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^{1}H and ^{13}C NMR Conformational Studies on Quaternary Nitrogen Derivatives of the Analgesic Drug Nefopam

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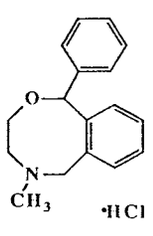
Nitrogen quaternization in the analgesic nefopam [(±)-3,4,5,6-tetrahydro-5-methyl-1-phenyl-1*H*-2,5,- benzoxazocine hydrochloride] by either *N*-trideuteriomethylation or *N*-oxidation affords reaction product diastereomeric mixtures differing in *N*-configuration. The axial to equatorial *N*-CH_3 product ratios were found to be *ca.* 3:2 (*N*-trideuteriomethylation) and approximately equimolar (*ca.* 48:52, *N*-oxidation). Both diastereomeric *N*-oxides have boat–(flattened chair) conformations of the octagonal ring in which the phenyl group is *exo*-oriented. The quaternary ammonium salts showed considerable line broadening in the ^{1}H NMR spectrum owing to rapid conformational equilibration. The same boat–(flattened chair) conformation is clearly the preponderant contributor to the time-averaged structure of nefopam methiodide in CD_2Cl_2 solution, similar to the case for the equatorial *N*-methyl isomer of the parent hydrochloride salt. Conformational assignments were based on the vicinal coupling constants in the —OCH_2CH_2N—fragment and on the finding of an NOE intensity enhancement for the benzhydrylic-*H* on irradiation of the equatorially oriented —O*CH*.

KEY WORDS Nefopam Analgesic Benzoxazocine Conformation ^{1}H NMR ^{13}C NMR Methylation Oxidation Difference NOE ^{1}H–^{1}H coupling constants

INTRODUCTION

Racemic nefopam hydrochloride [(±)-3,4,5,6-tetrahydro-5-methyl-1-phenyl-1*H*- 2,5-benzoxazocine hydrochloride,[1] (±**1**)] is a non-narcotic analgesic drug. The solution diastereomerization and the stereochemistry of nefopam hydrochloride in both the crystalline and solution states has been reported by Glaser and coworkers.[2–4] Structural studies on nefopam involved single-crystal x-ray diffraction,[2–4,5,6] NMR spectroscopy,[2–4] and molecular mechanics conformational modelling.[2–4] Nefopam hydrochloride exists in the crystalline state in a boat–(flattened chair) conformation (**1e**) with an equatorial *N*-methyl group and an *exo*-oriented phenyl ring.[2–4] Dissolution of either crystalline (±)**1e** or (+ or −)**1e** results in a prototropic shift/nitrogen inversion diastereomerization process forming an equilibrium mixture of equatorial (**e**) and axial (**a**) *N*-methyl isomers (**1e**, **a**) [**e**:**a** ratio *ca.* 1:1 (acidic D_2O, pD ≈ 1) and *ca.* 2:3 (CD_2Cl_2)].[2–4] The (1*R*,5*R*)-**1e** and (1*R*,5*S*)-**1a** diastereomeric pair resulting from the dissolution of crystalline (−)-(1*R*,5*R*)-**1e** is illustrated below.



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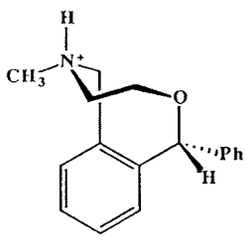
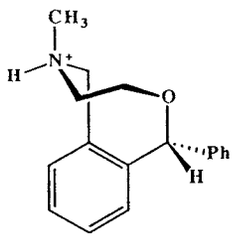


1e



1a

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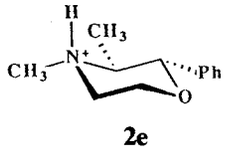
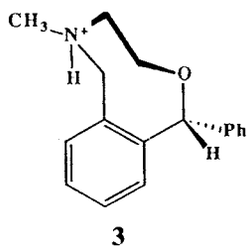
Using the chair conformation equatorial *N*-methyl diastereomer of phendimetrazine mesylate (**2e**) as a model, we have recently presented evidence pointing to the existence of a 'hidden partner' third species in rapid equilibrium (on the ^{1}H NMR time scale) with diastereomer **1e**.[7] While the molecular mechanics models of the boat–(flattened chair) **1e** and the twist-chair–(flattened chair) structure **3** were calculated and found to be very similar in energy,[4] the boat–(flattened chair) conformer is the major contributor to time-averaged species **1e** in solution.[3,7]



2e



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Differentiation of (−)-(1*R*,5*R*)-**1e**, (+)-(1*S*,5*S*)-**1e**, (−)-(1*R*,5*S*)-**1a**, (+)-(1*S*,5*R*)-**1a** *N*-methyl diastereomeric and (+,−)-enantiomeric stereoisomers was recently shown using modelling studies for the serotonin uptake area.[8] Nefopam is a potent inhibitor of the synaptosomal uptake of biogenic amines such as serotonin [5-hydroxytryptamine (5-HT)],[9] and recent animal studies

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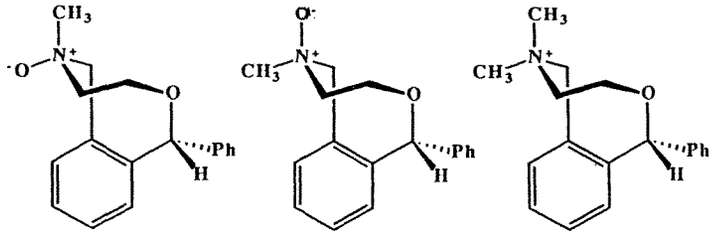
suggest that serotonergic pathways are involved in the antinociceptive activity of nefopam.[10]

Quaternization of the nitrogen in nefopam via *N*-oxidation or *N*-methylation involves reactions under kinetic approach control as opposed to the thermodynamically controlled diastereomerizations described above. *N*-Demethylation and *N*-oxidation are two of the metabolic pathways for nefopam.[11] Laboratory *N*-oxidation of (±)**1** yields two *d,l*-pairs of diastereomeric *N*-oxides, (±)**4** and (±)**5**.

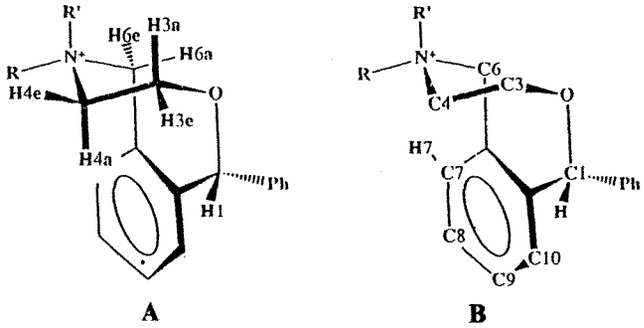


4 **5** **6**

This paper reports the structure determination of these two *N*-oxides using NMR spectroscopic methods. In addition, it is shown that *N*-methylated nefopam (**6**) affords broadened ^{1}H NMR spectral lines indicative of a rapid topomerization involving two octagonal-ring conformational species.

RESULTS AND DISCUSSION

Nefopam contains two chirotopic stereogenic[12] atoms: the benzhydryl carbon (C-1) and the labile nitrogen atom. Treatment of an ethanolic solution of nefopam free base with hydrogen peroxide results in the formation of two diastereomeric *N*-oxides (**4** and **5**) in almost equal amounts (*ca.* 48:52, respectively), while treatment with methyl iodide yields the corresponding quaternary ammonium salt (**6**). The aliphatic ^{1}H and ^{13}C NMR spectral parameters are listed in Tables 1 and 2. The numbering diagrams for nuclei in the boat–(flattened chair) conformations of the eight-membered ring for **4**, **5** and **6** are shown in structures **A** and **B**.



A **B**

Assignment of ^{1}H and ^{13}C NMR resonances

^{1}H and ^{13}C NMR spectra for the **4**,**5** diastereomeric mixture were measured in CD_3CN, and in CD_2Cl_2 for **6**. The partial ^{1}H NMR spectrum of the aliphatic regions for **4**,**5** is shown in Fig. 1. Two pairs of externally diastereotopic[13] singlets (benzhydryl-*H* and methyl-*H*) were readily differentiated by means of DEPT and XHCORR ^{13}C/^{1}H 2D-NMR correlation techniques. Each diastereomer contains three pairs of internally diastereotopic[13] methylene-*H*. Two-spin system H-6a,6e resonances are clearly differentiated from those of the four-spin system (H-3a,3e and H-4a,4e) by multiplicity. Multiplet assignments within a particular spin system were accomplished by homonuclear decoupling experiments. Within a particular four-spin system, two geminal protons each had resonances at lower field *vis-à-vis* those from their vicinal neighbours, and were assigned according to electronegativity effects as the adjacent-to-oxygen methylene-*H* pair H-3a,3e. The

Table 1. Aliphatic ^{1}H NMR spectral parameters for the axial *N*-methyl (1*R*,5*S*)/(1*S*,5*R*)-nefopam *N*-oxide (4) and equatorial *N*-methyl (1*R*,5*R*)/(1*S*,5*S*)-nefopam *N*-oxide (5) diastereomeric mixture, and for nefopam methiodide (6)

δ_H[a]	4[b]	5[b]	6[c]
H-1	5.83	5.79	5.80
H-3a	4.25	4.77	4.63
H-3e	4.03	3.91	4.11
H-4a	3.38	3.50	3.27
H-4e	3.20	3.02	3.98
H-6a	5.69	6.04	5.81
H-6e	4.41	4.30	4.72
axial-*N*-CH_3	3.42	—	3.73
equatorial-*N*-CH_3	—	3.07	3.40
J(HH)[d]			
3a–3e	−14.5 (1)	−13.3 (1)	−14.5 (1)
3a–4a	11.9 (3)	12.4 (1)	12.8 (1)
3a–4e	3.7 (1)	3.1 (1)	3.8 (1)
3e–4a	4.0 (5)	3.3 (2)	4.3 (2)
3e–4e	2.1 (4)	1.6 (1)	<1
4a–4e	−14.5 (4)	−14.1 (1)	−14.0 (2)
6e–6e	−12.2 (1)	−12.3 (4)	−12.4 (1)

[a] ppm downfield from tetramethylsilane.
[b] 200 MHz, CD_3CN, 298 K, **4**:**5** ratio ≈ 48:52.
[c] 300 MHz, CD_2Cl_2, 298 K.
[d] Hz; standard deviation in parentheses.

Table 2. Aliphatic ^{13}C NMR spectral parameters for the axial *N*-methyl (1*R*,5*S*)/(1*S*,5*R*)-nefopam *N*-oxide (4) and equatorial *N*-methyl (1*R*,5*R*)/(1*S*,5*S*)-nefopam *N*-oxide (5) diastereomeric mixture, and for nefopam methiodide (6)

δ_C[a]	4[b]	5[b]	6[c]
C-1	86.00	85.85	86.51
C-3	65.95	65.82	65.61
C-4	65.00	62.52	58.20
C-6	72.01	73.33	68.09
axial-*N*-CH_3	56.59	—	51.12
equatorial-*N*-CH_3	—	57.81	53.20

[a] ppm downfield from tetramethylsilane.
[b] 50 MHz, CD_3CN, 298 K, **4**:**5** ratio ≈ 48:52.
[c] 75 MHz, CD_2Cl_2, 298 K.

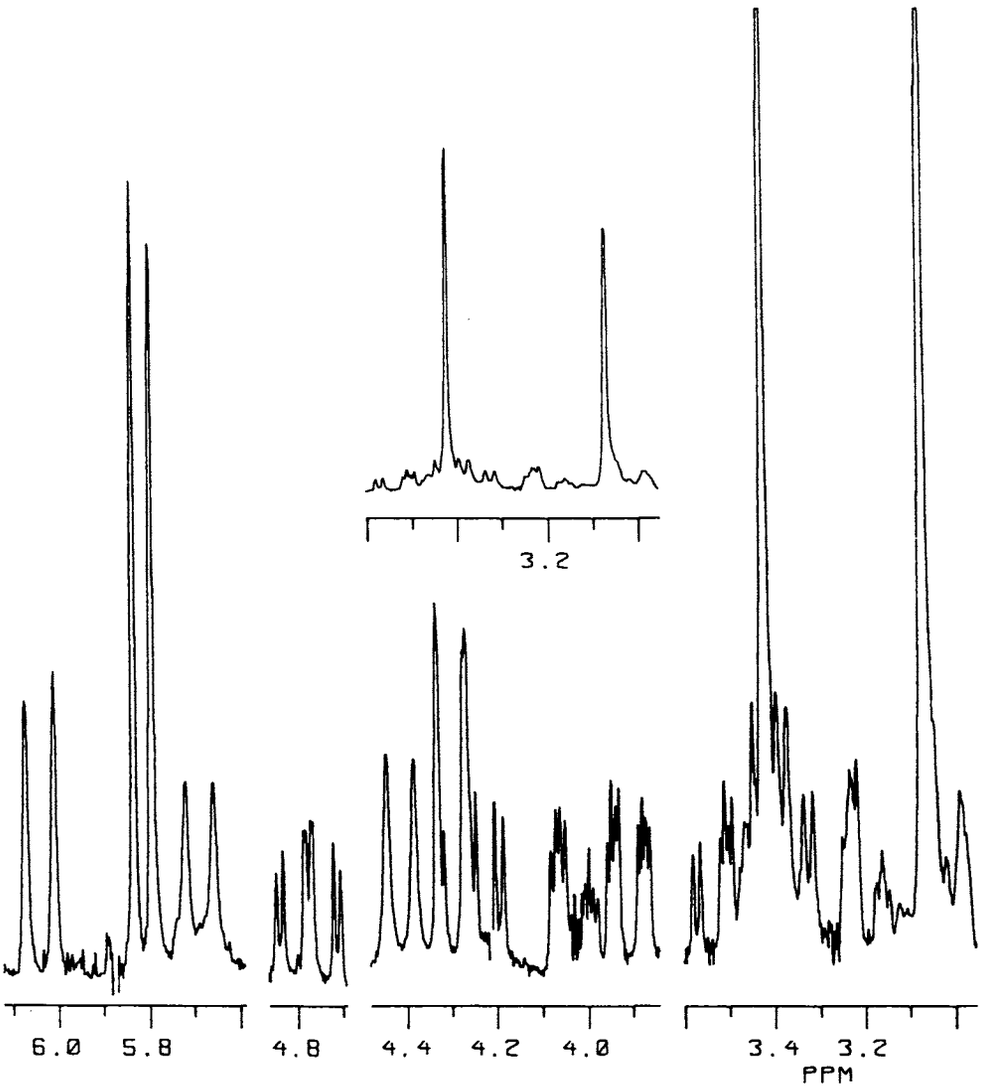


Figure 1. ^{1}H NMR partial spectra (200.1 MHz, CD_3CN, 298 K) of the aliphatic regions for the axial *N*-methyl (1*R*,5*S*)/(1*S*,5*R*)-nefopam *N*-oxide (**4**) and equatorial *N*-methyl (1*R*,5*R*)/(1*S*,5*S*)-nefopam *N*-oxide (**5**) diastereomeric mixture. The insert is plotted at one-eighth vertical scale to show the height of the *N*-CH_3 singlets truncated in the lower spectrum.

more downfield resonance for the diastereotopic H-6a, 6e pair was assigned to the spatially close *syn*-to-oxygen H-6a {$\Delta\delta$ 1.28[for H(6a,6e) in **4**], 1.74 (in **5**) and 1.09 ppm (in **6**)}.

In our previous work with **1e,a** diastereomeric mixtures, vicinal coupling constants involving $^+$N*H* permitted the assignment of proton resonances (and *N*-methyl stereochemistry) in the —$OCH_2CH_2N^+H(CH_3)CH_2$— fragment of each species. However, this facility is clearly lacking for the almost equimolar mixture of *N*-oxides **4** and **5** or for the diastereotopic methyls in **6**. Difference NOE intensity enhancements provide an alternative method based on spatially close interproton relationships within the molecule.

Only five of the eight lines [line numbers, high to low fields: 1, 2, 3, 4 (as a shoulder) and 7] from H-3a in **4**, the *A*-part of the *ABXY*-type four-spin system at 4.25 ppm, were readily identified at 200 MHz owing to overlap with the H-6e doublet from the other diastereomer. All eight H-3a transitions were located by means of spectral editing using a cycled, low-power irradiation technique[14] for the difference NOE spectrum {H-3a, transitions 1 and 2}. In this spectral editing difference NOE, the decoupler frequency is cycled over the non-overlapping lines of the multiplet at low power to eliminate or minimize irradiation spillover into nearby multiplets. As a result, usually all the transitions of the multiplet appear in the difference spectrum, despite the partial irradiation. The transitions of the irradiated multiplet appear with strong intensity and negative phases, while positive NOE enhancements are oppositely phased. The ordering of the transitions for H-3a in **4** was found to be 1, 2, 3, 5, 4, 6, 7, 8, hence all three coupling constants could be measured (at least once) even without recourse to the difference NOE spectrum. Similarly, there are three overlapping multiplets in the 3.3–3.6 ppm region (H-4a for both species and NCH_3 for **4**). All eight-lines of each H-4a multiplet were observed and measured using the difference NOE spectral editing technique. The eight transitions from H-4e in both species [the *X*-part of the *ABWX*- and *AMRX*-type four-spin systems in **4** and **5**, respectively]

were not adequately resolved and appeared as two broadened peaks with some fine structure. The midpoint of each broadened peak was used in the determination of spectral parameters.

Multiplicities of the resonances in the ^{13}C NMR spectrum were determined by comparison with those from DEPT spectra (pulse width 90° and 135°). Assignments were based on XHCORR 2D-NMR $^{13}C/^{1}H$ correlation experiments.

Stereochemistry of axial *N*-methyl (1*R*,5*S*)/(1*S*,5*R*)-nefopam *N*-oxide (4)

The finding of a 11.9 Hz vicinal coupling constant ^{3}J(3a, 4a) allowed the assignment of an antiperiplanar disposition to these nuclei in **4**. The two almost equal magnitude ^{3}J(3a, 4e) and ^{3}J(3e, 4a) values (3.7 and 4.0 Hz) were consistent with a synclinal (*gauche*) dihedral arrangement between axial–equatorial-type protons, while the lower 2.1 Hz ^{3}J(3e, 4e) value was also in agreement with that expected from synclinal equatorial–equatorial vicinal protons, see **A** (where R′ = CH_3 and R = O^-). Thus, the O—C-3—C-4—N dihedral angle in **4** (CD_3CN solution) could be calculated as 55.3 ± 2.0° using the *R*-factor method of Lambert.[15] This is reasonably similar to the 52.9 ± 1.5° value for this angle in the boat–(flattened chair) conformation of axial *N*-methyl nefopam hydrochloride (**1a**) measured in CD_2Cl_2 solution by the same technique.[2,3] Using a combination of x-ray crystallographic and molecular mechanics modelling, we have shown that this magnitude for the above dihedral angle is consistent with the boat–(flattened chair) benzoxazocine conformation (*ca.* 57 ± 3° for **1a,e**), and would be much larger for the inverted-sign O—C—C—N torsion angle twist-chair–(flattened chair) conformation [e.g. 80° for **3**].[4]

Observation of 1.3, 0.9 and 1.2% NOE {CH_3, 3.42 ppm} enhancements to H-3a,6a,6e resonances at δ 4.25, 5.69 and 4.41, respectively, allowed the determination of the adjacent-to-methyl two- and four-spin systems within the molecule. Moreover, the NOE noted for H-3a and H-6a (together with their absence in the corresponding {CH_3, 3.07 ppm} experiment, see below) is consistent with a *cis*-1,3-diaxial type relationship, and allowed the assignment of an axial descriptor for the *N*-methyl orientation in this diastereomer (**4**). A molecular mechanics model of boat–(flattened chair) **4** was calculated using the MMX88[16] program. The following distances measured in the model are consistent with the finding of NOE phenomena: $CH_3\cdots$H-3a 2.37 Å, $CH_3\cdots$H-6a 2.41 Å and $CH_3\cdots$H-6e 2.70 Å.

The assignment of the more downfield resonance to the spatially close *syn*-to-oxygen H-6a in the diastereotopic H-6a,6e pair (2.44 Å in model) was confirmed by the observation of a 3.8% NOE for a lone aromatic-*H* multiplet at 7.47 ppm on {H-6e} irradiation. This proton was assigned as H-7 (H-6e$\cdots$H-7 2.34 Å distance in model), and is downfield from the 7.1–7.4 ppm aromatic resonances. A similar effect was also observed for the parent axial *N*-methyl nefopam hydrochloride diastereomer **1a** (but not for the **1e** epimer).[3]

A 1.2% NOE {H-3e, 4.03 ppm} was found for H-1. This allowed the assignment of the 5.83 ppm benzhydryl-*H* resonance to diastereomer **4**. It also denotes an *exo* orientation for the phenyl group whereby H-1,3e are both on the same side of the eight-membered ring (H-1$\cdots$H-3e 2.23 Å distance in model for **4**). It is noted that H-1,3e are located on opposite sides of the ring in the twist-chair–(flattened chair) conformer **3**.[4] Molecular mechanics modelling has shown that an *exo* phenyl ring substituent is preferable to one in an *endo* orientation for nefopam hydrochloride in the boat–(flattened chair) conformation.[4]

Stereochemistry of equatorial *N*-methyl (1*R*,5*R*)/(1*S*,5*S*)-nefopam *N*-oxide (5)

In a manner similar to that discussed above, the magnitudes of the four vicinal coupling constants for the —OCH_2CH_2N—fragment in diastereomer **5** also denote a *gauche* O—C—C—N dihedral angle in which H-3a,4a are antiperiplanar, see structure **A** (where R′ = O^- and R = CH_3). Again, using Lambert's *R*-factor ratio method,[15] the O—C-3—C-4—N dihedral angle in **3** (CD_3CN solution) was calculated to be 58.1 ± 0.9°. Thus, the magnitude of this angle points to a boat–(flattened chair) conformation for **5** according to our previous x-ray and molecular mechanics studies.[4]

The 6.04 ppm lower field resonance in the two-spin system was assigned to the close-to-oxygen H-6a nucleus on the basis of the expected deshielding effect and on the non-observance of an NOE intensity enhancement for it on {CH_3, 3.07 ppm}. A 3.1% NOE was noted for H-6e in this experiment. The finding of an NOE enhancement only for H-6e and not for H-6a is consistent with the assignment of an equatorial orientation for the *N*-methyl in **5** (in the molecular mechanics model of **5**: $CH_3\cdots$H-6a 3.68 Å and $CH_3\cdots$H-6e 2.41 Å). A 1.3% NOE {H-3e, 3.91 ppm} was also found for H-1 (H-1$\cdots$H-3e 2.28 Å distance in model). This allowed the assignment of the singlet 5.79 ppm benzhydryl-*H* resonance to diastereomer **5**, and also was consistent with an *exo* orientation for the phenyl group in which H-1, 3e are both on the same side of the eight-membered ring.

Comparison of the ^{1}H chemical shifts for the externally diastereotopic *N*-CH_3 groups show the axial one to have a 0.35 ppm shift downfield from that of its equatorial analogue, compared with a 0.33 ppm shift downfield for the parent nefopam hydrochloride diastereomers **1e,a**.[2,3] Comparison of the ^{13}C chemical shifts for externally diastereotopic *N*-CH_3 nuclei show the axial one to have a 1.22 ppm shift upfield from that of its equatorial analogue, as expected. A similarly small upfield shift of 1.07 ppm was found for the analogous nefopam hydrochloride diastereomers **1e,a**.[2,3] It is noted that there is only one *cis*-1,3-diaxial interaction involving the axial *N*-methyl group in the boat–(flattened chair) 2,5-benzoxazocine ring, as opposed to two such interactions in *N*-methylpiperidine-type salts where the upfield shift is considerably larger.[7,17] In addition, the chemical shift of the γ-to-*N*-CH_3 nucleus, C-3, appears to be affected very little by the stereochemistry at nitrogen (perhaps changes in relative orientation effects of the nitrogen substituents balance each other out).

Stereochemistry of nefopam methiodide (6) and the kinetic course of *N*-methylation

The magnitudes of the four vicinal coupling constants for the NCH_2CH_2O fragment also point to a synclinal N—C—C—O arrangement. In this conformation, H-3a and H-4a are found to be antiperiplanar on the basis of their 12.8 Hz coupling constant. Whereas ^3J(3a, 4e) and ^3J(3e, 4a) were also readily ascertained, the small ^3J(3e, 4e) coupling constant between the two equatorial protons could not be measured owing to line broadening at ambient temperature. All the proton resonances of **6** [and for the diastereomeric *N*-CD_3 labelled isotopomers **8** and **9** (see below)] are considerably broadened. For example, both *N*-methyl proton singlets are *ca.* 3.3 times broader at half-height (3.3 Hz) compared with those in lines from diethyl ether methylene protons (a trace amount was present in the CD_2Cl_2 solution), see Fig. 2. Lowering the probe temperature to 230 K did not afford discernible resonances from a second species for **6**. Since the nefopam methiodide quaternary ammonium salt (**6**) is obviously incapable of exhibiting diastereomerism involving change of configuration at nitrogen, line broadening can indicate the presence of a rapid conformational equilibrium. Casy and Ogungbamila[18] noted broadening in the *N*-methyl ^{13}C resonances of *N*,*N*-dimethylpiperidinium derivatives, due to coupling with ^{14}N.[19] While this explanation of line broadening is an alternative to conformational interchange, we note that the benzhydrylic H-1 singlet resonance in **6**, **8** and **9** is similarly broadened, and this proton is located *five* bonds away from nitrogen.

A similar, but smaller, line-broadening effect has been noted for the equatorial *N*-methyl isomer of the parent hydrochloride salt, and has been discussed in terms of a 'hidden partner' [such as the putative twist-chair–(flattened chair) **3**] in rapid equilibrium with **1e**.[3] As with **1e**,[3] the vicinal coupling constants in the NCH_2CH_2O fragment together with an H-1 1.4% NOE enhancement {H-3e} point to a boat–(flattened chair) ring conformation as the major contributor to this equilibrium. The phenyl group has an *exo* orientation in this

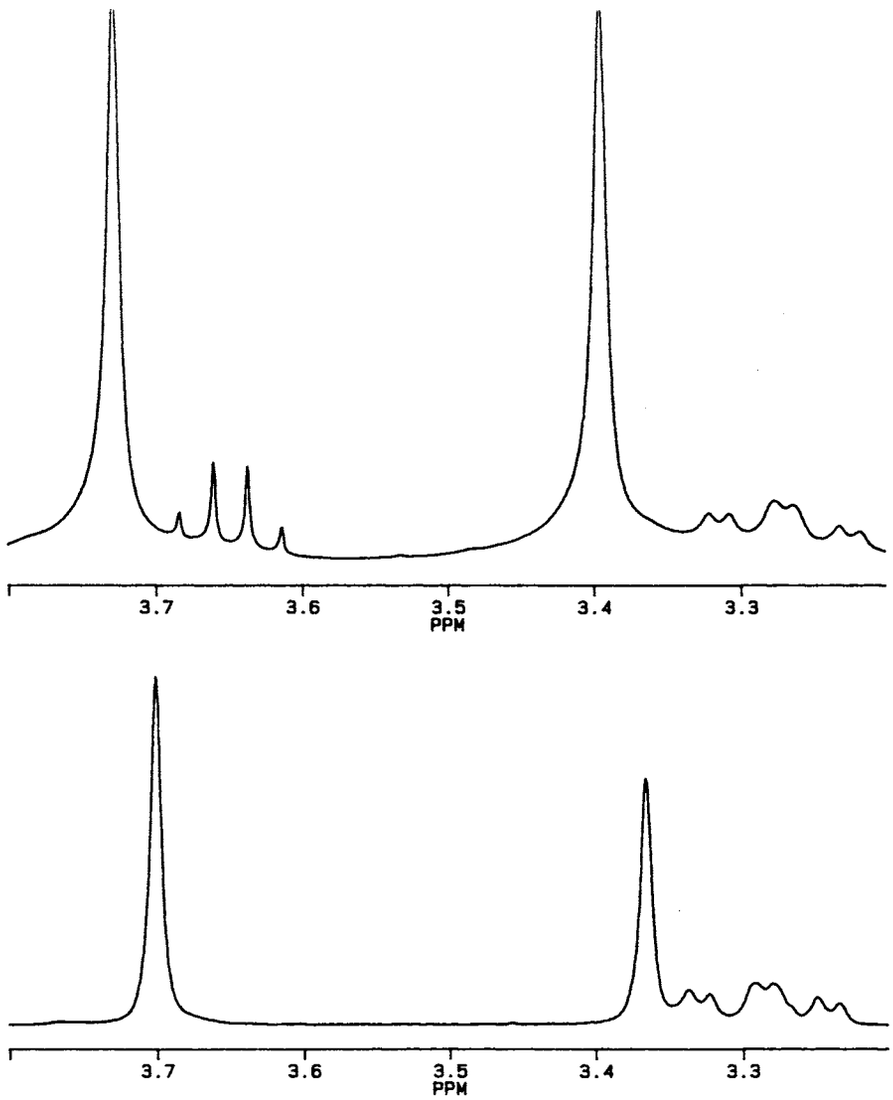
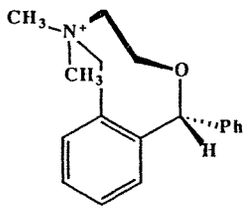


Figure 2. ^{1}H NMR partial spectra (300.1 NHz, CD_2Cl_2, 298 K, δ 3.8–3.2) showing the broadened *N*-methyl resonances of nefopam methiodide (**6**) (top) and of the isotopomeric nefopam trideuteriomethyl iodide diastereomeric mixture (**8**, **9**) (bottom) versus the narrower quartet arising from the OCH_2 protons of diethyl ether (top).

major contributor, and H-1,3e are located on the same side of the octagonal ring. Twist-chair–(flattened chair) **7** is the putative minor contributor to the conformational equilibrium.

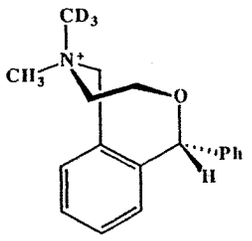
The conformational equilibrium inferred by solution-state ^{1}H NMR was observed in a recent single-crystal x-ray diffraction analysis on nefopam methiodide.[20] While there was a clear preponderance of the boat–(flattened chair) conformation **6** in solution, both conformations (**6** and **7**) were found in the crystalline state.[20] The positions of the two *N*-methyl groups and the C-4-methylene moiety represent the primary differences between the two conformations. These three groups were found to be disordered in the crystal, while the remainder of the molecular skeleton remained crystallographically well behaved.[20] As a result of this disorder, both eight-membered ring conformations were clearly observed with a *ca.* 50 : 50 occupancy for each.[20]



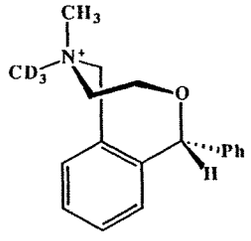
7

The internally diastereotopic *N*-methyl protons were assigned as axial and equatorial on the basis of difference NOE spectra. Irradiation of the 3.73 ppm *N*-CH_3 afforded a 1.2% NOE to axial H-3a (together with 1.0% and 2.6% NOE enhancements to H-6a,6e, respectively), and enabled it to be assigned as axial. The axial *N*-CH_3 resonance was 0.33 ppm downfield relative to that from the equatorial group. This difference was similar to the $\Delta\delta$ found for the externally diastereotopic groups in the parent nefopam salt and in the *N*-oxides. As expected, the XHCORR 2D-NMR spectrum showed the axial *N*-CH_3 resonance to be the one which is upfield (2.08 ppm) from that of its diastereotopic neighbour (this was also noted in the case of **1e,a**[3] and **4,5**).

A mixture of two diastereomeric *N*-CD_3 labelled isotopomers (**8** and **9**) was prepared by *N*-methylation with trideuteriomethyl iodide, and analysed by ^{1}H and ^{13}C NMR. A *ca.* 2 : 3 ratio of the kinetic approach controlled products **8** and **9**, respectively, was found by integration of the *N*-CH_3 resonances in the ^{1}H NMR spectrum (see Fig. 2). A similar ratio for the externally diastereotopic *N*-CH_3 nuclei was apparent in the ^{13}C NMR spectrum acquired by the DEPT-135 technique, see Fig. 3. Thus, *N*-methylation of nefopam free base proceeds with a slight preference for equatorial attack, while the direction of *N*-oxidation by hydrogen peroxide appears to be almost non-specific. Equatorial attack is also the preferred route for the *N*-methylation[21,22] and the *N*-oxidation[23] of tropane alkaloids (e.g. *N*-CH_3 axial to equatorial ratio of 4 : 1 for tropine trideuteriomethiodide,[22] and *N*-CH_3 axial to equatorial ratio of 3 : 1 for tropine *N*-oxide[23]). However, axial attack preponderates for *N*-methylation of simple *N*-methylpiperidines[22,24] and morpholines[22] (e.g. *N*-CH_3 axial to equatorial ratio of 1 : 4 for 2,4,6-trimethylmorpholine trideuteriomethiodide[22]). The existence of a minor second conformation (putative **7**) might be responsible for the lowered kinetic approach control selectivity in the *N*-quaternization reactions.



8



9

In conclusion, line broadening for **6** plus the similar effect found earlier for **1e** of the parent hydrochloride salt[3] points to the ability of the 2,5-benzoxazocine ring to attain a second, but minor, solution-state conformation in addition to the well characterized preferred boat–(flattened chair) for **1e**, **4** and **5**. Studies are in progress to force the nefopam 2,5-benzoxazocine ring into structures having a new stable conformation. Preliminary results have shown that appropriate derivatization of nefopam can afford compounds having predominantly the new twist-chair–(flattened chair) conformation.[25]

EXPERIMENTAL

A mixture of nefopam *N*-oxide diastereomers was prepared by hydrogen peroxide oxidation of the corresponding free base in ethanol by a method analogous to that described by Huber *et al.*[23] Nefopam methiodide and nefopam trideuteriomethiodide were prepared by reaction of nefopam free base with the corresponding alkyl iodide. Nefopam hydrochloride was a gift from 3M Riker (U.K.). Trideuteriomethyl iodide was obtained from Yeda (Rehovot, Israel). Elemental analyses commensurate with the proposed empirical formulae were obtained for the *N*-oxide diastereomeric mixture and for the quaternary ammonium salts.

^{1}H and ^{13}C NMR spectra (7.3 T, CD_2Cl_2, sealed 5-mm sample tube, 298 K) of the quaternary ammonium salts were obtained at 300.1 and 75.5 MHz, respectively, on a Bruker AM-300 Fourier transform spectrometer equipped with an Aspect 3000 data system. ^{1}H and ^{13}C NMR spectra (4.7 T, CD_3CN, sealed 5-mm sample tube, 298 K) of the *N*-oxide diastereomeric mixture were obtained at 200.1 and 50.3 MHz, respectively, on a Bruker WP-200-SY Fourier transform spectrometer equipped with an Aspect 2000 data system. The deuteriated solvent was used as an internal lock, and the residual dichloromethane ^{1}H resonance was used as an internal secondary reference (δ_H 5.32 and δ_C 53.8 relative to tetramethylsilane). Difference NOE spectra (Bruker NOEDIFF program) were obtained using the cycled, low-power irradiation technique[14] (12 irradiation periods of 0.4 s each per scan). ^{13}C NMR spectra were acquired using the broad-band proton decoupling mode and by the DEPT tech-

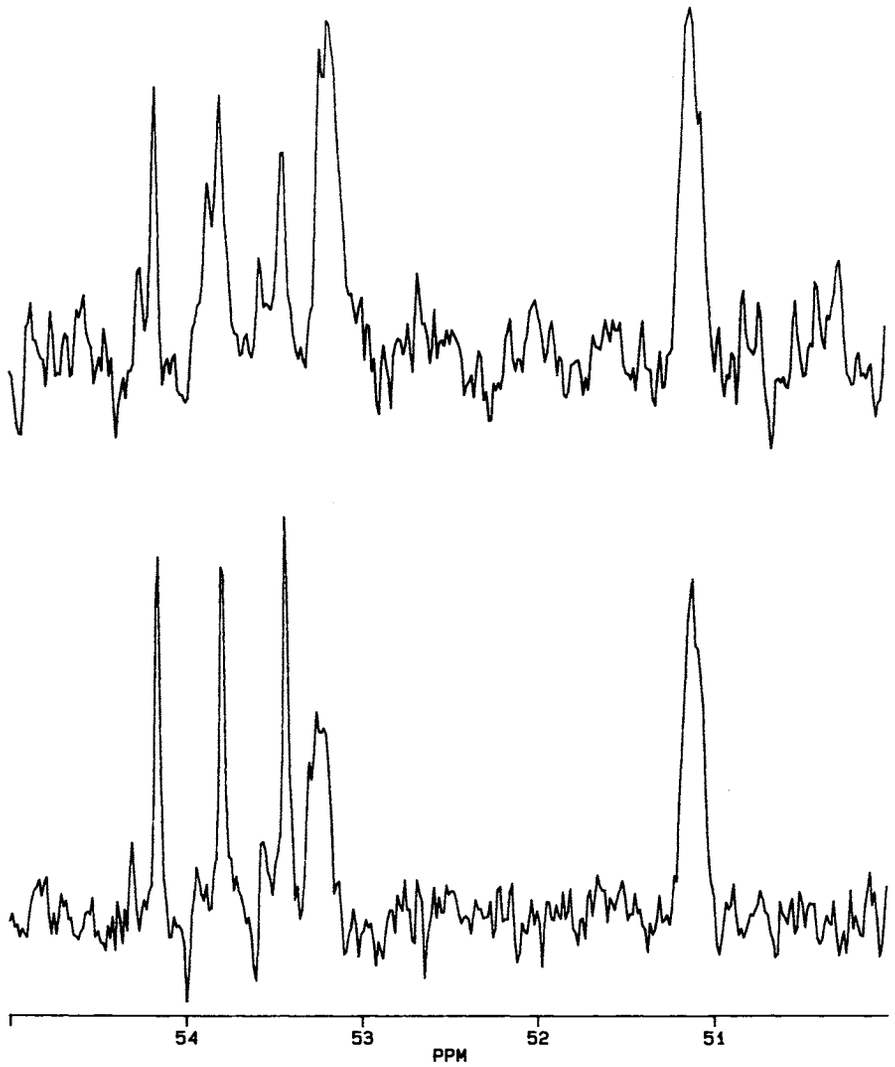


Figure 3. ^{13}C NMR partial spectra (75.5 MHz, DEPT 135° pulse width, CD_2Cl_2, 298 K, δ 55.0–50.0) showing the *N*-methyl resonances of nefopam methiodide (**6**) (top) and of the isotopomeric nefopam trideuteriomethyl iodide diastereomeric mixture (**8**, **9**) (bottom). The equal-intensity three-line signal at *ca.* 53.8 ppm arises from the residual isotopomeric $CHDCl_2$ species of the solvent.

nique (135° and 90° pulse width). Standard Bruker DEPT and XHCORR programs were used.

The minimized energy geometry of the molecular mechanics model compounds were determined by the MMX88 program,[16] and were performed on a MicroVAX-II computer under MicroVMS V4.5. MMX88 is an enhanced version of Allinger's MM2[26] program with MMP1 [27] π-subroutines incorporated for localized π-electron systems.

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