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STUDIES ON 4-PHENYLPIPERIDINE SERIES—IX[1]
THE STEREOCHEMISTRY OF THE QUATERNIZATION OF SOME N-ALKYL-4-PHENYL-4-FORMYLPIPERIDINES

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Abstract—The degree of stereoselectivity of the quaternization of some N-alkyl (or aralkyl) 4-phenyl-4-formylpiperidines with methyl iodide and that of N-methyl-4-phenyl-4-formylpiperidine with the corresponding halides has been followed from the proportions of the isomers present in the crude mixture. The preferred direction of attack, as previously found in analogous piperidinium salts, is axial to the piperidine ring provided that the incoming group has not a high steric requirement. NMR characteristics of the stereoisomers and particularly the chemical shifts of axial and equatorial N-Me groups have been used to assign configurations and probable conformations.

NUMEROUS reports have appeared concerning the preferred steric course of quaternization of piperidines or simple piperidine derivatives, and on the use of NMR spectroscopy for configurational and conformational assignments.[2-7]

In the present work we have examined the stereoselectivity of the quaternization of some N-alkyl(or aralkyl)4-phenyl-4-formylpiperidines (R = Et, nPr, iPr, nBu and CH_2Ph)[8] with methyl iodide (direct quaternization) and the quaternization of N-methyl-4-phenyl-4-formylpiperidine[8] with the corresponding halides (reverse quaternization).

In both cases we obtained a mixture of the two quaternary salts which can be formed in the course of the reaction; i.e., one with a 1-Me/4-Ph *cis* configuration (I) and another with a 1-Me/4-Ph *trans* configuration (II) (Fig. 1).

Quaternization was carried out by treatment of the piperidine base, dissolved in ether, with excess of an alkyl halide at room temperature, and then heated to complete the reaction. Direct quaternization always gave higher yield of quaternary salts (yields are almost theoretical), whereas the reverse quaternization gave lower yields (from 30 to 50%). When the incoming group was an isopropyl one, the reflux in ether failed to give a precipitate, and reflux was carried out in methyl ethyl ketone.

The ratio of the stereoisomers (I and II) was determined by NMR examination of the crude mixture, as the signals for axial and equatorial N-Me group generally appeared as separated singlets.

TLC on Alumina G, Merck, of each crude mixture, using acetone–methanol 9:1 as developing solvent, shows the presence of two spots which can be detected by iodine vapour. Particularly, the N-Me signal at higher field always belonged to the isomer which showed a lower affinity for the adsorbent.

UV spectroscopy was employed for the quantitative determination of the two stereoisomers, after separation by TLC and subsequent elution from the layers. The

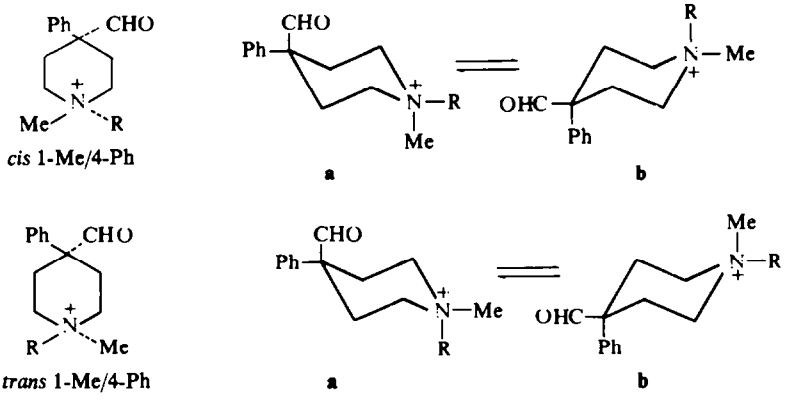

FIG. 1 Conformations of the 1-Me/4-Ph *cis* and *trans* 4-phenyl-4-formyl-N-methyl-N-alkyl-(or aralkyl)piperidinium salts.

adsorbance of the eluates was determined at 217–219 mμ and compared with standard curves obtained previously for each pair of stereoisomers.

Each series of quaternary iodides absorbs in the UV region and the adsorption maxima are at a wavelenth of 217–219 mμ; the molar adsorptivities (ε) are of the order of 10^4, varying between 15,000 and 20,000. No discernible shift in the value of λ_{max} is observed in the two series of stereoisomers. The adsorption peak must be related to the electron transition state $\pi \rightarrow n^*$ of iodide ion; in fact the quaternary chlorides display only a shoulder at 216 mμ: the adsorption band of the chloride ion appearing at lower wavelength.[9]

The chemical shifts of N-Me groups and isomer ratios are summarized in Table 1. The isomer ratios calculated by means of UV spectroscopy are in agreement with those obtained from integrals of NMR signals. Although the accuracy of both measurements was not very great, it was sufficient for the purpose to establish the relative proportions of the isomers obtained in direct and reverse quaternization.

The methiodide of N-methyl-4-phenyl-4-formylpiperidine does not exhibit *cis-trans* isomerism (I = II, R = Me) and exists largely in conformation with large Ph group in the equatorial position (Ia = IIa, R = Me) ($-\Delta G^\circ_X$ = 1·7 Kcal/mole at room temp corresponds to a population of 94% of the more stable e-phenyl conformer).[10,11,*] Hence the two observed chemical shifts of the two Me groups may be taken to represent axial and equatorial environment for this group (Table 2, No. 1).

The direct quaternization of the bases ($\diagdown\!\!\diagup$N—R + MeI) occurs with moderate degree of stereoselectivity, giving in major amount the stereoisomer with an higher field N-Me signal. When the compounds were not soluble in $CDCl_3$, spectra were run in D_2O or DMSO-d_6. Examination of the data summarized in Table 1 for the crude mixtures, and in Table 2 for the corresponding pure stereoisomers, reveals that change of solvent causes no appreciable change of the relative chemical shifts of axial and equatorial N-Me signal as in the case of N-propyl derivatives.[6,12]

* Approximate values for the conformational energy difference between equatorial and axial substituents ($-\Delta G^\circ_X$) in the two chair conformations were calculated from the data reported in ref. (10) (Table 1, pag. 44) for alkyl and phenyl substituents, and in ref. (11) for the formyl group.

TABLE 1. APPROXIMATE ISOMER RATIO OBTAINED IN DIRECT AND REVERSE QUATERNIZATION

Reaction	N-methyl chemical shift (τ; ppm) upper field	N-methyl chemical shift (τ; ppm) lower field	Isomer ratio[a] upper/lower signal	Isomer ratio[b] faster/slower spot
>N—Et + MeI	6·90	6·85[c]	1:0·65	—
>N—Me + EtI	6·90	6·85[c]	1:1·2	—
>N—nPr + MeI	6·60	6·53[d]	1:0·7	1:0·6
	7·04	6·99[e]		
>N—Me + nPrI	6·65	6·57[d]	1:1·4	1:1·4
	7·03	6·98[e]		
>N—nBu + MeI	6·62	6·53[d]	1:0·9	1:0·5
>N—Me + nBuI	6·62	6·53[d]	1:1·2	1:1·7
>N—iPr + MeI		6·72[d]		
	6·78	6·72[f]	1:0·9	1:0·5
>N—Me + iPrI[g]		6·78[d]		
	6·78	6·72[f]	1:0·3	1:0·4
>N—CH_2Ph + MeI		6·67[d]		
	0·57	0·45[d,h]	1:0·3	1:0·4
>N—Me + $PhCH_2Cl$		6·65[d]		
	0·57	0·45[d,h]	1:0·5	1:0·8
	6·77	6·70[f]		

[a] Estimated from integral of NMR signals of N-methyl protons. [b] Estimated from the relative intensity of absorption peaks at 217–219 mμ after separation of the isomers by TLC. Faster spots correspond to the isomers with higher field N-methyl signals. [c] In DMSO-d_6 with DSS as internal reference at 60 MHz. [d] In $CDCl_3$ with TMS as internal reference at 60 MHz. [e] In DMSO-d_6 with TMS as external reference at 100 MHz. [f] In D_2O with TMS as external reference at 60 MHz. [g] Quaternization has been carried out in methyl ethyl ketone. [h] Aldehydic proton.

Reverse quaternization occurs only partially with a moderate degree of stereoselectivity: the lower field N-Me signal predominates only when the incoming group is Et, nPr or nBu. When the entering group is as large as iPr or CH_2Ph group, the product ratio changes in favour of the stereoisomer with the higher field N-Me signal, approaching the same ratio obtained in the direct quaternization. That means that when the incoming group has an high steric requirement as do isopropyl or benzyl groups, the quaternization is less stereoselective and the entering group approaches the N atom prevalently from the side which can relieve the 1,3-R/H diaxial interactions: hence equatorial approach prevails. The more intense N-Me signal which is at higher field, belongs to the isomer with the two larger groups (4-phenyl and 1-isopropyl or 1-benzyl) equatorial to the piperidine ring (Ia), hence the chemical shift at higher field is assigned to the axial Me group.

A stronger signal at higher field (axial N-Me) can be observed in all the cases examined when the entering group is so small as a Me; i.e., axial approach predominates leading preferentially to the 1-Me/4-Ph *cis* isomers (I). Axial approach still predominates, and the 1-Me/4-Ph *trans* isomer is formed in major amount (lower field N-Me signal), when the incoming group is Et, nPr or nBu (Table 1).

Conformational assignments. All the quaternary salts listed in Table 2, having the 1-Me/4-Ph *cis* configuration will exist almost exclusively in conformation Ia: here the 1,3-Me/H and 4,2-CHO/H diaxial interactions are much smaller than the 1,3-R/H (R ≠ Me) and 4,2-Ph/H diaxial interactions of conformer Ib. (Approximate $-\Delta G^\circ_X$ values show that, at equilibrium at room temperature, populations of conformers Ia fall in the range of 96–99%).

Examination of the data summarized in Table 1 and in Table 2 No. 2–7 for two pairs of stereoisomers, respectively (I and II, R = nPr and nBu), shows that the aldehydic proton adsorbs at the same frequency in each pair, and so do the phenyl protons. Furthermore, difference of about 0·08 ppm in the chemical shift of N-Me protons (almost equal to that which separates axial and equatorial N-Me protons in (Ia = IIa, R = Me), can be observed. As an a-CHO and an e-Ph can support better the identity of these signals in both *cis* and *trans* isomers, we believe that in 1-Me/4-Ph *trans* isomers (II, R = nPr and nBu) conformation IIa predominates in all the solvents examined ($-\Delta G^\circ_X$ values calculated for the two chair conformers show that, at equilibrium at room temperature, conformer IIa will be present with a population of 89% for both *trans* N-propyl and N-butyl derivatives).

Examination of the NMR spectra in $CDCl_3$ of the crude mixtures obtained from $\rangle$N-CH_2Ph + MeI and $\rangle$N-Me + $PhCH_2Cl$ (Table 1) reveals that the two isomers give one signal for the Me group, and contemporaneously they show two signals for the aldehydric proton, 0·12 ppm apart (the higher field one prevailing in both mixtures), and two signals for the methylene benzyl protons, separated by 0·16 ppm (the one at lower field being the more intense signal). As we can see from Table 2, No. 11–12, the more intense signals belong to the *cis* isomer, which predominates in both mixtures. The different signals displayed by the *trans* isomer for the aldehydic proton at lower field is consistent with the suggestion that isomer (II, R = CH_2Ph) exists as an equilibrium of approximately equal proportion of conformations IIa and IIb: being the two forms in rapid interconversion, the chemical shift of the equatorial and axial substituents are the average value between axial and equatorial

TABLE 2. NMR CHARACTERISTICS OF 1-ME/4-PH *cis* and *trans* 4-PHENYL-4-FORMYL-N-METHYL-N-ALKYL(OR ARALKYL)PIPERIDINIUM IODIDES[a]

N°	R	Isomer	Solvent (MHz)	N-Me[b] upper f.	N-Me[b] lower f.	4-CHO[b] (hydrated)[c]	4-Ph	Others
1	Me	—	D_2O (60)	6·55	6·45	0·15 (4·60)	2·13[b]	
2	nPr	*cis*	D_2O (100)	6·63		0·20 (4·66)	2·19[b]	$N(CH_2)_2Me$ 8·64[d]
3	nPr	*trans*	D_2O (100)		6·56	0·20 (4·66)	2·19[b]	$N(CH_2)_2Me$ 8·70[e] (J7)
4	nPr	*cis*	DMSO-d_6 (100)	7·04		0·57	2·68[b]	$N(CH_2)_2Me$ 9·15[e] (J7)
5	nPr	*trans*	DMSO-d_6 (100)		6·98	0·56	2·68[b]	$N(CH_2)_2Me$ 9·18[e] (J7)
6	nBu	*cis*	$CDCl_3$ (100)	6·66		0·50	2·71[b]	$N(CH_2)_3Me$ 9·07[f]
7	nBu	*trans*	$CDCl_3$ (100)		6·60	0·50	2·71[b] 2·84[b]	$N(CH_2)_3Me$ 9·07[f]
8	iPr	*cis*	D_2O (60)	6·78		0·20	2·19[b]	$NCH(Me)_2$ 8·30[g] (J7)
9	iPr	*trans*	D_2O (60)		6·72	0·20	2·19[b]	$NCH(Me)_2$ 8·37[g] (J7)
10	CH_2Ph	*cis*	$CDCl_3$ (100)	6·70		0·56	2·70[h,i] 2·28[h,i]	NCH_2Ph 4·83[b]
11	CH_2Ph[j]	*cis*	$CDCl_3$ (60)	6·65		0·57	2·63[h,i] 2·27[h,i]	NCH_2Ph 4·77[b]
12	CH_2Ph[j,k]	*trans*	$CDCl_3$ (60)	6·65		0·45	2·62[h,i] 2·25[h,i]	NCH_2Ph 4·93[b]

[a] Chemical shifts in t units (ppm) from TMS (internal with $CDCl_3$ and external with D_2O and DMSO-d_6); spectra being measured at frequencies of 60 and 100 MHz; coupling constants in Hz; concentrations approx. 10%. [b] Singlet. [c] Ca. 40% under hydrated form. [d] Unsymmetrical triplet. [e] Triplet. [f] Multiplet (centre). [g] Doublet. [h] Main peak(s) of multiplet. [i] May include aryl protons of N-benzyl. [j] As Chloride. [k] Slightly soluble in $CDCl_3$ (peaks are clearer in the crude mixture).

environments. Axial and equatorial N-Me substituents show two signals, 0·07 ppm apart, in D_2O. Unfortunately, differences in aldehydic signal cannot be seen, as the aldehydic proton of *trans* isomer is completely hydrated in water and the signal falls in the region of spinning side bands of water.

cis and *trans* Isopropyl derivatives do not show difference in the chemical shift of aldehydic proton in $CDCl_3$ (where only the crude mixture has been examined, pure isomers being insoluble in this solvent) and in D_2O (Table 1, Table 2, No. 8–9). On the other hand, axial and equatorial N-methyl protons appear as a singlet in $CDCl_3$, and are 0·06 ppm apart in D_2O, as has been found for the N-benzyl analogues.

These results suggest that the contribution of conformer IIb for 1-Me/4-Ph *trans* (II, R = iPr) in the equilibrium mixture will be intermediate between that of IIb (R = nPr or nBu) and that of IIb (R = CH_2Ph). ΔG°_{iPr} found by Allinger and Hu,[13] 2·1 Kcal/mole, is of the same order as that for a n-propyl or n-butyl substituent. Winstein and Holness[14] reported for the same group 3·3 Kcal/mole, a value nearer that of a phenyl substituent. Results suggesting that an isopropyl substituent has a steric requirement of the same order than a benzyl group rather than an allyl group have been also reported.[4]

Our assignments for the N-Me signals are in agreement with those reported in earlier studies on piperidine derivatives,[2-4,6,7] that is: the N-Me signal at higher field is assigned to the conformation with an axial N-Me group, and the N-Me signal at lower field is assigned to the conformation with an equatorial N-Me group.

Particularly noteworthy is the relative small shift (0·1–0·06 ppm) between axial and equatorial N-Me signals in the two series here examined, compared with that reported for other piperidinium salts (see ref. cited above) which lack the presence of any oxygen function. House and Pitt[15] have reported that the presence and the nature of an oxygen function in quaternary salts of azabicycloalkanes can influence the relative positions of N-Me signals.

In order to obtain direct evidence of the influence of the formyl group, we converted it to an alcoholic secondary group with sodium borohydride in two pairs of stereoisomers: the N-propyl and the N-isopropyl derivatives. This reaction produced two new pairs of stereoisomers, namely: 1-Me/4-Ph *cis* and *trans* 4-phenyl-4-hydroxymethyl-N-methyl-N-propyl(or N-isopropyl)piperidinium iodides. Examination of the NMR in D_2O (60 MHz) of these compounds revealed that the chemical shift of the equatorial N-Me group (*trans* series) did not show any significant difference from that found in the corresponding formyl derivatives: τ 6·57 for the N-propyl derivative; Table 2, No. 3 τ 6·56; τ 6·72 for the N-isopropyl derivative, Table 2, No. 9 τ 6·72. On the other hand, the axial N-Me group (*cis* series) suffered an upfield shift in comparison with the signal of the corresponding formyl derivatives: τ 6·70 for the N-propyl derivative, Table 2, No. 2 τ 6·63; τ 6·92 for the N-isopropyl derivative, Table 2, No. 8 τ 6·78). The phenyl protons gave a singlet at τ 2·18–2·20, about the same chemical shift as in the formyl series.*

From these results it is evident that the CO group has a long range deshielding effect upon the axial methyl substituent. This differential shielding must be related to the possibility that the axial N-Me protons lie in the plane of the C=O double bond.

* Full detailed data of NMR spectra of hydroxymethyl derivatives will be reported in a next communication.

TABLE 3. 1-ME/4-PH *cis* AND *trans* 4-PHENYL-4-FORMYL-N-METHYL-N-ALKYL(OR ARALKYL) PIPERIDINIUM SALTS

Isomer	R	M.p. °C[a]		Found, %			Required, %		
				C	H	N	C	H	N
—	Me	215–217	$C_{14}H_{20}INO$	48·4	5·8	4·1	48·7	5·8	4·1
cis	nPr	110	$C_{16}H_{24}INO$	51·5	6·7	3·5	51·5	6·5	3·8
trans	nPr	218	$C_{16}H_{24}INO$	51·6	6·6	3·8	51·5	6·5	3·8
cis	iPr	198	$C_{16}H_{24}INO$	51·4	6·6	3·5	51·5	6·5	3·8
trans	iPr	b	$C_{16}H_{24}INO$	51·0	6·7	4·0	51·5	6·5	3·8
cis	nBu	131–132	$C_{17}H_{26}INC$	52·6	6·9	3·6	52·7	6·8	3·6
trans	nBu	200–202	$C_{17}H_{26}INO$	52·6	6·7	3·4	52·7	6·8	3·6
cis	CH_2Ph	193–196	$C_{20}H_{24}INO$	57·2	5·7	3·0	57·0	5·7	3·3
cis	CH_2Ph	222–224	$C_{20}H_{24}ClNO$	72·3	7·5	4·4	72·8	7·3	4·2
trans	CH_2Ph[c]	225–227	$C_{20}H_{26}ClNO_2$	68·9	7·8	4·0	69·1	7·5	4·0

[a] M.ps were determined with a Büchi–Tottoli appratus in capillary tubes and are uncorrected. [b] Hygroscopic amorphous powder. [c] The formyl group of this salt exists prevalently in the hydrate form: $\nu(C(OH)_2)$ KBr 1% 3250 cm^{-1}, weak band at 1710 cm^{-1}. All the other salts exhibit strong CO absorption at 1710 cm^{-1}.

The *cis* and *trans* piperidinium salts have been examined as inhibitors of acetylcholinesterase and serum cholinesterase. The results will be reported elsewhere.[16]

EXPERIMENTAL

The NMR spectra were recorded on a A-60 Spectrometer (60 MHz) and a Varian HA-100 (100 MHz). The UV spectra were recorded with a Beckman DK2 Spectrophotometer (EtOH as solvent).

Alkylation of piperidines. The N-alkylpiperidines were prepared as reported.[8] The following is new: 1-benzyl-4-phenyl-4-formylpiperidine, m.p. 86–87° from ether–pet.ether b.p. 40°. (Found: C, 81·80; H, 7·47; N, 4·95. $C_{19}H_{21}NO$ requires: C, 81·68; H, 7·58; N, 5·01%).

General procedure for quaternization of 4-phenyl-4-formyl-N-alkylpiperidines. A soln of the piperidine base in anhyd ether and an alkyl halide (1 mole excess) were kept at room temp for 24 hr and then heated under reflux (6–24 hr) until precipitation was complete. The solid was collected by filtration and washed with anhyd ether to remove any trace of unreacted starting material. Fractional crystallization of the crude salt from EtOH, acetone or mixture of these solvents with ether gave pure epimeric quaternary salts. The N-Et stereoisomers were obtained as a thick oil which defied all attempts at crystallization, even standing for periods longer than one year, and isolation of pure isomers were not attained. The steric correspondence of I($R = CH_2Ph$) as iodide and as chloride was established by converting the former into the latter by means of anion-exchange resin[4]; m.p. 222–224° from EtOH undepressed by a sample of *cis* isomer isolated from the reaction $\rangle N—Me + PhCH_2Cl$. Table 3 lists the physical data for the pure stereoisomers obtained by this method.

Thin layer chromatography. The composition of the mixtures and the purity of the isolated compounds were checked by TLC. Chromatoplates (5 or 10 cm × 10 cm) were made with a 0·25 mm layer of Alumina G, Merck, and dried at 105° for 1 hr. A mixture of acetone-MeOH 9:1 was used as eluent and the solvent was allowed to run to about 2 cm from the top of the plate. Spots were detected by placing the developed chromatoplates, dried at room temp, in a tank containing at the bottom crystals of I_2. The quaternary salts gave with iodine vapours brown spots. All the *trans* isomers were adsorbed more strongly than their epimers, and R_f differences were about 0·15. The N-benzyl stereoisomers as chlorides were better separated when eluted with a mixture of acetone-MeOH 8:2. The N-Et stereoisomers gave elongated spots and pure compounds were not separated. Preparative TLC was used to isolate the 1-Me/4-Ph *trans* N-isopropyl derivative from the enriched mother liquor, using thicker layers of Alumina and acetone-MeOH 9:1 as developing solvent. Working up gave a white powder which behaved as single compound. A sample of this material (dried under vacuum at 80°) was submitted for elementary analysis as all attempts at crystallization were unsuccessful.

UV measurements. The spots on the chromatoplates were outlined with a needle and, after drying the plates at 90° for 1 hr to send off all trace of iodine, the two areas were removed from the layer, collected on a suction filter and eluted with ethanol to a final volume of 25 ml. This procedure was always done in duplicate. The adsorbance of the eluates was determined at wavelength of 217–219 mμ and the mean value was compared with standard curves obtained for each pair of stereoisomers.

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