Compounds with Bridgehead Nitrogen. Part 70.[1] The Synthesis and Stereochemistry of the 12-Methyl- and 9-Ethyl-12-methylperhydropyrido-[1,2-*c*][1,3]benzoxazepines

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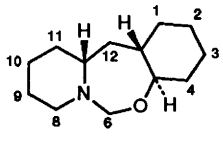
The diastereoisomeric 2-[1-(2-piperidyl)ethyl]cyclohexanols and the corresponding 2-[1-(5-ethylpiperidin-2-yl)ethyl]cyclohexanols were synthesised by reaction between the lithio derivatives of 2-ethylpyridine and 2,5-diethylpyridine and cyclohexene oxide followed by catalytic hydrogenation of the product. The individual amino alcohols were isolated and treated with formaldehyde to give the 12-methyl- and 9-ethyl-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepines. The configurations of these compounds were assigned by comparison of the NMR spectra with those of perhydropyrido-[1,2-*c*][1,3]benzoxazepines of known configuration. The *rel*-(4a*R*,12a*S*,12*R*,11a*R*) and *rel*-(4a*S*,12a*R*,12*R*,11a*R*)-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepines were shown to exist exclusively in the *trans*-fused conformation in $CDCl_3$ solution at room temperature. The *rel*-(4a*R*,12a*S*,12*S*,11a*R*) and *rel*-(4a*S*,12a*R*,12*S*,11a*R*)-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepines exist predominantly in the *trans*-fused conformations (*ca.* 75% and 72%, respectively) in equilibrium with *O*-inside *cis*-fused and *O*-outside *cis*-fused conformations, respectively. Equilibria positions for the corresponding 9-ethyl-12-methyl substituted compounds were also determined.

In contrast to the detailed studies on the conformational analysis of saturated bicyclic 6/5[2] and 6/6[3] ring fused azacyclic systems, the conformational equilibria in analogous 6/7 ring fused systems have been little explored.

Previous work[4] on the perhydropyrido[1,2-*c*][1,3]benzoxazepine system has resulted in the assignment of the *syn*- and *anti*-configurations (relative configurations of 11a-H, 12a-H) of **1** and **2** based on an X-ray study[5] of one (**4**) of the corresponding amino alcohols **3** and **4**. Estimates of the position of *trans*- ⇌ *O*-inside *cis*-fused conformational equilibria 1-*t* ⇌ 1-c_1 and 2-*t* ⇌ 2-c_1 have been made on the basis of NMR data and configurational and conformational assignments have been made to ring A substituted compounds.[2] The conformational equilibria positions of such compounds are, however, affected not only by the non-bonded interactions present in the various conformers but also by the predominant conformations of the partially pseudorotating seven-membered ring. This latter influence results from changes in the generalised anomeric effect.[6] Consequently it was decided to study the 12-methyl substituted derivatives **7**, **8**, **13** and **14** of **1** and **2**, since the substituent methyl is expected to alter the conformational mobility and average conformation of the seven-membered ring together with the balance of the non-bonded interactions and therefore in some cases the positions of *trans*-A/B ⇌ *cis*-A/B conformational equilibria.



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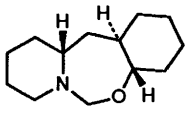

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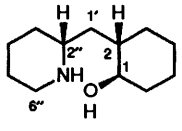

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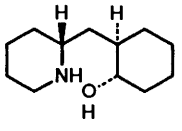

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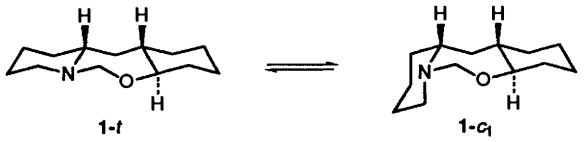
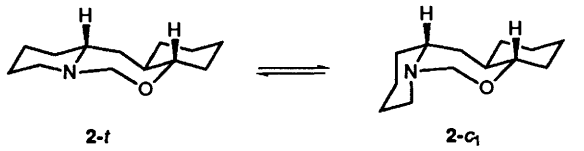


1-*t* **1-c_1**



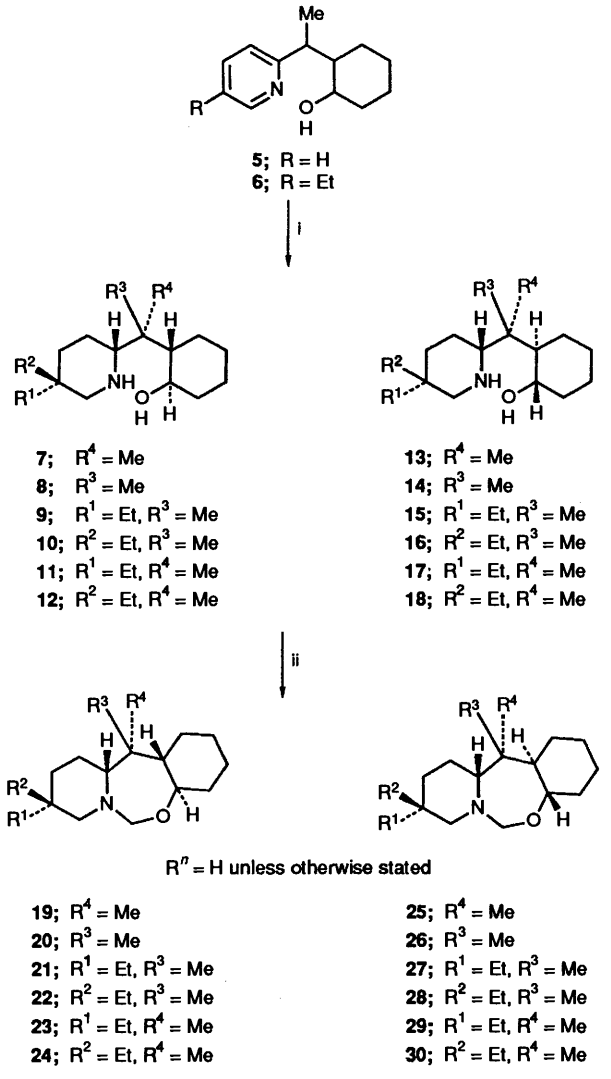
2-*t* **2-c_1**

In addition the 9-ethyl-12-methylperhydropyrido[1,2-*c*]-[1,3]benzoxazepines **21–24** and **27–30** (see Scheme 1), were chosen for study since the ring A ethyl substituent is expected to bias the positions of *trans*-A/B ⇌ *cis*-A/B equilibria. Comparisons of equilibria positions in the various series of compounds may then provide some information on the importance of substituents in the seven-membered ring on conformational equilibria.

Results and Discussion

Synthesis of Compounds.—The synthesis of the alkyl substituted 2-(piperidin-2-ylmethyl)cyclohexanols (**7–18**) is summarised in Scheme 1. Reaction between the lithio derivatives of either 2-ethylpyridine or 2,5-diethylpyridine and cyclohexene oxide gave mixtures of the corresponding alkyl derivatives (**5** and **6**) of 2-(pyridin-2-ylmethyl)cyclohexanol. Catalytic hydrogenation of the pyridine derivatives in glacial acetic acid solution in the presence of Adams' platinum oxide catalyst gave a mixture of isomers **7–18**. Separation of these was achieved by fractional recrystallisation and column chromatography.

The individual isomers of the alkyl substituted 2-(piperid-2-ylmethyl)cyclohexanols were treated with 40% aqueous formaldehyde solution to give the corresponding alkyl substituted perhydropyrido[1,2-*c*][1,3]benzoxazepines **19–30** (see Scheme 1). Only five of the possible diastereoisomers of 9-ethyl-

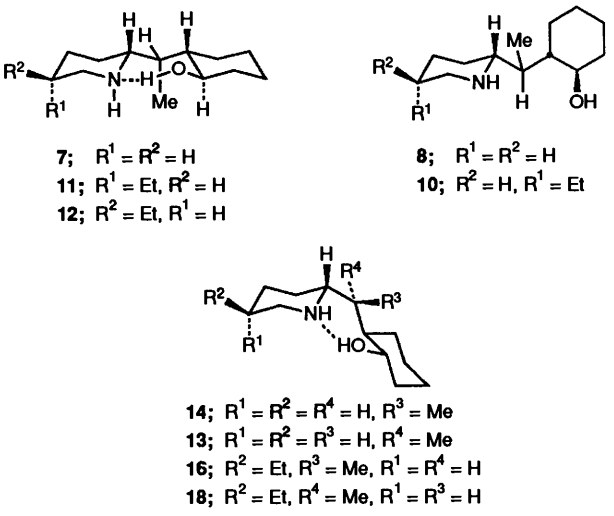


Scheme 1 Synthesis of the alkyl-substituted 2-(piperidin-2-ylmethyl)-cyclohexanols and of the alkyl-substituted perhydropyrido[1,2-*c*]-[1,3]benzoxazepines. *Reagents:* i, H_2/PtO_2; ii, CH_2O.

12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine were isolated.

Stereochemistry of the Alkyl Substituted 2-(*Piperidin*-2-*ylmethyl*)*cyclohexanols.*—The main stereochemical problem to be solved with the 2-[1-(2-piperidyl)ethyl]cyclohexanols (**7**, **8**, **13** and **14**) is the relative configurations about the C-2″, C-1′ and C-2 centres, since the *trans* stereochemistry about C-1 and C-2 has been fixed by the method of synthesis.[7]

The configurations of the aminoalcohols may be tentatively assigned from a comparison between selected ^{13}C NMR chemical shifts (Table 2) in the methyl substituted isomers and in the unsubstituted compounds **3** and **4**. As an initial approximation it may be assumed that the differences in shifts between these systems are a direct consequence of methyl substituent effects on shifts. Changes in the conformational equilibrium position between the two series of compounds resulting in differing orientation of heteroatoms and in deviations from the strictly axial and equatorial orientations of the substituent methyl are, however, expected and these will affect the comparisons to differing extents in the various structures. Thus, only approximate correlations may be expected. In addition, the IR and ^1H NMR spectra show that the conformation of isomer **8** is very different from those of the other isomers. In particular, although the IR spectra of three of the isomers **7**, **13** and **14** show the presence of strong intramolecular H-bonding (ν_{max} 3100 cm^{-1}), indicating as a first approximation the adoption of similar H-bonded conformations in solution (Scheme 2) to those adopted by **3** and **4**, the



Scheme 2 Predominant conformations of the aminoalcohols

spectrum of **8** indicates almost no intramolecular H-bonding and a significant amount of free OH stretching vibration (3622 cm^{-1}). Examination of Dreiding models of the various conformers does not show any of the H-bonded conformers to be particularly disfavoured but the conformer shown in Scheme 2 may be tentatively assigned to **8**. The ^1H NMR spectrum of this isomer (Table 1) showed a relatively upfield shift for H-2″.

Examination of Dreiding models, together with an examination of all the spectral data, suggests the conformations shown in Scheme 2 as predominant for the individual isomers. These assignments, although tentative, are supported by the stereochemical assignments made to the related but more conformationally restricted tricyclic derivatives **19**–**30**.

Configurational assignments to the 2-[1-(5-ethylpiperidin-2-yl)ethyl]cyclohexanols were based on the close agreement between the ^{13}C NMR spectra (Table 2) of isomers **10**, **11**, **12**, **16** and **18** with the corresponding isomers of 2-[1-(2-piperidyl)-ethyl]cyclohexanols, **7**, **8**, **13** and **14**.

Examination of the 6″-H signals in the ^1H NMR spectra (Table 1) of isomers **10**, **11**, **12**, **16** and **18** allowed assignment of equatorial substitution of ethyl at the C-5″ position for isomers **10**, **16**, **12** and **18** and axial substitution for isomer **11**. The shielding of C-3″ (δ 26.4) and CH_2–CH_3 (δ 22.5) nuclei in the ^{13}C NMR spectrum of isomer **11** relative to the corresponding nuclei of isomer **12** (δ 31.9 and δ 26.0, respectively) confirms the assignment of an axial 5″-ethyl substituent in isomer **11**. The configurations and predominant conformations for the five isomers are provided in Scheme 2.

Stereochemistry of the Alkyl Substituted Perhydropyrido[1,2-c]-[1,3]*benzoxazepines*

The 12-*Methylperhydropyrido*[1,2-c][1,3]*benzoxazepines.*—The conformational equilibria for the four possible diastereoisomers of 12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine **19**, **20**, **25** and **26** possessing a *trans*-B/C ring fusion are indicated in Scheme 3. For each individual isomer there exists a *trans*-A/B ring fused conformer, an *O*-inside *cis*-fused conformer and an *O*-outside *cis*-fused conformer, interconvertible in solution by nitrogen inversion and ring inversion. In addition a variety of conformations are possible for the tetrahydro-1,3-oxazepine ring.

Table 1 ^{1}H NMR chemical shifts (δ) and coupling constants (J/Hz) of the alkyl substituted 2-(piperidin-2-ylmethyl)cyclohexanols

Compound	1-H	6″-H_{eq}	6″-H_{ax}	2″-H	CH_2CH_3	Me
3	3.02	3.02 $J_{6''eq,6''ax} = -12.5$	2.52 $J_{6''ax,5''ax} = 12.5$ $J_{6''ax,5''eq} = 3.75$	2.52 $J_{2'',3''ax} = 9.3$ $J_{2'',3''eq} = 3.1$ $J_{2'',1'} = 8.75, 0$	—	—
4	3.09	3.09 $J_{6''eq,6''ax} = -12.5$	2.63 $J_{6''ax,5''ax} = 12.5$ $J_{6''ax,5''eq} = 3.75$	2.71 $J_{2'',3''ax} = 8.75$ $J_{2'',3''eq} = 3.75$ $J_{2'',1'} = 6.25, 4.40$	—	—
7	3.30 $J_{1,2=1,6ax} = 9.25$ $J_{1,6eq} = 4.70$	3.10 $J_{6''eq,6''ax} = -13.75$ $J_{6''eq,5''eq} = 2.20$ $J_{6''eq,5''ax} = 2.20$	2.56	2.56	—	0.85
8	3.37 $J_{1,2=1,6ax} = 10.0$ $J_{1,6eq} = 3.75$	3.10 $J_{6''eq,6''ax} = -11.9$ $J_{6''eq,5''ax} = 3.75$	2.58 $J_{6''ax,5''ax} = 11.9$ $J_{6''ax,5''eq} = 3.25$	2.34 $J_{2'',3''ax} = 11.0$ $J_{2'',3''eq} = 2.5$ $J_{2'',1'} = 10.0$	—	0.84
10	3.35 $J_{1,2=1,6ax} = 8.5$ $J_{1,6} = 4.6$	3.10 $J_{6''eq,6''ax} = -11.2$	2.17 $J_{6''ax,5''ax} = 11.2$	2.26 $J_{2'',3''ax=2'',1'} = 9.5$	0.90	0.83
11	3.30 $J_{1,2=1,6ax} = 9.4$ $J_{1,6eq} = 4.1$	2.90 $J_{6''eq,6''ax} = -14.0$ $J_{6''eq,5''eq} = 0$	2.77 $J_{6''ax,5''eq} = 3.0$	2.53 $J_{2'',3''ax} = 9.7$ $J_{2'',3''eq(1')} = 2.0$	0.90	0.85
12	3.30 $J_{1,2=1,6ax} = 9.3$ $J_{1,6eq} = 4.8$	3.08 $J_{6''eq,6''ax} = -13.5$ $J_{6''eq,5''ax} = 2.7$	2.25 $J_{6''ax,5''ax} = 10.0$	2.55 $J_{2'',3''ax} = 11.5$	0.85	0.85
13	3.32 $J_{1,2=1,6ax} = 10.0$ $J_{1,6eq} = 4.40$	3.10 $J_{6''eq,6''ax} = -12.5$ $J_{6''eq,5''eq} = 1.75$ $J_{6''eq,5''ax} = 1.75$	2.64 $J_{6''ax,5''ax} = 12.5$ $J_{6''ax,5''eq} = 2.5$	2.64	—	1.01
14	3.30 $J_{1,2=1,6ax} = 10.0$ $J_{1,6eq} = 5.0$	3.15 $J_{6''eq,6''ax} = -11.9$	2.60 $J_{6''ax,5''ax} = 11.9$ $J_{6''ax,5''eq} = 2.9$	2.56 $J_{2'',3''ax} = 10.6$ $J_{2'',3''eq} = 2.8$	—	0.97
16	3.30 $J_{1,2=1,6ax} = 9.7$ $J_{1,6eq} = 4.2$	3.15 $J_{6''eq,6''ax} = -11.3$ $J_{6''eq,5''ax} = 2.2$	2.23 $J_{6''ax,5''ax} = 11.3$	2.55 $J_{2'',3''ax} = 11.4$ $J_{2'',3''eq} = 4.4$ $J_{2'',1'} = 2.9$	0.87	1.00
18	3.30 $J_{1,2=1,6ax} = 10.0$ $J_{1,6eq} = 4.2$	3.10 $J_{6''eq,6''ax} = -12.3$ $J_{6''eq,5''ax} = 3.7$	2.25 $J_{6''ax,5''ax} = 10.8$	2.60 $J_{2'',3''ax} = 10.6$ $J_{2'',3''eq=2'',1'} = 3.2$	0.88	1.00

Table 2 ^{13}C NMR chemical shifts (δ) of alkyl substituted 2-(piperidin-2-ylmethyl)cyclohexanols

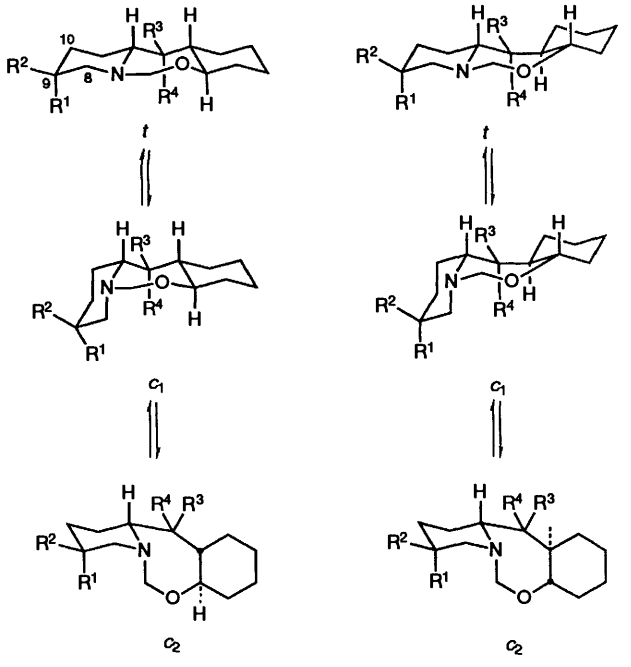
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2″	C-3″	C-4″	C-5″	C-6″	CH_2CH_3	CH_2CH_3	Me
3	74.6	46.7	33.7	26.9	25.0	35.2	45.7	56.9	35.0	24.8	25.9	46.3	—	—	—
4	74.1	40.9	33.6[b]	25.6	25.0	35.0	44.3	54.8	30.4[b]	24.8	25.8	46.8	—	—	—
7	68.2	52.5	32.4	27.1	25.3	35.5	44.7	62.05	32.1	24.9	26.3	46.2	—	—	7.1
8	71.1	46.2	25.1	26.6	25.3	36.65	37.7	59.4	31.1	25.2	25.9	47.2	—	—	11.65
10	71.2	46.2	25.1	25.4	25.85	36.5	37.5	59.3	31.05	31.6	38.6	52.8	27.2	12.0	11.3
11	68.2	52.3	32.6	26.2	24.8	35.4	44.4	62.0	26.4	28.4	33.6	48.9	22.5	12.1	7.0
12	68.05	52.15	31.3[a]	26.7[b]	24.7	35.2	43.9	61.8	31.9[a]	32.1[a]	38.9	51.3	26.0[b]	11.0	6.85
13	72.6	48.4	30.9[a]	26.0	25.2	35.6	43.6	59.8	29.4[a]	25.0	26.0	46.8	—	—	16.2
14	67.9	43.9	31.7[a]	25.4	25.0	35.6	43.0	60.5	29.7[a]	24.8	26.0	46.6	—	—	12.1
16	67.8	43.8	31.6	24.9	26.2	35.5	42.6	60.3	29.35	31.0	37.4	52.0	27.0	11.3	11.2
18	72.6	48.35	30.9	24.9	26.1	35.5	43.4	59.6	29.1	31.4	38.5	52.2	27.1	11.2	16.3

[a] Shifts may be interchanged. [b] These values have been altered from those in ref. 2.

As expected[8,9] the IR spectra of the four isomers show poorly defined Bohlmann absorption[10] but this at least indicated the presence of the *trans*-fused conformations.

The configurations and positions of conformational equilibria of the 12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepines were determined largely by comparison of the NMR parameters with those from the *syn*- and *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepines **1** and **2** which adopt equilibria containing *ca.* 97% **1**-*t* and *ca.* 73% **2**-*t*, respectively, in equilibrium with *O*-inside *cis*-fused conformations.[4] The methyl substituted isomers **19**, **20**, **25** and **26** are not, however, expected to adopt the same equilibria positions as **1** and **2** and in addition the substituent may alter the seven-membered ring conformation. Nevertheless such a comparison provides a necessary starting point for the stereochemical study especially since attempts to freeze the conformational equilibria for the 12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepines by low temperature ^{13}C NMR spectroscopy were unsuccessful.

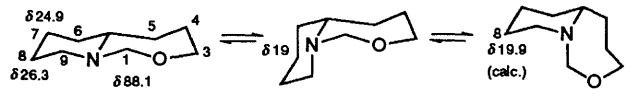
The ^{1}H and ^{13}C NMR spectra of the individual isomers are summarised in Tables 3 and 4, together with data on the *syn*- and *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepines **1** and **2**.[4] The ^{1}H NMR spectrum of isomer **19** showed a clear triplet of doublets for 8-H_{ax} at δ 2.65 consistent with the *trans*-conformation **19**-*t* ($J_{8ax,8eq} = -11.0$, $J_{8ax,9ax} = 11.0$ and $J_{8ax,9eq} = 3.25$ Hz) or with the equilibrium **19**-*t* $\rightleftharpoons$ **19**-c_2 since in this process the A ring does not invert. Comparison of the C-8 ^{13}C



R^n = H unless otherwise stated

19; R^4 = Me	**25**; R^4 = Me
20; R^3 = Me	**26**; R^3 = Me
21; R^1 = Et, R^3 = Me	**27**; R^1 = Et, R^3 = Me
22; R^2 = Et, R^3 = Me	**28**; R^2 = Et, R^3 = Me
23; R^1 = Et, R^4 = Me	**29**; R^1 = Et, R^4 = Me
24; R^2 = Et, R^4 = Me	**30**; R^2 = Et, R^4 = Me

Scheme 3 Conformational equilibria of alkylperhydropyrido[1,2-*c*][1,3]benzoxazepines. (The drawings provide a formal representation of the seven-membered ring conformation which may vary from compound to compound—see, for example, Fig. 1).

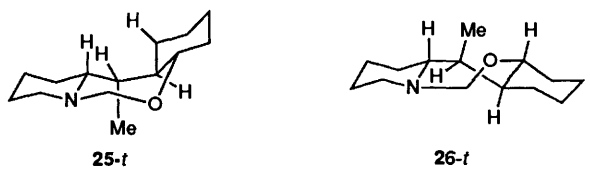


31-*t* **31-c_1** **31-c_2**

NMR chemical shifts in *trans*-fused perhydropyrido[1,2-*c*][1,3]oxazepine (**31**-*t*), with the corresponding C-9 shifts in *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine (**1**-*t*)[4] and in **19** shows à constancy of shifts indicating the absence of **19**-c_2 from the equilibrium. The ^{1}H NMR spectrum of isomer **19** shows a deshielding of 4a-H by 0.25 ppm relative to *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine (**1**-*t*)[4] indicating the presence of a near 1,3- *syn*-axial methyl group.[11] This is supported by the broadened doublet for 11a-H with $J_{11a,11ax}$ = 11.0 Hz.

Comparison of the ^{13}C NMR chemical shifts of isomer **19** with those of the *syn*-unsubstituted benzoxazepine (**1**-*t*), allowing for the methyl effect on the chemical shifts of relevant carbons, reveals generally good agreement with the conformation **19**-*t*. A difference of 5.3 ppm for C-4a is in agreement with an axial methyl substituent effect (γ_{ax} effect).[12] The reverse effect from C-4a and other steric interactions on the methyl group may account for the highfield shift (δ 9.15) of this group. Deshielding of C-11a and C-12a by 4.4 and 4.2 ppm, respectively, may also indicate a near axial methyl substituent (β_{ax} effect).[12]

The ^{1}H NMR spectrum of isomer **20** showed a multiplet at δ 2.74 for 8-H_{ax} ($J_{8ax,8eq}$ = −11.9, $J_{8ax,9ax}$ = 8.1 and $J_{8ax,9eq}$ = 4.4 Hz) inconsistent with the presence of a single conformer.



25-*t* **26-*t***

Fig. 1 Conformations of the *anti*-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepines

The *trans*-conformer (**20**-*t*), for example, is expected to show $J_{8ax,8eq}$ = −11.0, $J_{8ax,9ax}$ = 11.0 and $J_{8ax,9eq}$ = 2.9 Hz (see data for **19**-*t* in Table 3). Since the IR spectrum showed the presence of the *trans*-fused conformation the observed vicinal couplings must indicate the equilibrium **20**-*t* ⇌ **20**-c_1 in order for averaged couplings between the C-8 and C-9 methylene protons to be observed. Application of the Winstein–Holness equation[13] gives *ca.* 37% **20**-c_1 in the equilibrium. ^{13}C NMR spectroscopy may also be used to estimate the proportion of *O*-inside *cis*-conformer (**20**-c_1) by comparing the C-10 shift in **20** with the corresponding C-7 shifts in **31**-*t* and **31**-c_1. This gives an equilibrium containing *ca.* 31% **20**-c_1. The *O*-outside *cis*-conformer (**20**-c_2) may be shown to be absent from the equilibrium by the chemical shift of C-9 of δ 26.6 which is typical of *trans*- or *O*-inside *cis*-conformers.[4,9]

Examination of Dreiding models of the various conformers of isomer **26** suggests the predominance of the *trans*-fused conformer **26**-*t*. Comparison of the ^{13}C NMR shift of C-10 (δ 25.5) in the spectrum of **26** with that of the corresponding C-7 in the perhydropyrido[1,2-*c*][1,3]oxazepines (**31**-*t* and **31**-c_1) indicates the absence of any *O*-inside *cis*-fused conformer in the conformational equilibrium mixture. Comparison of C-9 (δ 24.5) in **26** with C-8 (δ 26.3) in **31**-*t*, however, indicates the presence of some *O*-outside *cis*-fused conformer. Using the Winstein–Holness expression[13] and the chemical shifts of C-8 (δ 26.3) in *trans*-perhydropyrido[1,2-*c*][1,3]oxazepine (**31**-*t*) and the calculated value (δ 19.9) in the corresponding *O*-outside *cis*-conformer **31**-c_2 provides an estimated position of equilibrium for **26** as *ca.* 72% *trans*-conformer (**26**-*t*) and *ca.* 28% *O*-outside *cis*-fused conformer (**26**-c_2).

The downfield shift ($\Delta\delta$ +0.36 ppm) of 4a-H (see **26** relative to **2**) indicates a near *syn*-axial relationship with the methyl substituent.[11] This is also reflected in the ^{13}C NMR chemical shift difference of C-4a ($\Delta\delta$ −7.4 ppm) (compare isomer **26** with **2**) which indicates a γ_{ax} type interaction between the methyl substituent and the C-4a methylene group. The appearance of a doublet of triplets at δ 2.44 with $J_{11ax,11a}$ = 10.0, $J_{11eq,11a}$ = 2.5 and $J_{11a,12'ax'}$ = 2.5 Hz for 11a-H in the ^{1}H NMR spectrum of isomer **26** is also consistent with the pseudoaxial orientation of the methyl group and the conformation shown in Fig. 1.

Dreiding models of the various conformers of isomer **25** suggest the predominance of the *trans*-conformer **25**-*t* with a pseudoaxial methyl group. As the observed shifts for C-9 in **25** and for the corresponding C-8 in **31**-*t* are very similar (δ 26.4 and δ 26.3, respectively) the presence of **25**-c_2 in the equilibrium may be ruled out. In addition, the shift of C-10 (δ 26.2) rules out the presence of the *O*-inside *cis*-fused conformer and shows isomer **25** to exist exclusively in the *trans*-fused conformation **25**-*t*. The pseudoaxial orientation of the methyl group is shown by the absorption of 11a-H in the ^{1}H NMR spectrum of isomer **25** as a near doublet of triplets with $J_{11a,11ax}$ = 9.75, $J_{11a,11eq}$ = 2.5 and $J_{11a,12'eq'}$ = 3.75 Hz.

A change of seven-membered ring conformation in **25** from that in **26**-*t* (Fig. 1) to minimise interactions involving the methyl group is indicated by the changes in the chemical shifts of 4a-H (δ 3.70), 6-H (δ 4.00) and 6′-H (δ 4.71) relative to

Table 3 ^{1}H NMR spectra of perhydropyrido[1,2-*c*][1,3]benzoxazepines

Compound	4a-H	6-H	6′-H	8eq-H	8ax-H	11a-H
1	2.91	4.45	4.52	2.87	2.71	2.47
2	3.04	4.25	4.31	2.97	2.50	2.69
19	3.16 $J_{4ax,4ax}$ = 10.0 $J_{4a,4eq}$ = 4.4 $J_{4a,12a}$ = 10.0	4.33 $J_{6,6'}$ = −12.1	4.48	2.88 $J_{8ax,8eq}$ = −11.0 $J_{8eq,9eq}$ = 2.9	2.65 $J_{8ax,9ax}$ = 11.0 $J_{8ax,9eq}$ = 3.25	2.4 $J_{11a,11ax}$ = 11.0
20	3.0 $J_{4a,4ax}$ = 8.75 $J_{4a,4eq}$ = 4.4 $J_{4a,12a}$ = 10.0	4.47	4.47	3.0	2.74 $J_{8ax,8eq}$ = −11.9 $J_{8ax,9ax}$ = 8.1 $J_{8ax,9eq}$ = 4.4	2.47 $J_{11a,11ax}$ = 8.5 $J_{11a,11eq}$ = 2.5 $J_{11a,12}$ = 8.5
22	2.95 $J_{4a,4ax=4a,12a}$ = 10.6 $J_{4a,4eq}$ = 4.0	4.61 $J_{6,6'}$ = −11.8	4.43	3.0 $J_{8eq,8ax}$ = −11.5 $J_{8eq,9ax}$ = 4.0	2.43 $J_{8ax,9ax}$ = 10.6	2.31 $J_{11a,11ax}$ = 10.8 $J_{11a,12'ax}$ = 7.9 $J_{11a,11eq}$ = 2.5
23	3.15 $J_{4a,12a=4a,4ax}$ = 10.6 $J_{4a,4eq}$ = 4.03	4.45 $J_{6,6'}$ = −11.9	4.31	2.71 $J_{8eq,8ax}$ = −11.2	2.84 $J_{8ax,9eq}$ = 2.9	2.47 $J_{11a,11ax}$ = 10.6 $J_{11a,11eq\ (or\ 12)}$ = 1.5
24	3.15 $J_{4a,12a=4a,4ax}$ = 10.3 $J_{4a,4eq}$ = 3.8	4.48 $J_{6,6'}$ = −11.7	4.36	2.86 $J_{8eq,8ax}$ = −10.8 $J_{8eq,9ax}$ = 4.0	2.30 $J_{8ax,9ax}$ = 10.8	2.36 $J_{11a,11ax}$ = 11.2
25	3.7 $J_{4a,4ax}$ = 10.0 $J_{4a,4eq}$ = 4.5 $J_{4a,12a}$ = 10.0	4.0 $J_{6,6'}$ = −12.5	4.71	2.8	2.8 $J_{8ax,9ax}$ = 11.0 $J_{8ax,9eq}$ = 2.9	2.55 $J_{11a,11ax}$ = 9.75 $J_{11a,11eq}$ = 2.5 $J_{11a,12}$ = 3.75
26	3.4 $J_{4a,4ax}$ = 10.0 $J_{4a,4eq}$ = 4.4	4.27 $J_{6,6'}$ = −11.0	4.34	3.0 $J_{8eq,8ax}$ = −11.5 $J_{8eq,9ax}$ = 4.0 $J_{8eq,9eq}$ = 3.1	2.6 $J_{8ax,9ax}$ = 11.5 $J_{8ax,9eq}$ = 3.75	2.44 $J_{11a,11ax}$ = 10.0 $J_{11a,11eq}$ = 2.5 $J_{11a,12}$ = 2.5
28	3.42 $J_{4a,12a=4a,4ax}$ = 10.35 $J_{4a,4eq}$ = 4.4	4.3		2.98 $J_{8eq,8ax}$ = −11.9 $J_{8eq,9ax}$ = 4.0	2.18 $J_{8ax,9ax}$ = 11.0	2.36 $J_{11a,11ax}$ = 11.5 $J_{11a,11eq\ (12)}$ = 2.4
30	3.68 $J_{4a,12a=4a,4ax}$ = 10.4 $J_{4a,4eq}$ = 4.8	4.74 $J_{6,6'}$ = −11.9	4.04	2.74 $J_{8eq,8ax}$ = −11.1 $J_{8eq,9ax}$ = 3.8	2.41 $J_{8ax,9ax}$ = 11.1	2.53 $J_{11a,11ax}$ = 10.6 $J_{11a,11eq=11a,12}$ = 3.0

Table 4 ^{13}C NMR chemical shifts (δ) of perhydropyrido[1,2-*c*][1,3]benzoxazepines

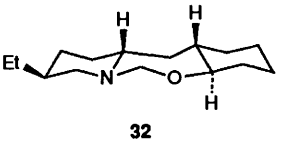
Compound	C-1	C-2	C-3	C-4	C-4a	C-6	C-8	C-9	C-10	C-11	C-11a	C-12	C-12a	CH_2	CH_3	Me
1	33.05	25.9	25.4	33.6	86.5	88.0	54.3	26.8	24.75	34.3	62.4	39.8	47.4	—	—	—
2	33.2	26.65	24.9	33.7	84.05	86.9	51.4	26.6	23.3	34.45	58.4	40.7	40.5	—	—	—
19	30.9	26.1	25.3	33.6	81.2	88.4	55.9	26.5	25.3	32.7	66.8	43.8	51.6	—	—	9.15
20	29.6[a]	26.2	25.3	34.3	84.0	86.1	53.25	26.6	23.4	30.0[a]	65.3	36.1	52.0	—	—	15.6
22	29.4[a]	26.2	25.3	34.1	85.9	87.1	61.6	38.2	31.8	30.0[a]	66.9	37.4	52.65	27.0	11.40	15.35
23	29.2	26.4	25.7	34.0	81.0	88.55	59.1	36.4	31.3	28.4	66.7	44.45	51.9	24.2	12.6	9.75
24	30.9	26.1	24.4	33.65	81.2	88.3	61.7	38.6	31.8	32.6	66.75	43.3	51.6	27.2	11.5	9.2
25	34.6	25.25	25.0	36.0	80.1	80.9	54.3	26.4	26.2	30.8	60.5	43.0	47.4	—	—	14.9
26	31.6	25.8	24.8	33.7	76.65	84.7	53.5	24.5	25.5	31.7	66.1	43.3	43.9	—	—	17.1
28	31.7	25.9	24.9	33.7	76.8	84.0	60.6	37.0	31.8	32.1	66.5	44.3[a]	42.8[a]	27.1	11.35	17.1
30	34.5	26.1	25.0	36.0	80.3	81.0	60.1	38.3	31.3	30.5	60.5	42.55	47.3	27.5	11.45	14.9

[a] These shifts may be reversed.

those (δ 2.98, δ 4.18 and δ 4.30, respectively) of the *trans*-fused 9-ethyl *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepine **33**.[4] Comparison of the ^{13}C NMR spectra of isomer **25** and **26** also indicates the change in the seven-membered ring conformation.

The syn-9-*Ethyl*-12-*methylperhydropyrido*[1,2-c][1,3]*benzoxazepines*.—The *syn*-isomers **23**, **24** and **22** obtained from isomers **11**, **12** and **10** are expected to adopt predominantly the *trans*-fused conformation. Examination of the ^{1}H NMR spectrum of isomer **23** shows absorption of 8-H_{ax} as a doublet of doublets ($J_{8ax,8eq}$ = −11.2 Hz, $J_{8ax,9eq}$ = 2.9 Hz) consistent with an axial ethyl substituent in the expected *trans*-fused conformation.

The ^{1}H NMR spectra of isomers **24** and **22** both show triplet absorption for 8-H_{ax} at δ 2.30 and δ 2.43, respectively, ($J_{8ax,8eq}$ = −10.8 to −11.4 and $J_{8ax,9ax}$ = 10.8 to 11.5 Hz) consistent with equatorial ethyl groups. Close correlation of ^{1}H NMR shifts of 8-H_{ax} of isomers **24** and **22** with that of the *syn*-9-ethylperhydropyrido[1,2-*c*][1,3]benzoxazepine **32**[2] indicates the extreme predominance of the *trans*-conformer in the equilibria of these isomers. The axial ethyl substituent in isomer **23** is indicated by upfield absorption of C-11 (δ 28.4) relative to isomer **24** (δ 32.6) and **32** (δ 32.85). Upfield absorption of C-4a in isomer **23** (δ 81.0) and **24** (δ 81.2) relative to that of **32** (δ 86.9) and isomer **22** (δ 85.9) is in accord with the pseudoaxial methyl substitution at C-12 in **23** which is also indicated by absorption of 11a-H as a broad doublet



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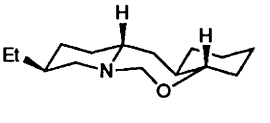

33

($J_{11a,11ax}$ = 10.6 – 11.2 Hz). Pseudoequatorial methyl substituent in isomer **22** is not expected to affect C-4a. Absorption of 11a-H in the spectrum of isomer **22** as a multiplet with $J_{11a,11ax}$ = 10.8, $J_{11a,12}$ = 7.9, $J_{11a,11eq}$ = 2.5 Hz is consistent with pseudoequatorial methyl substitution.

Examination of the NMR spectral data (Tables 3 and 4) for the 12-methyl and 9-ethyl-12-methyl *syn*-series of compounds shows in most cases almost identical chemical shifts, when the effect of ethyl substituent on NMR shifts is taken into account, suggesting structural and conformational similarity between the sets of compounds. The major expected difference, however, is between compounds **22** (existing as **22**-*t*) and **20** (existing as an equilibrium between 75% *trans*-fused and *ca.* 25% *O*-inside *cis*-fused conformer). The difference in conformational equilibria is confirmed by the C-10 absorption in both compounds. If allowance is made for the ethyl substituent effect on C-10 in **22**-*t* then the calculated C-10 shift for **20**-*t* is δ 25.2. The observed C-10 shift for isomer **20** is δ 23.4 showing an upfield shift due to a contribution to the equilibrium from **20**-c_1 (γ_{ax} effect between C-10 and C-12).

The anti-9-*Ethyl*-12-*methylperhydropyrido*[1,2-*c*][1,3]*benzoxazepines.*—The positions of conformational equilibria for the *anti*-isomers **28** and **30** are expected to resemble those of the B-ring unsubstituted analogues **26** (72% **26**-*t* ⇌ 28% **26**-c_2) and **25** (predominantly **25**-*t*), respectively. This is shown to be the case by the close similarity of ^{13}C shifts (Table 4) for the two sets of compounds, allowing for the ethyl substituent effect on C-8, C-9 and C-10. These similarities also point to similar B ring conformation for the pairs of compounds **28** and **26**, and **30** and **25**. In addition equatorial ethyl substitution is indicated by triplet absorption for 8-H_{ax} ($J_{8ax,8eq}$ = −11.1 to −11.9 Hz, $J_{8ax,9ax}$ = 11.0 to 11.1 Hz). Absorptions of 11a-H as doublets of triplets ($J_{11a,11ax}$ = 10.6 to 11.5 Hz, $J_{11a,11eq}$ = $J_{11a,12}$ = 2.4 to 3.0 Hz) in the spectra of both isomers **28** and **30** indicate pseudoaxial methyl substitution (compare Fig. 1 for ring A unsubstituted derivatives).

Conclusions

Substitution of a methyl substituent in the seven-membered ring of perhydropyrido[1,2-*c*][1,3]benzoxazepines may be expected to alter the positions of conformational equilibria from those in the unsubstituted systems **1** and **2** by the introduced Me/CH_2 non-bonded interactions [particularly Me/C(1)H_2 and Me/C(11)H_2 interactions] in the various conformers. In addition, the methyl substituent will cause changes in the average conformation of the seven-membered ring with concomitant changes in NCH_2O geometry and hence in the magnitude of the generalised anomeric effects[6] which will also affect the relative energies of the various conformers. The changes in positions of conformational equilibria in the *syn*-series of compounds **1**, **19** and **20** are readily rationalised. Thus, in **19** the highly unfavourable interaction between the pseudoaxial methyl group and the C(1) methylene in the *O*-inside *cis*-conformer **19**-c_1 will increase the preference for the *trans*-fused conformation (**19**-*t*) already favoured (**1**-*t*) by the parent system **1**. The relative shift (*ca.* 70% **20**-*t* ⇌ *ca.* 30% **20**-c_1) towards the *O*-inside *cis*-fused conformation for **20** must be an effect of ring B conformational changes with associated anomeric effect changes since non-bonded interactions between the pseudoequatorial methyl group and C(1)H_2 and C(11)H_2 are not expected to be markedly different in the two conformations **20**-*t* and **20**-c_1.

It has alaready been noted[4] that the equilibrium (*ca.* 73% **2**-*t* ⇌ *ca.* 27% **2**-c_1) for *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepine (**2**) shows a shift, relative to the equilibrium for the *syn*-isomer (**1**), towards the *cis*-fused conformer (**2**-c_1). This is reversed in **25**-*t* by the presence of the pseudoaxial methyl group which undergoes severe non-bonded interactions with the C(10) methylene group in the *O*-inside *cis*-fused conformation **25**-c_1.

The most striking observation, however, is the equilibrium for **26** which shows *ca.* 72% **26**-*t* in equilibrium with *ca.* 28% of the *O*-outside *cis*-fused conformation. *O*-outside *cis*-fused conformations in saturated 6/5 and 6/6 ring fused systems with nitrogen at a bridgehead position have never been reported. The NMR evidence indicates a pseudoaxial methyl substituent in **26**-*t* showing a change in B ring conformation from that in the epimer **25**-*t* and hence in **2**-*t*. These stereochemical situations are also expected in the *O*-inside *cis*-conformers with associated anomeric effect differences and models indicate a less favourable geometry in **26**-c_1 (pseudoaxial methyl group) for $n_o \rightarrow \sigma^*$ C–N interaction than in **2**-c_1.[4] The favoured geometry may well be presented in the alternative *O*-outside *cis*-conformation **26**-c_2. In view of the very small changes in conformation necessary to alter the NCH_2O geometry and hence the anomeric effect, these explanations of equilibria changes can only be regarded as tentative. Nevertheless the importance of the anomeric effect in these systems is demonstrated.

Experimental

Elemental analyses were carried out by Glaxo Group Research Ltd., Ware, Hertfordshire. Melting points were determined on a hot stage microscope. IR spectra were recorded on Perkin-Elmer 683 and 577 grating instruments as 0.005 mol dm^{-3} solutions in carbon tetrachloride using 1.0 cm matched silica cells. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution in 5 mm tubes, on a JEOL GSX-270 (^1H, ^{13}C) FT spectrometer at 270.16 (^1H) and 67.97 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and TMS as an internal standard. The most important measurement parameters were as follows: sweep width 3 (^1H) and 18 (^{13}C) KHz, pulse width 3 (^1H) and 4.2 (^{13}C) (*ca.* 40° and 45° flip angle), acquisition time 5.459 or 0.901 s, number of scans 16–320 (^1H) and 1–20 K (^{13}C), computer memory 32K. Light petroleum refers to the fraction boiling 40–60 °C.

2-(*Pyridin*-2-*ylmethyl*)*cyclohexanols.*—To a stirred suspension of small pieces of lithium (1 mol, 6.9 g) in sodium-dried diethyl ether (400 cm^3) contained in a three-necked flask was added bromobenzene (0.5 mol, 78.5 g) in sodium-dried diethyl ether (50 cm^3) at such a rate that a gentle reflux was maintained. The mixture was stirred until all the lithium had dissolved (2–3 h). A solution of the appropriately substituted pyridine (0.5 mol) in sodium-dried ether (30 cm^3) was then added over a period of 0.3 h and the resulting red solution was stirred for a further 0.6 h. The reaction mixture was cooled in ice, cyclohexene oxide (0.5 mol) was added dropwise over a period of 0.5 h, and the mixture was stirred until the red colouration disappeared. The mixture was acidified with hydrochloric acid (6 mol dm^{-3}), the separated aqueous layer basified with saturated sodium carbonate solution and extracted with chloroform (3 × 300 cm^3). The solvent was removed under reduced pressure, leaving the crude product, which was distilled *in vacuo* to yield the corresponding 2-(pyridin-2-ylmethyl)cyclohexanol. The following compounds were obtained: 2-[1-(pyridin-2-yl)-ethyl]cyclohexanol (**5**) (46.0 g, 45%) as a colourless liquid b.p. 120 °C at 0.35–0.40 mmHg (Found: C, 76.05; H, 9.3; N, 6.5 $C_{13}H_{19}NO$ requires C, 76.05; H, 9.35; N, 6.8%). 2-[1-(5-ethyl-pyridin-2-yl)ethyl]cyclohexanol (**6**) (67.6 g, 58%) b.p. 138 °C at 0.05 mmHg (Found: C, 77.2; H, 9.85; N, 6.0. $C_{15}H_{23}NO$ requires C, 77.2; H, 9.95; N, 6.0%).

2-(*Piperidin-2-ylmethyl*)*cyclohexanols*.—2-(Pyridin-2-ylmethyl)cyclohexanol (0.1 mol dm^{-3}, 20 g) was dissolved in glacial acetic acid (180 cm^3) and catalytically hydrogenated in a Parr apparatus (60 psi)* over Adams platinum oxide catalyst (1.27 g). After hydrogenation was complete (18 h) the catalyst was filtered off and the glacial acetic acid was removed from the filtrate under reduced pressure. The residue was basified (30% aqueous NaOH) and extracted with ether (8 × 60 cm^3). The ether layer was dried (Na_2SO_4), the ether was distilled off and the residue was treated with cold light petroleum when crystals were deposited. Three of the isomers (**7**, **8** and **13**) were separated by repeated fractional recrystallisation from light petroleum. The separation was monitored by TLC using Woelm aluminium oxide 60F 254 neutral (Type E) with chloroform–ethanol (65:35) as solvent. Fractions were also monitored by ^1H NMR spectroscopy. *rel*-(1*R*,2*S*)-2-[(1*R*,2*R*)-1-(piperidin-2-yl)ethyl]cyclohexanol (**7**) (*ca.* 5.0 g) was obtained as the least soluble isomer as rectangular crystals, m.p. 121–122 °C (Found: C, 73.9; H, 12.0; N, 6.7. $C_{13}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.65%). *rel*-(1*S*,2*R*)-2-[(1*R*,2*R*)-1-(piperidin-2-yl)ethyl]cyclohexanol (**13**) (*ca.* 8.0 g) was obtained next as needles, m.p. 127–128 °C (Found: C, 73.9; H, 12.0; N, 6.7. $C_{13}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.65%). Finally *rel*-(1*R*,2*S*)-2-[(1*S*,2*R*)-1-(piperidin-2-yl)ethyl]cyclohexanol (**8**) (*ca.* 6.0 g) was obtained as long rectangular crystals m.p. 101–102 °C (Found: C, 73.9; H, 12.0; N, 6.7. $C_{13}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.65%).

A small amount (0.014 g) of *rel*-(1*S*,2*R*)-2-[(1*S*,2*R*)-1-(piperidin-2-yl)ethyl]cyclohexanol (**14**) was obtained by preparative scale TLC, on aluminium oxide 60F 254 neutral (Type E), of the concentrated mother liquor using chloroform–ethanol (63:35) as eluent. A larger amount (0.2 g) of the latter isomer (**14**) was obtained as an oil (b.p. 123–125 °C at 0.35 mmHg) by column chromatography on Woelm alumina grade IV (5 g on 500 g alumina) using light petroleum–ether (100:0 to 63:37) as eluent. Separation on the column was monitored by TLC and ^1H NMR spectroscopy. (Found: C, 73.9; H, 12.0; N, 6.7. $C_{13}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.65%).

2-[1-(5-*Ethylpiperidin*-2-*yl*)*ethyl*]*cyclohexanols*.—The 2-[1-(5-ethylpyridin-2-yl)ethyl]cyclohexanol (*ca.* 20 g) was catalytically reduced as described for the ring A unsubstituted compounds. The 2-[1-(5-ethylpiperidin-2-yl)ethyl]cyclohexanols obtained were separated by flash column chromatography on silica, eluting with 2–25% ethanol–aqueous ammonium hydroxide (40%)–toluene (9:0.5:0.5) and 98–75% toluene. The isolated isomers were purified by fractional recrystallisation from ether–light petroleum. Only five isomers were obtained pure. Separation was monitored by TLC using alumina on aluminium plates with diethyl ether–ethanol (75:25) and silica on aluminium plates with ethanol (90%), aqueous ammonium hydroxide (4%) and dichloromethane (6%). The following compounds were obtained: *rel*-(1*R*,2*S*)-2-[(1*R*,2*R*,5*R*)-1-(5-ethylpiperidin-2-yl)ethyl]cyclohexanol (**11**) the first isomer to be eluted, (0.9 g, 30%), m.p. 62–64 °C (Found: C, 75.2; H, 12.2; N, 5.9. $C_{15}H_{29}NO$ requires C, 75.25; H, 12.2; N, 5.85%), *rel*-(1*R*,2*S*)-2-[(1*R*,2*R*,5*S*)-1-(5-ethylpiperidin-2-yl)ethyl]cyclohexanol (**12**), the second isomer to be eluted, (0.7 g, 23%) m.p. 100–102 °C (Found: C, 75.2; H, 12.1; N, 5.8. $C_{15}H_{29}NO$ requires C, 75.25; H, 12.2; N, 5.85%), *rel*-(1*S*,2*R*)-2-[(1*S*,2*R*,5*S*)-1-(5-ethylpiperidin-2-yl)ethyl]cyclohexanol (**16**), the third isomer to be eluted, (0.45 g, 15%) m.p. 117–119 °C (Found: C, 75.3; H, 12.2; N, 5.8. $C_{15}H_{29}NO$ requires C, 75.25; H, 12.2; N, 5.85%), *rel*-(1*S*,2*R*)-2-[(1*R*,2*R*,5*S*)-1-(5-ethylpiperidin-1-yl)ethyl]cyclohexanol (**18**), the fourth isomer to be collected pure, (0.21 g, 7%) m.p. 106–109 °C (Found: C, 75.25; H, 12.2; N, 5.8. $C_{15}H_{29}NO$ requires C, 75.25; H, 12.2; N, 5.85%), and *rel*-(1*R*,2*S*)-2-[(1*R*,2*R*,5*S*)-1-(5-*ethylpiperidin*-2-*yl*)*ethyl*]*cyclohexanol* (**10**), the fifth isomer to be collected pure, (0.15 g, 5%) m.p. 74–76 °C (Found: C, 75.15; H, 12.2; N, 5.9. $C_{15}H_{29}NO$ requires C, 75.25; H, 12.2; N, 5.85%).

Perhydropyrido[1,2-c][1,3]*benzoxazepines*.—The individual isomers of 2-[1-(piperidin-2-yl)ethyl]cyclohexanol (**7**, **8**, **13** and **14**) (0.005 mol dm^{-3}, 1.0 g) (except for isomer **14**, 0.001 mol dm^{-3}, 0.2 g) were treated with 40% aqueous formaldehyde (1 cm^3 and 0.2 cm^3, respectively). The mixtures were shaken for 0.5 h, after which they were basified with 30% aqueous sodium hydroxide and extracted several times with ether (4 × 10 cm^3). The ethereal extracts were combined, dried (Na_2SO_4) and the ether removed to give an oily residue. Each ring-closed isomer (**19**, **20**, **25**, **26**) was chromatographed in chloroform solution over a small chromatographic column packed with Woelm grade IV alumina (*ca.* 5.0 g) and eluted with light petroleum. Evaporation of the light petroleum left, in each case, a colourless oil. *rel*-(4a*R*,12a*S*,12*R*,11a*R*)-12-Methylperhydropyrido[1,2-*c*]-[1,3]benzoxazepine (**19**) (0.9 g) was obtained from isomer **7** (Found: C, 75.0; H, 11.55; N, 6.2. $C_{14}H_{25}NO$ requires C, 75.3; H, 11.3; N, 6.25%); *rel*-(4a*S*,12a*R*,12*R*,11a*R*)-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**25**) (0.9 g) was obtained from isomer **13** (Found: C, 75.0; H, 11.55; N, 6.2. $C_{14}H_{25}NO$ requires C, 75.3; H, 11.3; N, 6.25%); *rel*-(4a*R*,12a*S*,12*S*,11a*R*)-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**20**) (0.9 g) was obtained from isomer **8** (Found: C, 75.0; H, 11.55; N, 6.2. $C_{14}H_{25}NO$ requires C, 75.3; H, 11.3; N, 6.25%); *rel*-(4a*S*,-12a*R*,12*S*,11a*R*)-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**26**) (0.2 g) was obtained from isomer **14** (Found: C, 75.0; H, 11.55; N, 6.2. $C_{14}H_{25}NO$ requires C, 75.3; H, 11.3; N, 6.25%). In a similar way the following compounds were obtained from the ethyl-substituted derivatives: *rel*-(4a*R*,-9*R*,11a*R*,12*R*,12a*S*)-9-ethyl-12-methylperhydropyrido[1,2-*c*]-[1,3]benzoxazepine (**23**) b.p. 128 °C at 0.09 mmHg (Found: C, 76.4; H, 11.55; N, 5.6. $C_{16}H_{29}NO$ requires C, 76.4; H, 11.6; N, 5.6%); *rel*-(4a*R*,9*S*,11a*R*,12*R*,12a*S*)-9-ethyl-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**24**) b.p. 128 °C at 0.09 mmHg (Found: C, 76.45; H, 11.5; N, 5.6. $C_{16}H_{29}NO$ requires C, 76.4; H, 11.6; N, 5.6%); *rel*-(4a*S*,9*S*,11a*R*,12*R*,12a*R*)-9-ethyl-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**28**) b.p. 128 °C at 0.09 mmHg (Found: C, 76.3; H, 11.6; N, 5.6. $C_{16}H_{29}NO$ requires C, 76.4; H, 11.6; N, 5.6%); *rel*-(4a*R*,9*S*,-11a*R*,12*R*,12a*S*)-9-ethyl-12-methylperhydropyrido[1,2-*c*][1,3]-benzoxazepine (**30**) b.p. 128 °C at 0.09 mmHg (Found: C, 76.35; H, 11.5; N, 5.5. $C_{16}H_{29}NO$ requires C, 76.4; H, 11.6; N, 5.6%) and *rel*-(4a*R*,9*S*,11a*R*,12*S*,12a*S*)-9-ethyl-12-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**22**) b.p. 128 °C at 0.09 mmHg (Found: C, 76.3; H, 11.6; N, 5.65. $C_{16}H_{29}NO$ requires C, 76.4; H, 11.6; N, 5.6%).

* 1 psi ~ 6.894 757 × 10^3 Pa.

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