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Stereochemical Studies of the 4-Alkyl-4-Arylpiperidine Class of Opioid Ligand

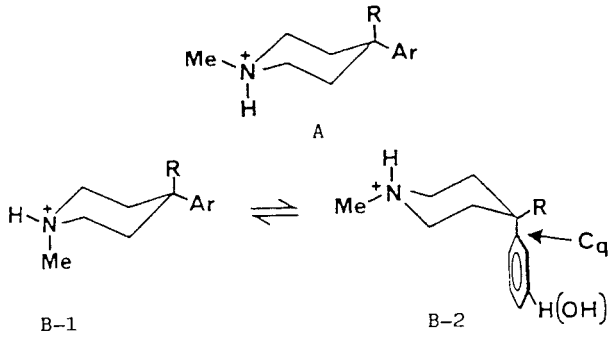
A. F. Casy,* G. H. Dewar and Omar A. A. Al-Deeb
School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK

The ^{1}H (270, 400 MHz) and ^{13}C (67.5 MHz) NMR spectra of some 4-methyl- (also 4-*n*-propyl- and -isobutyl)-4-(3-hydroxy- and 3-methoxy-phenyl)piperidines and their 3-methyl diastereoisomers are reported. Many of the compounds had opioid ligand activities. The data were analysed in terms of preferred conformation and configuration (3-methyl derivatives). Only compounds with preference for axial 4-aryl chair conformations displayed marked agonist properties and the one potent antagonist, *cis*-1,3,4-trimethyl-4-(3-hydroxyphenyl)piperidine, favoured an equatorial 4-aryl chair.

KEY WORDS 4-Alkyl-4-arylpiperidines Opioid ligands ^{1}H NMR ^{13}C NMR Stereochemistry Conformational analysis

INTRODUCTION

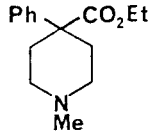
There is much recent interest in opioid ligands based on 4-alkyl-4-arylpiperidines (where aryl = 3-hydroxyphenyl), a group which includes both agonists and antagonists.[1–3] This study was undertaken to establish the stereochemistry (configuration and solute conformation) of such agents in an attempt to identify steric characteristics which may govern their pharmacological activity. Previously we have examined the conformational equilibria of hydrochloride salts of pethidine (**1**), ketobemidone (**2a**) and the 4-methyl derivative **2b** in D_2O by analysis of their ^{1}H and ^{13}C NMR spectra.[4] Interpretation of the data in terms of mixtures of protonated epimers at equilibrium was justified by pK_a evidence of the extensive protonation (>95%) in water of piperidine bases of this kind, and the fact that spectral appearance did not change with time. The equatorial 4-aryl chair conformer A proved to be the major protonated epimer of pethidine and ketobemidone, and the minor form in the case of **2b**.



RESULTS AND DISCUSSION

In this paper we extend our studies of 4-alkyl-4-arylpiperidines to include the 4-*n*-propyl (**2d**) and 4-isobutyl (**2e**) derivatives, together with diastereoisomeric pairs of the 3-methylpiperidines **3a–f**. The ^{1}H and ^{13}C NMR spectra of **2d**, **2e** and **2f** hydrochlorides in D_2O displayed well resolved duplicate resonances typical of binary epimeric mixtures (Tables 1 and 2). Evidence that the major epimer is the axial 4-aryl chair B-2 and the minor the 4-equatorial aryl chair A is provided by the relative intensities of the following:

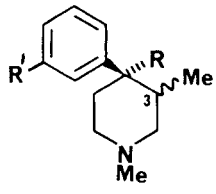
1. the two aromatic Cq (C-1′) resonances: the more intense higher field signal (143.5 ppm) is assigned to the more sterically polarized Cq of B-2 and the less intense lower field signal (148.5 ppm) to Cq of A;[5]
2. the two α-carbon resonances of the 4-R substituent (higher field in the *minor* epimer A);[6]
3. the two *N*-methyl proton resonances: the contribution of B-1 to the conformational equilibrium moves the *N*-methyl chemical shift upfield (in general axial *N*-methyl protons resonate to high field of related equatorial protons in piperidine derivatives);[7,8] and



1

2

	R	R′
2a	COEt	H
2b	Me	H
2c	Me	Me
2d	*n*-Pr	H
2e	*i*-Bu	H
2f	*i*-Bu	Me



3

	R	R′
3a	Me	OH
3b	Me	OMe
3c	*n*-Pr	OH
3d	*n*-Pr	OMe
3e	*i*-Bu	OH
3f	*i*-Bu	OMe
3g	Me	H

* Author to whom correspondence should be addressed.

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Table 1. ^{13}C NMR chemical shifts of some 4-alkyl-4-arylpiperidines[a]

Compound and solvent	C-2,6	C-3,5	C-4	4-R CH_2CH_2CH	Me(Me_2)	*N*-Me	Ar C-1′	Ar C-3′
2d (4-*n*Pr), base in $CDCl_3$	52.0	34.8	39.0	α52[b] β16.6	14.5	45.7	147.1	157.3
2d, HCl in D_2O	51.3 (50.1)	32.3 (31.3)	38.4 (36.7)	α46.9 (37.4) β15.9 (16.1)	13.5	42.6 (42.1)	143.6 (148.5)	155.9 (155.5)
2f (4-*iso*-Bu),[c] base in $CDCl_3$	52.0	36.1	39.3	α52 β23.6	24.75	46.0	∼148	∼160
2f,[c] HCl in D_2O	51.0 (53.8)	33.1 (32.2)	38.8 (∼37)	α50.0 (43.7) β ∼ 24	24.1 (23.0)	42.6 (42.1)	143.6[d]	159.3[d]
2e, base in $CDCL_3$	51.9	35.5	39.3	α51.9 β23.8	24.9	45.7	∼148	157.2
2e, HCl in D_2O	51.0 (53.7)	33.0 (32.1)	38.7 (36.8)	α50.1 (43.7) β23.0 (23.5)	24.06 (23.8)	42.7 (42.1)	143.3 (148.4)	156.0 (155.5)

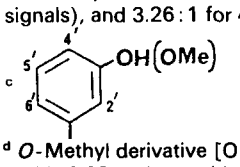
[a] In ppm from TMS [methanol (48.45 ppm), internal reference]; values in parentheses refer to the minor component of epimeric pairs.
[b] Overlaps C-2,6 signal.
[c] *O*-Methyl derivative (OMe base, 54.8 ppm; HCl salt, 55.0 ppm).
[d] Epimeric resonances not resolved.

Table 2. ^1H NMR characteristics of some 4-alkyl-4-arylpiperidines[a,b]

Compound and solvent	H-2,6	H-3,5	*N*-Me	R $CH_2CH_2(CH)$	$Me(Me)_2$	Aryl protons[c]
2d (4-*n*-Pr), HCl in D_2O	eq: 3.35 brd, 12.5 (3.42 brd, 12.5) ax: 2.69 brt, 13.0, (3.24 brt, 13.0)	eq: 2.48 brd, 14.8 (2.18 brd, 15) ax: 1.81 dt, 14.3, 14.3, 2.5 (2.14 dt, 14.3, 14.3, 2.5)	2.63 s (2.89 s)	α1.33 m (1.62 m) β0.8 m	0.53 t, 7 (0.61 t, 7)	5′: 7.19 t, 7.7 (7.10 t, 8) 6.73–6.8 m 4′: (6.7 dd, 8, 2)
2f (4-*i*-Bu),[d] HCl in D_2O	eq: 3.43 brd, 12.5 (minor not resolved) ax: 2.78 brt, 12.5 (3.34 brt, 12.5)	eq: 2.56 brd, 14.6 (2.26 brd, 14.5) ax: 1.95 brt, 14.4 (2.04 brt 14.4)	2.71 s (2.96 s)	α1.42 approx. d, 4.9 (1.74 br m) β1.29 m	0.49 d, 6.4 (0.56 brd)	5′: 7.29 t, 7.9 (7.15 brt) 6′: 6.92 d, 7.6 2′: 6.88 brs 4′: 6.82 d, 7.9 (6.68 brd)
2e, HCl in D_2O	eq: 3.37 brd, 12.5 (3.43 brd, 12.5) ax: 2.75 brt, 12.5, (3.26 brt, 12.5)	eq: 2.53 brd, 14.6 (2.21 brd, 14.9) ax: 1.88 dt, 14.2, 14.2, 4 (1.91 dt, 14.2 14.2, 4)	2.67 s (2.91 s)	α1.38 d, 5.5 (1.68 d, 5.5) β1.26 m	0.49 d, 6.7 (0.54 d, 6.7)	5′: 7.19 t, 7.9 (7.10 t, 7.9) 2′: 6.83 brs 6.80–6.75 m 4′: (6.71 dd, 8, 2)
2f (4-*i*-Bu),[d] MeI in DMSO-d_6	Unres.	Unres.	3.18 s[e] 3.02 s	α1.58 brs β1.28 m	0.58 d, 6.7	5′: 7.30 t, 7.9 6′: 6.99 d, 8 2′: 6.93 brs 4′: 6.84 dd, 8, ∼2

(TMS as reference)

[a] Chemical shifts in ppm from DSS (D_2O), coupling constants or line separations (Hz) follow signal descriptions. Abbreviations: br, broad; *s*, singlet; d, doublet; t, triplet; m, multiplet, plus combinations, e.g. dt, doublet of triplets; eq, equatorial; ax, axial. Most data recorded at 400 MHz.
[b] Data in parentheses refer to minor component of epimeric pairs. Ratios for 4-*n*-Pr derivatives were 2.85:1 (*N*-Me, eq H-3,5, α-CH_2, γ-Me signals), and 3.26:1 for 4-*i*-Bu derivatives (HAr-5′, eq H-3,5, αCH, γMe_2 signals).



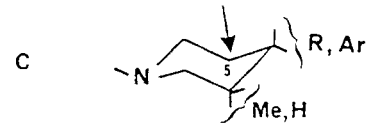
[d] *O*-Methyl derivative [OMe: 3.76 s (3.70 s)].
[e] *3.20, 3.03 in the methiodide of* **2c** (4-Me 1.26 s).

4. the two equatorial H-3,5 signals: the protons giving rise to the more intense lower field signal (2.55 ppm) will be deshielded by 4-Ar when conformation B-2 is favoured.[9,10]

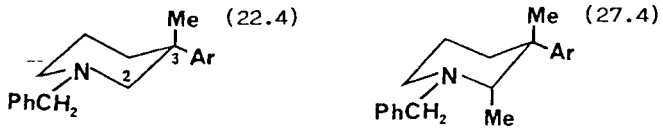
Integration of the better resolved pairs of proton resonances (for details, see Table 2, footnote b) gave epimeric ratios of 2.85:1 for the 4-*n*-propyl and 3.26:1 for the 4-isobutyl derivatives in favour of epimer B (cf. 2.2:1 for the 4-methyl derivative **2b**).[4]

3-Methyl derivatives

Diastereoisomeric pairs of the 3-methylpiperidines **3a–f** were isolated in all cases by fractional crystallization of the hydrochloride salts of either the 4-(3-methoxyphenyl) or 4-(3-hydroxyphenyl) derivatives. ^{13}C and ^{1}H NMR characteristics of bases and HCl salts are given in Tables 3 and 4, respectively. The conformational preferences of the 3-methyl substituents were established from (1) comparative ^{13}C chemical shifts of C-5 of the major and minor isomer and the des-3-methyl derivative (when 3-methyl is axial the C-5 chemical shift moves

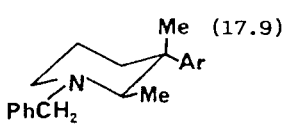


upfield as a result of steric polarization, see C[5,6]) and (2) coupling magnitudes of the H-3 proton signal after decoupling the 3-methyl resonance (values diagnostic of axial or equatorial protons were observed).[11] NOED experiments, as used successfully in the analysis of 3-aryl-3-piperidine spectra,[6] failed to give unequivocal results in the case of several of the **3** derivatives, presumably owing to rapid chair–chair interconversion rates. Assignment of the 4-alkyl/4-aryl conformational preferences of the diastereoisomers **3** (and concomitant elucidation of configuration) was therefore based on the NMR features of the aromatic Cq (C-1′) and 4-$\underline{CH_2}$R (α) signals, as already outlined for the des-3-methyl derivatives (**2**), supplemented by evidence of the influence of vicinal *cis* (D) and *trans* (E) methyl on the ^{13}C chemical shifts of axial 4-methyl as derived from studies of 3-aryl-2,3-dimethylpiperidines (see **4a–4c**).[6]



^{13}C chemical shifts (ppm) in parentheses; Ar = 3—OMe—C_6H_4

4a 4b

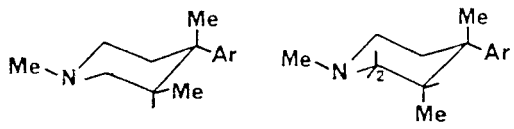


4c

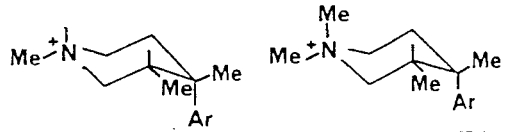
Computational studies have shown that equatorial 4-aryl chairs are favoured in derivatives of type **3a** over their invertomers, at least in the case of bases.[12] As will be described, supporting evidence of stereochemistry was derived from the aromatic proton resonance pattern, and observation of epimeric mixtures in the case of *cis*-**3a** and *trans*-**3c** and **-3e** hydrochlorides (configurational terms *cis* and *trans* refer to 3-Me and 4-Ar).

3,4-Dimethyl derivatives (3a, 3b and 3g)

^{13}C Cq (C-1′), 4-methyl and C-5 chemical shifts (Table 3) and the appearance of the H-3 resonances after irradiation of the 3-methyl signal (broad singlet for major, dd of separations 3.8 and 13.6 Hz for minor) characterize the major isomer as the *cis* derivative E (Ar = 3-OH/OMe-C_6H_4) and the minor as the *trans* form D (Ar = 3-OH/OMe-C_6H_4). Further ^{1}H NMR evidence was derived from the relative 3-Me/4-Me chemical shifts (both at lower field in the spectra of *E* because of mutual deshielding[13]) and analysis of the ring proton signals, e.g. axial H-2 minor isomer 3.2 ppm (t) with two large separations; major broad doublet downfield of 3.2 ppm, deshielded by axial 3-Me.[14] It was noted that the aromatic ^{1}H signals of the major **3a** hydrochloride were at higher field than the corresponding signals of the minor isomer. This fact proved of empirical value to the assignment of isomers **3c** and **3e** (see Fig. 1, and later).



D E



(Ar = 3—OH—C_6H_4) (Ar = 3—OH—C_6H_4)

5 6

The presence of both epimers of *cis*-**3b**·HCl was evident from its ^{1}H NMR spectrum in $CDCl_3$ (ratio *ca.* 2:1; much greater in D_2O); the minor epimer favours conformation **5** as judged from H-3, 3-Me and *N*-Me NMR characteristics (Table 4). The NMR spectrum of the methiodide of the major isomer of **3b** also provided evidence for its *cis* configuration and indicated that the axial 4-aryl chair **6** was its preferred conformation in DMSO-d_6/$CDCl_3$ (see ^{13}C C-1′ and C-5, and ^{1}H *N*-Me chemical shifts).[8]

When 4-phenyl analogues of **3a** were prepared, only the *cis* isomer was isolated. It had NMR features close to those of *cis*-**3a** and a sample provided by Dr D. M. Zimmerman.

3-Methyl-4-*n*-propyl and 3-methyl-4-isobutyl derivatives

The stereochemical characterization of the isomeric diastereoisomers of **3c** and **3e** was possible by similar methods to those used with the 4-methyl derivatives (in particular see Tables 3 and 4 for details of ^{13}C C-1′, C-5, 4-αCH_2R and H-3 resonances). The aromatic proton resonance features provided further evidence. Thus, those of the major isomer of **3c/d** were upfield of signals of the minor isomer and close to those of *cis*-**3a**;

Table 3. ^{13}C NMR chemical shifts of some 4-alkyl-4-aryl-3-methylpiperidines[a]

Compound and solvent	C-2	C-3	C-4	C-5	C-6	C-4-alkyl	C-3-Me	*N*-Me	Ar C-1′	Ar C-3′
4-Methyl series:										
cis-**3b** (OMe), base in $CDCl_3$	58.4	38.7	37.9	30.6	52.1	27.3	16.3	46.5	151.8	159.4
cis-**3b** (OMe), HCl in D_2O	56.0	36.1	36.6	26.9[b]	50.4	25.7[c]	14.0	43.4	149.4	158.9
cis-**3b**, methiodide in $CDCl_3$ + DMSO-d_6	64.2	35.5	37.5	31.7[d]	59.3	28.7	14.1	50.2[d] (ax) 54.9[d] (eq)	143.5	158.7
cis-**3a**, base in $CDCl_3$	58.4	38.7	37.7	30.6	52.0	27.3	16.0	46.2	151.0	156.4
cis-**3a**, HCl in D_2O[e]	56.2	36.0	36.4	26.7	50.6	25.4	13.6	43.2	149.0	155.4
trans-**3a**, HCl in D_2O	55.8	36.4	36.6	37.7	50.8	14.0[f]	11.7[f]	42.9	149.0	155.4
cis-**3g**, HCl in D_2O[g]	56.7	36.4	36.8	27.1	51.0	26.0	14.2	43.5	~148	—
4-n-Propyl series:										
cis-**3d** (OMe), base in $CDCl_3$	58.4	39.0	41.3	26.4	51.9	αCH$_2$ 40.2 βCH$_2$ 16.6 γMe 14.6	16.4	46.6	149.7	159.3
cis-**3c**, base in $CDCl_3$	58.4	39.4	41.2	26.3	51.7	αCH$_2$ 40.0 βCH$_2$ 16.9 γMe 14.7	16.3	46.6	149.1	156.6
cis-**3c**, HCl in D_2O	56.0	36.4	39.9	23.0	50.2	αCH$_2$ 38.3 βCH$_2$ 16.2 γMe 13.4	13.7	43.2	147.3	155.5
trans-**3c**, base in $CDCl_3$	59.2	38.9	42.0	32.7	52.0	αCH$_2$ 32.7[h] βCH$_2$ 16.4 γMe 13.7	14.6	46.2	148.1	159.3
trans-**3c**, HCl in D_2O	55.6 (57.3)	39.5 (31.7)	40.8 (40.7)	27.0 (40.0)	50.3 (51.3)	αCH$_2$ 42.4 (26.5) βCH$_2$ 16.1 (15.5) γMe 13.4 (13.2)	12.4 (11.1)	43.0 (42.7)	144.9 (146.4)	155.7 (155.3)
4-Isobutyl series:										
trans-**3f** (OMe), base in $CDCl_3$	59.6	38.7 broad	42.6	31.9	52.1	αCH$_2$ 31.9[h] βCH 23.8 γMe$_2$ 24.9, 24.8	14.7	46.4	148.1	159.3
cis-**3f** (OMe), base in $CDCl_3$	58.3	39.6	41.4	26.6	52.0	αCH$_2$ 46.0 βCH 24.0 γMe$_2$ 24.4, 24.7	16.25	46.3	149.5	159.3
trans-**3f** (OMe), HCl in D_2O	57.3 (55.7)	33.0 (40.5)	41.1 (41.3)	30.2 27.4	51.2 (50.6)	αCH$_2$ 49.2 (32.3) βCH 22.8 (23.6) γMe$_2$ 23.9 (23.7) 23.6 (22.9)	13.0 (11.5)	43.3 (42.8)	144.4 (146.5)	159.2 (158.5)
trans-**3e**, base in $CDCl_3$	59.3	38.9 br	42.3	31.6	52.3	αCH$_2$ 31.6[h] βCH 23.9 γMe$_2$ 24.9	14.5	46.1	147.9	156.8
cis-**3e**, base in $CDCl_3$	58.3	39.9	41.3	26.4	51.9	αCH$_2$ 45.8 βCH 24.3 γMe$_2$ 25.2, 24.6	16.2	46.5	149.0	156.6
trans-**3e**, HCl in D_2O	57.4 (55.8)	33.0 (40.6)	40.9 (41.2)	27.5 (30.2)	51.3 (50.7)	αCH$_2$ 49.2 (32.4) βCH 23.6 (22.8) γMe$_2$ 23.9 (23.7)	13.0 (11.5)	43.2 (42.8)	144.5 (146.5)	155.8 (155.2)

Table 3 (*continued*)

Compound and solvent	C-2	C-3	C-4	C-5	C-6	C-4-alkyl	C-3-Me	*N*-Me	Ar C-1′	Ar C-3′
cis-**3e**, HCl in D_2O	56.2	37.3	40.0	23.35	50.6 αCH_2	44.3	13.65	43.2	147.5	155.3
					βCH	23.7				
					γMe_2	23.8				

[a] Footnote a in Table 1 applies.
[b] Value in 3-desmethyl analogue 33.7 (33.6).[4]
[c] Value in 3-desmethyl analogue 23.4 (equatorial 4-aryl chair epimer).[4]
[d] Broad signal, as often encountered with methiodide ^{13}C NMR spectra.[8]
[e] Some low-intensity epimeric signals also seen.
[f] Higher field values of *trans* isomer are evidence of a *gauche* interaction between 3-Me and 4-Me.
[g] 4-Phenyl analogue of *cis*-**3a**; spectrum similar to that of sample LY109836 supplied by Dr D. M. Zimmerman.
[h] Overlaps C-5 resonance.
[i] From spectrum of a *cis–trans* mixture.

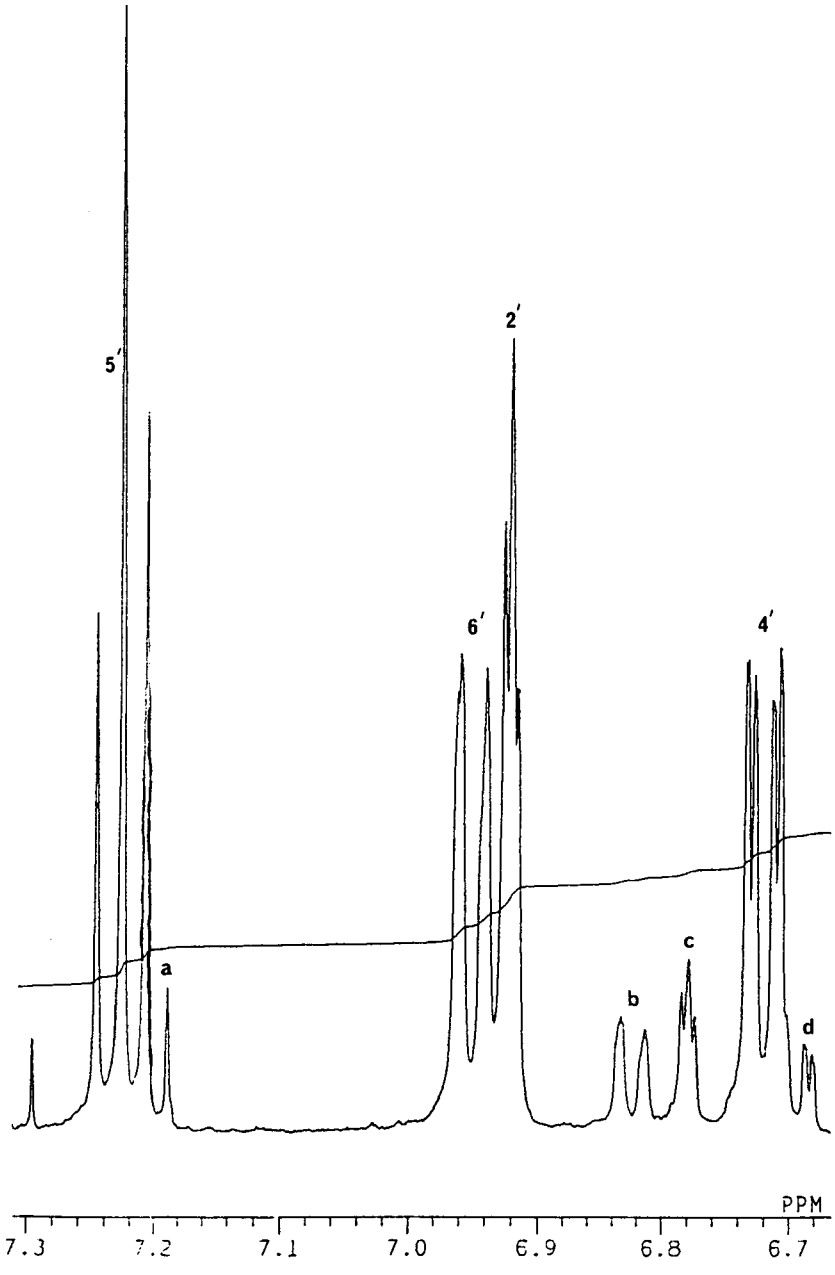
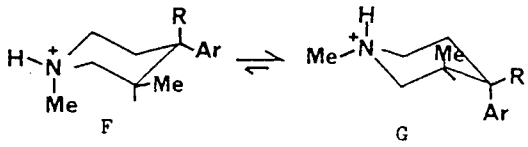


Figure 1. Part of the 400 MHz ^1H NMR spectrum of *trans*-1,3-dimethyl-4-(3-methoxyphenyl)-4-*n*-propylpiperidine (**3d**) containing a small amount of the corresponding *cis* diastereoisomer. Aromatic proton signals of the major component are numbered. Minor signals: a (highest field line of 5′ t); b, 6′; c, 2′, d (higher field half of 4′ dd). Solvent: $CDCl_3$.

when the 4-isobutyl isomers (**3e/f**) were compared, the major aromatic signal corresponded with those of *trans*-**3a**. NMR spectra of *trans*-**3c** and *trans*-**3e** displayed signal duplication indicative of binary epimeric mixtures, which was not seen in the spectra of related *cis* isomers. This result may be anticipated for *trans* isomers **3** with bulky substituents at C-4 (larger than methyl, see above), since the equatorially protonated epimer F may invert to G with relief of non-bonded



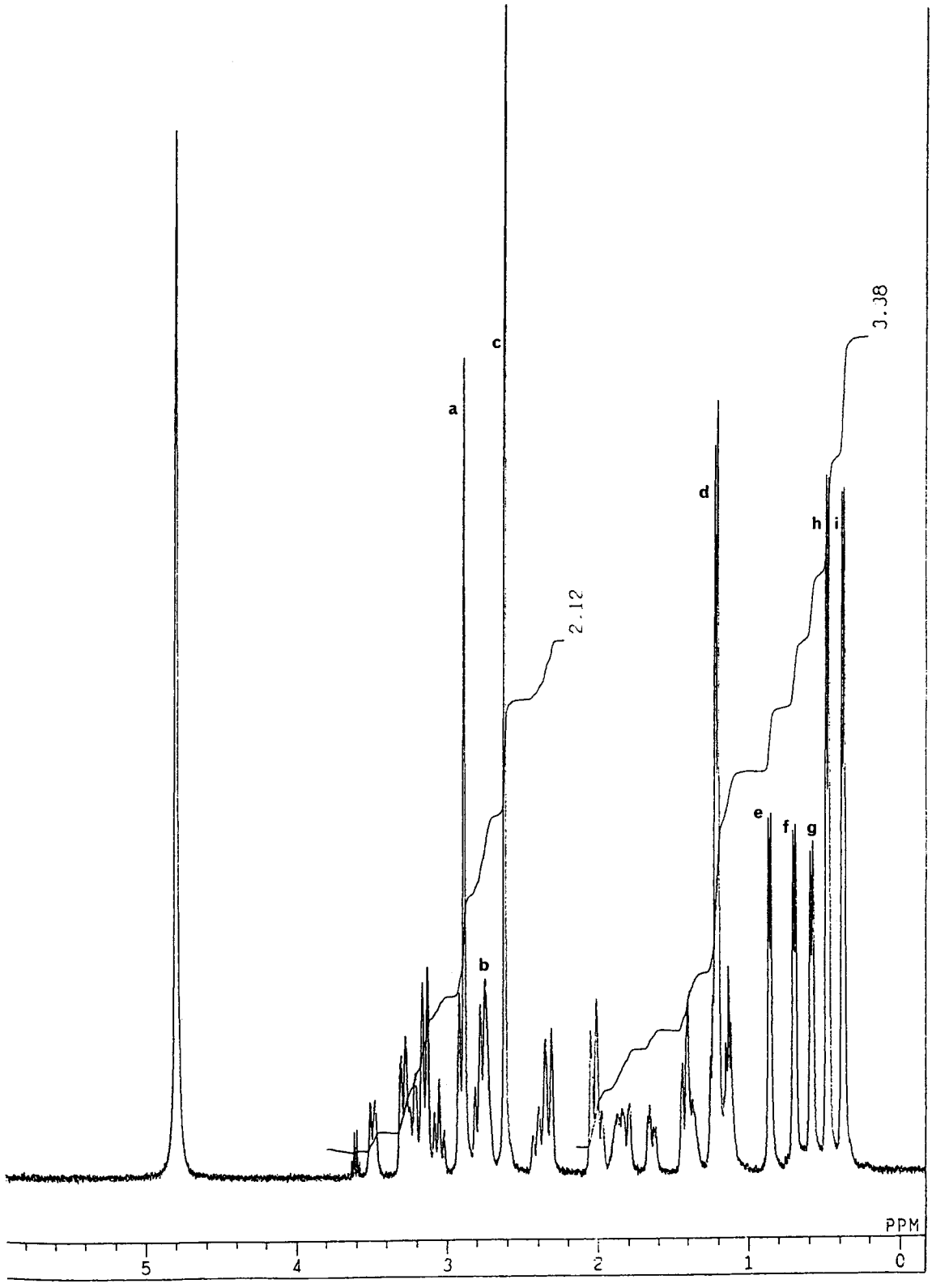


Figure 2. Part of the 400 MHz ^{1}H NMR spectrum of *trans*-1,3-dimethyl-4-(3-hydroxyphenyl)-4-isobutylpiperidine (**3e**) hydrochloride in D_2O. Annotated epimeric resonances: a, c, *N*-Me; b, multiplet including major H-3; d, major 3-Me; e, f, minor $CH_2CH\underline{Me}_2$; g, minor 3-Me; h, i, major $CH_2CH\underline{Me}_2$.

Table 4. ^{1}H NMR characteristics of some 4-alkyl-4-aryl-3-methylpiperidines[a]

Compound and solvent	H-2	H-3	H-5	H-6	3-Me	4-R	*N*-Me	Aryl protons
4-Me series:								
cis-**3b** (OMe),[b] base in $CDCl_3$	Unres.	1.95–2.05 m	ax: unres. eq. 1.6 brd	Unres.	0.79 d, 7.1	1.3 s	2.27 s	5′: 7.22 t, 8.1 6′: ~6.9 *dt*, 7.7 2′: ~6.85 t, 2.2 4′: ~6.7 ddd, 8, 2, <1
cis-**3b** (OMe), HCl in D_2O	ax: 3.47 brd, 11 eq: 3.25 brd, 13.5	Unres.	ax: unres. eq: 1.94 brd (14.7)	Unres.	0.70 d, 7.3 (0.60)	1.37 s (1.34 s) int. ratio 27:2.5	2.86 s (2.76) int. ratio 28:1	5′: 7.33 t, 7.9 6′: 6.96 brd, ~8 2′, 4′: 6.84–6.92 m
3b · HCl in $CDCl_3$[c]	Unres.	2.3 m, eq[d] (2.7 m, ax)[e]	Unres.	Unres.	1.05 d, 7 (1.25 d, 7)[f] int. ratio 10:7	1.45 s (1.42) s int. ratio 10:6	~2.9 d, 4–5 (~2.7 d, 4–5)	7.26–7.3 m 6.76–6.96 m
3b · MeI in DMSO-d_6 $CDCl_3$ (TMS as reference)	Unres.	2.05 m (overlaps another signal)	ax: ~1.75 brt	Unres.	0.73 d, 7	1.08 s	3.12 s, eq 2.99 s, ax[g]	5′: 6.88 t, 7.9 6′: 6.52 dd, 2, 8 2′: 6.43 t, 2.1 4′: 6.39 dd, 7.9, 2.4
cis-**3a**,[h] HCl in D_2O	3.45–3.55 m	2.3–2.45 m, eq[d]	eq: 1.9 brd, 15 ax: 2.3–2.45 m	3.1–3.32 m	0.69 d, 7.3 (1.12 d, 6.1)	1.34 s (1.31 s) int. ratio 86:7	2.85 s (2.75 s) int. ratio 100:7	5′: 7.24 t, 7.9 6′: 6.87 brd, 7.9 2′: 6.79 t, 2.5 4′: 6.73 dd, 7.3, 2.5 (epimer signals nr 6.9 and 7.0)
trans-**3a**, HCl in D_2O	ax: 3.01 t, 12.6 eq: 3.16–3.45 m	2.42 m, ax[i]	ax: 2.08 dt, 15, 15, 6 eq: 1.66 dt, 15, 2, 2	ax: 3.20 t, 13, 13, 3 eq: 3.16–3.45 m	0.59 d, 6.7	1.29 s	2.88 s	5′: 7.26 t, 8.0 6′: ~7.2 brd, 7.9 2′: 6.93 t, 2.2 4′: ~6.77 dd, 7.9, 2.4
cis-**3g**,[j] HCl in D_2O	3.3–3.4, 3.45–3.6 m	2.4–2.55 m[d]	ax: 2.4–2.55 m eq: 1.99 brd, 14.7	ax: 3.3–3.4 m eq: 3.45–3.6 m	0.73 d, 7.3 (0.60 d, 7.1) int. ratio 74:11	1.41 s (1.37 s) int. ratio 80:10	2.91 s (2.75) s	7.25–7.55 m
4-n-Pr series:								
cis-**3d** (OMe),[b] base in $CDCl_3$[k]	ax: 2.48 brd, 12 eq: 2.58 dd, 12, 3	1.95 m[d]	ax: 1.37 dt, 13,13, 4 eq: 1.78 brd, 12	ax: 2.2m eq: 2.76 brd, 12	0.73 d, 6.8	αCH_2 2.2 m βCH_2 0.63–1.05 m γMe 0.77 t, 7.2	2.27 s	5′: 7.21 t, 8 6′: 6.82 brd, 8 2′: 6.78 t, 2 4′: 6.7 ddd, 8, 2, >1
cis-**3c**, base in $CDCl_3$	ax: 2.6 brd, 12 eq: 2.7 dd, 12, 3	1.95 m[d]	ax: 1.4 dt, 13, 13, 4 eq: 1.8 brd, 12	ax: 2.2 m eq: 2.9 brd, 12	0.67 d, 7	αCH_2 2.2 m βCH_2 1.06–1.22 m γMe 0.76 t, 7.1	2.32 s	5′: 7.1 t, 7.9 6′: 6.73 brd, 7.9 2′: 6.65 t, ~2 4′: 6.60 dd, 7.9, 2

cis-**3c**, HCl in D_2O	ax: 3.46 brd, ∼13 eq: 3.3 brd, ∼13	2–2.4 m	ax: 1.52 dt, 13.5, 13.5, 3 eq: 2–2.4 m	ax: 3.23 dt, 13 13, 3.7 eq: 3.59 dd, 13, 2.6	0.72 d, 7.1	αCH_2 2–2.4 m βCH_2 0.45–0.9 m γMe 0.71 t, 6.6	2.83 s	5′: 7.1 t, 7.9 6′: 6.85 brd, 7.9 2′, 4′: 6.7–6.8 m
trans-**3c**, HCl in D_2O[l]	Unres.	2.76 m[m]	Unres.	Unres.	0.63 d, 7.0 (1.24 d, 7.3)[m]	αCH_2 unres. βCH_2 unres. γMe 0.98 t, 6.8 (0.69 t, 6.8)	2.85 (2.6) int. ratio 76:74	5′: 2 t near 7.3, ∼8 6′: overlapping d near 7.0 2′: 6.9 brs 4′: 2 d near 6.81, ∼8
4-i-Bu series:								
trans-**3f**, (OMe),[b] base in $CDCl_3$	Unres.	Unres.	Unres.	Unres.	0.96 d	αCH_2 unres. βCH unres. γMe_2 0.71 d, 6.6	2.19	5′: 7.2′ t, 7.9 6′: 6.98 d, 8.2 2′: 6.96 brs 4′: 6.72 dd, 8, ∼2
trans-**3f**, (OMe)[b] HCl in D_2O[l]	Unres.	∼2.7 m (∼1.8 m)	Unres.	Unres.	1.24 d, 7.3 (0.61, d, 6.7)	αCH_2 unres. βCH unres. γMe_2 0.39, 0.48 d, 6.7 (0.89, 0.72 d, 6.7)	2.63 s (2.90 s)	5′: 7.30 t, 7.9 (7.22 t, 8.2) 6′: 6.97 d, 7.6 (7.0 d, 7.6) 2′: 6.98 brs (6.94 brs) 4′: 6.85 dd, 8, ∼2 (6.77 dd, 8, ∼2)
trans-**3e**, base in $CDCl_3$	Unres.	Unres.	Unres.	Unres.	0.87 brs	αCH_2 unres. βCH unres. γMe_2 0.71 d, 6.4	2.24 s	5′: 7.12 t, 8 6′, 2′: 6.82–6.9 m 4′: 6.63 dd, 8, ∼2
cis-**3e**, base in $CDCl_3$	Unres.	1.9 m[d]	Unres.	Unres.	0.63 d, 7.0	αCH_2 2.16, 1.43 dd, 14, 4.5 βCH 1.3 m γMe_2 0.47, 0.85 d, 6.7	2.32 s	5′: 7.11 t, 8 6′: 6.75 d, 8 2′: 6.68 brs 4′: 6.61 dd, 8, ∼2
trans-**3e**, HCl in D_2O[l]	Unres.	∼2.8 m (∼1.9 m)[n]			1.21 d, 7.3 (0.58 d, 7.0)	αCH_2 unres. βCH unres. γMe_2 0.38, 0.48 d, 6.4 (0.86, 0.70 d, 6.4)	2.62 s (2.89) s	5′: 7.20 t, 7.9 (7.13 t, 7.9) 2′, 6′: 6.84–6.96 m 4′: 6.75 brd, ∼8 (6.72 brd, ∼8)
cis-**3e**, HCl in D_2O	ax: 3.58 dd, 13, 4 eq: 3.26 d, 12.5	2.26 m[d]	Unres.	ax: 3.25 dt, 12.5, 12.5, 4.5 eq: 3.46 brd. ∼13	0.67 d, 7.3	αCH_2 2.12, 1.15 dd, 15, 5 βCH 1.2 m γMe_2 0.41, 0.79 d, 6.7	2.85 s	5′: 7.24 t, 8 6′: 6.89 d, 8 2′: 6.80 brs 4′: 6.74 dd, 8, ∼2

[a] Footnote a of Table 2 applies; unres., unresolved.
[b] OMe s ∼ 3.8.
[c] Evidence of epimeric mixture (minor features in parentheses) including duplicate NH (11.5, 12.4 brs) and OMe (∼3.8) signals.
[d] Collapsed to, or appearance of, brs when Me d irradiated.
[e] Collapsed to dd (∼12, 5) when 1.25 Me d irradiated.
[f] Relation to H-3 resonances established by COSY experiment.
[g] Cf. values 3.18 and 3.02 for methiodide of **2f** (Table 2).
[h] Some low intensity duplicate signals present.
[i] Collapsed to dd, 13.6, 3.8 when 0.59 Me d irradiated.
[j] 4-Phenyl analogue, minor features in parentheses.
[k] Isolated from oxalate salt which separated from *cis–trans* mixture.
[l] Epimer signals in parentheses.
[m] 2.76 m and 1.24 d linked by spin decoupling experiment; brs emerged from 2.76 m when 1.24 d irradiated.
[n] 2.8 m and 1.21 d linked by COSY and decoupling experiments; brs emerged from 2.8 m when 1.21 d irradiated.

interactions of R (ax → eq) and removal of the Me/Ar interaction. In contrast, the corresponding pair of *cis* invertomers are both unfavoured (one by 1,3-diaxial methyl and the other by 3-Me/4-Ar and 3-Me/4-R interactions).

Part of the ^{1}H NMR spectrum of *trans*-**3e**·HCl is shown in Fig. 2. Assignment of duplicate 3-Me and terminal 4-$CH_2\underline{CHMe_2}$ (two sets of doublet pairs) was aided by COSY and decoupling experiments. The principal epimer was identified as G (R = *i*-Bu) on the basis of its *N*-Me and H-3 chemical shifts (H-3 is deshielded by 4-Ar in G and has a notably low-field resonance) and ^{13}C NMR features, especially those of C-5, 3-Me and 4-$\underline{CH_2}CHMe_2$. In G the 4-R protons will fall within the aromatic shielding zone as the group R rotates about its bond to C-4 (see also B-2), a consideration which accounts for the greater intensity of the higher field pair of terminal methyl resonances in the spectrum in Fig. 2. Epimeric ratios were approximately 1:1 for *trans*-**3c** and 2:1 (1.6–2.3) for *trans*-**3e** hydrochlorides from integrals of a variety of ^{1}H NMR signals.

Details of the opioid ligand activities of phenolic compounds **2d** and **2e** and the diastereoisomers **3a**, **3c** and **3e** are reported elsewhere.[15] It is significant that only derivatives with favoured axial 4-aryl chair conformations displayed agonist activities, while the single notable antagonist identified was *cis*-**3a** with a preferred equatorial 4-aryl conformation.

EXPERIMENTAL

The preparation of compounds **2d** and **2e** and diastereoisomers **3a–f** is reported elsewhere.[15]

Methiodides of **2c**, m.p. 235–236 °C (found, C 49.75, H 6.75, N 3.8; $C_{15}H_{24}NOI$ requires C 49.9, H 6.7, N 3.9%), **2f**, m.p. 203 °C (found, C 53.8, H 7.6, N 3.4; $C_{18}H_{30}NOI$ requires C 53.6, H 7.5, N 3.5%) and *cis*-**3b**, m.p. 205–207 °C (found, C 51.0, H 6.9, N 3.65; $C_{16}H_{26}NOI$ requires C 51.2, H 7.0, N 3.7%) were obtained by treating the corresponding bases in acetone with excess of methyl iodide and crystallizing the products which separated from methanol or ethanol. Treatment of 1,2,5,6-tetrahydro-1,5-dimethyl-4-phenylpyridine (**5g**)[16] in THF (50 ml) with *n*-butyllithium (24 ml, 1.4 M in hexane) followed by dimethyl sulphate, as described elsewhere for the preparation of **3a**,[15] gave a mixture of the corresponding 4-methylenamine base and methosulphate. The base (80 mg) was hydrogenated at room temperature over 5% Pd–C in the usual manner to give *cis*-4-phenyl-1,3,4-trimethylpiperidine (**3g**) isolated, as the hydrochloride, m.p. 193-194 °C, from ethanol–diethyl ether (a sample supplied by Dr D. M. Zimmerman had m.p. 188–189 °C, mixed m.p. 184–188 °C). Additional material was derived from the enamine methosulphate (treatment of the corresponding methochloride with sodium thiophenate gave the enamine hydrochloride which was reduced with $NaBH_4$).

The ^{1}H NMR spectra of the bases were measured on a Jeol GX 270 spectrometer, and those of the salts on both the GX 270 and Jeol GX 400 spectrometers. Samples (approximately 10 mg) were dissolved in D_2O (0.5 ml, DSS reference) or $CDCl_3$ (0.5 ml, TMS reference), and examined without degassing at the ambient probe temperature (20 °C) and employing the standard conditions of 32K data points with digital resolution of 0.18 Hz per point. The homonuclear ^{1}H–^{1}H chemical shift correlated 2D diagrams were obtained using the standard COSY-45 pulse sequence.[17] Before Fourier transformation the data were multiplied with an unshifted sine-bell, and zero filling was applied in the F_1 dimension. The ^{13}C NMR spectra were recorded at 67.8 MHz (Jeol GX 270 spectrometer) and spectral analyses were aided by DEPT experiments.

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REFERENCES

1. A. F. Casy and R. T. Parfitt, *Opioid Analgesics: Chemistry and Receptors*, Chapt. 7. Plenum Press, New York and London (1986).
2. D. M. Zimmerman, R. Nickander, J. S. Horng and D. T. Wong, *Nature (London)* **275**, 332 (1978).
3. G. Loew, J. A. Lawson, E. Uyeno, L. Toll, G. Frenking, W. Polgar and L. Y. Y. Ma, *Mol. Pharmacol.* **34**, 363 (1988).
4. A. F. Casy, G. H. Dewar and O. A. A. Al-Deeb, *J. Chem. Soc., Perkin Trans. 2*, in press.
5. A. J. Jones, A. F. Casy and K. M. J. McErlane, *Can. J. Chem.* **31**, 1782 (1973).
6. A. F. Casy, M. A. Iorio and A. E. Madani, *Magn. Reson. Chem.* **25**, 524 (1987).
7. A. F. Casy, *PMR Spectroscopy in Medicinal and Biological Chemistry*, Chapt. 4. Academic Press, London (1971).
8. A. F. Casy and F. O. Ogungbamila, *Org. Magn. Reson.* **18**, 171 (1982).
9. N. L. Allinger and M. T. Tribble, *Tetrahedron Lett.* 3259 (1971).
10. E. L. Eliel and Sr. M. C. Knoeber, *J. Am. Chem. Soc.* **90**, 3444 (1968); D. J. Hodgson, U. Rychlewska, E. L. Eliel, M. Manoharan, D. R. Knox and E. M. Olefirowicz, *J. Org. Chem.* **50**, 4838 (1985).
11. S. Sternhell, *Rev. Pure Appl. Chem.* **14**, 15 (1964); *Q. Rev. Chem. Soc.* **23**, 236 (1969).
12. M. Froimowitz, *J. Med. Chem.* **25**, 1127 (1982).
13. A. F. Casy and F. O. Ogungbamila, *J. Chem. Soc., Perkin Trans. 1* 749 (1982).
14. H. Booth, *Tetrahedron* **22**, 615 (1966).
15. A. F. Casy, G. H. Dewar and O. A. A. Al-Deeb, *Chirality*, in press.
16. A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef', *Tetrahedron* **21**, 3387 (1965).
17. G. A. Morris, *Magn. Reson. Chem.* **24**, 371 (1986).