·94[d](J7)		—	—
IIb(R′ = H)	$CDCl_3$–pyridine (1HCl:0·17 base)	8·48[c](J7)	2·68[b]	4·27[h](W_H7·5)	8·92[h](W_H11·5)		—	—
IIb(R′ = H)	$CDCl_3$–piperidine (1HCl:0·17 base)	8·51[c](J7)	2·65[b]	4·22[h](W_H7)	8·93[d](J6·5)		—	−0·2[b]
IIb(R′ = H)	$CDCl_3$–piperidine (1HCl:1·1 base)	8·84[c](J7)	2·67[b]	4·11[c](J3·5)	9·02[d](J7)		—	—
IIb(R′ = H)	D_2O	8·17[c](J8)	2·13[b]	3·75[h](W_H10)	8·58[h](W_H7)		—	—
IIb(R′ = H)	N/10 HCl–H_2O	8·47[c](J7·5)	—	—	8·77[d](J7)	8·98[d](J6·5)	1·9:1·6	—
IIc(R′ = H)	$CDCl_3$	5·58[e](N–CH_2Ph)	2·67[e]	4·28[h](indistinct)	8·82[i](W_H12)	9·12[i](W_H13.5)	1·4:1·7	—
IId(R′ = H)	$CDCl_3$	6·62[e](N–CH_2CH_2Ph)	2·69[b]	4·28[h](W_H11)	8·81[h](W_H13)	9·05[h](W_H15)	0·9:1·1	—
IId(R′ = H)	$CDCl_3$–D_2O	6·62[e]	2·67[b]	4·3[h](W_H9·5)	8·94[i](J6·5)		—	—
Base-CF_3CO_2H	$CDCl_3$	6·58[e]	2·67[b]	4·28[h](W_H11)	8·90[i](J7)	9·08[i](J6·5)	—	—
IIe(R′ = H)	$CDCl_3$	(see $\overset{+}{N}$—H)	2·67[b]	4·18[c](J4)	8·87[d](J6)		—	−1·0 (2 protons)
IIe(R′ = H)	$CDCl_3$–D_2O		2·7[b]	4·23[c](J3)	8·95[d](J6)		—	—
IIb(R′ = *o*-Me)[l]	$CDCl_3$	8·43[c](J7)(N–CH_2Me)	2·75[f]	4·45[h](W_H8·5)	8·90[i](W_H12)	9·17[i](J7)	1·0:2·3	−2·3[h]
IIb(R′ = *o*-Me)[l]	$CDCl_3$–D_2O	8·43[c](J7)	2·78[f]	4·43[c](J3·5)	9·08[i](J7)		—	—

IIc(R′ = *o*-Me)[i]	$CDCl_3$	5·53[a](N–CH_2Ph)	2·47, 2·83[k]	4·48[a](W_H8·5)	8·97[f](J6·5)	9·22[f](J6)	1·0:3·0	—
IIc(R′ = *o*-Me)[i]	$CDCl_3$–D_2O	5·52[d](J3)	2·48, 2·83[k]	4·5[h](W_H5·0)	9·13[f](J6·5)		—	—
IIb(R′ = *m*-Me)[i]	$CDCl_3$	8·47[f](J7)(N–CH_2Me)	2·85[e]	4·28[a](W_H10)	8·73[d](J6·5)	9·08[d](J7)	1·0:1·0	−2·3[h]
IIb(R′ = *m*-Me)[i]	$CDCl_3$–D_2O	8·48[c](J7)	2·85[e]	4·28[a](W_H6·5)	8·93[f](J7)		—	—
IIb(R′ = *p*-Me)[i]	$CDCl_3$	8·45[f](J7)(N–CH_2Me)	2·85[b], 2·9[b]	4·32[h](W_H12)	8·85[d](J7)	9·06[d](J7)	0·8:0·9	—
IIb(R′ = *p*-Me)[i]	$CDCl_3$–D_2O	8·48[c](J7)	2·88[b]	4·3[e](J3)	8·93[d](J3)		—	—
IIc(R′ = *p*-Me)[i]	$CDCl_3$	5·57[h](N–CH_2Ph)	2·47, 2·87[k]	4·2[h](indistinct)	8·82[c](J6)	9·17[f](J6·5)	1·1:1·5	—
IIc(R′ = *p*-Me)[i]	$CDCl_3$–D_2O	5·55[d](J4)	2·47, 2·82[k]	4·33[h](indistinct)	8·98[c](J6)		—	—

[a] chemical shifts in tau units, coupling constants and widths at half height (W_H) in c/s
[b] singlet.
[c] triplet.
[d] doublet.
[e] main peak of multiplet.
[f] peak of broad singlet.
[g] two closely overlapping singlets.
[h] centre of multiplet.
[i] deformed doublet.
[j] two closely overlapping triplets.
[k] two main peaks of multiplet.
[l] aryl-methyl signal τ7·65–7·67 (singlet).
[m] may include aryl protons of N-substituent.



IV

Integral data shows the two epimers A and B to be present in approximately equal proportions in all but *o*-tolyl derivatives (Table 3). Evidence that equilibrium conditions had been reached before the NMR spectra were recorded is provided by the

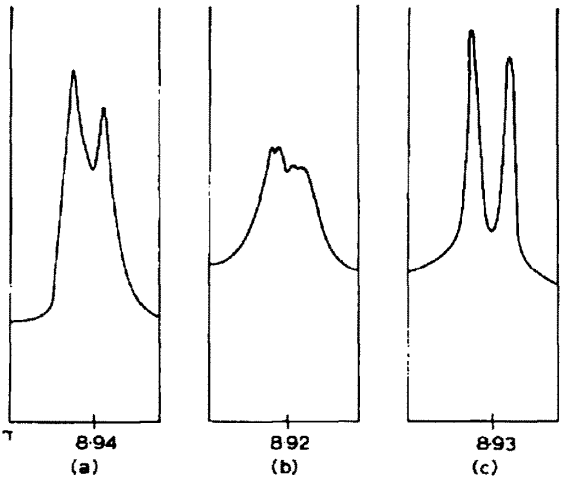


Fig. 3. Part of the NMR spectra of 1-ethyl-5-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (IIb, R′ = H) hydrochloride; (a) in $CDCl_3$–D_2O; (b) in $CDCl_3$–pyridine (1 mole IIb, R′ = H: 0·17 mole pyridine); (c) in $CDCl_3$–piperidine (1 mole IIb, R′ = H: 0·17 mole piperidine).

fact that the spectra of solutions of IIb (R′ = H and *o*-Me) hydrochlorides in $CDCl_3$ remained unchanged during storage for 6 days and from spectral data recorded under conditions of accelerated proton exchange (see below).

Rate of proton exchange

The sharp nature of the two 5-methyl doublets in the hydrochlorides (IIa; R′ = H and IIb; R′ = H, *m*-Me and *p*-Me) and the aromatic pair of singlets in IIa and IIb (R′ = H) indicates that the rate of proton exchange between the epimers A and B (resulting in their interconversion) must be relatively slow in $CDCl_3$. The nature of the $\overset{+}{N}$—H signal also provides evidence for this conclusion; it forms a broad band near τ 1–2 indicative of extensive spin–spin coupling which must occur if the N—H bond is relatively permanent. When the proton exchange rate was accelerated by addition of a small amount of D_2O, the two methyl doublets coalesced (to give one doublet) or collapsed to give an unresolved signal, centred near τ8·9 in $CDCl_3$ (Table 3 and Fig. 1).

In the case of the hydrochloride (IIb; R′ = H), exchange promoted by pyridine and piperidine [both in the molar ratio base catalyst: (IIb; R′ = H); 0·17 to 1] was

also studied; the rate was faster with piperidine than with pyridine as is evident from the appearance of the 5-methyl signals (the doublet, clearly defined in piperidine—$CDCl_3$ is ill-defined in pyridine—$CDCl_3$, Fig. 3), in accord with piperidine being the stronger base. When the molar proportion of piperidine was increased to 1·1, the spectrum of the hydrochloride (IIb; R′ = H) was identical with that of the corresponding free base, piperidine (the stronger base) thus competing successfully with IIb (R′ = H) for protons. While proton exchange clearly occurs when the alkene (IIb; R′ = H) hydrochloride is dissolved in D_2O alone (the 5-methyl signal is an unresolved band centred at τ8·58) it is slow when a large excess of hydrogen ions are present (the 5-methyl signal is composed of two clear doublets centred at τ8·77 and 8·98 respectively in N/10 HCl–H_2O). Because the chemical shift of 5-methyl in the hydrochlorides (II; not *o*-tolyl derivatives) falls almost midway between the low and high field values (representing axial and equatorial environments respectively) when proton exchange is accelerated, the populations of the epimers A and B must be approximately equal at equilibrium (proton exchange allows the epimers to equilibrate). Integral data gives similar results for epimer populations in solutions of the hydrochlorides (II; not *o*-tolyl derivatives) in $CDCl_3$ to which a proton-exchange catalyst has *not* been added; hence freshly prepared solutions of the salts in $CDCl_3$ must also be at equilibrium.

Cases where the 5-methyl signal of hydrochlorides (II) *consists entirely or mainly of a single doublet*

Proton addition to the alkene (IIe; R′ = H) does not render the basic centre asymmetric and, if the above interpretations are valid, it follows that the NMR spectrum of the hydrochloride of this alkene should exhibit a single doublet due to the 5-methyl group. The configurations A and B become identical when R = H and conversion of A-1 (≡B-1) to A-2 (≡B-2) results in a less pronounced 1,3-diaxial interaction than is the case when nitrogen bears a substituent. Hence the populations of the 5-axial and 5-equatorial methyl conformers should be almost equal and be independent of the rate of proton exchange. In accord with these arguments, the 5-methyl signal of the hydrochloride (IIe; R′ = H) is one doublet (τ8·87 in $CDCl_3$) with a chemical shift close to that of 5-methyl of N-substituted analogues where proton exchange has been accelerated.

In the hydrochloride of the 4-*o*-tolyltetrahydropyridine (IIb, R′ = *o*-Me) the factor favouring an axial 5-methyl group in 4-phenyl, *m*- and *p*-tolyl derivatives loses its significance since in this case a planar conjugated system is unfavoured by *o*-methylpiperidine ring proton interactions even when the 5-position of the piperidine ring is unsubstituted.[8] Hence the unfavourable diaxial hydrogen-methyl interaction of conformation A-1 is no longer offset by resonance stabilization gained through increased conjugation, and thus conformation B-2 (1-ethyl and 5-methyl both equatorial) would be expected to predominate. In accord with this interpretation, the NMR spectra of IIb(R′ = *o*-Me) and IIc(R′ = *o*-Me) hydrochlorides display 5-methyl doublet pairs in which the higher is much larger than the lower field doublet (from integral data the ratio is approx. 2·5 to 1). The chemical shift values of both higher field [τ9·17 (N–Et) and 9·22 (N–Bz)] and lower field [τ8·9 (N–Et) and 8·97 (N–Bz)] 5-methyl doublets, upfield relative to the corresponding members of methyl doublet pairs in 4-phenyl, *m* and *p*-tolyl analogues, are consistent with the 5-methyl group

receiving increased degrees of screening by the aromatic group in the *o*-tolyl compounds as already discussed.

Close agreement between observed 5-methyl chemical shifts recorded under conditions of accelerated proton exchange, using D_2O as catalyst (τ9·08 and 9·13 for IIb and c; R′ = *o*-Me, respectively) and those calculated from integral data relating to solutions in $CDCl_3$ lacking a proton-exchange catalyst (corresponding values are τ9·09 and 9·16) further indicates that equilibrium conditions are established in freshly prepared solutions of the hydrochlorides (II) before their spectra are recorded (see also discussion under 'Rate of proton exchange').

The vinylic proton signal

In the hydrochlorides (II; all except IIe, R′ = H), signals due to the C-3 vinylic and C-2 methylene protons appear as broad unresolved bands. The broad nature of the vinylic signal is probably a result of overlap between signals (comparable in intensity) due to the *trans* and *cis* isomers A and B respectively; the signal is narrower, but still unresolved, when proton exchange is accelerated (Table 3), as is to be expected if interconversion of approximately equi-populated conformers (A-1 and B-2) is now permitted. Even when proton-exchange is catalysed, the C-2 methylene protons do not become equivalent, a fact which must follow from their being adjacent to an asymmetric centre (the protonated nitrogen of the ring); thus an unresolved vinylic signal results. In contrast, the vinylic signal of the hydrochloride of the secondary base (IIe; R′ = H) is a fairly well resolved triplet, in accord with the symmetry of the protonated nitrogen and the probable equi-populations of type 1 and 2 conformers (as previously discussed) rendering the C-2 methylene protons virtually equivalent. The vinylic signal is also a triplet (J 3·5c/s) in all the free bases of type II, rapid inversion about the nitrogen atom contributing to the equivalence of the C-2 methylene protons in this case. The ethiodide and methiodide of IIa (R′ = H) give vinylic signals (W_H 7–8c/s) that are narrower than those given by related hydrochlorides (W_H 10–11c/s) in accord with the signal from the quaternary salts arising largely from one conformer (that with an equatorial 5-methyl group).

The chemical shift of vinylic hydrogen in the bases of type II falls in the range τ4·12–4·15 with the exception of the secondary base (IIe; R′ = H; τ4·05) and *o*-tolyl derivatives (τ4·5); this range of values demonstrates the deshielding influence of the 4-aryl group (cf. vinylic hydrogen in 1-methylcyclolohexene, τ4·68 in CCl_4)[7] which is maximum when the aryl group is coplanar with, and minimum when at right angles to, the plane of the double bond.[8] In all alkenes II, except *o*-tolyl derivatives, the vinylic signal is moved upfield ($\Delta\tau$0·13–0·18) when the base is protonated. This result is consistent with a higher proportion of conformations of type B-2 (in which vinylic hydrogen is less deshielded by the 4-aryl group) being present in solutions of the salt than in those of the base. In corresponding *o*-tolyl derivatives, the aryl group is even more deflected out of the plane of the double bond than it is in 4-phenyl derivatives, and the higher field chemical shift of vinylic protons in *o*-tolyl alkenes ($\tau \simeq 4{\cdot}5$) reflects their being less deshielded. In contrast with other results, vinylic chemical shifts in *o*-tolyl bases and hydrochlorides (II) are almost identical, it being probable, therefore, that the orientation of the *o*-tolyl group with respect to the plane of the double bond suffers little change upon adding a proton to the basic centre.

Signals due to substituents on nitrogen

Isomerism arising as a result of a protonated basic centre having two possible configurations has previously been reported for hydrochlorides of 1,2-dimethylpyrrolidine and pseudotropine.[9,10] Isomers of this type are comparable to N-isomeric quaternary salts[11,12] and differ in the conformation of the N-substituents.

In the present examples, however, the N-substituents are equatorial in both type A-1 and B-2 epimeric hydrochlorides and show little difference in chemical shift values as a result of their similar environments (Fig. 2). The N-methyl signals of A and B in the hydrochloride (IIa; R′ = H), for example, are separated by only 5–6 c/s, while in contrast, signals due to axial and equatorial N-methyl in the methiodide of IIa(R′ = H) show a 14 c/s separation. The chemical shifts of N-substituents in the salts are downfield with respect to those in the corresponding bases as a result of increased deshielding by positively charged nitrogen (Tables 1 and 3). Increased complexity of N-substituent signals in the salts results not only from small environmental differences between epimers but also from spin–spin coupling with the acidic proton on nitrogen (J values of about 3 c/s are observed); when proton exchange is accelerated the appearance of the signals closely resembles the corresponding signals in the free bases.

From spectroscopic evidence to be presented elsewhere, it is concluded that conformation A-1 (minus the proton) predominates in the free bases (II) and it is of interest that proton addition to these compounds may influence the orientation of the 4-phenyl group in respect to the C-3 double bond of the ring (coplanarity, essentially complete in molecules of the bases, only obtains to the extent of approximately 50% in molecules of the protonated bases). This phenomenon may have significance in biological systems where conditions of proton exchange prevail, e.g. the addition or removal of a proton from a drug at a biological surface may change the conformation of the molecule in a position remote from the basic centre.

EXPERIMENTAL*

General method for the preparation of 4-aryl-3-methyl-4-piperidinols (I). The N-substituted 3-methyl-4-piperidone (1 mole) was added drop-wise with stirring to a cooled solution of a Li-aryl in ether prepared from Li (2·4 atoms) and an aryl bromide (1·2 mole). The mixture was stirred for 2 hr at room temp and then added to crushed ice and excess of glacial acetic acid. The solid which separated was washed with ether, the base liberated with strong aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the solvent was removed and the residue (distilled in some cases) crystallized from hydrocarbon solvents such as n-hexane and pet. ether mixtures (Table 4). The yield of piperidinol was improved when the Li-aryl–piperidone reaction mixture was decomposed with crushed ice (no acetic acid) and the alkaline product extracted with ether.

General method for the dehydration of the piperidinols I. A mixture of I (8 g, approx, 0·04 mole), conc. HCl (66 ml) and glacial acetic acid (124 ml) was heated under reflux overnight (approx. 12 hr). (Alcohols were detected in mixtures heated for reflux periods of 4 hr or less but not in those heated overnight.) Most of the solvent was removed by distillation under red. press. the residue dissolved in water and the solution made alkaline with NH_4OH and extracted with ether. The ether was dried (Na_2SO_4) and evaporated to give the crude mixture of II and III (NMR data of Table 2 refers to these

* M.ps are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford. Equiv. ws of bases and salts were determined by titration with 0·02N perchloric acid in glacial acetic acid (mercuric acetate added in the case of salts) using Oracet Blue B as indicator.

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TABLE 4. 4-ARYL-3-METHYL-4-PIPERIDINOLS (I)

Compound	Form	m.p.	Mol. formula	Found				Required				Absorption of base in 990–1020 cm^{-1} region[a]
				C	H	N	Equiv. wt.	C	H	N	Equiv. wt.	
1a(R′ = H)	base	101–102°[a]	—	—	—	—	—	—	—	—	—	998 cm^{-1}
1b(R′ = H)	base	109–111°[b]	$C_{14}H_{21}NO$	76·9	9·85	6·6	222	76·7	9·6	6·4	219	1000 cm^{-1}
1b(R′ = *o*-Me)	base	68–72°[b]	$C_{15}H_{23}NO$	76·2	9·9	6·3	231	77·2	9·8	6·0	233	1000 cm^{-1}
1b(R′ = *m*-Me)	base	76–79°[b]	$C_{15}H_{23}NO$	77·6	9·8	6·1	233	77·2	9·8	6·0	233	1000 cm^{-1}
1b(R′ = *p*-Me)	base	89°[b]	$C_{15}H_{23}NO$	76·9	9·9	6·0	236	77·2	9·8	6·0	233	1003 cm^{-1}
1c(R′ = H)	HCl	188–189°[c]	$C_{19}H_{24}NO$	72·7	7·5	4·2	317	72·0	7·6	4·2	317	1012 cm^{-1} (liquid film)
1c(R′ = *o*-Me)	base	100·5°[b,f]	$C_{20}H_{25}NO$	81·3	8·5	4·7	—	81·3	8·6	4·7	—	1015 cm^{-1}
1c(R′ = *p*-Me)	HCl	212–213°[c]	$C_{20}H_{26}ClNO$	71·8	7·7	4·3	—	72·4	7·8	4·2	—	1013 cm^{-1} (liquid film)
1d(R′ = H)	base	105–106°[g]	—	—	—	—	—	—	—	—	—	1000 cm^{-1}
1e(R′ = H)	HCl	186°[d,h]	$C_{13}H_{17}ClNO$	62·9	7·8	6·3	—	63·3	7·9	6·15	—	[i]

[a] = α-prodine alcohol Ref. 4
[b] = from petroleum ether b.p. 40–60°
[c] = from ethanol
[d] = from ethanol–ether
[e] = Nujol mull unless otherwise indicated
[f] = prepared by Dr. G. Kirk
[g] = ref. 13
[h] = prepared by catalytic debenzylation of 1c(R′ = H)
[i] = not examined

[13] A. H. Beckett, A. F. Casy and G. Kirk, *J. Med. pharm. Chem.* **1**, 37 (1959).

TABLE 5. 4-ARYL-5-METHYL-1,2,5,6-TETRAHYDROPYRIDINE (II) HYDROCHLORIDES

Compound	m.p.	Mol. formula	Found			Required		
			C	H	N	C	H	N
IIa(R′ = H)	196°[a]	—	—	—	—	—	—	—
IIb(R′ = H)[b]	226°	$C_{14}H_{20}ClN$	70·95	8·6	5·7	70·8	8·5	5·9
IIb(R′ = *o*-Me)[c]	192°	$C_{15}H_{22}ClN$	71·7	8·8	5·6	71·7	8·7	5·5
IIb(R′ = *m*-Me)[d]	171–173°	$C_{15}H_{22}ClN$	70·7	8·6	5·5	71·7	8·7	5·5
IIb(R′ = *p*-Me)	209°	$C_{15}H_{22}ClN$	71·5	8·6	5·55	71·7	8·7	5·5
IIc(R′ = H)	246–247°	$C_{19}H_{22}ClN$	76·4	7·55	4·7	76·1	7·4	4·7
IIc(R′ = *o*-Me)	225–226°	$C_{20}H_{24}ClN$	76·2	7·7	4·7	76·5	7·7	4·5
IIc(R′ = *p*-Me)	227–229°	$C_{20}H_{24}ClN$	76·0	7·7	4·1	76·5	7·7	4·5
IId(R′ = H)	229–230°[e]	$C_{20}H_{24}ClN$	75·9	7·9	4·7	76·5	7·7	4·5
IIe(R′ = H)	140–141°	$C_{12}H_{16}ClN$	68·54	7·7	6·7	68·7	7·7	6·7

[a] = reported[8] m.p. 187–188°;
[b] = Found: equiv. wt. 240; required: 238;
[c] = Found: equiv. wt. 250; required: 251;
[d] = Found: equiv. wt. 246; required; 251:
[e] = reported[8] m.p. 224–225°

TABLE 6. 4-ARYL-3-METHYL-1,2,5,6-TETRAHYDROPYRIDINE (III) HYDROCHLORIDES

Compound	m.p.	Mol. formula	Found			Required		
			C	H	N	C	H	N
IIIa(R′ = H)	189–190°	$C_{13}H_{18}ClN$	69·5	8·2	6·0	69·8	8·05	6·3
IIIb(R′ = H)	188°	$C_{14}H_{20}ClN$	70·6	8·4	6·05	70·8	8·5	5·9
IIIb(R′ = *p*-Me)	175°	$C_{15}H_{22}ClN$	71·3	9·1	5·4	71·7	8·8	5·5
IIIc(R′ = H)	175–176°	$C_{19}H_{22}ClN$	76·2	7·25	4·8	76·1	7·4	4·7
IIIc(R′ = *p*-Me)	158°	$C_{20}H_{24}ClN$	76·6	7·6	4·2	76·5	7·7	4·5

mixtures, distilled in some cases). The mixture was treated with excess of ethanolic HCl and diluted with dry ether. The hydrochloride which separated, after storage at room temp or in the refrigerator, was fractionally crystallized from the same solvent mixture to give the pure hydrochlorides of II and III (Tables 5 and 6). Alternatively, the alkene mixture in ether was treated with excess of ether saturated with HCl and the precipitate, freed from solvent by decantation, fractionally crystallized

from EtOH, EtOH–ether or acetone. The pure bases II (NMR data given in Table 1) and III were liberated from corresponding hydrochlorides.

The methiodides of IIa and b (R′ = H) were prepared by adding MeI (1–2 mole excess) drop-wise to ethereal solutions of IIa and IIb respectively. The solids which separated after the mixtures had stood for several hr were recrystallized from EtOH to give the *methiodide of* IIa (R′ = H), m.p. 206–207° (Found: C, 51·0; H, 6·5; N, 4·1; $C_{14}H_{20}IN$ requires: C, 51·1; H, 6·1; N, 4·25%), and the methiodide of IIb (R′ = H), m.p. 167–168°. (Found: C, 52·3; H, 6·6; N, 4·0; $C_{15}H_{22}IN$ requires: C, 52·5; H, 6·5; N, 4·1%.)

The NMR spectra were obtained on a 60 M.c Varian A-60 instrument (with tetramethylsilane as internal standard) at the normal operating temp; $CDCl_3$ was used as solvent unless otherwise stated (Tables 1 and 3). The IR spectra were measured on a Unicam S.P.100 spectrophotometer.

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