Conformational studies of some 5,9-dimethyl-6,7-benzomorphan diastereoisomers and related compounds

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The proton magnetic resonance characteristics of some α/β diastereoisomeric 5,9-dimethyl-6,7-benzomorphans are reported for free base, hydrohalide, and methiodide forms, and differences between α- and β-signals are interpreted in terms of the piperidine ring fragment of the β-salts adopting skew-boat conformations. The steric course of quaternization of benzomorphan isomers is discussed from results of alkylations using trideuteriomethyl iodide and other experiments. A possible correlation between conformational and potency differences in analgesically active benzomorphan diastereoisomers and related compounds is discussed.

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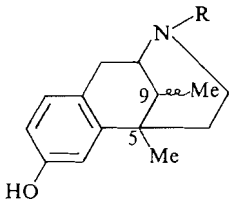
This paper reports a comparative conformational study of some 6,7-benzomorphan derivatives **1** that are diastereoisomeric with respect to the C-5 and C-9 alkyl substituents. The relative



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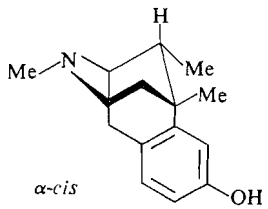
5,9-dialkyl configurations of several pairs of benzomorphan isomers are known (α-*cis* and β-*trans* with reference to the hydroaromatic ring) from rates of quaternization and proton magnetic resonance (p.m.r.) data (1), and a recent X-ray analysis of the α-*N*-allyl derivative **1** (R = CH_2-$CH{=}CH_2$) supports these assignments (2). Stereochemical data upon these compounds are of interest in view of the marked analgesic properties found in this class and because of the influence of the 5,9-dialkyl geometry upon analgesic potency (3) (β-diastereoisomers are generally more active than the α-forms).

Evidence of conformation, as in related work upon other classes of analgesic (4*a–c*), has been derived from p.m.r. data, characteristics of two α/β benzomorphan pairs (**1**, R = H and Me) in free base, hydrohalide, and quaternary salt forms being compared. Most of the data refer to solutions in DMSO-d_6 because this was the only convenient solvent which dissolved all forms, and chemical shift values (recorded at 60 MHz) are given in Hz from TMS. Stereochemical information of most value derives from the 5,9-dimethyl and *N*-methyl p.m.r. signals; this information is given in Table I. Differences between α- and β-signals are initially interpreted in terms of the piperidine-chair forms **2** and **3** respectively.



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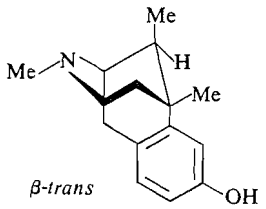

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Bases

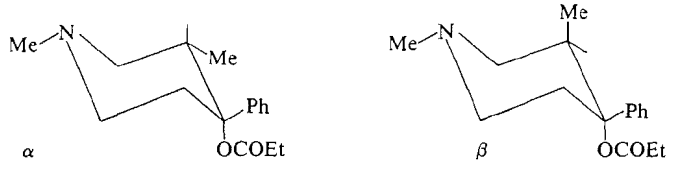
The chemical shifts of the α- and β-5-methyl signals are similar and their low field values (near 70 Hz) compared with the usual *t*-methyl positions near 54 Hz (5) are consistent with both groups lying near the plane of, and fairly close to, the 6,7-fused benzene ring (as in **2** and **3**), a position in which they are subject to aromatic deshielding (6). In the case of the 9-methyl signals, however, α-signals are higher field by over 20 Hz, β-signals being near-coincident with the 5-methyl resonance position. May's group (1*a*) obtained similar results for the *N*-methyl pair in $CDCl_3$ and interpreted differences in terms of differential aromatic shielding (α-9-methyl is shielded because it lies within the diamagnetic screening zone, whereas the β-group is too far removed to be affected by phenyl). The proximity of the nitrogen lone-pair to the

TABLE I

Proton magnetic resonance characteristics of some 5,9-dimethyl-6,7-benzomorphans **1**

R	Isomer*	Form	Solvent	Chemical shift†			Difference (salt–base)¶	
				N-Me—‡	5-Me—§	9-Me—‖	5-Me	9-Me
H	α	Base	DMSO-d_6	—	71	40	5.5	5
		HCl	DMSO-d_6	—	76.5	45		
H	β	Base	DMSO-d_6	—	69	65.5	6	7.5
		HCl	DMSO-d_6	—	75	73		
Me	α	Base	$CDCl_3$	145	78	48		
		Base	DMSO-d_6	131	71	42	7	5.5
		HCl	DMSO-d_6	163	78	47.5		
		HCl	D_2O	172	81	49.5		
		MeI	DMSO-d_6	202 194.5	83	50	12	8
		CD_3I	DMSO-d_6	192	82	49	11	7
CD_3	α	CD_3I	DMSO-d_6	—	81	49	10	7
Me	β	Base	$CDCl_3$	141	78	74.5		
		Base	DMSO-d_6	128	67.5	64.5		
		HCl	DMSO-d_6	161	72.5	75.5	5	11
		HBr	D_2O	173	81	77.5		
		MeI	DMSO-d_6	188 170	77	75.5	9.5	11
		CD_3I	DMSO-d_6	186.5	78.5	81	11	16.5
CD_3	β	CD_3I	DMSO-d_6	—	77	74.5	9.5	10

*α-*cis*- and β-*trans*-5,9-di-Me with respect to the hydroaromatic ring.
†In Hz from TMS (internal with $CDCl_3$ and DMSO-d_6, external with D_2O as solvent) spectra being measured at a frequency of 60 MHz.
‡Singlet except in some salts where spin–spin coupling with $\overset{+}{N}H$ proton occurs to give a doublet ($J \simeq 5$ Hz).
§Singlet.
‖Doublet ($J = 6.5$–7 Hz).
¶DMSO-d_6 solvent data.



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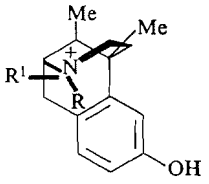
β-9-methyl group in benzomorphan bases is probably also of significance in regard to the α/β 9-Me chemical shift difference in view of demonstration of the greater deshielding influence of the lone-pair orbital upon axial than upon equatorial 3-methyl substituents in *trans* quinolizidines (7).

Hydrohalides

Both α- and β-5-methyl signals move downfield by about 6 Hz when basic centers are protonated. Lower field positions (relative to free base signals) also occur for α- and β-9-methyl signals in the protonated bases, the β-shift (7–11 Hz) being a few cycles larger than the α-value (5–5.5 Hz) in DMSO-d_6. 9-Methyl signals of α- and β-hydrohalide salts in D_2O show little difference from corresponding base resonance positions in $CDCl_3$.

9-Methyl-nitrogen geometry in α/β benzomorphans is analogous to that of 3-methyl-nitrogen in α- and β-prodine, (α- and β-**4**) respectively. In these and related compounds, the α-3-methyl signal suffers only a small change when the base is protonated (2–3 Hz downfield shift) while pronounced shifts (14–18 Hz) are observed for the β-signals *in the feebly polar solvent* $CDCl_3$. These differences have provided some of the evidence for the preferred chair conformations of both α- and β-prodine etc. in $CDCl_3$, 3-methyl being close to the deshielding $\overset{+}{N}H$ function in protonated β-**4** but further removed in α-**4** (4*a*). Hence the differences between the α- and β-

downfield shifts of the 9-methyl groups of the benzomorphans (induced on protonation) are smaller than those expected on the basis of the chair conformations **2** and **3**. The energy of the β-chair **3** will be raised when the base accepts a proton in a polar solvent through 1,3-diaxial non-bonded interactions between the solvated charged nitrogen and the 9-methyl group (axial with respect to the piperidine chair).[1] This interaction may be relieved in flexible conformations such as the skew-boat **5** and an increase in the population of such forms would explain the reduced influence of $\overset{+}{N}H$ upon the 9-methyl chemical shift since these two functions are further removed in **5** than in the chair **3**. There is similar evidence that skew-boat conformers



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are preferred for hydrochlorides of β-prodine (and related esters) and its parent alcohol (β-prodinol) when dissolved in D_2O (4*b*) or DMSO-d_6.[2] In these cases solubility properties of the salts allowed measurements to be made in the feebly polar solvent $CDCl_3$ when clear evidence for chair conformations was obtained (4*a*, *b*). It is probable that greater 9-methyl salt–base chemical shift differences might have been observed in the β-benzomorphans if $CDCl_3$, rather than DMSO-d_6, could have been used as solvent. A further assessment of conformational, solvent, and anion influences upon the chemical shifts of methyl substituents in these piperidine and benzomorphan salts will be given elsewhere.

Further evidence for skew-boat conformations in β-benzomorphans has been obtained by a study of $\overset{+}{N}H$ and $\overset{+}{N}$—Me p.m.r. signals in hydrochloride and quaternary salts. If skew-boat populations are significant in the β-secondary base **1** (R = H) hydrochloride, the difference between the chemical shifts of the two $\overset{+}{N}$—H protons would be expected to be greater than that between the α-$\overset{+}{N}H_2$ pair since one of the β-$\overset{+}{N}H$ protons (R = H in **5**) falls close to and above the plane of the aromatic ring in the skew-boat **5** (R = R′ = H). A shielding factor difference of about 0.8 p.p.m. (48 Hz at 60 Hz) between pseudo-*a* and *e*-$\overset{+}{N}H$ (or $\overset{+}{N}$Me) groups in **5** (R = R′ = H or Me) is anticipated on the basis of Johnson and Bovey's table of aromatic shielding values (6).[3] In fact, while the α-$\overset{+}{N}H_2$ signal formed a two proton multiplet centered at 570 Hz, the β-salt showed two distinct $\overset{+}{N}H$ signals, at 571 and 525 Hz, the latter, higher field value, being consistent with the aromatic screening of one of the protons, as anticipated for **5** (R = R′ = H). The broad nature of these signals (α-w_H 14, β, 24 and 26 Hz) differentiated them from the sharper phenolic OH signals. The latter fell within the aromatic multiplet in bases and hydrohalide salts as confirmed by comparing spectra of salts of α-**1** (R = H) and the corresponding *O*-methyl ether but were moved downfield in methiodides (forming isolated singlets) possibly as a result of hydrogen bonding of OH to iodide. $\overset{+}{N}H$ signals in the α/β *N*-methyl salts (**1**, R = Me) could not be clearly resolved.

Quaternary Salts

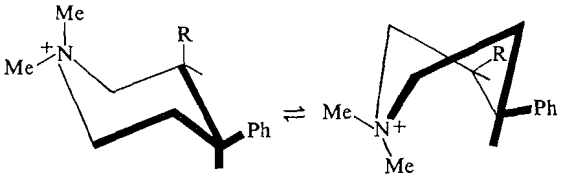
Non-chair conformations of the piperidine ring in methiodides of β-benzomorphans **1** (R = alkyl) are even more probable than in corresponding hydrohalide salts because of the axial 1,3-dimethyl interactions which must arise in the chair forms. This expectation is given point by the case of the 4-phenylpiperidine methiodides **6***a* and *b* where separation of the *N*-Me p.m.r. signals in $CDCl_3$ is reduced from 12 (**6***a*) to 3.5 Hz (**6***b*) when an axial 3-methyl substituent is present.[4] This result demonstrates the smaller environmental difference between

[1]Although no previous studies have been reported in DMSO-d_6, there is evidence that the effective size of $\overset{+}{N}H$ protons is increased by the presence of tightly held water molecules of hydration (8).

[2]Chemical shift differences (salt–base) for the prodinols in DMSO-d_6 are 7 Hz for the α- and 11 Hz for the β-isomer (unpublished results).

[3]$\overset{+}{N}H_2$ chemical shifts are unlikely to be averaged through proton exchange because the rate of this process is slow in hydrogen bonding solvents such as DMSO-d_6 (9).

[4]A. F. Casy and A. P. Parulkar. Unpublished results.



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

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the *N*-Me groups in the 3-methyl derivative as would result from comparable populations of the *e*-Ph chair **6***b* and skew-boat **7***b* (the population of the inverted chair form of **6***b* is likely to be low because of the large $-\Delta G_x^0$ value of phenyl) (10).

Methyl iodide rapidly methylated the α-benzomorphan **1** (R = Me), but a much longer reaction period was required to quaternize completely the corresponding β-isomer, as expected from reported reaction rates (1). The p.m.r. spectrum of the α-methiodide displayed distinct *N*-methyl signals at 202 and 194.5 Hz, whereas that of the β-isomer showed *N*-methyl bands at 188 and 170 Hz (Fig. 1A and D). The greater separation of the β-signals (18 compared with 7.5 Hz for α-) and the unusually high field position of one of the signals is consistent with the β-methiodide having the skew-boat conformation **5** (R = R′ = Me) in DMSO-d_6 with one *N*-methyl group falling well within the aromatic shielding zone. The deshielding influence of charged nitrogen upon the β-9-methyl signal is only a little greater than upon the α-9-methyl resonance ($\nu_{methiodide} - \nu_{base}$: α, 8 Hz; β, 11 Hz), again a result expected for a favored skew-boat rather than piperidine chair β-conformation (cf. argument relating to the conformation of the β-hydrochloride salts).

Quaternization of the α- and β-bases **1** (R = Me) was also carried out using trideuteriomethyl iodide to aid spectral analysis and provide evidence of reaction stereochemistry. In the α-series, the lower field *N*-methyl signal was absent in the mono-*N*-CD_3 iodide, while ring proton signals, hidden in the *N,N*-dimethyl form, were revealed in the *N,N*-di-CD_3 derivative (Fig. 1, B and C). Identification of the *N,N*-dimethyl signals of the β-methiodide itself is equivocal because more than two signals fall in the *N*—Me resonance region (Fig. 1D). One must be the unusually broad 170 Hz band because of its complete absence in the mono-*N*-CD_3 compound, while the other is the 188 Hz signal, as both this and the 170 Hz signal are missing from the spectrum of the *N,N*-di-CD_3 derivative (Fig. 1, E and F). Signals near 192 Hz which remain in the last spectrum must be due to ring protons.

There is good evidence that axial rather than equatorial approach is the preferred reaction pathway for the quaternization of cyclic nitrogen compounds, provided the group already attached to nitrogen is not markedly smaller than the incoming group (11, 12). Hence the *N*-methyl signal in the α-*N*-Me,*N*-CD_3 salt is probably due to an equatorial group. This is the higher field member of the *N,N*-dimethyl quaternary salt (Fig. 1, A and B), thus the lower field signal (202 Hz) is assigned to axial *N*-methyl. In monocyclic *N,N*-dimethyl piperidine salts, the axial *N*-methyl group generally has the *higher* field position (11, 12), and anisotropic effects of the fused hydroaromatic system (influencing *e*- rather than *a*-*N*-methyl) are most probably responsible for the reversal noted in the α-benzomorphan case. In the β-series the lower field methyl signal of the *N,N*-dimethyl salt remains in the *N*-Me,*N*-CD_3 salt.[5] This result further supports a radical conformational difference between the methiodide of α- and β-**1** (R = Me) since, if the β-chair **9** were favored, the *higher* field *N*-methyl signal should persist in the mono-*N*-CD_3 compound (as it does in the corresponding α-isomer).

Taking the skew-boat **5** (R′ = R = Me) as the favored β-methiodide conformation, two reaction pathways for quaternization of the β-base **1** (R = Me) with CD_3I may be formulated:

1) axial approach of CD_3I upon the chair conformation **8** and subsequent conformational change of the quaternary chair **9** to the skew-boat **10**;

2) pseudo-axial approach of CD_3I upon the

[5]Hence, assuming the skew-boat conformation **5** (R = R′ = Me), relative positions of pseudo-axial and pseudo-equatorial *N*-methyl chemical shifts are as seen in monocyclic piperidines. The pseudo-equatorial group still falls under the influence of the fused aromatic system (it has a chemical shift close to *e*-*N*-methyl in the α-salt) but the pseudo-axial group is even more subject to the same screening influence.

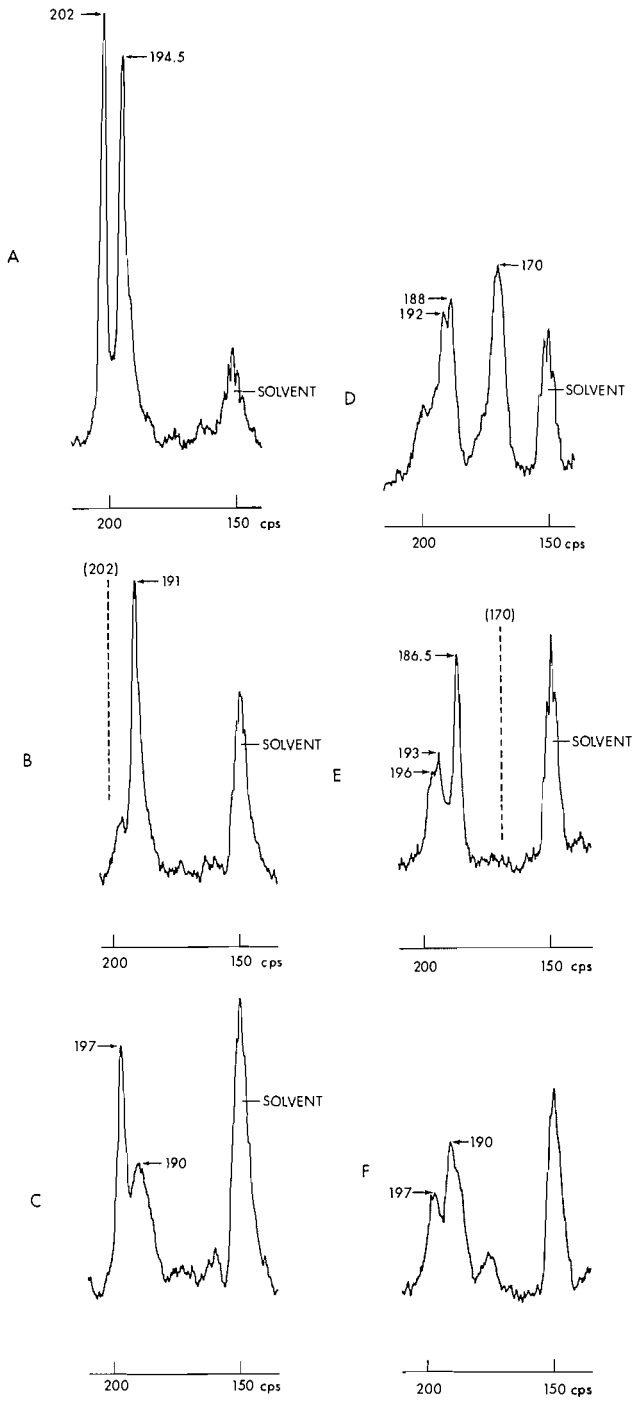
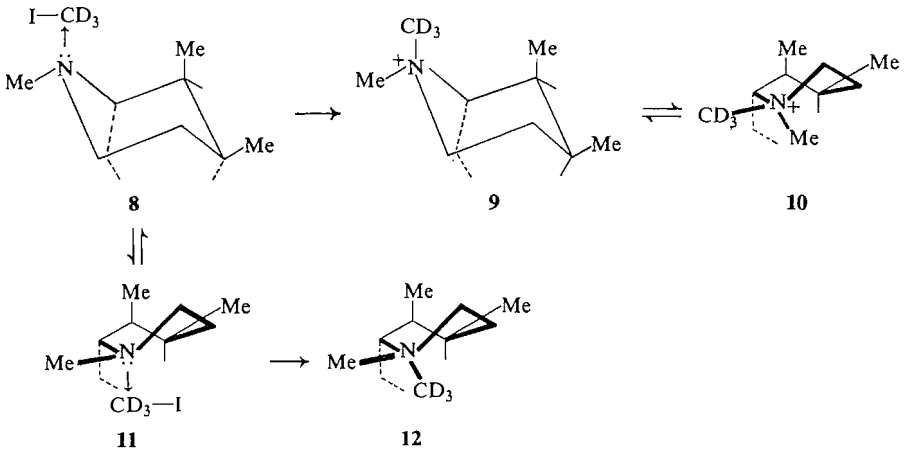


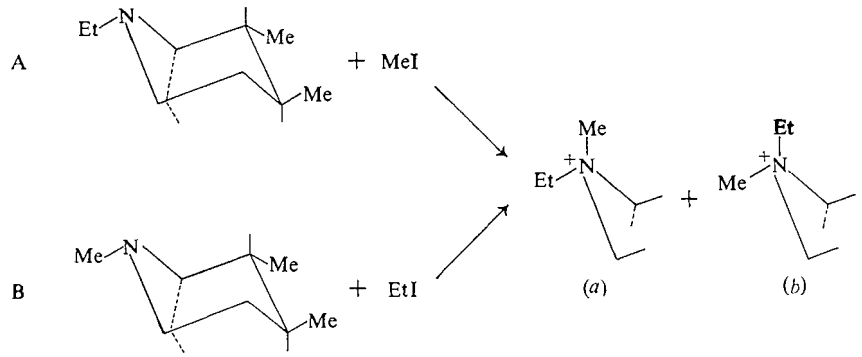
FIG. 1. Part of the proton magnetic resonance spectra of A, *N*,*N*-di-Me; B, *N*-Me,*N*-CD_3; C, *N*,*N*-di-CD_3 iodide salts of α-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan in DMSO-d_6. D, E, and F are spectra of the corresponding salts of the β-isomer. Spectral amplitudes are 12.5 (A), 25 (D), 32 (B and E), and 80 (C and F). Relative signal intensities may be gauged by comparison with solvent signals near 150 Hz. Chemical shifts are in Hz from TMS at a 60 MHz frequency.



skew-boat conformation **11** of the β-base with direct formation of the favored quaternary salt conformer **12.**

In the former case, the *higher* field *N*-Me signal will remain whereas in the latter, the *lower* field signal; results obtained thus support pathway *2.*

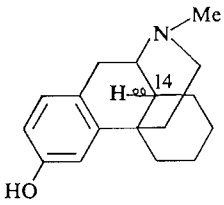
Further evidence for axial *N*-methyl having a lower field chemical shift than equatorial *N*-methyl in α-benzomorphan methohalides was obtained from the results of the methylation of α-**1** (R = Et) (reaction A), and the ethylation of α-**1** (R = Me) (reaction B). Two isomers may result in each case; viz.,



Only one *N*-Me signal (201 Hz) was resolvable in the total product of reaction A and the minor *N*-Me signal (185 Hz) was identified in the spectra of recrystallized samples. The same *N*-Me signals were found for the total product of reaction B but major and minor values were reversed. Hence assuming axial approach of quaternizing reagent (11, 12), the major product of reaction A is the axial *N*-methyl isomer (*a*) (lower field) while that of reaction B is the equatorial isomer (*b*) (higher field).

Ethylation of the β-*N*-methylbenzomorphan **1** (R = Me) (complete only after a 14 day reflux period) gave a total product showing sharp *N*-Me signals at 203 and 184 Hz (a broad band at 195 Hz situated between these signals is provisionally assigned to ring protons) of separation comparable with that found for the *N*-Me signals of the β-**1** (R = Me) methiodide.

The morphinan **13***a* and isomorphinan **13***b* derivatives are close analogues of the α- and β-benzomorphans **1** (R = Me) and similar evidence for favored skew-boat conformations in **13***b* methiodide (in the chair conformation, the 8-methylene group bears a 1,3-diaxial relationship to an *N*-methyl group) derives from



13*a* 14-H *cis* to nitrogen bridge
13*b* 14-H *trans* to nitrogen bridge

N–Me p.m.r. signals. In the methiodide of 3-hydroxy-*N*-methylmorphinan **13***a* (no 8-methylene – *N*-Me interaction), *N*-Me signal separation (8 Hz) approximates to that found in the α-benzomorphan **1** (R = Me) methiodide, whereas a separation of 13.5 Hz (closer to that of the β-benzomorphan analogue) is obtained for the isomorphinan derivative. However, the NMe_2 chemical shift separation of the isomorphinan is not as large as that of the β-benzomorphan methiodide and the higher field member is not moved upfield so markedly; these facts indicate skew-boat conformers to be less favored in **13***b* methiodide than in the corresponding β-benzomorphan salt.

It is attractive to speculate upon a possible correlation between α/β benzomorphan conformational differences and variations in isomeric analgesic potencies, which may arise as a result of the influence of conformation upon drug–receptor interactions and/or processes governing the transport and distribution of isomeric pairs. In the α-derivatives, 9-alkyl groups enhance activity in the 5-methyl series but reduce it in 5-ethyl and 5-propyl analogues (1). In β-derivatives, 9-Me, Et, and Pr substituents yield analgesics of high potency in all examples studied (1, 13). From the present evidence, skew-boat populations are probably high in all the β-derivatives when protonated in aqueous media and it is possible that conformers of this type allow a more effective drug–receptor association than do the chair forms of the α-benzomorphans or are subject more readily to processes governing the transport and distribution of isomeric pairs. These considerations may also be important in regard to the higher potency of isomorphinan over morphinan derivatives (14) and to the remarkably high potency of certain 14-acyloxycodeinones (15).

Experimental

The p.m.r. spectra were recorded on a Varian A-60 spectrometer operating at the normal running temperature with TMS as standard (internal with $CDCl_3$ and DMSO-d_6 and external with D_2O as solvent). Supply of the following chemicals is gratefully acknowledged: α- and β-**1** (R = Me) (Dr. E. L. May, National Institutes of Health); α- and β-**1** (R = H) and the *O*-methyl ether hydrochloride of α-**1** (R = H) (Dr. N. F. Albertson, Sterling Winthrop Research Institute, Rensselaer, New York); dextrorphan (Roche Laboratories, Welwyn Garden City, Herts); (−)-3-hydroxy-*N*-methylisomorphinan (Dr. M. Gates, University of Rochester, Rochester, New York).

The α- and β-benzomorphans **1** (R = H) gave hydrochlorides, m.p. 292–295° decomp. (lit. (16) 290–294° decomp.) and 312–314° decomp., respectively.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.25; H, 7.9. Found: C, 66.15; H, 7.6.

Isomeric 2,5,9-Trimethylbenzomorphans ***1*** *(R = Me) and Derivatives*

A mixture of α-**1** (R = H) (3.27 g), 40% formaldehyde solution (2.25 ml), 5% palladized charcoal (0.6 g), and EtOH (20 ml) was shaken with hydrogen (atmospheric pressure and room temperature) until gas absorption ceased. The product was filtered and the filtrate concentrated to give α-**1** (R = Me), m.p. 231–233° from EtOH, lit. 228–233° (17). Reductive methylation of β-**1** (R = H) gave β-**1** (R = Me), m.p. 220–221.5°, lit. 215–217.5° (17), hydrochloride, m.p. 313–315°, lit. 269–272° (17).

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.3; N, 5.2. Found: C, 67.0; H, 7.9; N, 5.3.

Methiodides

A mixture of α-**1** (R = Me) (0.2 g), MeI (1 ml), and $CHCl_3$ (300 ml) was stirred at 38° (±2°) under reflux for 5 days (solid separated after 8–9 h), then concentrated to 25 ml, and diluted with ether. The solid which separated was recrystallized from EtOH–ether to give α-**1** (R = Me) *methiodide*, m.p. 268–268.5°.

Anal. Calcd. for $C_{16}H_{24}INO$: C, 51.5; H, 6.5; N, 3.75. Found: C, 51.2; H, 6.3; N, 3.5.

β-**1** (R = Me) *methiodide* (it separated from the reaction mixture after 2–3 days) had m.p. 279–281°. Found: C, 51.3; H, 6.4; N,3.7.

N-Trideuteriomethyl Derivatives

A mixture of α-**1** (R = Me) (0.15 g), CD_3I (0.11 g), and $CHCl_3$ (100 ml) was stirred at 33° (±2°) under reflux for 4 days. The methiodide of α-**1** (R = CD_3) which separated had m.p. 250–254°. Similar treatment of β-**1** (R = Me) gave the methiodide of β-**1** (R = CD_3), m.p. 118°. Treatment of α-**1** (R = H) (0.11 g) with CD_3I (0.2 g) gave the trideuteriomethiodide of **1** (R = CD_3), m.p. 254–258° decomp. after a 7 day reaction period. The β-*N*,*N*-di-CD_3 analogue had m.p. 287–288° from EtOH. The p.m.r. spectra of these products closely resembled those of the corresponding *N*,*N*-dimethyl derivatives in all respects save those of the *N*-Me resonance region (Fig. 1).

N-Ethyl-N-methyl Quaternary Salts of ***1*** *(R = H)*

A mixture of α-**1** (R = Me) (0.4 g), EtI (2 ml), and $CHCl_3$ (250 ml) was heated under reflux for 4 days. The solvent was evaporated and the residue recrystallized

from EtOH–ether to give an isomeric mixture of *N*-ethyl-*N*-methyl **1** (R = H) iodides, m.p. 265–266.5° decomp.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.7; H, 6.8; N, 3.5. Found: C, 52.4; H, 6.5; N, 3.6.

Reductive ethylation of α-**1** (R = Me) using MeCHO instead of formaldehyde gave **1** (R = Et), m.p. 155–157° from $CHCl_3$–ether, lit. m.p. 158–160° (18). The *hydrochloride*, m.p. 166–168° displayed duplicate *N*-CH_2Me (quartets centered on 212 and 217 Hz from TMS, J = 7 Hz) and *N*-CH_2Me (triplets centered on 65.5 and 67 Hz, J = 7 Hz) p.m.r. signals in DMSO-d_6, indicative of similar populations of $\overset{+}{N}$—H epimers (unfavorable 1,3-diaxial interactions of an *a*-*N*-Et group must be balanced by interactions between *e*-*N*-Et and one of the C-8 methylene protons).

Anal. Calcd. for $C_{16}H_{24}ClNO{\cdot}H_2O$: C, 64.1; H, 8.7; N, 4.7. Found: C, 64.3; H, 8.4; N, 4.3.

The α-base **1** (R = Et) with MeI gave a quaternary salt mixture, m.p. 165° whose p.m.r. spectrum closely resembled that of the mixture obtained from **1** (R = Me) in all respects save the *N*-Me resonance region (see text). *N*-Ethylation of β-**1** (R = Me) (complete after a 14 day reflux period) gave an *N*-ethyl-*N*-methyl quaternary mixture, m.p. 241–242° from EtOH–ether. Found: C, 52.8; H, 6.9; N, 3.6.

Morphinan and Isomorphinan Methiodides

Dextrorphan (**13***a*) (0.1 g), MeI (2 ml), ether (200 ml), and EtOH (15 ml) were stirred under reflux at 35° (±2°) for 4 days. The solid which separated was recrystallized from $CHCl_3$–EtOH to give *dextrorphan methiodide*, m.p. 285–286°.

Anal. Calcd. for $C_{18}H_{26}INO$: C, 54.1; H, 6.6; N, 3.5. Found: C, 53.75; H, 6.6; N, 3.7.

The analogue derived from (−)-3-hydroxy-*N*-methylisomorphinan (**13***b*) had m.p. 248–250°. Found: C, 53.9; H, 6.6; N, 3.2. *N*-Methyl p.m.r. characteristics in DMSO-d_6 of **13***a* methiodide: singlets at 195.5 and 187.5 Hz from TMS; and **13***b* methiodide: singlets at 184 and 197.5 Hz.

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