Compounds with Bridgehead Nitrogen

48†—Stereochemistry of the 5-Methylperhydropyrido[3,2,1-*i,j*][3,1]-benzoxazines

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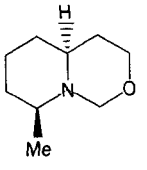
Six of the eight possible diastereoisomeric 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines have been synthesized, and the utility of the C-3 methylene proton NMR parameters [*J*(3ax3eq) and Δ3ax3eq] in the assignment of configurations has been demonstrated.

INTRODUCTION

Following the observation of the marked analgesic activity of *cis*-(H-4a, H-8)8-methylperhydropyrido-[1,2-*c*][1,3]oxazine (**1**), the synthesis of the related but conformationally locked 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines (**2**) was undertaken.



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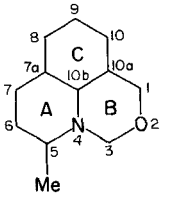

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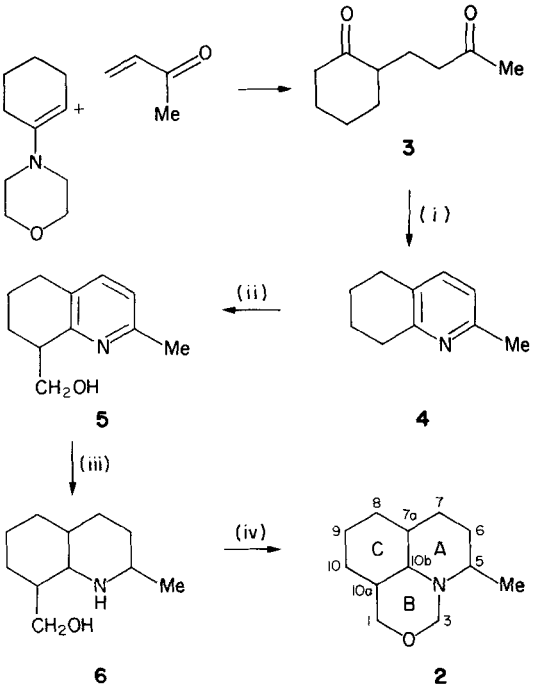
(**1** showed marked analgesic activity at a dose of 100 mg kg^{-1} on the hot plate and phenylquinone-induced writhing tests carried out by Glaxo Group Research Limited.) A study of the ^{1}H NMR spectra of the isomers of **2** was made in order to make configurational assignments.

SYNTHESIS OF COMPOUNDS

The reaction sequence for the synthesis of the isomeric 5-methylperhydropyrido[3, 2, 1-*i, j*][3, 1]benzoxazines (**2**) is given in Scheme 1. The synthesis of 2-methyl-5,6,7,8-tetrahydroquinoline (**4**) proceeded via the diketone **3**, prepared by reaction between methyl vinyl ketone and 1-morpholinocyclohex-1-ene. The ring closure of **3** with hydroxylammonium chloride gave **4** in good yield.

Compound **4** was heated with excess of paraformaldehyde to give 8-hydroxymethyl-2-methyl-5,6,7,8-tetrahydroquinoline (**5**). Two isomeric 5-methylperhydro[3,2,1-*i,j*][3,1]benzoxazines (**2a** and **2b**) were produced by catalytic hydrogenation of **5** followed by ring closure with aqueous formaldehyde of the resultant 8-hydroxymethyl-2-methyldecahydroquinolines



Scheme 1. Reagents: (i) $NH_2OH{\cdot}HCl$; (ii) paraformaldehyde; (iii) Na EtOH or Pt–H_2; (iv) aq. HCHO.

(**6**). Isomer **2a** was eluted first from a chromatographic column of grade III Woelm alumina.

The reduction of **5** with sodium in ethanol gave a mixture of the 8-hydroxymethyl-2-methyldecahydroquinolines (**6**), which was readily ring closed with formaldehyde to give a mixture of isomeric 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines (**2**). This was separated by column chromatography over alumina to give six isomers, **2a–2f**.

RESULTS

Stereochemistry of 5-methylperhydropyrido[3,2,1-*i,j*]-[3,1]benzoxazines (2)

There are eight possible diastereoisomers of **2** and six of these (**2a–2f**) were isolated by the route shown in

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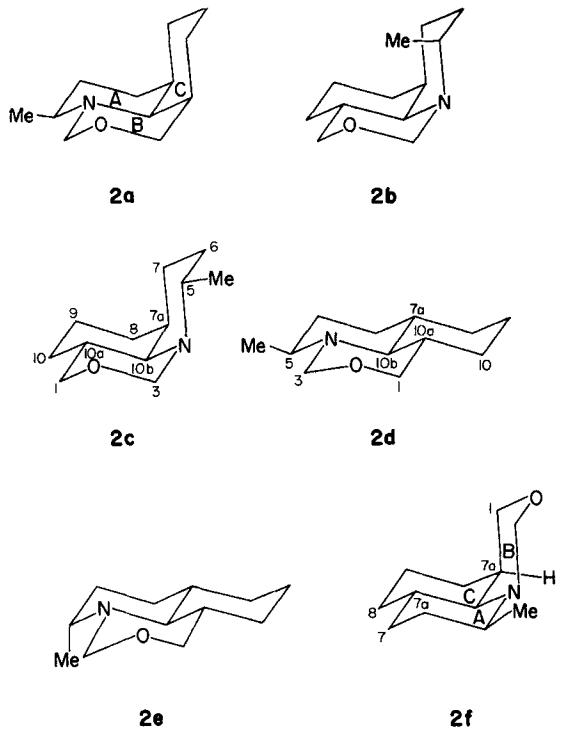

Scheme 1. Their configurations were assigned on the basis of the 270 MHz NMR data provided in Tables 1 and 2.

r-5,c-7a,c-10a,c-10b-5-Methylperhydropyrido[3,2,1-*i,j*]-[3,1]benzoxazine (2a). In the NMR spectrum of **2a** the C-3 geminal coupling of −7.55 Hz[2] and the large difference (1.40 ppm) in chemical shift between the 3eq- and 3ax-protons are consistent with the *trans*-A/B ring fusion in which the nitrogen lone pair is *trans* and axial to the 3ax-proton.[3] The vicinal coupling between the 1eq-proton (δ 3.62) and the 10a-proton is 0.0 Hz, and the 1ax-proton signals (δ 3.57) show a vicinal *J*(1ax10a) value of 3.2 Hz, indicating a *cis*-B/C ring fusion. The 10b-proton signal (δ 2.25) appears as a broad singlet, clearly showing no *J*(axax) couplings to the 7a- or 10-protons, confirming the *cis*-B/C ring fusion. The high-field absorption for the 5-proton indicates its axial orientation and the equatorial nature of the methyl substituent.

Strong Bohlmann bands[4] in the 2800–2600 cm^{-1} region of the IR spectrum of **2a** indicate the three axial C—H bonds (3ax, 5ax and 10b) *trans* to the axial nitrogen lone pair.

r-5, c-7a, t-10a, c-10b-5-Methylperhydropyrido[3, 2, 1-*i,j*]-[3,1]benzoxazine (2b) and r-5,t-7a,c-10a,t-10b-5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazine (2c). The magnitude (−10.8 Hz) of *J*(3ax3eq) in the NMR spectrum of **2b** indicates the *cis*-A/B ring fused structure in which the nitrogen lone pair bisects the C-3 methylene group, and the very small Δ3eq3ax value (0.05 ppm) supports this. Analysis of the 5-proton signals (δ 3.28 in $CDCl_3$) gave vicinal couplings of 7 Hz to the methyl group protons and vicinal couplings between the 5-proton and the 6-methylene protons of 7 Hz and 0 Hz. The magnitudes of these *J*(56) couplings eliminate the possibility of an axial proton and indicate that the structure of the isomer corresponds to **2b** with an axial methyl group. This is expected as a result of the synthetic sequence with predominant *cis*-hydrogenation of a 5,6,7,8-tetrahydroquinoline intermediate. The observed *J*(56) values of 7 Hz and 0 Hz are consistent with dihedral angles of *ca* 30° and 90°, respectively. Dreiding models show that this geometry can be realised by a distortion of the chair A ring as a result of minimizing non-bonded interactions involving the axial methyl group. This distortion places the 5ax-methyl close to the oxygen lone pair which,[5] together with the effect of two *syn* axial interactions,[6] accounts for the deshielding of the methyl group protons (δ 1.35) relatice to isomer **2a** (δ 1.06). Since the

Table 1. ^{1}H NMR spectra of the isomeric 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines (2a–2f) in $CDCl_3$

Compound	Chemical shifts (δ)										
	3eq	3ax	1eq	1ax	5eq	5ax	7a	10a	10b	10ax	CH_3
2a	4.71	3.31	3.62	3.57	—	2.1	—	—	2.25	—	1.06
2b	4.55	4.50	3.90	3.22	3.28	—	—	2.25	2.74	0.68	1.35
2c	4.80	4.30	3.89	3.24	—	3.26	—	—	—	—	1.12
2d	4.71	3.42	3.81	3.05	—	1.95	—	—	—	0.89	1.06
2e	4.28	3.89	3.78	3.03	3.10	—	—	—	—	—	0.94
2f	4.34	4.30	3.63	3.60	—	2.91	1.99	2.25	2.65	—	1.14

Table 2. ^{1}H NMR spectra of the isomeric 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines (2a–2f) in $CDCl_3$

Compound	Coupling constants (Hz)														
	J(3ax3eq)	*J*(1ax1eq)	*J*(1ax10a)	*J*(1eq10a)	*J*(5ax6ax)	*J*(5ax6eq)	*J*(5eq6ax)	*J*(5eq6eq)	*J*(H-5,CH_3)	*J*(10a10b)	*J*(10b7a)	*J*(10ax10eq)	*J*(10ax9ax)	*J*(10ax10a)	*J*(10ax9eq)
2a	−7.55	−11.0	3.2	0.0	—	—	—	—	6.8	—	—	—	—	—	—
2b	−10.8	−11.3	11.3	4.8	—	—	7.0	0.0	7.0	11.5	4.5	−12.0	12.0	11.3	4.0
2c	−11.1	−11.2	11.2	4.2	—	—	—	—	—	—	—	—	—	—	—
2d	−7.65	−11.0	11.6	5.3	11.0	2.75	—	—	6.0	—	—	−12.4	12.4	12.4	4.0
2e	−7.8	−11.2	11.2	4.5	—	—	2.5	2.5	6.7	—	—	—	—	—	—
												J(7a7ax)	*J*(7a8ax)	*J*(7a10b)	*J*(7a8eq)
2f	−8.0	—	—	5.6	11.9	2.5	—	—	7.3	4.9	10.9	11.3	11.3	11.3	3.6
												J(7a7eq)			
												3.6			

methyl group seemed particularly hindered by the 10a-proton, an NOE difference spectrum was run, saturating the 10a-proton multiplet at δ 2.25. Differential peaks were obtained for the 1eq-, 10b-, 1ax- and 7ax-protons as expected, together with a *ca* 5% enhancement of the methyl doublet at δ 1.35, giving further proof of structure **2b**. The four lines of the 10b proton absorption at δ 2.74 show a small *J*(10b7a) of *ca* 4.5 Hz and a large *J*(10a10b) of 11.5 Hz. Added to this, the *J*(10a1ax) of 11.3 Hz, *J*(10a,10ax) of 11.3 and the *J*(10a,1eq) of 4.8 Hz confirm the stereochemistry **2b**. The complete lack of Bohlmann bands in the IR spectrum of **2b** shows the absence of C—H bonds *trans* diaxial to the nitrogen lone pair and supports the assigned stereochemistry.

As in the case of **2b**, the value of *J*(3ax3eq) of −11.1 Hz in the NMR spectrum of **2c** and the lack of Bohlmann bands in the IR spectrum indicated the *O*-inside *cis*-A/B ring fusion shown in the structure. The methyl group was located in the equatorial position since, relative to that in **2b**, the 3eq-proton shows deshielding (*ca* 0.25 ppm) by the *peri*-type methyl group[7] and the absorption for the methyl group protons is 'normal' at δ 1.12. The 5ax-proton is deshielded relative to that in **2a** and **2d** by the C-3—O bond and by a *syn*-axial 'alkyl' group (the C10b-substituent).

***r*-5, *t*-7a, *t*-10a, *c*-10b-5-Methylperhydropyrido[3, 2, 1-*i*,*j*]-[3,1]benzoxazine (2d) and *r*-5,*c*-7a,*c*-10a,*t*-10b-5-methylperhydropyrido[3,2,1-*i*,*j*][3,1]benzoxazine (2e).** The *trans*-A/B ring fusion and the equatorial methyl substituent in **2d** was indicated by the close similarity between the 3-methylene parameters in **2d** and in **2a**. The high-field absorption of the 5-proton (δ 1.95) confirmed the equatorial orientation of the methyl substituent and the *trans*-B/C fusion in **2d** shown by the coupling constants involving the 10a-proton (Table 2).

The magnitude (−7.8 Hz) of *J*(3ax3eq) for **2e** taken with the values of the vicinal coupling constants between the 1-methylene protons and H-10a, and the low-field absorption (δ 3.10) for the 5-proton, indicate either structure **2e** or the axial methyl epimer of **2f**. The latter is, however, eliminated by the high-field absorption of H-10b (to high-field of δ 2.0).[3] Accordingly, structure **2e** is assigned to this isomer.

***r*-5,*t*-7a,*c*-10a,*c*-10b-5-Methylperhydropyrido[3,2,1-*i*,*j*]-[3,1]benzoxazine (2f).** The very small Δ3ax3eq of 0.04 ppm, together with the *J*(3ax3eq) value of −8.0 Hz, indicated[3] the *O*-outside *cis*-A/B structure for **2f**. The *trans*-A/C ring fusion was shown by the coupling constants involving the 7a- and the 10b-protons, and analysis of the splitting pattern for the 5-proton showed the equatorial orientation of the methyl substituent.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded for 10% solutions in $CDCl_3$ on a Bruker WH-270 spectrometer (sweep width 3 kHz, number of scans 100, accumulation 4K or 16K data points, Fourier transform over 8K data points). Chemical shifts are in ppm downfield from internal TMS and are considered accurate to ±0.2 ppm, and coupling constants to ±0.2 Hz. Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic.

4-(1-Oxocyclohex-2-yl)butan-2-one

Methyl vinyl ketone (70 g) and 1-morpholinocyclohex-1-ene (167 g) were refluxed for 4 h in benzene (150 ml). After removal of benzene *in vacuo* the residue was distilled, giving 4-(1-oxocyclohex-2-yl)butan-2-one (67 g, 42%), b.p. 105 °C at 0.5 mmHg (lit.,[8] 156–157 °C at 10 mmHg).

2-Methyl-5,6,7,8-tetrahydroquinoline

4-(1-Oxocyclohex-2-yl)butan-2-one (55 g) and hydroxylammoniun chloride (23 g) in ethanol (150 ml) were boiled under reflux. After removal of the ethanol *in vacuo*, the residue was neutralized with sodium carbonate and extracted with diethyl ether. The ether was removed *in vacuo* and the residue distilled, giving 2-methyl-5,6,7,8-tetrahydroquinoline (25 g, 62%), b.p. 70 °C at 0.1 mmHg (lit.,[9] 110 °C at 10 mmHg).

8-Hydroxymethyl-2-methyl-5,6,7,8-tetrahydroquinoline

2-Methyl-5,6,7,8-tetrahydroquinoline (25 g) and paraformaldehyde (15 g) were heated for 100 h in a lightly sealed flask on a boiling water-bath (100 °C). After cooling, hydrochloric acid (100 ml, 20%) was added and the solution filtered. The filtrate was basified with aqueous sodium hydroxide solution and then extracted with benzene. After removal of the benzene *in vacuo* the remaining liquid was distilled, giving *8-hydroxymethyl-2-methyl-5,6,7,8-tetrahydroquinoline* (3 g, 12%) as a colourless mobile liquid, b.p. 130 °C at 0.1 mmHg. (Found: C, 74.0; H, 8.4; N, 7.8%. $C_{11}H_{15}NO$ requires C, 74.6; H, 8.5; N, 7.9%).

5-Methylperhydropyrido[3,2,1-*i*,*j*][3,1]benzoxazine. Isomers 2a and 2b

A solution of 8-hydroxymethyl-2-methyl-5,6,7,8-tetrahydroquinoline (9 g) in glacial acetic acid (30 ml) to which Adams catalyst (PtO_2, 1 g) had been added was shaken under hydrogen in a Parr hydrogenator until the calculated uptake of hydrogen had been achieved. After filtering off the catalyst the bulk of the acid was removed *in vacuo* and the residue basified with sodium hydroxide. The solution was extracted with diethyl ether and the separated ether layer dried over anhydrous sodium sulphate. After removing the ether, a mixture of isomeric 8-hydroxymethyl-2-methyldecahydroquinolines (8 g, 87%) was obtained, which could not be separated by fractional crystallisation.

Table 3. Boiling points, yields and elemental analyses of the isomeric 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines

Compound	Configuration	B.p. (°C)	Yield (g)	Analysis (%)[a]
2a	*r*-5,*c*-7a,*c*-10a,*c*-10b	75–76 (0.15 mmHg)	0.1	C, 73.6; H, 10.9; N, 7.15
2b	*r*-5,*c*-7a,*t*-10a,*c*-10b	78–80 (0.1 mmHg)	0.2	C, 73.55; H, 11.0; N, 7.0
2c	*r*-5,*t*-7a,*c*-10a,*t*-10b	77–78 (0.1 mmHg)	0.11	C, 73.7; H, 11.0; N, 7.2
2d	*r*-5,*t*-7a,*t*-10a,*c*-10b	73–74 (0.1 mmHg)	1.25	C, 73.6; H, 10.7; N, 7.25
2e	*r*-5,*c*-7a,*c*-10a,*t*-10b	80–81 (0.15 mmHg)	0.62	C, 73.8; H, 10.9: N, 7.2
2f	*r*-5,*t*-7a,*c*-10a,*c*-10b	78–80 (0.1 mmHg)	0.15	C, 73.95; H, 10.8; N, 7.3

[a] $C_{12}H_{21}NO$ requires C, 73.8; H, 10.8; N, 7.2%.

The mixture of isomers (7 g) was shaken with 40% aqueous formaldehyde (20 ml) for 30 min, basified with 30% aqueous sodium hydroxide and extracted with diethyl ether. The dried ether extracts were distilled to give a colourless mobile liquid consisting of a mixture of isomers of 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazine (5 g, 71%), b.p. 121–150 °C at 760 mmHg. The mixed isomers (3 g) were chromatographed over grade III Woelm neutral alumina (250 g). The column was packed in carbon tetrachloride and eluted with light petroleum (b.p. 30–40 °C) until no further carbon tetrachloride remained. The sample was loaded in light petroleum (b.p. 30–40 °C) and eluted with diethyl ether–light petroleum (b.p. 30–40 °C) containing increasing amounts of diethyl ether from 0 to 50%. Thirty fractions (50 ml) were taken. Fractions 1–4 yielded isomer **2a**, *r-5,c-7a,c-10a,c-10b-5-methylperhydropyrido*[3, 2, 1-*i,j*][3, 1]*benzoxazine* (0.8 g), b.p. 108 °C at 760 mmHg. (Found. C, 74.1; H, 10.7; N, 7.2%. $C_{12}H_{21}NO$ requires C, 74.0; H, 10.8; N, 7.2%.) Fractions 9–14 yielded isomer **2b**, *r-5,c-7a, t-10a, c-10b-5-methylperhydropyrido*[*3, 2, 1-i,j*]-[*3,1*]*benzoxazine* (0.7.g), b.p. 162 °C at 760 mmHg. (Found: C, 73.8; H, 10.7; N, 7.1%. $C_{12}H_{21}NO$ requires C, 74.0; H, 10.8; N, 7.2%.) No further isomers were found on continued elution.

2-Methyldecahydroquinolin-8-ylmethanol

A solution of 2-methyl-5,6,7,8-tetrahydroquinolin-8-ylmethanol (0.133 M, 23.5 g) in absolute ethanol (300 ml) was boiled under reflux and sodium metal (45 g) added slowly over 1.5 h. The solution was boiled under reflux for a further 2 h before being cooled to room temperature. The solution was acidified carefully with hydrochloric acid and then basified with 30% aqueous sodium hydroxide solution and extracted with diethyl ether (3 × 100 ml). The combined ethereal extracts were dried (Na_2SO_4), evaporated, and the residue was distilled *in vacuo* to give *2-methyldecahydroquinolin-8-ylmethanol* (12.4 g, 51%) as a colourless oil, b.p. 96–98 °C at 0.1 mmHg (Found: C, 72.1; H, 11.4; N, 7.7%. $C_{11}H_{21}NO$ requires C, 72.1; H, 11.55; N, 7.6%.)

5-Methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazine

The mixture of isomeric 2-methyldecahydroquinolin-8-ylmethanols (0.055 M, 10 g) prepared by the sodium in ethanol reduction was shaken with excess of 36% aqueous formaldehyde solution (10 ml) for 1 h. The solution was basified, extracted with diethyl ether (4 × 40 ml) and the combined ether extracts were dried (Na_2SO_4), concentrated and the residue was distilled *in vacuo* to give an isomeric mixture of 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazines (6.3 g, 59%) as a colourless oil, b.p. 86–87 °C at 0.1 mmHg. The individual isomers were separated by column chromatography on a column of H-type grade 3 alumina (800 g) [elution with 1.5–15% diethyl ether in light petroleum (b.p. 40–60 °C); 50 ml fractions]. Table 3 shows the boiling points, yields and elemental analyses of the six isomers of 5-methylperhydropyrido[3,2,1-*i,j*][3,1]benzoxazine in order of elution.

REFERENCES

1. P. M. R. Barkworth, T. A. Crabb and P. Robinson, *J. Chem. Soc., Perkin Trans. 1* 2807 (1983).
2. J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.* **42**, 1339 (1965).
3. T. A. Crabb, R. F. Newton and D. Jackson, *Chem. Rev.* **71**, 109 (1971).
4. F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).
5. T. A. Crabb and M. J. Hall, *J. Chem. Soc., Perkin Trans. 2* 1419 (1974).
6. H. Booth, *Tetrahedron* **22**, 615 (1966).
7. R. J. Abraham and S. J. E. Holker, *J. Chem. Soc.* 806 (1963).
8. W. C. Thompson, *J. Am. Chem. Soc.* **53**, 3160 (1931).
9. J. Epstajn, W. E. Hahn and B. Tosik, *Rocz. Chem.* **43**, 807 (1969).

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