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THE STRUCTURE AND NMR SPECTRA OF SOME N-SUBSTITUTED-4-(CYANOPHENYLMETHYLENE)-PIPERIDINES

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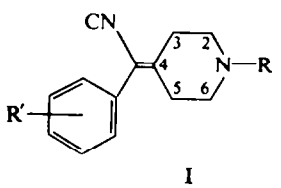
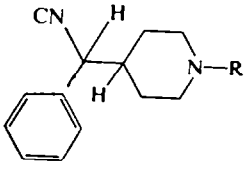
Abstract—Seven N-substituted-4-(cyanophenylmethylene)piperidines were synthesized by the condensation of N-substituted-4-piperidones with ring substituted benzyl nitriles. Hydrolysis or modification of the cyano group of these compounds was unsuccessful. Their structures were confirmed by analyses, and IR and UV data; spectral evidence indicates that the benzene ring is out of the plane of maximum conjugation due to non-bonded interaction between the *ortho* hydrogens of the phenyl ring and methylene protons of the heterocyclic ring.

The NMR spectrum of N-benzyl-4-(cyanophenylmethylene)piperidine is unexpectedly simple with the eight ring protons appearing as a four-proton singlet (2·46 ppm δ) and a symmetrical four-proton multiplet (2·74 ppm). The piperidine ring shows ready conformational interchange and there is fortuitous coincidence of the long range, anisotropic and inductive effects of the phenyl ring, nitrile group, double bond and substituted nitrogen atom so that the four protons on the same side as the phenyl ring become equivalent and form an A_4 singlet. The protons on the same side as the cyano group have different chemical shifts and interact to produce an A_2B_2 multiplet. The NMR spectra of compounds related to N-benzyl-4-(cyanophenylmethylene)piperidine confirm these conclusions.

AS PART of work on the structure-action relationships in analgesics, seven new N-substituted-4-(cyanophenylmethylene)piperidines I were prepared by condensation of N-substituted-4-piperidones with ring substituted benzyl nitriles (cf. Anker and Cook[1]); the reaction products were characterized as the hydrochlorides or hydrobromide salts (Table 1).



I



II

N-benzyl-4-(cyanophenylmethylene)piperidine Ia was hydrogenated in methanol (Pd–C) with uptake of hydrogen equivalent to the addition of four hydrogen atoms to yield II (R = H). Alkylation of the secondary amine group was achieved by refluxing the base with the required alkyl halide (benzyl chloride or phenethyl bromide) in absolute ethanol in the presence of sodium carbonate.

Numerous unsuccessful attempts (Experimental) were made to hydrolyse or modify the cyano group of Ia both in acid and alkaline media, but the product was either unchanged starting material or an intractable tar. Anker and Cook[1] reported that they were unable to hydrolyse N-methyl-4-(cyanophenylmethylene)piperidine under acid or alkaline conditions. In contrast, N-benzyl-4-piperidylphenylacetonitrile (II, R = benzyl) was converted in 80% sulphuric–ethanol to the corresponding

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[1] R. Anker and A. H. Cook, *J. Chem. Soc.* 806 (1948).

TABLE 1. UV AND IR SPECTRA OF THE SALTS OF COMPOUNDS OF TYPE I

I	R	R′	Salt	λ_{max} mμ	ε	—C≡N cm⁻¹	>C=C< cm⁻¹
(a)	Benzyl	H	HCl	250	12,600	2200	1615
(b)	Benzyl	*p*-Cl	HCl	256	13,200	2200	1630
(c)	Benzyl	*p*-F	HCl	250	10,400	2210	1630
(d)	Benzyl	*m*-Cl	HBr	247	11,400	2210	1630
(e)	Benzyl	*p*-OCH_3	HBr	272	9,600	2200	1600
(f)	Phenethyl	H	HCl	250	11,400	2210	1615
(g)	Phenethyl	*p*-Cl	HCl	255	12,600	2210	1630

amide but not to the ester (pethidine nitrile is converted to pethidine under the same conditions[2]). The lack of reactivity of the nitrile group of N-benzyl-4-(cyanophenylmethylene)piperidine may be due to electronic factors in which the π cloud of the conjugated system plays a part or to steric factors.[3]

IR *and* UV *spectra of compounds of types* I *and* II

The IR spectra of compounds of type I show a sharp band around 2200 cm^{-1} for the conjugated nitrile group[4] and a medium strength one between 1630–1600 cm^{-1} for the conjugated >C=C< double bond[4] (Table 1).

The UV spectra of the salts of compounds of Type I in ethanol (Table 1) show a similar shape to the spectrum of styrene but exhibit none of the styrene fine structure found between 275–300 mμ.[5] The UV extinction of both substituted and unsubstituted compounds of type I is less than that of styrene, (λ_{max} 248, ε 14,600).[5]

This decrease in UV extinction is probably due to non-bounded interactions between the *ortho* hydrogens of the benzene ring and the C5 methylene hydrogens of the piperidine ring.[6–8] This interaction can be relieved by stretching of the double bond or twisting of the planar benzene ring out of the van der Waal's radius of the substituent; the latter possibility is more favoured energetically.[9] This rotation about the C—C bond removes the benzene ring from the plane of maximum conjugation with the double bond and decreases the UV extinction.[8–11] It is difficult to calculate the angle of distortion from the plane of the conjugated system using Braude's equation[9,10] due to lack of suitable reference compounds, but the angle observed in Catalin models of compounds of type I is about 35°.

[2] O. Eisleb, US Patent No. 2,167,351 (1939).
[3] V. Migridichain, *Chemistry of Organic Cyanogen Compounds* ACS monograph No. 105; p. 39 (1947).
[4] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Edition) pp. 34, 363. Methuen, London (1958).
[5] C. G. Overberger and D. Tanner, *J. Amer. Chem. Soc.* **77**, 369 [1955).
[6] D. C. Cram, *J. Amer. Chem. Soc.* **71**, 3883 (1949).
[7] M. Barbieux and R. H. Martin, *Bull. Soc. Chim. Belg.* **73**, 703 (1964).
[8] M. Barbieux, N. Defay, J. Percher and R. H. Martin, *Bull. Soc. Chim. Belg.* **73**, 716 (1964).
[9] H. H. Jaffe and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy* pp. 384–449. Wiley, N.Y. (1962).
[10] E. A. Braude and F. Sondheimer, *J. Chem. Soc.* 3754 (1955).
[11] E. L. Allred, J. Sonnenberg and S. Winstein, *J. Org. Chem.* **25**, 26, (1960).

Insertion of substituents in the *para* position of the phenyl ring which are in conjugation with the ring *and* double bond leads to a *bathochromic* shift due to the extended conjugation. Insertion of a group into the *meta* position of the phenyl ring causes a slight *hysochromic* shift (Table 1).

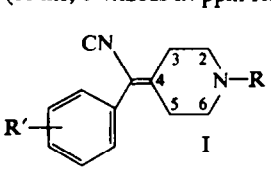
The IR and UV data indicate that in compounds of type I the benzene ring is conjugated with the double bond though there is some deviation from coplanarity of these two groups.

The IR spectra of compounds of type II show no double bond band but have a band for the nitrile group[4] at 2230–2250 cm^{-1}; UV spectral data (Experimental) are consistent for the assigned structures and show only low benzenoid extinction.

The NMR *spectra of* N-*substituted*-4-(*cyanophenylmethylene*)*piperidines*

It was expected that the NMR spectrum of compounds of type I would show a complicated group of signals for the eight heterocyclic ring protons as the chemical shifts of the four sets of protons might be different. However, the NMR spectrum of

TABLE 2. NMR SPECTRA OF N-SUBSTITUTED-4-(CYANOPHENYLMETHYLENE)PIPERIDINES I IN $CDCl_3$ (60 mc, δ VALUES IN ppm FROM TMS)



I

I	R′	R	Ring protons at C_5 and C_4	Ring protons at C_2 and C_3	—N—CH_2—	Aromatics
(a)	H	benzyl	2·46 (S, 4H)	2.74 (M, 4H)	3·54	7·31 (S, 10H)
(b)	*p*-Cl	benzyl	2·45 (S, 4H)	2·72 (M, 4H)	3·54	7·33 (M, 9H)
(c)	*p*-F	benzyl	2·44 (S, 4H)	2·72 (M, 4H)	3·55	7·17 (M, 9H)
(d)	*m*-Cl	benzyl	2·47 (S, 4H)	2·72 (M, 4H)	3·52	7·32 (S, 9H)
(e)	*p*-OCH_3	benzyl	2·45 (S, 4H)	2·72 (M, 4H)	3·52	7·00 (D, 2H)
						7·20 (D, 2H)
			(methoxy group 3·78)			7·31 (S, 5H)
(f)	H	phenethyl	2·49 (S, 4H)	plus CH_2CH_2—N 2·76 (M, 8H)	—	7·32 (M, 10H)
(g)	*p*-Cl	phenethyl	2·49 (S, 4H)	plus CH_2CH_2—N 2·76 (M, 8H)	—	7·28 (M, 9H)
(h)[1]	H	methyl	2·43 (S, 4H)	2·71 (M, 4H)	(N—CH_3 2·31)	7·35 (S, 5H)

S = singlet, D = doublet, M = multiplet

N-benzyl-4-(cyanophenylmethylene)piperidine (Ia; Table 2) is very simple and the eight ring protons appear as a four-proton *singlet* (2·46 ppm δ) and a symmetrical four-proton *multiplet* (2·74 ppm; Fig. 1). The two-proton singlet at 3·54 ppm is assigned to the methylene protons of the benzyl group while the signal of the ten aromatic protons appears as a singlet at 7·31 ppm.

NMR studies of Ia at 100 mc gave singlet-multiplet patterns similar to the above and the 60 mc spectrum of Ia in pyridine, benzene and deuterodimethylsulfoxide showed analogous patterns. The 3- and 4-chloro, 4-fluoro and 4-methoxy analogues of N-benzyl-4-(cyanophenylmethylene)piperidine also gave similar results (Table 2).

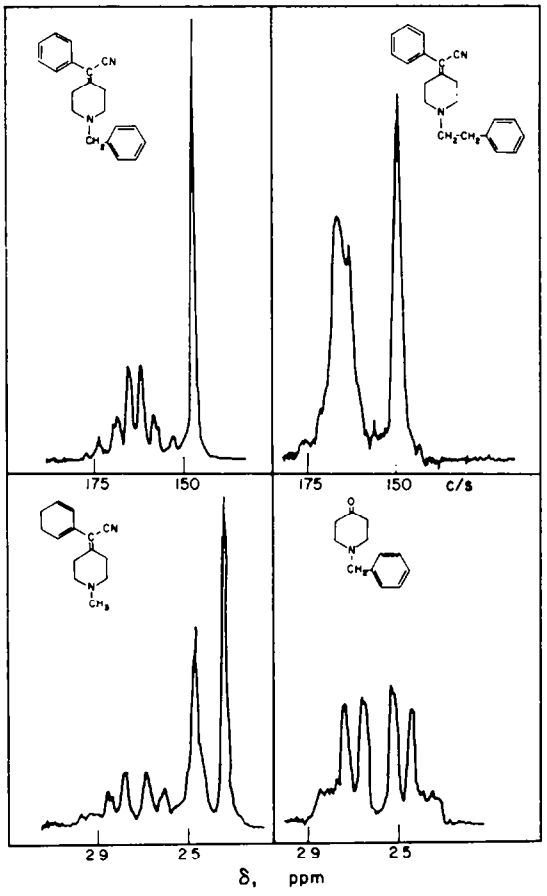


FIG. 1

The origin of the NMR *spin-coupling pattern in* N-*substituted*-4-(*cyanophenylmethylene*)-*piperidines* I

The phenomenon may be explained as follows. Each of the signals, integrating for four protons, must be the result of interaction between protons on either C2 and C3 *or* C5 and C6 since the "insulating" nature of the piperidine nitrogen and the double bond will allow interaction only between protons on each side of the ring.

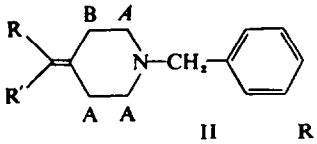
Bible[12] has pointed out that, in a series R—CH_2CH_2—R′, patterns from A_2X_2 to A_2B_2 to A_4 can be obtained by holding J_{AB} constant (ca. 6 c/s) and decreasing the chemical shift difference ($\Delta\nu$) between the two groups of methylene protons by varying substituents R and R′. Thus the spectrum of the methylene groups of Cl—CH_2CH_2—OH appears as a A_2B_2 multiplet[13] similar to that of I and the four methylene protons of NC—CH_2CH_2—$COOCH_3$ appear as a sharp singlet.[14] The

[12] R. H. Bible, *Interpretation of* NMR *Spectra* p. 77. Plenum Press, N.Y. (1965).
[13] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, NMR *Spectra Catalog* Vol. I; No. 12. (1962).
[14] Ref. 13. No. 106.

NMR spectra of N-substituted 4-(cyanophenylmethylene)piperidines are unusual in that the *same* six-membered ring gives rise to *both* an A_2B_2 and an A_4 pattern.

The four-proton singlet ($w\frac{1}{2}$, peak width at half height = 1·5–2·0 c/s) in the NMR spectrum of I requires the chemical shift of four protons on one side of the ring (at C2 and C3 *or* C5 and C6) to be equivalent. The fact that this A_4 pattern appears, indicates that the six-membered ring is in rapid conformational change so that there is no distinction between *axial* and *equatorial* protons and thus the two protons of the four sets of ring protons (at C2, C3, C5 and C6) are equivalent.

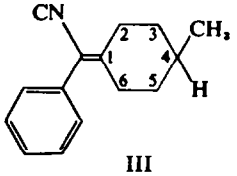
The other side of the ring consists of two protons (*A*) next to the nitrogen (which must have a slightly different δ than A) that couple with the two protons on the carbon atom adjacent to the double bond (B) and form an A_2B_2 pattern.



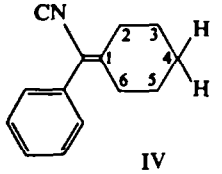
II R = Phenyl or CN
R′ = CN or Phenyl

To clarify the role of conformational interchange in the production of the singlet-multiplet pattern of the NMR spectra of I and to determine which ring protons produced the singlet and which ring protons produced the multiplet, the NMR spectra of model compounds were investigated; assignments of the chemical shifts of the ring protons in Table 2 are based on the NMR spectra of these compounds.

NMR *spectra of model compounds*



III



IV

The NMR spectrum of 4-*methyl*-1-(*cyanophenylmethylene*)*cyclohexane* III shows the expected three-proton doublet (J = 5·5 c/s) for the methyl group at 0·90 ppm but only an unassignable group of signals (10 protons) between 1·0–3·3 ppm (Fig. 2). In III the conformation having the methyl group *equatorial* will be preferred and thus the nonequivalent *axial* and *equatorial* ring protons give rise to a complicated NMR spectrum.

When the methyl group in III is absent (compound IV), both chair conformations of the alicyclic ring are energetically equivalent and conformational interchange between the two conformations results in the *axial* and *equatorial* protons becoming magnetically equivalent. The simple NMR spectrum of 1-(cyanophenylmethylene)-cyclohexane[15] (IV; Fig. 2) having two multiplets (2 protons each) at 2·29 ppm ($w\frac{1}{2}$ = 10 c/s) and 2·71 ppm ($w\frac{1}{2}$ = 13 c/s) and a broad ($w\frac{1}{2}$ = 7 c/s) six-proton singlet at 1·61 ppm, is in accord with this deduction. The broad singlet, in reality an unresolved multiplet, is assigned to the six ring protons on C3, C4, and C5; its value differs slightly from the δ of cyclohexane (1·43 ppm). Both two-proton multiplets must

[15] J. A. McCrae and R. H. G. Manske, *J. Chem. Soc.* 486 (1928).

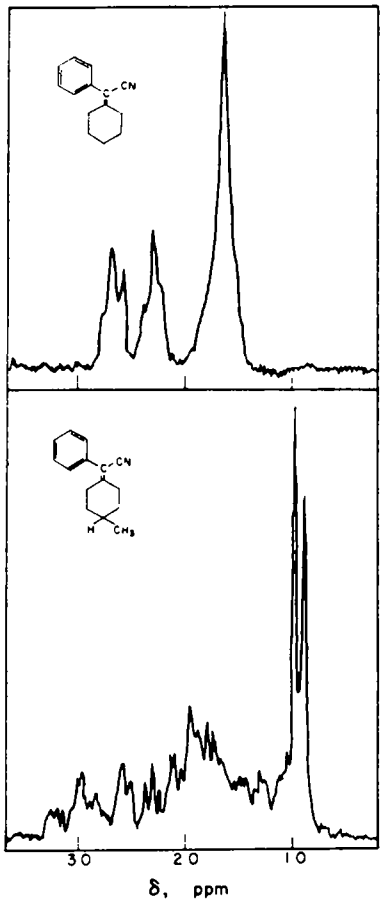


FIG. 2

arise from the ring protons on C2 and C6 having unequal chemical shifts due to the different long range shielding effects of the phenyl ring and the nitrile group. Comparisons of the NMR spectra of III and IV show that the latter spectrum is simpler and approaching the singlet-multiplet pattern of I. However, a substituted nitrogen atom in the 4 position of IV is required before the singlet-multiplet pattern as for I is seen in the NMR spectrum. The nitrogen atom has both an inductive effect and an effect on the conformational interchange of the six-membered ring; these factors are now considered.

Conformational interchange in N*-substituted piperidines and derivatives*

Six-membered ring compounds with trigonal bonds at C4 (>C=C< or >C=O) and a substituted nitrogen atom in the 1 position (e.g. I and V) would be expected to undergo conformational interchange readily due to two factors. One is the absence of the C4 proton which eliminates the 2–4 and 4–6 *diaxial* interactions found in cyclohexane. The second factor is that the inherent tendency of a trigonal nitrogen atom to

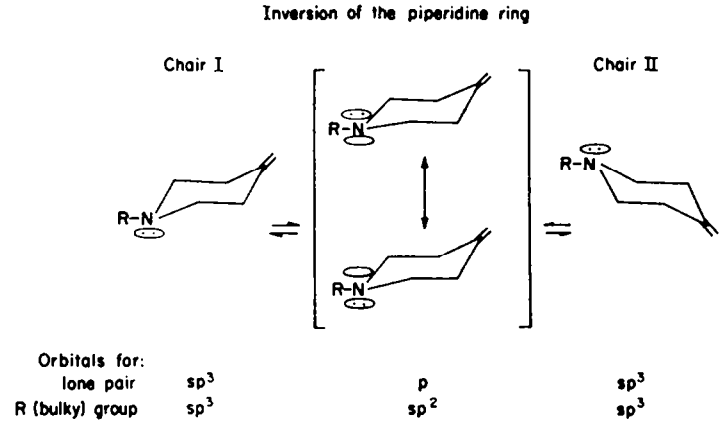
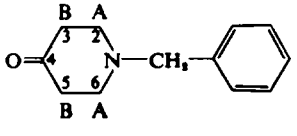


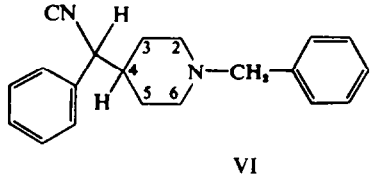
FIG. 3

invert is not prevented by a bulky group bonded to it;[16] this group will adopt the preferred *equatorial* position in *both* chair forms of the piperidine ring (Fig. 3).

The NMR spectrum of N-benzyl-4-piperidone (V; Fig. 1) shows a $2(A_2B_2)$ pattern arising from the equivalent protons adjacent to the nitrogen on C2 and C6 (A) coupling with those on C3 and C5 which have a different chemical shift (B) due to the C4 carbonyl group. Comparison of the NMR spectrum of V with those of cyclohexanone and N-benzyl piperidine suggest that the lower field multiplet (2·73 ppm) is due to the protons next to the nitrogen atom and the higher field multiplet (2·49 ppm) is due to the protons next to the carbonyl group. While the ability to interchange conforma-



V



VI

tionally is similar in V and Ia, their NMR spectral patterns are different (Fig. 1); thus different chemical shifts for the protons on each side of the ring must be important in the NMR singlet-multiplet phenomenon shown by compounds of type I.

Chemical shifts of ring protons in compounds of type I

It was shown for compound IV that the two sets of protons of the six-membered ring immediately adjacent to the substituted double bond had different chemical shifts (Fig. 2); the same situation would be expected in compounds of type I. A different NMR spectrum is expected for the saturated analogue of Ia, N-*benzyl α-piperidylphenylacetonitrile* VI for two reasons. One is the relative freedom of rotation around the bond between the piperidine ring and the carbon bearing the benzene ring and cyano group. This leads to averaging of the long range effects of the phenyl ring and the nitrile group so that the protons on C3 and C5 have similar chemical shifts. The second factor is the fixing of the piperidine ring in one preferred chair conformation with the bulky group at C4 in an *equatorial* position.

[16] W. N. Speckamp, U. K. Pandit and H. O. Huisman, *Tetrahedron Letters* 3279 (1964).

The NMR spectrum of VI shows a ten-proton aromatic singlet at 7·30 ppm and a two-proton singlet at 3·46 ppm for the methylene group of the benzyl side chain; these signals appear in about the same position as in the unsaturated parent compound Ia. The presence of two additional protons compared with Ia is indicated in the total integral; a one-proton doublet at 3·58 ppm (J = 6 c/s) is assigned to the proton on the carbon attached to the phenyl ring and nitrile group; the long range and inductive effects of both these groups account for the downfield position of this proton. It is split into a doublet by the proton on C4; the coupling constant is typical for a vicinal proton with free rotation, i.e. 6–8 c/s.

The proton at C4 cannot be independently distinguished from the protons at C3 and C5 which appear at about 1·7 ppm (five-proton integral). A two-proton doublet at 2·9 ppm results from the two *equatorial* protons on C2 and C6 indicating the fixed conformation of the piperidine ring.[17] These *equatorial* protons are split primarily into a doublet (J = 12 c/s) by coupling with the geminal proton with further small splittings due to the adjacent methylene groups (J values for geminal protons are 12–15 c/s). The signals for the *axial* protons on C2 and C6 appear at higher field (about 2·0 ppm) than the *equatorial* protons; the $\Delta\nu$ (ca. 1·0 ppm) between the *axial* and *equatorial* hydrogens on C2 and C6 is greater than that usually found (0·1–0·7 ppm)[18] and is probably due to the magnetic anisotropy of the unshared pair of electrons of the adjacent nitrogen atom.[19]

Allocations of the chemical shifts to the ring protons of compounds of type I

The above discussion indicates that facile conformational interchange and a difference in the chemical shifts of the protons on each side of the piperidine ring are required for the spin-pattern seen in the NMR spectrum of compounds of type I in which the phenyl and nitrile groups play a special part in their effect on the chemical shifts of the piperidine ring protons.

The protons on C2 and C6 are downfield compared with cyclohexane (1·43 ppm) due to the adjacent substituted nitrogen atom. N-benzylpiperidine has a four-proton multiplet ($w\frac{1}{2}$ = 21 c/s) at 2·42 ppm for the C2 and C6 protons and the six C3, C4 and C5 protons appear at 1·50 ppm ($w\frac{1}{2}$ = 15 c/s). The presence of the substituted nitrogen atom thus causes a *paramagnetic* shift of about 0·1 ppm for the C3 and C5 protons and a *paramagnetic* shift of about 1·0 ppm for the C2 and C6 protons.

In compounds of type I the C4 double bond should *deshield* the C3 and C5 protons equally and have little effect on the C2 and C6 protons.

The long range effect of the nitrile group on the ring protons can be shielding or deshielding depending on the orientation of the protons with respect to the C—N bond axis.[20–22] The magnitude of this effect is dependent on the distance of the protons from the nitrile group. The conformational flexibility of the alicyclic ring and the difficulty

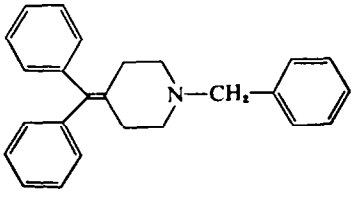
[17] N. S. Bhacca, D. P. Hollis, L. F. Johnson and E. A. Pier, NMR *Spectra Catalog* Vol. II; Nos. 477, 478, 479 (1963).
[18] N. S. Bhacca and D. H. Williams, *Applications of* NMR *Spectroscopy in Organic Chemistry* p. 47. Holden-Day, San Francisco (1964).
[19] H. P. Hamlow and S. Okuda, *Tetrahedron Letters* 2553 (1964).
[20] G. S. Reddy, J. H. Goldstein and L. Mandell, *J. Amer. Chem. Soc.* **83**, 1300 (1961).
[21] G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.* **39**, 3509 (1963).
[22] A. D. Cross, *J. Amer. Chem. Soc.* **85**, 3223 (1965).

of obtaining an accurate value of $\Delta\chi$ for the nitrile group make calculations difficult. Qualitative calculations[20–22] suggest that the nitrile group *shields* most strongly at C5, less at C6 and *deshields* the protons on C2 and C3 slightly.

Calculation of shielding or deshielding of the ring protons by the phenyl ring depends on knowledge of the distance of the protons from the centre of the benzene ring and their distance above the plane of the ring. Qualitative calculations[23] based on the benzene ring being about 35° out of the plane of maximum conjugation suggest that the benzene ring *deshields all* ring protons with the greatest effect at C5.

It is impossible to calculate the exact chemical shifts of each set of ring protons because of the lack of quantitative data on the relative importance of the above effects.

To determine which set of protons gives the singlet and which set gives the multiplet, modifications of compound I were attempted to see what effect this had on the NMR spectra; unfortunately, all attempts to modify the nitrile group of Ia were unsuccessful (cf. exp.). However, N-*benzyl*-4-(*diphenylmethylene*)*piperidine* VII was synthesized



VII

from 4-benzhydriledinepiperidine.[24] The NMR spectrum of VII shows a ten-proton singlet at 7·10 ppm assigned to the two benzene rings attached to the double bond; a five-proton aromatic singlet at 7·28 ppm for the aromatic protons of the benzyl group and a two-proton singlet at 3·51 ppm assigned to the methylene protons of the benzyl group.

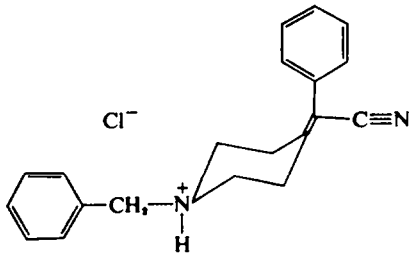
In addition, there is an *eight-proton singlet* ($w\frac{1}{2}$ = 2 c/s) at 2·45 ppm which is in the same position as the four-proton singlet in compounds of type I (Table 1). This A_8 singlet results from the *fortuitous* equivalence of the eight ring protons in VII. The position and multiplicity of the ring protons in the diphenyl compound (VII) indicate that A_4 singlet seen in the NMR spectrum of I is due to the protons on the same side as the phenyl ring. The A_2B_2 multiplet is therefore formed by the four protons on the same side of the ring as the cyano group. Examination of the NMR spectra of compounds of type I in light of these findings shows that the protons on C3 are in a region of more *net* deshielding than the protons in C5.

The NMR *spectra of modified compounds of type* I

Protonation of the heterocyclic nitrogen atom of N-benzyl-4-(cyanophenylmethylene)piperidine (Ia) gives VIII which is expected to be in a fixed chair conformation with the benzyl group in the *equatorial* position in a non basic solvent such as deuterochloroform, assuming only a slow intermolecular proton interchange. The NMR spectrum of VIII shows the two-proton singlet for the N—CH_2-protons at about 4·4 ppm while the singlet multiplet pattern of Ia is completely obliterated due to

[23] C. E. Johnson and F. S. Bovey, *J. Chem. Phys.* **29**, 10212 (1958).
[24] K. W. Wheeler, J. K. Seyler, F. P. Palopoli and F. J. McCarty, US Patent 2,898,339 (Aug. 4, 1957).

fixing of the alicyclic ring in a chair conformation and the change in chemical shifts of the ring protons due to the positive charge on the nitrogen.



VIII

In the NMR spectrum of N-*β-phenethyl*-4-(*cyanophenylmethylene*)*piperidine* If and its *p*-chloro analogue Ig (Table 2; Fig. 1), the pattern is not as clear as in the case of the benzyl analogues because the signals of the four ring protons and the four side chain protons are found together as an eight-proton multiplet (2·8 ppm). The four-proton singlet, however, remains in about the same position as in the N-benzyl analogues.

In the N-benzyl analogues (Ia–Ie), the side chain methylene protons are subjected to the inductive and long range effects of *both* the nitrogen atom *and* the phenyl ring; consequently their signal is found far downfield (ca. 3·5 ppm). In the N-*β*-phenethyl analogues (If and Ig), each set of methylene side chain protons is subjected to the inductive and long range effect of *only* the heterocyclic nitrogen atom *or* the phenyl ring and their signal is shifted upfield (relative to the benzyl protons) to 2·7 ppm and thus overlaps the ring proton multiplet.

Surprisingly, there are only minor changes in the singlet-multiplet pattern of the NMR spectrum, when the benzyl group is replaced by a methyl group. The appearance of the multiplet of the N-methyl derivative Ih in $CDCl_3$ (Fig. 1) is similar to that of the N-benzyl compound Ia in benzene. The nature of the nitrogen substituent does not seem to play an important part in the production of the singlet-multiplet phenomenon seen in the NMR spectra of N-substituted-4-(cyanophenylmethylene) piperidines I.

EXPERIMENTAL

I *Synthesis of compounds*

A. *Preparation of compounds of type I* (HCl *or* HBr *salts*)

N-benzyl (or N-phenethyl)-4-piperidine was dissolved in MeOH and added to a solution of Na metal and the required nitrile in MeOH (mole ratios of piperidone–Na–nitrile were about 1·0:0·8:2·0) and the mixture heated under reflux for 0·5 hr. After cooling the reaction mixture was poured into cold water, the solution then acidified with conc. HCl and extracted with ether; the crude product formed on cooling the aqueous phase. These base hydrochlorides were recrystallized from 96% EtOH or EtOH–ether. The hydrobromides were prepared from the free bases with 10% ethanolic HBr and recrystallized from EtOH–ether.

Compound Ia (R = benzyl, R′ = H) crystallized as white plates, m.p. 214–215·5°. (Found: C, 74·0; H, 6·4; N, 8·5. $C_{20}H_{21}N2Cl$ requires: C, 73·95; H, 6·5; N, 8·6%.)

Compound Ib (R = benzyl, R′ = *p*-Cl) crystallized as pale yellow granules, m.p. 221–222·5°. (Found: C, 66·85; H, 5·7; N, 8·0. $C_{20}H_{20}N_2Cl_2$ requires: C, 66·85; H, 5·6; N, 7·8%.)

Compound Ic (R = benzyl, R′ = *p*-F) crystallized as pale cream needles, m.p. 215–217°. (Found: C, 69·4; H, 5·6; N, 8·2. $C_{20}H_{20}N_2FCl$ requires: C, 70·1; H, 5·8; N, 8·2%.)

Compound Id [R = benzyl, R′ = m-Cl) crystallized as colourless needles, m.p. 211·5–212·5°. (Found: C, 59·5; H, 5·1; N, 6·95. $C_{20}H_{20}N_2BrCl$ requires: C, 59·5; H, 5·0; N, 6·9%.)

Compound Ie (R = benzyl, R′ = *p*-OCH_3) monohydrate crystallized as white granules, m.p. 227·5–228·5°. (Found: C, 59·5; H, 5·9; N, 6·5. $C_{21}H_{22}N_2OBr \cdot H_2O$ requires: C, 60·0; H, 5·9; N, 6·7%.)

Compound If (R = phenethyl, R′ = H) crystallized as white granules, m.p. 206–207·5°. (Found: C, 72·8; H, 7·2. $C_{21}H_{22}NCl$ requires: C, 73·5; H, 7·1%.)

Compound Ig (R = phenethyl, R′ = *p*-Cl) crystallized yellow granules, m.p. 225–227°. (Found: C, 67·8; H, 6·1; N, 7·7. $C_{21}H_{22}N_2Cl_2$ requires: C, 67·6; H, 6·0; N, 7·5%.)

B. *Preparation of compounds of type* II

(1) 4-*Piperidylphenylacetonitrile* HBr (II, R = H). Pd (10% on C, 2·5 g) was added to a solution of N-benzyl-4-(cyanophenylmethylene)piperidine (4·32 g) in abs EtOH and the mixture hydrogenated at room temp and atm. press. The calculated volume of H_2 was absorbed after 1 hr; the catalyst was filtered off and the filtrate evaporated to dryness (water pump vacuum) yielding a brown oil which was distilled (b.p. 190–192°, 0·1 mm), yield 70%. The base was dissolved in excess 10% ethanolic HBr and the solution diluted with dry ether; the solid which crystallized on standing recrystallized from EtOH–ether as colourless cubes, m.p. 266·5–268·5°. (Found: C, 55·8; H, 5·9; N, 10·3. $C_{13}H_{17}N_2Br$ requires: C, 55·5; H, 6·05; N, 10·0%), UV (EtOH λ 252 mμ (ε 150), λ 258 mμ (ε 300), λ 264 mμ (ε 160), IR (nujol) 2240, 1562 cm^{-1}.

(2) N-*Benzyl-4-piperidylphenylacetonitrile* HBr (II, R = *benzyl*). 4-Piperidylphenylacetonitrile (16 g) was dissolved in abs. EtOH (100 ml and Na_2CO_3 (10 g) and benzyl chloride (9·6 g) added; the mixture was heated under reflux for 24 hr. After cooling, the inorganic matter was filtered off and the filtrate evaporated to dryness; the residual oil solidified on cooling and was recrystallized from acetone as colourless crystals, m.p. 76·5–77·5°. The hydrobromide was prepared by dissolving the base in excess 10% ethanolic HBr, diluting the solution with ether and recrystallizing the solid which formed upon standing from EtOH–ether as colourless microprisms, yield 95%, m.p. 183–184°. (Found: C, 64·45; H, 6·4; N, 7·5. $C_{20}H_{23}N_2Br$ requires: C, 64·65; H, 6·2; N, 7·55%), λ 256 mμ (ε 370), λ 261 mμ (ε 200), IR nujol 2250 1600 cm^{-1}.

(3) N-β-*Phenethyl-4-piperidylphenylacetonitrile* HBr (II, R = *phenethyl*). The compound, prepared in a manner similar to that above using phenethyl bromide and n-propanol crystallized as colourless microprisms, yield 80%, m.p. 201–202°. (Found: C, 65·45; H, 6·3; N, 7·3. $C_{21}H_{25}N_2Br$ requires: C, 65·4; H, 6·5; N, 7·3%), UV (EtOH) λ 251 mμ (ε 320), λ 256 mμ (ε 290), λ 261 mμ (ε 420), IR (nujol) 2230, 1590 cm^{-1}.

(4) N-*Benzyl-4-piperidylphenylacetamide* HBr. N-Benzyl-4-piperidylphenylacetonitrile (5 g) was dissolved in 80% w/w H_2SO_4 in EtOH (40 ml) and the solution stored at room temp for 48 hr before it was poured on to ice. After the ice had melted, the solution was basified and filtered and the collected base dissolved in 10% ethanolic HBr; the solid which crystallized on cooling was recrystallized from water as colourless cubes, yield 19%, m.p. 305–306°. (Found: C, 61·6; H, 6·5; N, 7·2. $C_{20}H_{25}N_2OBr$ requires: C, 61·7; H, 6·4; N, 7·2%.)

C. *Preparation of* 4-*methyl*-1-(*cyanophenylmethylene*)*cyclohexane* III

4-Methylcyclohexane (11·2 g, 0·1 mole), Na (2·3 g, 0·1 mole) and benzylcyanide (11·7 g, 0·1 mole) were reacted in the manner described by Macrae and Manske.[15] The compound was distilled as a colourless oil. b.p. 136–138°, yield 10 g 49%. (Found: C, 86·4; H, 8·0; N, 7·1. $C_{15}H_{16}N$ requires: C, 85·7; H, 7·6; N, 6·7%.)

D. *Preparation of* N-*benzyl-4-benzhydrylidinepiperidine* VII

4-benzhydrilidinepiperidine[24] (prepared from α,α, diphenyl-4-piperidine-methanol[25]; 378 mg) was warmed in 60% NaOH aq (5 ml); benzoyl chloride (0·5 ml) was added with shaking; an exothermic reaction ensued and an oil separated. This oil was extracted with ether (2 × 10 ml) and the combined ether extracts dried ($MgSO_4$) and LAH (0·2 g) added over a period of 10 min. The reaction mixture was stirred for 40 min and the complex decomposed by addition of sat sodium potassium tartrate solution (10 ml). The organic layer was filtered off, washed with ether and the ether washings added

[25] E. L. Schumann, M. G. Van Campen Jr. and R. C. Pogge, US Patent 2,804,422 (Aug. 27, 1957).

to the filtrate. The combined filtrate and washings were dried ($MgSO_4$) and the solvent evaporated, leaving a yellow oil which solidified on standing. The product was recrystallized from aqueous acetone as colourless needles, m.p. 93–94°, yield 120 mg. (Found: C, 88·2; H, 7·4; N, 4·1. $C_{25}H_{25}N$ requires: C, 88·4; H, 7·4; N, 4·1%), UV (λ 243 mμ, ε 3500 in EtOH), MW. 340, equiv. wt. (non aqueous titration) 341. TLC shows single spot by UV inspection and spraying with iodoplatinic acid in the following systems:

Silica gel: ($CHCl_3$, 5: MeOH, 1) R_f 0·73
Silica gel: (AcoEt) R_f 0·76

II. *Unsuccessful attempts to modify the nitrile group of* N-*benzyl*-4-(*cyanophenylmethylene*)-*piperidine* Ia *included*

CN Cleavage (sodamide–toluene); Stephen reaction (Stannous Chloride–HCl–ether); and hydrolysis (KOH–H_2O_2, 50% H_2SO_4 in MeOH, NaOH–acetone, NaOH–acetone–water, 40% H_2SO_4 in EtOH. All above procedures gave either starting material or a black tar.

III. *Physical measurements*

IR spectra of the compounds as nujol mulls were determined on a Unicam SP200 and UV spectra in EtOH were determined on a Unicam SP800 spectrometer. The NMR spectra were determined on a Varian A-60 or HR 100, about 10% w/v solutions in $CDCl_3$ (unless otherwise noted) with TMS as internal reference.

Note added in proof

N. S. Bhacca and L. F. Johnson of Varian Associates, Palo Alto, Calif have very kindly run 230 mc. NMR spectra of Ia and VII (Fig. 4). The higher ratio of $\Delta\nu$ to

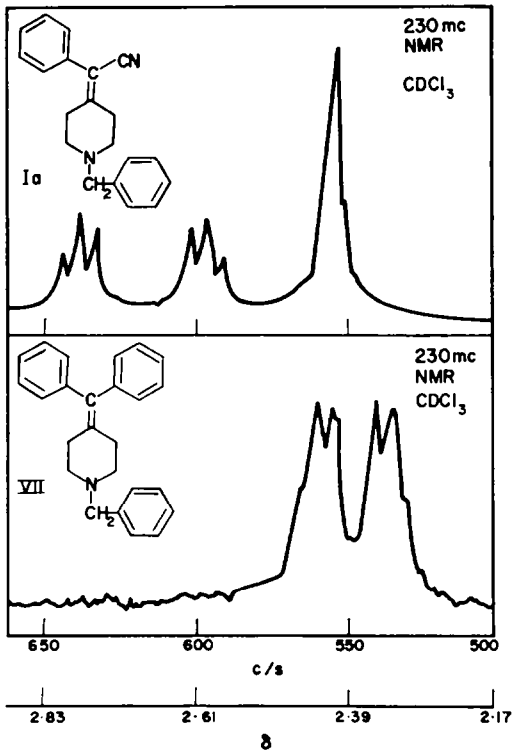


FIG. 4

J[12] has resulted in the four proton A_2B_2 multiplet of Ia at 60 mc appearing as an A_2X_2 pattern ($J = 6$ c/s, $\Delta\nu = 42$ c/s) in the 230 mc spectrum. When $\Delta\nu/J$ is less than 6, first order spin patterns do not appear;[12] calculation of $\Delta\nu/J$ for the different NMR spectra shows why only 230 mc spectra will give a first order A_2X_2 pattern: [230 mc, $(42/6 = 7)$, 100 mc $(18/6 = 3)$, 60 mc $(11/6 = 1{\cdot}8)$]. The four-proton singlet (2·46 ppm at 60 mc) remains a singlet (with about the same band width as the two-proton singlet in Ia) at 230 mc indicating that the four protons on same side as the phenyl ring in Ia are *very nearly* equivalent (coincidence $\leq \frac{1}{2}$ c/s at 60 mc). However, in model compound VII, the eight-proton singlet seen in the 60 mc spectrum now appears as an A_2B_2 pattern in the 230 mc spectrum.

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