Compounds with Bridgehead Nitrogen

42†—^{1}H NMR and Stereochemistry of Isomeric 6a-Methylperhydroindolo[3,2,1-*i,j*]benzoxazines and the Position of Conformational Equilibrium in Perhydropyrrolo[1,2-*c*][1,3]oxazine

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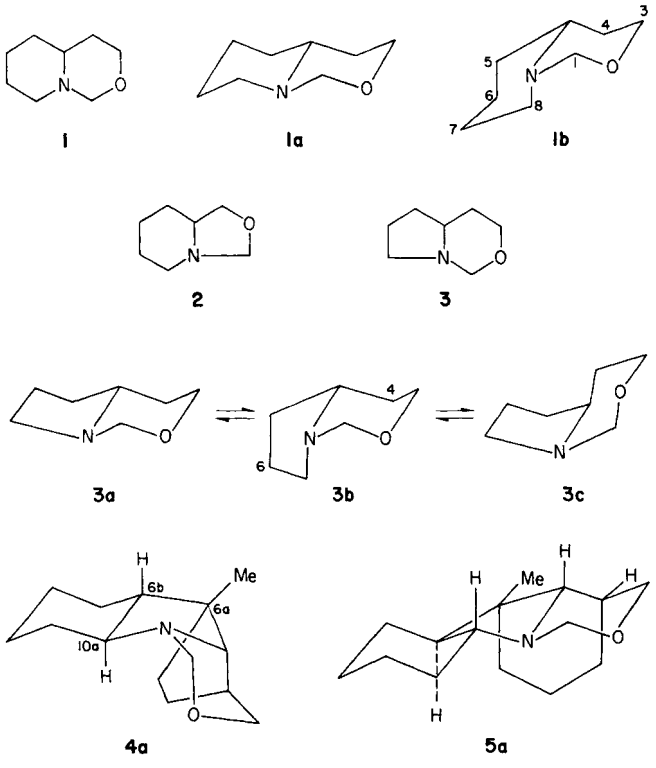
The ^{1}H NMR parameters of the NCH_2O protons in the spectrum of perhydropyrrolo[1,2-*c*][1,3]oxazine show its existence in solution at room temperature in the *O*-inside *cis*-fused conformation. *rel*-(3a*S*,6a*S*,6b*R*,10a*S*,11a*S*)-6a-Methylperhydroindolo[3,2,1-*i,j*]benzoxazine and *rel*-(3a*S*,6a*S*,6b*S*,10a*R*, 11a*S*)-6a-methylperhydroindolo[3,2,1-*i,j*]benzoxazine are shown to adopt *cis*- and *trans*-fused conformations, respectively, for the corresponding bicyclic moiety.

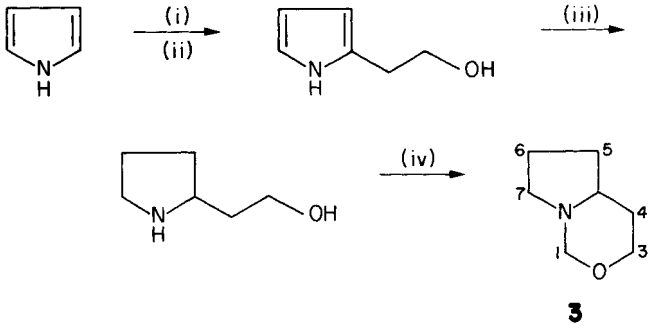
INTRODUCTION

Whereas conformational equilibria in perhydropyrido[1,2-*c*][1,3]oxazine (**1**)[2,3] and in perhydrooxazolo[3,4-*a*]pyridine (**2**)[4–7] have been extensively studied, no conformational studies of perhydropyrrolo[1,2-*c*][1,3]oxazine (**3**) have been described. Accordingly, **3** and the conformationally locked isomeric 6a-methylperhydroindolo[3,2,1-*i,j*]benzoxazines (**4** and **5**) were synthesized for stereochemical and ^{1}H NMR studies.



SYNTHESIS OF COMPOUNDS

Perhydropyrrolo[1,2-*c*][1,3]oxazine (**3**) was synthesized by the route shown in Scheme 1, and two isomers (**4** and **5**) of 6a-methylperhydroindolo[3,2,1-*i,j*]benzoxazine by the route shown in Scheme 2. The *cis*-relationship between the 6a-Me and C-3a—H in both isomers is expected, since this is present in *trans*-1-hydroxymethyl-4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole, the synthesis of which followed published procedures.[8,9]



Scheme 1. Reagents: (i) C_2H_5MgBr; (ii) ethylene oxide; (iii) H_2/PtO_2; (iv) 40% aqueous formaldehyde.

RESULTS AND DISCUSSION

Perhydropyrrolo[1,2-*c*][1,3]oxazine (**3**) may exist in solution as an equilibrium between the *trans*-fused conformer (**3a**), the *O*-inside *cis*-fused conformer (**3b**) and the *O*-outside *cis*-fused conformer (**3c**). Since in

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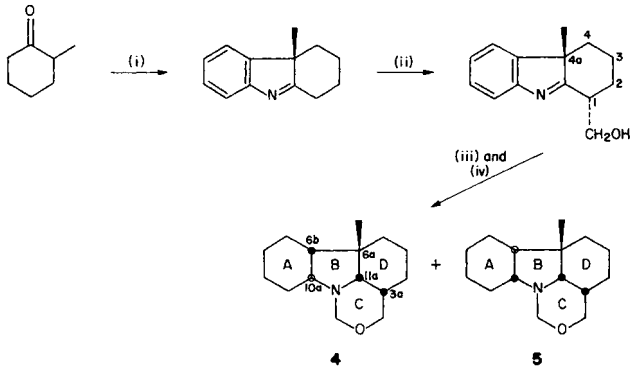
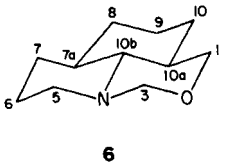


Scheme 2. Reagents: (i) phenylhydrazine; (ii) paraformaldehyde/dry dioxane; (iii) H_2/PtO_2; (iv) 40% aqueous formaldehyde.

these types of systems the geminal coupling constant [$J(gem)$] between the NCH_2O protons is sensitive to the orientation of the heteroatom lone pairs of electrons with respect to the C—H bonds of the methylene group,[10] then the magnitudes of $J(gem)$ in **3a** and **3c** and in **3b** are expected to be similar to that (−7.55 Hz) in *r*-7a, *c*-10a,*t*-10b-perhydropyrido[3,2,1-*i*,*j*][3,1]-benzoxazine (**6**)[3] (parallel nitrogen lone pair/CH geometry) and to that (−10.8 Hz) in the *r*-7a,*t*-10a,*c*-10b isomer (**7**)[3] (bisecting nitrogen lone pair/CH_2 geometry), respectively. In fact, the ^{1}H NMR spectrum of **3** (Table 1) showed $J(gem) = -10.2$ Hz (cf. −10.8 Hz in **7**) indicating the *O*-inside *cis*-fused conformation (**3b**).

To provide additional confirmation of this preference for the *cis* conformation, the ^{1}H NMR spectra of the conformationally locked 6a-methylperhydroindolo[3,2,1-*i*,*j*]benzoxazines (**4** and **5**) were recorded.

The ^{1}H NMR spectrum of **5** shows $J(NCH_2O) = -6.7$ Hz, a larger value than that observed for *trans*-fused perhydropyrido[1,2-*c*][1,3]oxazines (cf. −7.55 Hz in **6**) but which can only be reconciled with a *trans*-fused perhydropyrrolo[1,2-*c*][1,3]oxazine moiety. This conformation is also supported by the large difference in chemical shift (Δ_{ae})[11] between the NCH_2O protons and by the presence of strong absorption in the 2800–2600 cm^{-1} region of the IR spectrum.[11] The remainder of the NMR data are consistent with the stereochemistry shown in **5a**. In particular, the vicinal coupling constants involving the 3a- and 11a-protons define the B/C/D fusions and the H-10a parameters the *trans*-A/B junction. (The 11a-proton, unobservable in the spectrum of **5** in C_6D_6, was clearly visible as a doublet in the spectrum recorded in DCl solution).



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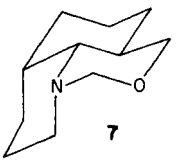

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The absence of Bohlmann bands in the IR spectrum of isomer **4**, together with the small Δ_{ae} of 0.25 ppm for the NCH_2O protons, suggest the *O*-inside *cis*-fused perhydropyrrolo[1,2-*c*][1,3]oxazine moiety (*cis*-B/C junction). The $J(gem)$ for the NCH_2O protons of −9.5 Hz also supports this stereochemistry, although slightly larger than the value (−10.2 Hz) observed for **3b**. The *O*-inside *cis*-conformation is confirmed by the low field shift of H-10a (1,3-*syn*-axial to oxygen and to the C-4 methylene), and the B/C/D fusions shown in **4a** by the vicinal coupling constants involving H-3a and H-11a. The *trans*-A/B junction is suggested by the vicinal coupling constants involving H-10a.

The *O*-inside *cis*-conformational preference for **3** is in direct contrast to that for perhydropyrido[1,2-*c*][1,3]oxazine (**1**), which favours the *trans*-conformation (**1a**) (*ca.* 90% **1a** ⇌ *ca.* 10% **1b**).[3] This must be due in

Table 1. ^{1}H NMR spectra of perhydropyrrolo[1,2-*c*][1,3]oxazine (3), *rel*-(3a*S*,6a*S*,6b*R*,10a*S*,11a*S*)-6a-methylperhydroindolo[3,2,1-*i*,*j*]benzoxazine (4) and *rel*-(3a*S*,6a*S*,6b*S*,10a*R*,11a*S*)-6a-methylperhydroindolo[3,2,1-*i*,*j*]benzoxazine (5)

		Chemical shifts (δ)							
Compound	Solvent	1ax	1eq	3ax	3eq	4ax	CH_3	10a	11a
3[a]	CCl_4	3.70	4.03	3.49	3.94				
4[b]	CCl_4	4.40	4.62	3.29	3.58	2.20	1.0	2.80	2.95
	C_6D_6	4.44	4.69	3.48	3.76	2.23	0.93	2.76	2.87
5[b]	CCl_4	3.42	4.36	3.30	3.60	1.90	0.85	2.20	1.82
	C_6D_6	3.58	4.66	3.37	3.75	2.10	0.80	2.04	—
	DCl	4.45	5.22	3.85	3.97	2.11	1.20	3.45	3.29

		Coupling constants (Hz)[c]													
Compound	Solvent	J(1ax, 1eq)	J(3ax, 3eq)	J(3ax, 3a)	J(3ax, 4ax)	J(3ax, 4eq)	J(3eq, 4ax)	J(4ax, 3a)	J(4ax, 4eq)	J(4ax, 5ax)	J(4ax, 5eq)	J(10a, 6b)	J(10a, 10ax)	J(10a, 10eq)	J(11a, 3a)
3[a]	CCl_4	−10.2	−11.8		11.5	2.5	5.0								
4[b]	C_6D_6	−9.5	−10.6	3.0								8.9	13.3	4.6	4.6
5[b]	C_6D_6	−6.7	−11.3	2.6				13.7	−13.7	−13.7	3.8	10.5	13.7	4.7	
	DCl	−8.1	−12.2	2.9								11.5	11.8	6.0	2.5

[a] Spectrum determined at 100 MHz.
[b] Spectra determined at 270 MHz.
[c] Coupling constants were of the same magnitude in spectra recorded in CCl_4 and in C_6D_6.

part to the reduction in the C-6/C-4 *gauche* butane type interaction in **3b** relative to **1b**. In addition, **3a** is presumably destabilized relative to **1a** by ring fusion strain (cf. relative stability of hydrindanes and decalins[12]).

EXPERIMENTAL

NMR spectra were recorded for 10% solutions (at *ca.* 18 °C) in CCl_4, C_6D_6 or DCl (see Table 1) on a Bruker WH-270 spectrometer (sweep width 3 kHz, number of scans 100, accumulation 4K data points, Fourier transform over 8K data points). Chemical shifts are in ppm downfield from internal TMS or, in the case of DCl solution, from DSS. Coupling constants are considered to be accurate to ±0.1 Hz. IR spectra were recorded on a Perkin–Elmer 297 spectrometer for 0.2 M solutions in $CDCl_3$ using 0.2 mm matched cells. Elemental analyses were carried out by the Analytical Section, Portsmouth Polytechnic.

Perhydropyrrolo[1,2-*c*][1,3]oxazine. Ethyl bromide (60 g, 0.55 M) in dry diethyl ether (50 ml) was added to magnesium (12 g, 0.50 M) in the same solvent (50 ml). When formation of the Grignard reagent was complete, pyrrole (33 g, 0.49 M) in dry diethyl ether (20 ml) was added dropwise. The reaction mixture was cooled, dry benzene (50 ml) added and the mixture heated to 40–45 °C. Ethylene oxide (22 g, 0.50 M) was added at a rate such that reflux was maintained. When addition had been completed, the reaction mixture was kept at 100 °C for 2 h, then cooled and excess of water added. After shaking and separation of the benzene layer, the aqueous layer was acidified with dilute sulphuric acid and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), concentrated and distilled to give 2-(2-hydroxyethyl)-pyrrole as a viscous oil (6 g, 11.0%), b.p. 96–100 °C at 0.15 mmHg. This (5 g, 0.045 M) was dissolved in glacial acetic acid (200 ml) and platinum oxide (1 g) added. Hydrogenation was carried out at 60 lb in.$^{-2}$ in a Parr hydrogenator until uptake was complete. After filtration the acetic acid was evaporated and the residue basified with sodium hydroxide solution and extracted with diethyl ether. After drying (Na_2SO_4) and removal of the solvent, the residue was distilled to give 2-(2-hydroxyethyl)pyrrolidine as a viscous oil (3.5 g, 67.6%), b.p. 96–100 °C at 0.25 mmHg. This oil (3 g, 0.026 M) was shaken with formaldehyde solution (40%, 3 ml, 0.04 M) for 30 min. The mixture was basified, extracted with diethyl ether and the extract dried (Na_2SO_4) and concentrated. Distillation of the residue gave *perhydropyrrolo*[1,2-*c*][1,3]*oxazine* (**3**) as a colourless viscous oil (0.35 g, 10.6%), b.p. 80–83 °C at 24 mmHg. (Found: C, 66.4; H, 10.1; N, 11.1. $C_7H_{13}NO$ requires C, 66.1; H, 10.3; N, 11.0%).

4a-Methyl-1,2,3,4-tetrahydro-4a*H*-carbazole. This was prepared[8] from phenylhydrazine and 2-methylcyclohexanone in 50% yield, b.p. 98–100 °C at 0.25 mmHg (lit.,[13] 98–100 °C at 0.3 mmHg).

***trans*-1-Hydroxymethyl-4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole.** This was prepared[9] from 4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole and paraformaldehyde in dry dioxane in 34% yield, m.p. 96–97 °C (lit.,[9] 28%, m.p. 96–99 °C).

***trans*-1-Hydroxymethyl-4a-methyl-1,2,3,4,6b,7,8,9,10,10a-decahydro-4a*H*-carbazoles.** *trans*-1-Hydroxymethyl-4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole (5.0 g, 0.023 M) was dissolved in glacial acetic acid (200 ml) and Adams catalyst (0.5 g) added. The mixture was hydrogenated at 60 lb in^{-2} in a Parr hydrogenator until the calculated uptake of hydrogen was achieved (24 h). The catalyst was removed by filtration and washed with water. The combined filtrates were evaporated, using a rotary evaporator, on a water-bath at ≤35 °C. The residue was basified with sodium hydroxide solution (10%) and extracted with chloroform. After drying ($MgSO_4$) and evaporation, there remained, as a sticky colourless oil, a mixture of 1-hydroxymethyl-4a-methyl-1,2,3,4,6b,7,8,9,10,10a-decahydro-4a*H*-carbazoles, which was used directly in the next stage without further purification.

***rel*-(3a*S*,6a*S*,6b*R*, 10a*S*, 11a*S*)-6a-Methylperhydroindolo-[3,2,1-*i*,*j*]benzoxazine (4) and *rel*-(3a*S*,6a*S*,6b*S*,10a*R*, 11a*S*)-6a-methylperhydroindolo[3,2,1-*i*,*j*]benzoxazine (5).** The mixture of 1-hydroxymethyl-4a-methyl-1,2,3,4,6b,7,8,9,10,10a-decahydro-4a*H*-carbazoles (see above) was shaken with an excess of formaldehyde solution for 30 min. The mixture was then basified with dilute sodium hydroxide solution, extracted with diethyl ether, dried (Na_2SO_4) and concentrated. The viscous residue was chromatographed on Woelm alumina (90 g, grade IV), eluting with light petroleum (b.p. 40–60 °C). *rel*-(3a*S*,6a*S*,6b*R*,10a*S*,11a*S*)-6a-Methylperhydroindolo[3,2,1-*i*,*j*]benzoxazine (**4**) was eluted first as a colourless oil. (Found: C, 76.3; H, 10.6; N, 6.1. $C_{13}H_{25}NO$ requires C, 76.5; H, 10.7; N, 6.0%). *rel*-(3a*S*,6a*S*,6b*S*,10a*R*,11a*S*)-6a-Methylperhydroindolo[3,2,1-*i*,*j*]benzoxazine (**5**) was also obtained as a colourless oil. (Found: C, 76.4; H, 10.6; N, 6.2. $C_{13}H_{25}NO$ requires C, 76.5; H, 10.7; N, 6.0%).

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