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STUDIES OF THE ELIMINATION OF 4-ARYL-3-METHYL-4-PIPERIDINOLS—III[1]

$\pi \rightarrow \pi^*$ TRANSITIONS IN SOME 4-ARYL-3-(AND 5)-METHYL-1,2,5,6-TETRAHYDROPYRIDINES

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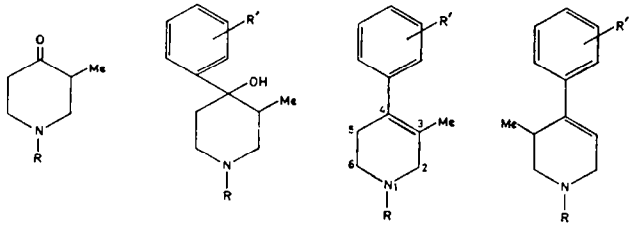
Abstract—The electronic absorption characteristics of some 4-phenyl- and 4-substituted-phenyl-3(and 5)-methyl-1,2,5,6-tetrahydropyridines are shown to differ from those of corresponding hydrochloride salts. These differences are interpreted in terms of the influence of steric and electronic factors upon the $\pi \rightarrow \pi^*$ transitions of the styrenoid chromophore present in the bases.

IN THE preceding paper[1] the influence of charged nitrogen upon the $\pi \rightarrow \pi^*$ electronic transitions of the styrenoid chromophore of some 4-aryl-1,2,5,6-tetrahydropyridines was examined. These studies are now extended to 3- and 5-methyl analogues, an analysis of the electronic absorption spectra of these compounds requiring consideration of steric, in addition to electronic, factors.

Preparation of compounds and spectral data. Acid-catalysed elimination of the 3-methyl-4-piperidinols (II) derived from I and an organic-metallic reagent, gave binary



I II III IV

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

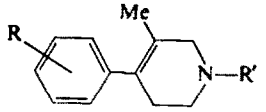
mixtures of the 3- and 5-methyltetrahydropyridines (III and IV) which were separated by fractional crystallization of the corresponding hydrochloride salts as previously described.[2] The *p*-dimethylaminophenylpiperidinol (IIc, R′ = *p*-NMe_2) required the same elimination conditions, in contrast with analogues unsubstituted at C-3 and 5 which lose water when acidified with ethanolic hydrogen chloride at room temperature.[1] The isomeric 3- and 5-methyltetrahydropyridines (III and IVd, R′ = *p*-OMe) and III and IVc (R′ = *p*-NMe_2) were characterized by PMR spectroscopy. The isomer ratio obtained from the *p*-dimethylaminophenylpiperidinol (IIc, R′ = *p*-NMe_2) was similar to those obtained from 4-phenylpiperidinols previously studied (5-Me, major isomer) while that from the *p*-methoxyphenyl derivative (IId, R′ = *p*-OMe) was similar to those obtained from *p*-tolyl-analogues (3-Me, major isomer).[2] Epimeric forms of the 5-methyltetrahydropyridines[2] were evident in acidic solvents. The electronic absorption

[1] Part II, A. H. Beckett, A. F. Casy, R. G. Lingard, M. A. Iorio and K. Hewitson, *Tetrahedron*, **22**, 2735 (1966).

[2] A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef, *Tetrahedron* **21**, 3387 (1965).

spectra of the III and IV hydrochlorides (recorded in EtOH before and after the addition of ammonia) are given in Tables 1 and 2.

TABLE 1. UV ABSORPTION CHARACTERISTICS OF SOME 4-ARYL-3-METHYL-1,2,5,6-TETRAHYDROPYRIDINES IN ETHANOL

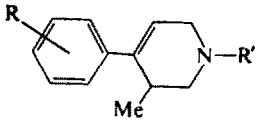


Compound[a]	R	R'	λ_{max} mμ (log ε) Base	Hydrochloride	Δλ mμ[b]
1	H	H	237 (3·87)	230 (3·89)	−7
2	H	Me	235 (3·89)	230 (3·92)	−5
3	H	Et	235 (3·88)	230 (3·91)	−5
4	H	CH_2Ph	234·5 (3·96)	230·5 (3·95)	−4
5	*p*-Me	Et	237 (4·0)	234 (4·02)	−3
6	*p*-Me	CH_2Ph	234·5 (3·96)	230·5 (3·95)	−4
7	*p*-OMe	CH_2Ph	239 (4·12)	241 (4·11)	+2
8	*p*-NMe_2	Et	269 (4·20)	277·5 (4·18)	+8·5

[a] Compds 2–6, Ref. 2.

[b] $\Delta\lambda = \lambda_{max}$ HCl − λ_{max} Base; +ive value represents a *red* shift, −ive value, a *blue* shift upon protonation of the base.

TABLE 2. UV ABSORPTION CHARACTERISTICS OF SOME 4-ARYL-5-METHYL-1,2,5,6-TETRAHYDROPYRIDINES IN ETHANOL



Compound[a]	R	R'	λ_{max} mμ (log ε) Base	Hydrochloride	Δλ mμ[b]
1	H	H	240 (4·05)	237 (4·05)	−3
2	H	Me	240 (4·07)	238 (4·06)	−2
3	H	Et	239·5 (4·03)	237·5 (4·03)	−2
4	H	CH_2Ph	241 (4·11)	237 (4·11)	−4
5	H	$(CH_2)_2Ph$	241 (4·09)	238 (4·09)	−3
6	*p*-Me	Et	243 (4·13)	243 (4·13)	0
7	*p*-OMe	CH_2Ph	249·5 (4·16)	250 (4·15)	+0·5
8	*p*-NMe_2	Et	280·5 (4·28)	290 (4·26)	+9·5

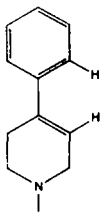
[a] Compds 1–6, Ref. 2.

[b] See footnote *b*, Table 1.

DISCUSSION

4-aryl-3-methyl-1,2,5,6-tetrahydropyridines (III; Table 1). The absorption maxima of the 4-phenyl-3-methyl derivatives (Table 1, compds 1–4) are at wavelengths 10·5–12·5 mμ shorter than those of corresponding 3-unsubstituted compounds and their extinction coefficients are lower.[1] The blue shifts in absorption maximum and reduction in intensity that follow replacement of vinylic hydrogen in the tetrahydropyridines (V)

by a methyl group are considered to be due to steric effects. Models reveal that, while the coplanar structure (V) entails little or no non-bonded interactions, that of the 3-methyl analogue (VI) does since the methyl substituent and an *ortho* hydrogen of the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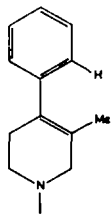
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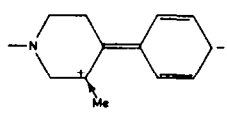
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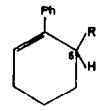
VIII

aromatic ring are in close proximity in the planar conformation. Interaction between these groups may be relieved by rotation of the aromatic ring out of the plane of the double bond. It is probable, therefore, that in the 3-methyl derivatives, the population of conformations with a planar styrenoid chromophore is less than that obtaining in the unsubstituted analogues.

The blue shifts (4–7 mμ) in absorption maxima observed when the bases (Table 1, compds. 1–4) are protonated are larger than those obtained in the case of the unsubstituted tetrahydropyridines (1·5–3 mμ).[1] It is probable that the bias in the bases towards dipolar resonance forms with a positive change at C-3 is more pronounced in the 3-methyl derivatives because of the form (VII) will be stabilized by the methyl substituent; if such is the case the destabilizing influence of protonated nitrogen upon this form would be expected to have a correspondingly greater effect in 3-methyl derivatives than in corresponding unsubstituted analogues. The greater influence of charged nitrogen upon electronic transitions in 3-methyltetrahydropyridines as compared with unsubstituted derivatives is also seen in the two *p*-tolyl derivatives (Table 1, compds 5 and 6).* In these compounds, the bias towards contributors with a positive charge at C-3 (as in VII) is probably offset somewhat by the electron donation of the aromatic methyl group. In the *p*-methoxy- and *p*-dimethylamino-phenyl derivatives (Table 1, compds 7 and 8) the electron donating influence of the aryl substituent must overide that of the 3-methyl group in this respect since red shifts are obtained when these bases are protonated. The shift of 8·5 mμ noted with the 3-methyl derivative (Table 1, compd 8) is 1·5–2·5 mμ less than that obtained with unsubstituted derivatives and this difference is consistent with a small reduction in charge accumulation at C-3 in the dipolar excited taste (as a result of 3-methyl opposition) which in turn leads to the excited state being correspondingly less influenced by charged nitrogen.

4-Aryl-5-methyl-1,2,5,6-tetrahydropyridines (IV: Table 2). The absorption maxima of the 4-phenyl-5-methyl-1,2,5,6-tetrahydropyridines (Table 2, compds 1–5) are at wavelengths 6·5–8 mμ shorter than those of corresponding derivatives in which a 5-methyl substituent is absent and their extinction coefficients are somewhat smaller.[1] The changes in absorption characteristics which follow insertion of a methyl group into the 5-position of the heterocyclic ring of the tetrahydropyridines (V) are also considered to be a consequence of steric interactions, these being less pronounced than

* No change in absorption maxima is observed when corresponding derivatives without a 3-methyl substituent are protonated.

TABLE 3. PMR CHARACTERISTICS OF 4-ARYL-3 (AND 5)-METHYLTETRAHYDROPYRIDINES[a]

Compound	Form	N—R″	4-Aryl	C-3-H(vinylic)	C-3-Me	C-5-Me
IIIa	base	—	2·68, 2·72, 2·77[b]	—	8·45[c]	—
(R′ = H)	HCl	—	2·65[b]	—	8·38[c]	—
III and IVd	total[f]	6·35[c]	2·64, 2·75, 2·95,	very small	8·46[c]	9·02[e]
(R′ =	elimination	(N—$\underline{CH_2}$Ph)	3·08[b]	signal near		(J6)
p-OMe)	product		6·21[d]	4·17		
	(base)					
IVd	base	6·37[c]	2·63[c]	4·2[h]	—	8·99[e,i]
(R′ =		(N—$\underline{HC_2}$Ph)	2.78, 3·07, 3·22[g]	(J 3·5)		(J 6·5)
p-OMe)			6·23[d]			
IIId	base	6·43[c]	2·65[c],	—	8·5[c]	—
(R′ =		(N—$\underline{CH_2}$Ph)	3·00, 3·15, 3·25, 3·4[g]			
p-OMe)			6·32[d]			
	HCl	5·59[e]	2·5, 2·55, 2·63[b]	—	8·44[c]	—
		(J5)	2·8, 2·95, 3·07, 3·22[g]			
			6·2[d]			
III and IVc	total[f]	8·92[h]	2·77. 2·93, 3·08,	4·32[j]	8·44[c]	8·98[e]
(R′ =	elimination	(J7)	3·33, 3·48[b]			(J7)
p-NMe_2)	product	(N—$CH_2\underline{Me}$)	7·1[k]			
	(base)					
IVc	base	8·87[h]	2·61, 2·75, 3·15,	4·15[j]	—	8·97[e,m]
(R′ =		(J7)	3·3[g]			
p-NMe_2)		(N—$CH_2\underline{Me}$)	7·03[k]			
IIIc	base	8·84[h]	2·79, 2·93, 3·19,	—	8·4[c]	—
(R′ =		(J7)	3·33[g]			
p-NMe_2)		(N—$CH_2\underline{Me}$)	7·07[k]			

[a] Chemical shifts in tau units, coupling constants in c/s; solvent, $CDCl_3$ unless otherwise stated.
[b] main peak(s) of multiplet
[c] singlet (may be broad)
[d] OMe singlet
[e] doublet
[f] integral ratio 3-Me: 5-Me; 18:5 approx.
[g] peaks of A_2B_2 quartet
[h] triplet
[i] in $CDCl_3$–CF_3CO_2H the 5-methyl signal is composed of two doublets at 8·94 and 9·09 (J7).
[j] multiplet
[k] NMe_2 singlet
[l] in CCl_4; integral ratio 3-Me:5-Me; 10:15 approx.
[m] the 5-methyl signal is composed of two doublets in 0·1N—HCl—H_2O, at 8·82 and 9·01 (J7).

those obtaining when the 3-position is similarly substituted. Steric inhibition of the coplanarity of the double bond—phenyl chromophore is likely to be least when the 5-methyl substituent is axial[3] (inspection of Catalin models indicates that an equatorial methyl group is in closer proximity to an *ortho* hydrogen atom of the aromatic ring than is an axial group when the molecule adopts a coplanar conformation) and, on these grounds, this conformation may be preferred.

Evidence is available regarding the conformation of related 6-substituted 1-phenylcyclohexenes (VIII) from the widths at half-height of the C-6 proton resonance bands.[3]

[3] E. W. Garbisch, Jr., *J. Org. Chem.* **27**, 4243, 4249 (1962).

Bulky substituents (e.g. t-butyl. phenyl and nitro) were found to prefer the axial conformation, and these results were rationalized in terms of an axial 6-substituent interfering less with the coplanar styrenoid chromophore of the cyclic system as explained above for a methyl group. The PMR method was not applicable to 6-methyl derivatives (the signal of the extensively spin-spin coupled C-6 proton is difficult to resolve) but evidence of models and of UV absorption data of some of the 1-phenylcyclohexenes, discussed below, leads to the conclusion that this group also prefers an axial conformation in these systems. The absorption maxima of the derivatives (VIII) in which the 6-substituent is bulky and axial, fall in the range 238–240 mμ while those of the bulky equatorial analogues lie near 236 mμ.[3] The positions of the absorption peaks of the 6-isopropyl (λ_{max} 239·5 mμ) and 6-methyl derivatives (λ_{max} 242 mμ) indicate the degree of planarity of their styrenoid systems to be at least as great as those obtaining in cyclohexenes with 6-axial substituents, while the absorption maximum of 6,6-dimethyl-1-phenylcyclohexene (227 mμ) has a value demonstrating the adverse effect of a 6-equatorial methyl group upon styrenoid planarity.

The close agreement between the chemical shift values of 6-methyl in the cyclohexene (VIII, R = Me) (τ 9·09)[3] and 5-methyl in the 4-phenyltetrahydropyridines (Table 2, compd 1–5) (τ 8·98–9·00)[2] is evidence for the methyl substituents in both the tetrahydropyridines and the cyclohexene having similar environments and thus having the same preferred conformation.* The destabilizing 1,3 interaction in the tetrahydropyridine bases (Table 2, compd 1–5) with an axial 5-methyl conformation is small, being between a methyl group and a lone-pair of electrons on nitrogen. When the lone-pair is replaced by hydrogen,[4] as in hydrochloride salts, the 1,3-interaction becomes large enough to reduce the population of axial methyl conformers to approximately 50 per cent in deuterochloroform solution (PMR data),[2] a percentage which is probably less in more polar solvents, such as ethanol, where solvation of protonated nitrogen may increase the 1,3 interaction. The population of axial 5-methyl conformers should be least in the methohalides of the tetrahydropyridines (Table 2, compd 2–5) on account of the even greater 1,3 interaction (Me/Me) obtaining in quaternary salts. Hence the degree to which the styrenoid systems of the tetrahydropyridines (Table 2, compds 2–5) deviate from planarity should *increase* in the order base < hydrochloride < quaternary salt as a result of increasing populations of conformers with equatorial 5-methyl groups. These conclusions are supported by UV data (Table 2); the absorption maxima of the salts (Table 2, compd 1–5) are 2–3 mμ less than those of the corresponding free bases while the methochloride of compound 4 of Table 2 absorbs at 235·5 mμ (cf. the corresponding hydrochloride 237 mμ).†

* The small downfield shift of 5-methyl in the tetrahydropyridines relative to the 6-methyl signal in the cyclohexene may be attributed to the deshielding action of the piperidine nitrogen atom and/or to a solvent effect (the cyclohexene was examined in CCl_4 and the tetrahydropyridines in $CDCl_3$). The last effect is likely to be small, however, because in the case of the derivative IVc (R′ = H) the chemical shifts of 5-methyl in $CDCl_3$ and CCl_4 were identical.

† Data relating to methiodides cannot be used since their spectra are complicated by iodide absorption bands.

[4] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones and A. R. Katritzky, *Proc. Chem. Soc.* 257 (1964); N. J. Allinger, J. G. D. Carpenter and F. M. Karkowski, *Tetrahedron Letters* No. 45, 3345 (1964); N. J. Allinger and J. Chow Tai, *J. Amer. Chem. Soc.* **87**, 1227 (1965); N. J. Allinger, J. G. D. Carpenter and F. M. Karkowski, *J. Amer. Chem. Soc.* **87**, 1232 (1965).

These shifts cannot be attributed entirely to steric effects, however, since displacements (base to salt) of similar magnitudes are observed with tetrahydropyridines which carry no C-5 substituent and in which, therefore, no steric factor can operate. However, a decrease in the coplanar nature of the styrenoid chromophore (with a concomittant fall in dipolar character) must reduce the significance of the destabilizing action of charged nitrogen upon excited states having a positive or negative charge at C-3.

In accord with these considerations, the red shifts (base to salt) observed in the cases of the *p*-methoxy and *p*-dimethylaminophenyl derivatives (Table 2, compds 7 and 8) are somewhat smaller than those noted with the analogues lacking a 5-methyl substituent,[1] spectral changes in these compounds being largely governed by electronic rather than steric influences. Hence the consequence of steric and electronic factors upon the styrenoid chromophone in salts of the 5-methyl derivatives (Table 2, compds 1–5) are not necessarily additive and it is probable that both contribute to the overall magnitude of the blue shifts observed. A *para*-methyl substituent in the 4-phenyl group of the tetrahydropyridine (Table 2, compd 3) appears to offset the destabilizing influences that arise when the basic centre is protonated, the absorption characteristics of the base (Table 2, compd 6) and its salt being alike.

EXPERIMENTAL

4-Aryl-3-methyl-4-piperidinols were prepared and dehydrated by methods described,[1,3] the following new compounds being prepared: the *4-p-methoxyphenylpiperidinol* (IId, R′ = *p*-OMe) *hydrochloride*, m.p. 189–191° from EtOH. (Found: C, 68·7; H, 7·1; N, 3·8. $C_{20}H_{26}ClNO_2$ requires: C, 69·1; H, 7·5; N, 4·0%); the *4-p-dimethylaminophenylpiperidinol* (IIc, R′ = *p*-NMe_2) *dihydrochloride*, m.p. 225–231° from EtOH. (Found: C, 57·6; H, 8·6; N, 8·5. $C_{16}H_{28}Cl_2ON_2$ requires: C, 57·3; H, 8·4; N, 8·35%); the *4-phenyl-3-methyltetrahydropyridine* (IIIa, R′ = H) *hydrochloride*, m.p. 78° from acetone–ether. (Found: C, 66·4; H, 7·8; N, 6·1. $C_{12}H_{16}NCl$. 0·5 H_2O requires: C, 65·9; H, 7·8; N, 6·4%), ν_{max} 3400 cm^{-1} (H_2O); the *4-p-methoxyphenyl-3-methyltetrahydropyridine* (IIId, R′ = *p*-OMe) *hydrochloride* m.p. 223° from acetone–EtOH. (Found: C, 72·8; H, 7·3; N, 4·2. $C_{20}H_{24}ClNO$ requires: C, 72·8; H, 7·3; N, 4·2%); the *4-p-dimethylaminophenyl-3-methyltetrahydropyridine* (IIIc, R′ = *p*-NMe_2) *dihydrochloride*, m.p. 228° from acetone–EtOH. (Found: C, 58·6; H, 8·5; N, 8·6. $C_{16}H_{28}Cl_2N_2$. 0·5 H_2O requires: C, 58·9; H, 8·3; N, 8·6%), ν_{max} 3300 cm^{-1} (H_2O); the *4-p-methoxyphenyl-5-methyltetrahydropyridine* (IVd, R′ = *p*-OMe) *hydrochloride*, m.p. 221° from EtOH. (Found: C, 73·0; H, 6·8; N, 4·0. $C_{20}H_{24}ClNO$ requires: C, 72·8; H, 7·3; N, 4·2%); the *4-p-dimethylaminophenyl-5-methyltetrahydropyridine* (IVc, R′ = *p*-NMe_2) *dihydrochloride*, m.p. 238° (dec) from EtOH. (Found: C, 61·0; H, 8·05; N, 8·9. $C_{16}H_{28}Cl_2N_2$ requires: C, 60·6; H, 8·3; N, 8·8%.) The PMR characteristics of the above tetrahydropyridines are given in Table 3.

The UV absorption spectra were recorded in EtOH on a Beckman D.K.2 spectrophotometer and the PMR spectra on a Varian A-60 instrument in $CDCl_3$ with TMS as internal standard.

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