Conformational Equilibra of Hydrochloride Salts of Pethidine, Ketobemidone, and Related Central Analgesics of the 4-Arylpiperidine Class

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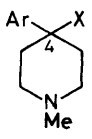
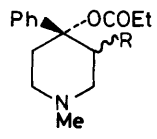
The n.m.r. (^{1}H, ^{13}C) spectra of hydrochloride salts of pethidine, ketobemidone, 4-*m*-hydroxyphenyl-1,4-dimethylpiperidine, and the reversed ester of pethidine and its analogues are reported. Analysis of the data shows that, apart from the reversed esters, both *N*-protonated epimers are significantly populated when the salts are dissolved in D_2O. The equatorial 4-aryl chair conformer is the major epimer of pethidine and ketobemidone, but the minor form in the case of the 1,4-dimethyl derivative. Little evidence for axial 4-aryl chair epimers has been found for solutes of the reversed esters of pethidine. The results corroborate previous computational studies, and are discussed in terms of differing binding modes of the two classes of 4-arylpiperidine ligand at opioid receptors.

There is much interest in the conformation of central analgesics of the 4-arylpiperidine class with regard to their interactions with opioid receptors.[1] This group of analgesics may be subdivided into derivatives with carbon substituents at C-4 of the piperidine ring such as pethidine (**1a**) and ketobemidone (**1b**), and those with oxygen substituents such as the reversed ester of pethidine (**2a**) and the prodines (**2b**) and (**2c**). Antinociceptive activity of the former group is enhanced by the presence of a *m*-phenolic substituent in the 4-aryl group[2] while that of the oxygenated derivatives (**2**) is depressed.[3,4] This unusual difference in structure–activity relationships may be explained by postulating that the active (bound) conformation of pethidine and its C-4 carbon analogues is an axial 4-aryl chair



(1)

(**a**) Ar = Ph, X = CO_2Et
(**b**) Ar = *m*-OHC_6H_4, Y = COEt
(**c**) Ar = *m*-OHC_6H_4, X = Me

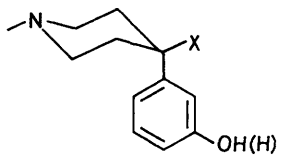


(2)

(**a**) R = H
(**b**) R = Me
(**c**) R = Me

(**3**) thereby mimicking the 4-aryl piperidine fragment of morphine (**4**) (partial structure), while that of the C-4 oxgyen group is an equatorial 4-aryl chair (**5**). From an energetic point of view these proposals are supported by the computational studies of Froimowitz[5] who showed that the axial 4-aryl chair conformers of pethidine and ketobemidone free-bases differ in energy from corresponding equatorial 4-aryl chairs by only 0.6–0.7 kcal mol^{-1},* while those of the reversed esters (**2**) have substantially higher energies (1.9–3.4 kcal mol^{-1}) than conformers with equatorial aryl substituents.

We now report the ^{1}H and ^{13}C n.m.r. spectra of derivatives (**1**) and (**2**) as hydrochlorides in D_2O and show that these data provide physical evidence of conformation which supports the conclusions of the computational studies. The data are interpreted in terms of mixtures of protonated epimers at equilibrium in which proton exchange is slow on the n.m.r. time scale. This approach is justified by the fact that the bases will be extensively protonated (>95%) in water (and D_2O) as judged by reported pK_a values (pethidine 8.72, ketobemidone 8.7,



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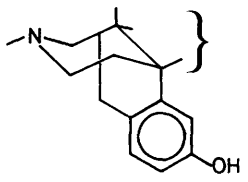

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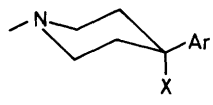


(5)

ketobemidone 8.7, alphaprodine 8.51, betaprodine 8.56)[1] and the observation that the appearance of spectra did not change with time.

Experimental

^{1}H N.m.r. spectra were recorded on JEOL GX270 and GX400 MHz spectrometers. Samples (*ca.* 10 mg) were dissolved in D_2O (0.5 cm^3, external TMS reference) or $CDCl_3$ (0.5 cm^3, TMS reference), and examined without degassing at the ambient probe temperature (20 °C), employing the standard conditions of 32K data points with digital resolution of 0.18 Hz per point. The ^{13}C n.m.r. spectra were recorded at 67.8 MHz using a JEOL GX270 MHz spectrometer, and the number of protons attached to carbon atoms were established by DEPT experiments.

Sources of compounds (HCl salts) were as follows: pethidine (May and Baker); ketobemidone (Dr. A. H. Stead, Home Office Forensic Science Service); 4-aryl-4-methylpiperidine (**1c**) (Dr. D. M. Zimmerman, Eli Lilly, material also synthesized from 4-*m*-hydroxyphenyl-1-methyl-1, 2,5,6-tetrahydropyridine);[6] the reversed ester of pethidine (**2a**) and its 4-acetoxy- and *m*-hydroxyphenyl analogues were synthesized from 1-methyl-4-piperidone;[4,7] and α- and β-prodine were synthesized from 1,3-dimethyl-4-piperidone.[8]

* 1 cal = 4.184 J.

Table 1. ^{1}H N.m.r. characteristics of pethidine hydrochloride and related compounds.

Compound*	H(2,6)	H(3,5)	NMe	CH_2[b]	Me[b]	Ar
Pethidine (**1a**)·HCl	eq: 3.63 br d, 13.0 (3.48 br d, *ca.* 13) ax: (3.10 dt, 13.2, 13.2, 1.4)[c]	eq:[d] ax: 2.15 dt, 14, 14, 4 (2.47 br t, *ca.* 14, 14)	2.9 s (2.73 s)	4.18 q, 7.1 (4.06 q, 7.1)	1.17 t, 7.1 (1.11 t, 7.1)	7.4–7.6 m
(in $CDCl_3$)	eq: 3.60 (br, d, *ca.* 11 (3.48 br d, *ca.* 11) ax:[d]	*d*	2.86 d, 4.9[f] (2.70 d, 4.9)	4.21 q, 6.8 (4.06 q, 6.8)[e]	1.20 t, 6.8 (1.15 t, 6.8)[g]	7.2–7.5 m
Ketobemidone (**1b**)·HCl	eq: 3.55 br d, 13.1 (3.47 br d, 13.4) ax: 3.00 dt, 13.3, 13.3, 2 (2.91 dt, 13.3, 13.3, 2)	eq:[i] ax: 2.07 dt, 14.2, 14.2, 3.5 (2.18 dt, 14.2, 14.2, 3.5)	2.83 s (2.72 s)	2.36 q, 7.0 (2.33 q, 7.0)	0.78 t, 7.1 (0.73 t, 7.1)	2′ 6.75 t, 2 5′ 7.27 t, 8.0 (7.33 t, 8.3) 6′ (6.97 br d 7.9) *h*
(**1c**)·HCl	eq: 3.36 br d, 13.0 (3.43 br d, 13.0) ax: 2.80 dt, *ca.* 13.5, 13.5, 1.5 (3.27 dt, 13, 13, 3)	eq: 2.56 br d, 14.1 (2.12 br d, *ca.* 14) ax: 1.89 dt, 14, 14, 3 (2.03 dt, 13.6, 13.6, 4)	2.67 s (2.88 s)	—	4Me 1.19 s (1.32 s)	5′ 7.31 t, 7.8 (7.28 t, 7.8) 2′ nr 6.88 4′ nr 6.78 } *j* 6′ nr 6.98
(**2a**)·HCl	eq: 3.53 br d, *ca.* 12.5 ax: 3.36 dt, *ca.* 12, 12, 2	eq: 2.72 br d, 14 ax: 2.29 dt, 14, 14, 4	2.93 s (2.89)	2.48 q, 7.5	1.06 t, 7.5 (0.99 t)	7.35–7.45 m
4-Acetoxy analogue of (**2a**)·HCl	eq: 3.51 d, 12.5, plus small couplings ax: 3.38 dt, 12.5, 12.5, 1.5	eq: 2.71 br d, 14 ax: 2.26 dt, 14, 14, 3	2.90 s (2.83 s)	—	2.11s (2.01 s) OCOMe	7.35–7.45 m
4-*m*-OHC_6H_4 analogue of (**2a**)·HCl	eq: 3.59 br d, 12.5 ax: 3.41 t, 12.5, 12.5, plus small couplings	eq: 2.78 br d, 14 ax: 2.32 t, 14, 14, plus small couplings	2.97s	2.52 q, 7.5	1.11 t, 7.5	2′ 6.95 br s 4′ 6.91 dd, 8.2 5′ 7.36 t, 8 6′ 7.05 br d, 7.5
Alphaprodine (**2b**)·HCl	2(H) eq: 3.43 br d, 9.3 ax: 3.28 br t, 12.5, 12.5	3(H) ax: 2.13 m[k]	2.95 s	*ca* 2.6[d]	1.19 t, 8 (3-Me, 0.8 d, 7)	7.3–7.5 m
	6(H) eq: 3.59 br d, 11 ax: 3.18 br t, 13.5, 13.5	5(H) eq: 3.07 br d, 16 ax: *ca.* 2.6[d]				
Betaprodine (**2c**)·HCl	2(H) eq: 3.57 br d, 13 ax: 3.74 dd, 12.9, 3.6	3(H) eq: 2.64 m[l]	2.92 s	2.46 q, 7.6	1.04 t, 7.6 (3-Me, 0.74 d, 7.6)	7.3–7.5 m
	6(H) eq: 3.41 br d, 13 ax: 3.22 dt, 13.6, 13.6, 2.9	5(H) eq: 2.95 br d, 16 ax: *ca.* 2.75 dt, 15, 15, 4.3				

[a] In D_2O unless otherwise stated. Chemical shifts in ppm from external TMS followed by multiplicity and line separations of signals; data for minor epimer in parentheses. Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; plus combinations such as dt, doublet of triplets; br, broad; nr, near; eq, equatorial; ax, axial. [b] Of 4-CO_2Et, COEt, or OCOEt. [c] Major signal overlaps *eq* 3,5(H) and N-Me signals. [d] Unresolved. [e] Integral ratio 4.5:1. [f] Coupled to $^+$NH proton (12.5 ppm, br d). [g] Integral ratio 4.6:1. [h] Minor 2′, major and minor 4′ and major 6′ signals overlap, m 6.8–6.9 ppm. [i] Overlaps N-Me signal at 2.83 ppm. [j] Major and minor signals overlap. [k] Forms dd (12.3, 4.2 Hz) when 3-Me signal irradiated. [l] Forms br s when 3-Me signal irradiated.

Results and Discussion

4-Arylpiperidines with C-4 Linked to a Carbon Function.— The 400 MHz ^{1}H n.m.r. spectrum of pethidine hydrochloride in D_2O clearly demonstrates that the salt exists as a mixture of protonated epimers whose interconversion rates must be slow on the n.m.r. time scale. Thus duplicate resonances were recorded which were well-resolved in many cases (Table 1). The epimeric ratio is judged to be *ca.* 2.5:1 from the relative intensities of the better separated signal pairs. The ^{13}C n.m.r. spectrum of (**1a**)·HCl was also typical of an epimeric mixture (Table 2). Evidence that the major epimer is the equatorial 4-phenyl chair (**6**) and the minor the 4-axial phenyl chair (**7a**) in rapid equilibrium with its invertomer (**7b**) is provided by the following.

(*a*) The relative intensities of the two aromatic C_q ^{13}C resonances: the more intense lower field signal (140.4 ppm) is assigned to C_q of (**6**) and the less intense higher field signal (136 ppm) to C_q of (**7**) to which (**7a**) with a more sterically polarized C_q contributes [the same argument may be made with regard to the carbonyl C_q pair, the more intense higher field signal at 174.6 ppm being assigned to epimer (**6**) with an axial CO_2Et function].[9]

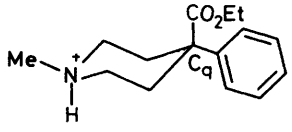
(*b*) The greater intensity of the lower field member of the duplicate ^{1}H ethyl ester resonances (q CH_2, t Me); corresponding higher field resonances are assigned to the ethyl group of epimer (**7**) since these protons fall within the shielding zone of the 4-phenyl group when it is axial (**7a**) and orthogonal to the mean plane of the piperidine ring.[10]

(*c*) The relative intensities of the two *N*-methyl proton resonances: the higher field signal (2.75 ppm) is attributed to

Table 2. Carbon-13 n.m.r. chemical shifts of pethidine hydrochloride and related compounds.[a]

Compound	C(2,6)	C(3,5)	C(4)	CH_2[b]	Me[b]	C_q(Ar)	C_q(CO)[d]	NMe
Pethidine (**1a**)·HCl	52.3 (50.6)	30.9 (28.8)	47.3 (46.4)	63.0	13.0	140.4[c] (136)	174.6 (175.5)	42.9 (42.1)
(in $CDCl_3$)	52.5 (52.0)	31.1 (28.6)	47.7	61.7	13.9 (13.8)	140.3[e]	173.1[e]	43.5 (42.6)
Ketobemidone (**1b**)·HCl	51.6 (52.0)	29.5 (28.2)	52.0	30.4 (30.0)	7.4 (7.2)	141.4 (137.4)[f]	214.5 (214.7)	42.5 (42.3)
(**1c**)·HCl	51.6 (50.8)	33.7 (33.6)	35.3	—	4-Me 32.3 (23.4)	145.9 (151.1)[g]	—	42.7 (42.6)
(**2a**)·HCl	50.0	32.6	77.1	28.0	8.1	141.6	175.6	42.9
4-Acetoxy analogue of (**2a**)·HCl	49.9	32.5	77.4	—	21.1 (OCO*Me*)	141.5	172.6	42.8

[a] In D_2O unless otherwise stated; chemical shifts in ppm from external TMS:[2] data for minor epimer in parentheses. [b] Of 4-CO_2Et, COEt, or OCOEt. [c] Quaternary C′ carbon of 4-Ar; other aromatic signals: 129.2 (129.5), 128.3 (12.7), 125.4. [d] Quaternary carbon of 4-CO_2Et, COEt or OCOEt. [e] Minor resonance not recorded. [f] Other aromatic signals: 155.9 (156.3), 130.4 (130.7), 117.6 (119.4), 114.8 (114.3), 112.5. [g] Other aromatic signals: 156.1 (155.7), 130.5 (130.1), 118.3 (117.0), 113.4 (113.2), 112.1.



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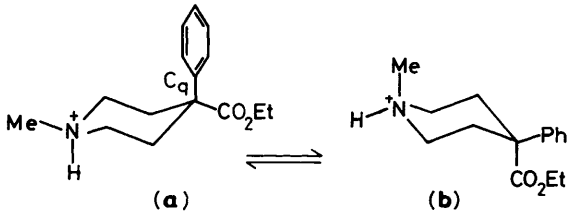
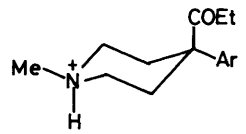


(7)

the contribution of invertomer (**7b**) which carries an axial *N*-methyl substituent (in general axial *N*-methyl protons resonate to high field of related equatorial protons in piperidine derivatives).[11]

Epimeric resonances of ester ethyl protons were particularly well resolved in the ^{1}H n.m.r. spectrum of pethidine HCl in $CDCl_3$ and provided the epimeric ratio of about 5:1 (details in Table 1).

In the solid-state, pethidine hydrochloride and hydrobromide salts adopt the equatorial 1-methyl 4-phenyl chair conformation (**6**).[12] N.m.r. spectra of ketobemidone (**1b**)·HCl in D_2O were comparable to those of pethidine·HCl with regard to evidence of epimeric nature. In the 400 MHz ^{1}H n.m.r. spectrum the duplication of all resonances was apparent including those of the aromatic signals (Table 1 and Figure) while the ^{13}C n.m.r. spectrum also presented many signals in duplicate (Table 2). It was concluded from intensity and chemical shift comparisons, as outlined above, that the epimer (**8**) preponderated with a preferred equatorial 4-aryl chair conformation, but the population difference between epimers (ratio *ca.* 1.2:1) was less than that found in the case of pethidine. Solvation of the protonated nitrogen centre must have a major influence on the conformational equilibria of salts (**1**) since the ^{1}H n.m.r. spectrum of (**1b**) in $CDCl_3$ showed little evidence of an epimeric pair [*cf.* also the result for (**1a**) in $CDCl_3$].



(8)

The ^{1}H n.m.r. spectra of analogues of ketobemidone·HCl, in which *N*-methyl was replaced by hexyl and heptyl,[13] examined in $CDCl_3$ (solubility was low in D_2O), were incompletely resolved but gave evidence of the compounds existing in solution as epimeric mixtures (ratio *ca.* 4:1) from duplication of signals due to $^+$NH, aromatic and some ring protons, and ethyl of the 4-propionyl group. Epimeric features of the *N*-hexyl derivative (typical of both compounds) were:* $^+$NH br m 10.6 (10.4); 5′-H t, 7.14 (7.24); 2′-H br s, 6.97 (7.23?); 6′-H dd, 6.91 (6.85); 4′-H br d, 6.56 (6.74); eq 3-H br d, 3.62 (3.50); and $COCH_2$*Me* t, (0.81)—major signal unresolved.

Froimowitz[5] also included the 4-aryl-4-methylpiperidine (**1c**) in his calculations and found that the axial 4-aryl chair was in fact preferred over its equatorial invertomer by 0.7 kcal mol^{-1}. This deduction is supported by the n.m.r. characteristics of (**1c**)·HCl in D_2O; both its ^{13}C and ^{1}H spectra showed clearly-defined duplicate signals characteristic of an epimeric mixture. In the case of the ^{13}C spectrum (Table 2), the higher field aromatic C_q (directly attached to C-4) signal had the greater intensity, evidence that the epimer (**9**) preponderated over the equatorial 4-aryl chair (**10**). The 4-methyl chemical shifts were in support; the more intense lower field signal (32.3 ppm) is assigned to 4-Me of (**9**) [which receives a contribution from equatorial 4-Me of (**9a**)], and the less intense higher field resonance (23.8 ppm) to the more sterically polarized axial methyl group of epimer (**10**).[14]

* See footnote *a*, Table 1 for details of notation.

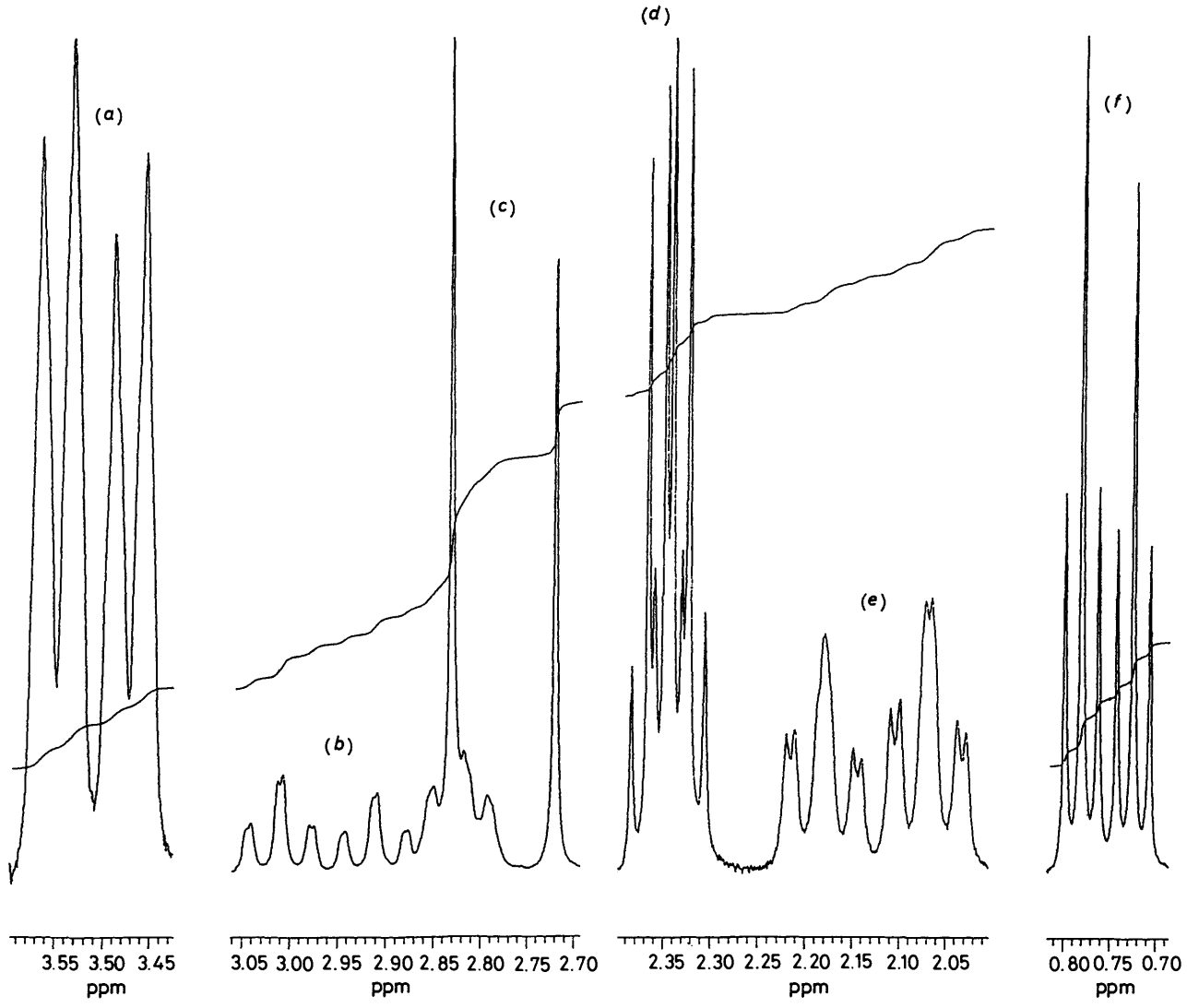
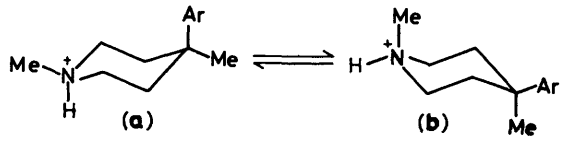
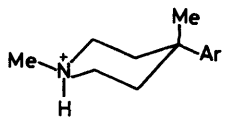


Figure. Parts of the 400 MHz ^{1}H n.m.r. spectrum of ketobemidone·HCl (**1b**) in D_2O showing epimeric signals due to: (*a*) eq 2,6-H; (*b*) ax 2,6-H; (*c*) N-Me; (*d*) OCH_2Me; (*e*) ax 3,5-H; and (*f*) OCH_2Me. Differing degrees of expansion have been used.



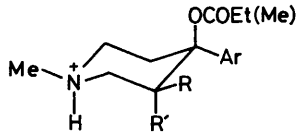
(**9**)



(**10**)

Details of the duplication of the ^{1}H n.m.r. signals of (**1c**)·HCl are shown in Table 1, and the epimer ratio calculated to be *ca.* 2.2:1 from integration of the *N*-methyl and 4-methyl signals. The major epimer had the higher field *N*-methyl resonance [moved upfield by the contribution from the axial *N*-methyl conformer (**9b**)], axial 2,6-H signal [these protons are subject to aromatic shielding in conformation (**9a**)], and axial 3,5-H signals [protons deshielded by axial 4-methyl in epimer (**10**)].[15] Similar n.m.r. results were found for the HCl of the *O*-methyl derivative of (**1c**) with the addition of duplicate OMe proton signals (3.81 and 3.80 ppm).

4-Arylpiperidines with C-4 *Linked to an Oxygen Function.*— N.m.r. data on hydrochlorides of the reversed ester of pethidine (**2a**) and its 4-*m*-hydroxyphenyl and 4-acetoxy analogues, and of α-(**2b**) and β-(**2c**) prodine in D_2O are presented in Tables 1 and 2. In all cases spectra were consistent with the preponderance of one *N*-protonated solute species which, from computational,[5] *X*-ray crystallographic (prodines),[16] and n.m.r. studies of *t*-2-Me, *r*-4-Ar analogues with a preferred axial 4-aryl conformation,[17] is undoubtedly an equatorial *N*-methyl-4-phenyl chair (**11**). In the case of the reversed ester of pethidine (**2a**) and its 4-acetoxy analogue, the ^{1}H n.m.r. spectra gave evidence of the presence of a minor epimer from low intensity signals due to acyl and *N*-methyl protons, and unresolved multiplets close to the major ring proton resonances. *N*-Methyl signals of (**2a**) were in the ratio 100 (2.93 ppm):7 (2.89 ppm) (other minor signals could not be quantitated accurately). From ^{1}H n.m.r. spectral data, alphaprodine (**2b**) prefers exclusively the chair conformation (**11**; R = Me, R^1 = H), as does betaprodine



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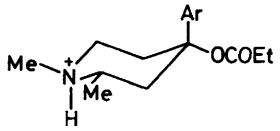

(12)

(**2c**). Coupling constant magnitudes show that the equatorial 4-phenyl chair (**11**; R = H, R^1 = Me) is maintained even when an axial 3-methyl substituent is present.

The 1954 proposal[18] that pethidine adopts a conformation which mimics the 4-arylpiperidine fragment of morphine at the opioid receptor received no support from subsequent structure–activity relationship studies and conformational analyses directed, chiefly, at the reversed ester of pethidine and its analogues.[19] The results of the present n.m.r. analyses together with the computations of Froimowitz[5] not only revive interest in the original concept, but also corroborate the view (based on differing structure–activity studies) that pethidine, ketobemidone, and related 4-arylpiperidine analgesics with C-4 carbon substituents differ from ligands of the reversed ester type in their mode of binding to opioid receptors. Whether differences in binding of the two classes arise from conformational factors as discussed or may be attributed to differential influences of the C-4 carbon and oxygen substituents remains to be established. The fact that the 2-methyl analogue of the reversed ester of pethidine, with a preferred axial 4-aryl chair conformation (**12**), lacks the antinociceptive properties of its 4-phenyl parent,[17] indicates that the nature of the non-aryl 4-substituent is the determinant factor, as does also the similar influence of a 3-methyl substituent on the action of pethidine and its reversed ester (potency raised by 3-methyl *cis* to 4-Ph, little changed by *trans* 3-Me in each case).[19]

Acknowledgements

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