Compounds with Bridgehead Nitrogen. Part. 69.[1] The NMR Spectra and Stereochemistry of Perhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines

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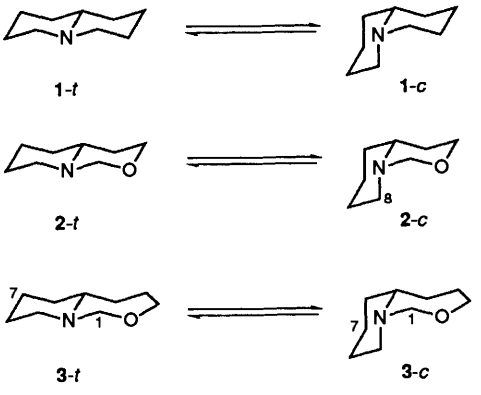
The positions of conformational equilibria in a series of perhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines have been determined by ^1H and ^{13}C NMR spectroscopy. In contrast with *syn*- and *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepine which favour the *trans*-fused conformers the equilibria for the cyclopenta analogues show marked shifts towards the *O*-inside *cis*-fused conformers (71% *cis* conformer for the *syn* isomer, 78% *cis* conformer for the *anti* isomer).

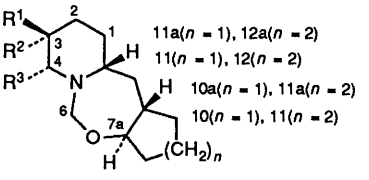
Conformational equilibria in reduced 1,3-heterocyclic systems are dominated by the generalised anomeric effect.[2] For example, whereas ΔG°_{298} for the quinolizidine equilibrium[3] **1**-*t* ⇌ **1**-*c* is 2.6 kcal mol^{-1},† the corresponding equilibrium **2**-*t* ⇌ **2**-*c* for perhydropyrido[1,2-*c*][1,3]oxazine[4] shows a shift towards the *cis* conformer **2**-*c* (ΔG°_{203} 1.3 kcal mol^{-1}) as a result of a favourable anomeric effect and the smaller non-bonded interaction between the oxygen atom and the C-8 methylene in **2**-*c* as opposed to a *gauche*-butane type interaction in **1**-*c*. Such factors also contribute to the position of conformational equilibrium **3**-*t* ⇌ **3**-*c* for the corresponding seven-membered ring analogue but the conformational mobility of the seven-membered ring makes an assessment of anomeric effects and non-bonded interactions difficult.

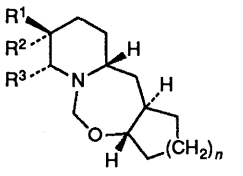


In fact **3** shows[5] a greater preference (74% **3**-*t* ⇌ 26% **3**-*c* at 298 K) for the *cis* conformer (**3**-*c*) than does the six-membered ring analogue (*ca.* 90% **2**-*t* at 298 K). This may represent a situation where both $n_O \rightarrow \sigma^*$ C–N and $n_N \rightarrow \sigma^*$ C–O anomeric effects stabilise the *cis* conformer **3**-*c* as in **2**-*c* but in which the $n_O \rightarrow \sigma^*$ C–N interaction (stabilising **2**-*t*) is absent in **3**-*t* as a result of loss of the necessary antiperiplanar relationship between an oxygen lone pair and the C–N bond.

The sensitivity of *cis* ⇌ *trans* conformational equilibria to such types of seven-membered ring conformational changes is shown by the differing equilibria in *syn*- and *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepines **8** and **16**.[6] Whereas the *syn* isomer adopts predominantly the *trans* fused conformation **8**-*t* the *anti* isomer adopts a similar equilibrium position (*ca.* 73% **16**-*t* ⇌ *ca.* 27% **16**-*c*) to that (**3**-*t* ⇌ **3**-*c*) adopted by the bicyclic system.

In order to explore such effects the cyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines **4**–**7** and **12**–**15** were selected for study. Comparison of the equilibria positions for these compounds with those of the corresponding six-membered C-ring analogues **8**–**11** and **16**–**19** should then indicate the effect of the differing size of the cycloalkano-ring on the equilibria positions. The compounds were synthesised by a similar sequence of reactions to that adopted for the cyclohexano analogues.[6] Separation of the isomers was achieved by fractional recrystallisation and column chromatography.





4 $R^1 = R^2 = R^3 = H$, $n = 1$
5 $R^1 = R^2 = H$, $R^3 = Me$, $n = 1$
6 $R^1 = Et$, $R^2 = R^3 = H$, $n = 1$
7 $R^2 = Et$, $R^1 = R^3 = H$, $n = 1$
8 $R^1 = R^2 = R^3 = H$, $n = 2$
9 $R^1 = R^2 = H$, $R^3 = Me$, $n = 2$
10 $R^1 = Et$, $R^2 = R^3 = H$, $n = 2$
11 $R^2 = Et$, $R^1 = R^3 = H$, $n = 2$

12 $R^1 = R^2 = R^3 = H$, $n = 1$
13 $R^1 = R^2 = H$, $R^3 = Me$, $n = 1$
14 $R^1 = Et$, $R^2 = R^3 = H$, $n = 1$
15 $R^2 = Et$, $R^2 = R^3 = H$, $n = 1$
16 $R^1 = R^2 = R^3 = H$, $n = 2$
17 $R^1 = R^2 = H$, $R^3 = Me$, $n = 2$
18 $R^1 = Et$, $R^2 = R^3 = H$, $n = 2$
19 $R^2 = Et$, $R^1 = R^3 = H$, $n = 2$

Results and Discussion

The *syn*-/*anti*-configurations of the perhydropyrido[1,2-*c*]-[1,3]benzoxazepines have been determined[7] by an X-ray structure determination of 1*R*, 2*S*, 2″*S*-2-(piperidin-2-ylmethyl)cyclohexanol (**20**) from which **16** is obtained by ring closure with formaldehyde. Similarly, configurational assignments were made to the parent unsubstituted cyclopentano compounds **4** and **12** on the basis of their preparation from the 2-(piperidin-2-ylmethyl)cyclopentanols **21** and **22** of known configuration.[7] Estimates of the positions of conformational equilibria of the cyclohexano derivatives **8**–**11** and **16**–**19** have been made largely from a comparison of the ^{13}C NMR shifts of C-2‡ in the various derivatives with the corresponding C-7 shifts in **3** (δ 24.9 in **3**-*t*, δ 19.0 in **3**-*c*).[5] Low temperature (−100 °C) NMR spectroscopy of these compounds and of the five-membered ring analogues described in this paper did not result in a 'freezing' of the equilibria.

† 1 cal = 4.184 J.

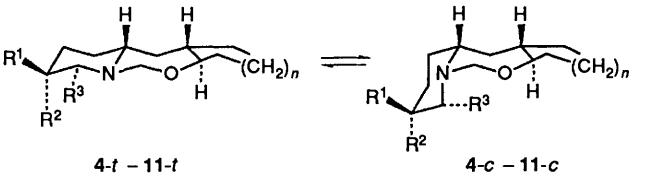
‡ The numbering system for the five-membered ring compounds described in this paper deviates from the IUPAC system in order to facilitate comparison of spectral data on **8**–**11** and **16**–**19**.

Table 1 ^{13}C NMR chemical shifts of the perhydrocycloalkano[*f*]pyrido[1,2-*c*][1,3]oxazepines **4**–**19** in $CDCl_3$

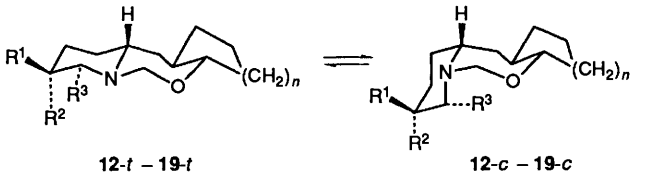
	δ_C															
Compound	C-1	C-2	C-3	C-4	C-6	C-7a	C-8	C-9	C-10	C-10a	C-11	C-11a	C-12	C-12a	C-CH_2	C-CH_3
4	33.2	20.7	26.3	47.8	84.3	85.5	31.1[a]	21.3	30.55[a]	43.4	36.2	59.5	—	—	—	—
5	33.5	25.1	31.4	56.0	77.4	87.8	29.4	20.3	29.4	44.8	39.3	61.7	—	—	—	20.8
6	33.4	31.3	38.1	58.5	87.8	88.4	31.0	20.7	29.7	42.7	38.1	60.0	—	—	27.0	11.2
7	33.9	26.1	38.9	51.35	83.8	84.8	30.5	21.7	30.9	43.0	35.1	58.7	—	—	27.4	11.4
8	33.05	24.75	26.8	54.3	88.0	86.5	34.3	25.4	25.9	—	33.6	47.4	39.8	62.4	—	—
9	32.7	25.4	33.35	55.9	80.9	86.5	36.2	25.9	25.7	—	34.9	48.6	39.8	63.3	—	20.7
10	32.85	31.8	38.9	61.1	88.7	86.9	34.4	28.85	25.4	—	33.4	47.9	39.7	62.6	27.05	11.4
11	31.1	26.9	38.0	52.0	83.0	84.05	34.6	25.8	25.4	—	34.0	44.2	38.05	60.2	26.5	11.65
12	32.1	20.3	26.5	48.8	88.6	86.1	32.2	22.1	31.5	44.8	35.2	57.1	—	—	—	—
13	35.4	23.0	33.9	54.4	82.3	87.05	30.7	20.6	31.0	42.4	38.5	59.45	—	—	—	21.4
14	34.7	31.3	39.1	58.8	85.0	87.3	31.15	20.5	31.3	44.3	42.1	57.8	—	—	26.3	11.5
15	32.9	25.5	38.7	52.7	88.8	85.2	32.6	22.75	30.5	45.8	34.0	55.5	—	—	27.35	11.4
16	33.2	23.3	26.6	51.4	86.9	84.05	34.45	24.9	25.65	—	33.7	40.5	40.7	58.4	—	—
17	33.9	24.85	33.8	56.6	78.0	83.1	37.75	25.7	25.1	—	34.7	39.4	42.6	59.35	—	20.9
18	33.1	31.3	38.3	59.2	85.7	84.3	34.1	24.7	25.4	—	33.3	39.7	42.0	59.4	26.9	11.3
19	31.1	25.6	38.5	51.3	89.4	82.9	34.7	24.7	25.4	—	34.4	42.3	35.8	54.5	27.05	11.4

[a] These assignments may be interchanged.

Comparison of the C-2 shifts (Table 1) for the *syn*- and *anti*-cyclopentano and cyclohexano systems **4** and **12** and **8** and **16** show marked differences. Thus whereas *syn*- and *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepine show C-2 values of δ 24.75 and δ 23.3 respectively corresponding to equilibria containing >97% **8**-*t* and *ca.* 73% **16**-*t* the analogous cyclopentano compounds show shifts of δ 20.7 and δ 20.3 indicating a predominance of the *cis*-fused conformers (**4**-*c* and **12**-*c*). If the C-7 shifts of **3**-*t* and **3**-*c* are taken as indicative of the *trans*-fused and *cis*-fused conformers of the cyclopentano compounds **4** and **12**, and assuming that the fusion of the cyclopentane ring on to **3** does not affect the C-2 shift, then the equilibria positions may be estimated[8] as *ca.* 29% **4**-*t* ⇌ 71% **4**-*c* for **4** and *ca.* 22% **12**-*t* ⇌ 78% **12**-*c* for **12**.



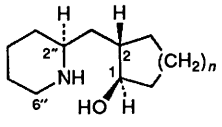
4-*t* – **11**-*t* **4**-*c* – **11**-*c*



12-*t* – **19**-*t* **12**-*c* – **19**-*c*

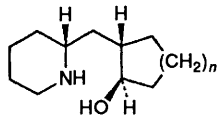
These estimates are supported by the small Δae [= $\delta(H_{eq}) - \delta(H_{ax})$] values (Table 2) for the C-4 methylene protons of −0.13 and −0.23 ppm for the *syn*- and *anti*-compounds respectively (*cf.* Δae of 0.16 and 0.47 ppm in the *syn*- and *anti*-cyclohexano analogues **8** and **16**). The distinction between the C-4 axial and equatorial proton signals in the NMR spectra of **4** and **12** was made on the basis of the near triplet of doublets ($J_{4ax,4eq} \simeq J_{4ax,3ax} \simeq 11$ Hz, $J_{4ax,3eq} \simeq 4$ Hz) for the axial proton and the near doublet of triplets ($J_{4e\,4ax} \simeq 11$ Hz, $J_{4eq,3ea} \simeq J_{4eq,3ax} \simeq 4$ Hz) for the equatorial proton. In addition the low field resonances of 11a-H of δ 2.98 and 3.26 in **4** and **12** (*cf.* δ 2.47 and 2.69 for 12a-H in **8** and **16**) indicate the *gauche* relationship between the nitrogen lone pair and the angular proton in **4**-*c* and **12**-*c*.[9] The predominance of the *cis*-fused conformer **4**-*c* was supported by nuclear Overhauser effects between 7a-H and the C-4 methylene protons.

The two isomers of 4-methylperhydrocyclopenta[*f*]pyrido-[1,2-*c*][1,3]oxazepine obtained are expected to possess the *cis*-(4-H,12a-H) configuration as a consequence of the predominance of *cis*-addition of hydrogen in the reduction of the substituted pyridine.[10] The ^1H NMR spectrum of one isomer (m.p. 90 °C) of 6″-methyl-2-(piperidin-2-ylmethyl)cyclopentanol showed a multiplet at δ 2.70 ($J_{6''ax,5''ax} = 10.6$ Hz; $J_{6''ax,Me} = 6.25$ Hz; $J_{6''ax,5''eq} = 2.5$ Hz) assigned to 6ax-H, permitting location of the methyl group in the equatorial position. Comparison with the ^1H NMR spectrum of *rel*-(1*R*,2*S*,2″*S*)-2-(piperidin-2-ylmethyl)cyclopentanol (**21**), especially with the multiplet splitting pattern of the 2″-H signal, allowed the *anti*-configuration (**13**) to be assigned to the 4-



rel (1*R*, 2*S*, 2″*S*)

20 *n* = 2
21 *n* = 1



rel (1*R*, 2*S*, 2″*R*)

22 *n* = 1

methylperhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepine obtained by formaldehyde ring closure of the amino alcohol. The ^1H NMR spectrum of **13** showed the presence of the equatorially orientated methyl group and thus the *trans*-fused conformation **13**-*t*. Similarly the second isomer **5** was assigned the predominantly *trans*-fused conformation **5**-*t*. The equatorial orientation of the methyl group is supported by the upfield shift of C-6 in **5** and **13** relative to C-6 absorption in **6** and **14**.

Two of the four diastereoisomeric 3-ethyl substituted derivatives (**6**, **7**, **14**, **15**) are expected to adopt the *trans*-fused conformations **6**-*t* and **14**-*t* and two the *cis*-fused conformations **7**-*c* and **15**-*c* in order to minimise non-bonded interactions in conformations **6**-*c*, **14**-*c*, **7**-*t* and **15**-*t* containing axial ethyl groups. One of the isomers was readily assigned the configuration depicted in **7** and the *cis*-fused conformation **7**-*c* on the basis of the similarity of its ^{13}C NMR spectrum to that of **4**-*c* and allowing for the substituent effect of the ethyl group[11] on the shifts of C-2, C-3 and C-4. The *cis*-fused conformers **7**-*c* for **7** and **15**-*c* for **15** were indicated by the chemical shifts (δ 26.1 and δ 25.5) of C-2 (γ ax effect with C-11 methylene)

Table 2 Selected ^{1}H NMR parameters of the perhydrocycloalkano[*f*]pyrido[1,2-*c*][1,3]oxazepines **4**–**19** in $CDCl_3$

	δ_H(*J*/Hz)						
Compound	4-H$_{eq}$	4-H$_{ax}$	6-H$_{eq}$	6-H$_{ax}$	7a-H	Bridgehead proton (11a-H,12a-H)	Me
4	2.83[a]	2.96[b]	4.49 ($J_{6eq,6ax}$ − 11.25)	4.53	3.72 ($J_{7a,10a}$ 8.8) ($J_{7a,8ax'} = J_{7a,8eq'}$ 8.1)	2.98[b]	—
5	—	2.75[b]	4.52 ($J_{6eq,6ax}$ − 12.5)	4.27	3.36 ($J_{7a,8eq'} = J_{7a,8ax'} = J_{7a,10a}$ 8.8)	2.74[b]	1.21
6	3.03	2.15	4.28 ($J_{6eq,6ax}$ − 11.25)	4.21	3.55	2.44	—
7	2.88 ($J_{4eq,4ax}$ − 11.25) ($J_{4eq,3ax}$ 3.8)	2.50	4.49 ($J_{6eq,6ax}$ − 11.25)	6.63	3.78 ($J_{7a,10a} = J_{7a,8eq'} = J_{7a,8ax'}$ 8.1)	3.06[c]	—
8	2.87 ($J_{4eq,4ax}$ − 10.6) ($J_{4eq,3ax}$ 10.0)	2.71 ($J_{4ax,3ax}$ 10.6) ($J_{4ax,3eq}$ 3.8)	4.52 ($J_{6eq,6ax}$ − 11.9)	4.45	2.91 ($J_{7a,11a} = J_{7a,8ax}$ 9.6) ($J_{7a,8eq}$ 3.8)	2.47	—
9	—	2.76 ($J_{4ax,3ax}$ 11.5) ($J_{4ax,3eq}$ 1.9)	4.93 ($J_{6eq,6ax}$ − 13.1)	4.37	2.85 ($J_{7a,11a} = J_{7a,8ax}$ 10.6) ($J_{7a,8eq}$ 3.8)	2.62	1.17
10	2.93 ($J_{4eq,4ax}$ − 11.5) ($J_{4eq,3ax}$ 3.2)	2.30 ($J_{4ax,3ax}$ 11.5)	4.58 ($J_{6eq,6ax}$ − 11.5)	4.46	2.88 ($J_{7a,11a} = J_{7a,8ax}$ 9.7) ($J_{7a,8eq}$ 4.1)	2.30	—
11	2.68 ($J_{4eq,4ax}$ − 12.1)	2.51[d] ($J_{4ax,3eq}$ 8.9)	4.47 ($J_{6eq,6ax}$ − 11.5)	4.34	307 ($J_{7a,11a} = J_{7a,8ax}$ 9.6) ($J_{7a,8eq}$ 4.5)	2.81	—
12	2.66 ($J_{4eq,4ax}$ − 10.6)[e] ($J_{4eq,3ax}$ 4.4) ($J_{4eq,3eq}$ 3.8)	2.89 ($J_{4ax,3ax}$ 9.4) ($J_{4ax,3eq}$ 2.5)	4.42 ($J_{6eq,6ax}$ − 11.25)	4.30	3.62 ($J_{7a,10a}$ 8.8) ($J_{7a,8ax'} = J_{7a,8eq'}$ 8.1)	3.26 ($J_{11a,1ax}$ 10.0) ($J_{11a,11'}$ 7.5) ($J_{11a\,11}$ 3.8)	—
13	—	2.66 ($J_{4ax,3ax}$ 12.5) ($J_{4ax,3eq}$ 3.8) ($J_{4ax,Me}$ 6.3)	4.59 ($J_{6eq,6ax}$ − 11.9)	4.18	3.52 ($J_{7a,10a} = J_{7a8ax'} = J_{7a,8eq'}$ = 8.8)	2.88 · ($J_{11a,1ax}$ 11.9) ($J_{11a,11}$ 6.3) ($J_{11a,11'}$ 6.9)	1.18
14	3.03	2.38	4.43 ($J_{6eq,6ax}$ − 12.5)	4.36	3.03[c] ($J_{7a,10a} = J_{a,8ax'} = J_{7a,8eq'}$ 8.8)	2.44[c]	
15	2.81 ($J_{4eq,4ax}$ − 11.9) ($J_{4eq,3ax}$ 4.4)	2.46 ($J_{4ax,3ax}$ 11.9)	4.51 ($J_{6eq,6ax}$ − 11.25)	4.31	3.71 ($J_{7a,10} = J_{7a,8ax'} = J_{7a,8eq'}$ 7.5)	3.47[c]	—
16	2.97 ($J_{4eq,4ax}$ − 11.9)	2.50 ($J_{4ax,3ax}$ 8.8) ($J_{4ax,3eq}$ 3.8)	4.31 ($J_{6eq,6ax}$ − 10.6)	4.25	3.04 ($J_{7a,11a} = J_{7a,8ax}$ 11.25) ($J_{7a,8eq}$ 3.8)	2.69	—
17	—	2.60	4.60 ($J_{6eq,6ax}$ − 11.9)	4.24	3.15 ($J_{7a,11a} = J_{7a,8ax}$ 9.6) ($J_{7a,8eq'}$ 3.8)	2.69	1.18
18	2.98 ($J_{4eq,4ax}$ − 10.8)	2.11 ($J_{4eq,3ax}$ 10.8)	4.34 ($J_{6eq,6ax}$ − 11.6)	4.19	3.00 ($J_{7a,11a} = J_{7a,8ax}$ 10.6) ($J_{7a,8eq}$ 3.8)	2.47	
19	2.65	2.65	4.49 ($J_{6eq,6ax}$ − 11.9)	4.32	3.22 ($J_{7a,11a} = J_{7a,8ax}$ 9.6) ($J_{7a,8eq}$ 3.8)	3.33	

[a] First-order analysis inappropriate. [b] Overlapping signals precluded extraction of coupling constants. [c] Ill defined multiplet. [d] Designated 3-eq assuming a *trans*-fused A/B conformation. [e] These *J* values represent an average.

which after allowance is made for a βeq ethyl effect of 6.6 ppm gives C-2 shifts of δ 19.5 and 18.9 close to that (δ 19.0) in **3**-*c*.

Additional evidence for the *cis*-fused conformers **7**-*c* and **15**-*c* comes from the Δae values of the C-4 methylene protons of 0.38 and 0.35 ppm for the *syn*- and *anti*-compounds respectively. These are larger than for **4** and **12** as a result of preferential shielding of 4ax-H by the equatorial ethyl group by *ca.* 0.4 ppm[12] but still indicate *cis*-fused conformers. The axial C-4 protons resonate as triplets ($J_{4ax,4eq} = J_{4ax,3ax}$ = 11.25 Hz) and the equatorial protons as doublets of doublets ($J_{4eq,4ax}$ = 11.25 Hz, $J_{4eq,3ax}$ = 3.8 Hz) showing the equatorial orientation of the ethyl group. The 11a-H resonance is also typical of *cis*-fused conformers (δ 3.06 for **7** and δ 3.47 for **15**).

Evidence for the predominance of *cis*-A/B fusion in **7** and **15** was strengthened by nuclear Overhauser effects between the C-4 methylene protons and the C-6 equatorial proton. In the *syn*-compound (**7**) effects between 7a-H and the C-4 axial proton indicated a preference for the B-ring geometry depicted in **7**-*c*. Effects between the C-6 axial proton and both 7a-H and 11a-H were noted in the spectrum of the *anti*-isomer **15** supporting the stereochemistry **15**-*c*.

The predominance of the *trans*-fused conformer **6**-*t* for isomer **6** was indicated by the C-2 shift δ 31.3 (*cf.* δ 31.8 for the *trans*-fused six-membered ring analogue **10**-*t*), the large chemical shift difference between the C-4 methylene protons (Δae 0.88 ppm) (*cf.* 0.63 ppm in **10**), and the angular 11a-H shift of δ 2.44. Similar parameters confirmed the predominance of conformer **14**-*t* for isomer **14**.

Table 3 Estimates of equilibria positions in perhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines

Compound	Equilibrium based on ^{13}C NMR parameters			'Calculated' equilibrium position[a]			'Calculated' equilibrium position[b]		
	% *trans*	% *cis*	ΔG° [c]	% *trans*	% *cis*	ΔG° [c]	% *trans*	% *cis*	ΔG° [c]
6	97	3	2.03	89	11	1.27	92	8	1.47
4	29	71	−0.53	29	71	−0.53	29	71	−0.53
7		>99%		2	98	−2.33	1.4	98.6	2.5
14	97	3	2.03	85	15	1.05	89	11	1.25
12	22	78	−0.75	22	78	−0.75	22	78	−0.75
15		>99%		2	98	−2.55	1	99	−2.75

[a] Based on conformational free energy of ethyl group of 1.8 kcal mol^{-1}. [b] Based on conformational free energy of ethyl group of 2.0 kcal mol^{-1}. [c] ΔG° refers to the *trans* $\rightleftharpoons$ *cis* equilibrium.

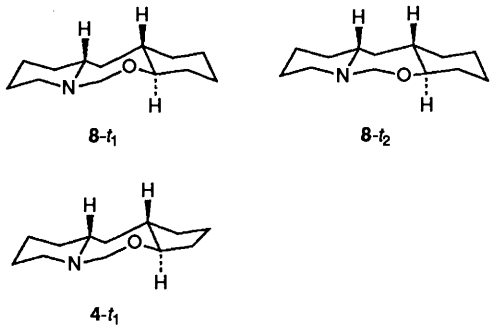


Fig. 1 B-ring conformations of *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine and of the cyclopenta-analogue

Rationalisation of Conformational Equilibria in Perhydrocyclopenta[f]*pyrido*[1,2-c][1,3]*oxazepines.*—NMR measurements have been used to estimate the positions of conformational equilibria in the perhydrocyclopenta[*f*]pyrido[1,2-*c*]-[1,3]oxazepines shown in Table 3. These are based on assumptions regarding ethyl substituent effects[11] on ^{13}C NMR shifts and the application of the Winstein–Holness equation.[8] Such methods may lead to significant errors in the estimates since in some cases very small differences in numbers are involved. It is important therefore to test these results against some of the basic principles of conformational analysis to see whether the changes in equilibria positions with substitution are reasonable.

For the *syn*-series of compounds, ΔG° for the equilibrium **4**-*t* $\rightleftharpoons$ **4**-*c* should differ from that for the ethyl substituted derivatives **6**-*t* $\rightleftharpoons$ **6**-*c* and **7**-*t* $\rightleftharpoons$ **7**-*c* by the magnitude of the interactions between the axial ethyl substituent in **6**-*c* and **7**-*t* and the C-11 methylene and the nitrogen lone pair. The magnitude of this effect is not known but may be taken as similar to the conformational free energy of the 3-methyl substituent in 1,3-dimethylpiperidine which is reported as 1.8 kcal mol^{-1} [12] and 1.5 kcal mol^{-1} [13] and assuming the conformational free energy of the ethyl group to be equal to that of the methyl group.[6] With reference to Table 3 the natural starting point for an estimate of $\Delta G^{\circ}_{trans \rightleftharpoons cis}$ in the perhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines is compound **4** since the equilibrium for this does not lie at an extreme. From the estimates of equilibrium ΔG° for **4** is *ca.* −0.53 kcal mol^{-1}. Taking the effect of the ethyl substituent as the higher value of 1.8 kcal mol^{-1} then gives an equilibrium for **6** of −0.53 + 1.8 = 1.27 kcal mol^{-1} corresponding to 89% *trans* conformer. This is lower than the estimate based on NMR data. In a similar manner the equilibrium for **7** is estimated as *ca.* 98% *cis*-conformer. Similar calculations were made for the *anti* series based on the observed position of equilibrium for **12** and the results are provided in Table 3. These calculated equilibria positions match those obtained by NMR spectroscopy more closely by utilising a larger value (2.0 kcal mol^{-1}) for the conformational free energy of the ethyl group.

Examination of Dreiding models shows two reasonable conformations (**8**-t_1 and **8**-t_2) for the *trans-syn-trans*-cyclohexano compound **8** as shown in Fig. 1 but the **8**-t_1 structure seems favoured on the basis of the anomeric effect. In this conformation the B/C ring fusion involves equatorial bonds from the cyclohexane ring. If the favourable **B** ring geometry is to be preserved in the cyclopentano analogue **4**-t_1 then ring fusion strain will be involved, as in *trans*-hydrindane. This may provide the basis for the preference of the cyclopentano compound **4** for the *cis*-conformer **4**-*c*. In contrast with the six-membered compound **16** which adopts a 73% **16**-*t* $\rightleftharpoons$ 27% **16**-*c* equilibrium the five-membered ring compound **12** favours the *cis* conformer (22% **12**-*t* $\rightleftharpoons$ 78% **12**-*c*). This again may be attributed to strain in the *trans*-fused 5/7 ring junction in **12**-*t*.

Experimental

Elemental analyses were carried out by the Butterworth Microanalytical Consultancy, Teddington, Middlesex. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution (*ca.* 0.05 mol dm^{-3}) 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 tetramethylsilane as internal standard. Chemical shifts were independent of concentration over the range of dilute solutions used. 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) μs (*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. The ^{13}C NMR assignments were made on the basis of electronegativity effects on chemical shifts. In addition, CH and CH_3 signals were distinguished from CH_2 signals by a pulse sequence technique[14] or attached proton test (APT) technique.[15] The assignment of ring A ^{13}C NMR signals was assisted by comparison with the shifts in piperidines and related systems and on the basis of methyl[16] and ethyl[11] substitution effects. Stereochemically dependent ^{13}C NMR shifts were assigned by comparison with the shifts observed at 193 K [5] for *trans*-fused and *O*-inside *cis*-fused perhydropyrido[1,2-*c*][1,3]oxazepine taking into consideration the appropriate substituent effect.

2-(*Pyridin*-2-*ylmethyl*)*cyclopentanols.*—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 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, the cyclopentene oxide (0.5 mol) added dropwise over a period of 0.5 h, and the mixture 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 evaporated leaving the crude product which was distilled *in vacuo* to yield the corresponding 2-(pyridin-2-ylmethyl)cyclopentanols. The following compounds were obtained: 2-(*6-methylpyridin-2-ylmethyl*)*cyclopentanol* (24%) b.p. 105 °C at 0.45 mmHg (Found: C, 75.2; H, 8.8; N, 7.2. $C_{12}H_{17}NO$ requires C, 75.35; H, 9.0; N, 7.3%); 2-(*5-ethylpyridin-2-ylmethyl*)*cyclopentanol* (29%) b.p. 120–130 °C at 0.3 mmHg (Found: C, 76.0; H, 9.5; N, 6.9. $C_{13}H_{19}NO$ requires C, 76.05; H, 9.3; N, 6.8%).

2-(*Piperidin-2-ylmethyl*)*cyclopentanols*.—A solution of the 2-(pyridin-2-ylmethyl)cyclopentanol (20 g) in glacial acetic acid (200 cm^3) was shaken with hydrogen at *ca.* 60 psi on a Parr hydrogenator at room temperature in the presence of Adams platinum oxide catalyst (1.5 g). After absorption of the calculated volume of hydrogen, the catalyst was filtered off and the acetic acid removed *in vacuo*. The residue was basified with 30% aqueous sodium hydroxide and extracted with ether (8 × 50 cm^3). The solution was dried (Na_2SO) and the solvent removed leaving mixtures of isomeric 2-(piperidin-2-ylmethyl)-cyclopentanols. The following compounds were obtained: 2-(*6-methylpiperidin-2-ylmethyl*)*cyclopentanol* (90%) m.p. 85 °C (Found: C, 72.8; H, 11.6; N, 7.0. $C_{12}H_{23}NO$ requires C, 73.0; H, 11.75; N, 7.1%); 2-(*5-ethylpiperidin-2-ylmethyl*)*cyclopentanol* (90%) b.p. 115–120 °C at 0.3 mmHg (Found: C, 73.9; H, 11.8; N, 6.5. $C_{13}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.6%).

Perhydrocyclopenta[f]*pyrido*[1,2-c][1,3]*oxazepines*.—The appropriate 2-(*piperidin-2-ylmethyl*)*cyclopentanol*, either as a single isomer or a mixture of diastereoisomers, was shaken with an excess of 37% aqueous formaldehyde for 0.5 h. The mixture was basified with 30% aqueous sodium hydroxide and extracted with ether (5 × 50 cm^3). The ethereal solution was dried (Na_2SO_4), concentrated and distilled *in vacuo* to give the required perhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines. Ring closure of the 2-(piperidin-2-ylmethyl)cyclopentanols **21** and **22** gave rel-(7aR,10aS,11aR)*perhydrocyclopenta*[f]*pyrido*-[1,2-c][1,3]*oxazepine* (**4**) (40%) b.p. 90–91 °C at 0.07 mmHg (Found: C, 73.75; H, 10.9; N, 7.2. $C_{12}H_{21}NO$ requires C, 73.8; H, 10.8; N, 7.2%) and rel-(7aS,10aR,11aR)*perhydrocyclopenta*[f]-*pyrido*[1,2-c][1,3]*oxazepine* (**12**) (28%) b.p. 90–91 °C at 0.07 mmHg (Found: C, 73.8; H, 10.75; N, 7.1. $C_{12}H_{21}NO$ requires C, 73.8; H, 10.8; N, 7.2%). Ring closure of the 2-(6-methylpiperidin-2-ylmethyl)cyclopentanols (2.0 g) gave a mixture of the 4-methylperhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines **5** and **13** (0.5 g) b.p. 109–110 °C at 0.07 mmHg. Column chromatography over Grade IV Woelm alumina (50 g) using light petroleum (b.p. 40–60 °C) as the eluent gave rel-(4R,7aR,10aS,11aR)-4-*methylperhydrocyclopenta*[f]*pyrido*[1,2-c][1,3]-*oxazepine* (**5**) (*ca.* 0.25 g) (Found: C, 74.9; H, 11.1; N, 6.7. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.1; N, 6.7%) together with rel-(4R,7aS,10aR,11aR)-4-*methylperhydrocyclopenta*[f]*pyrido*[1,2-c][1,3]*oxazepine* **13** (*ca.* 0.1 g) (Found: C, 74.6; H, 11.05; N, 6.65. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.1; N, 6.7%). Ring closure of the mixture of diastereoisomeric 2-(5-ethylpiperidin-2-ylmethyl)cyclopentanols gave a mixture of the diastereoisomeric 3-ethylperhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepines **6**, **7**, **14** and **15** (4.0 g) b.p. 100–102 °C at 0.4 mmHg. Column chromatography over Grade IV Woelm alumina (500 g) using 5% ether in light petroleum (b.p. 40–60 °C) as the eluent gave (fractions 95–105) rel-(3R,7aS,10aR,11aR)-3-*ethylperhydrocyclopenta*[f]*pyrido*[1,2-c][1,3]*oxazepine* **15** (0.025 g) (Found: C, 74.0; H, 11.85; N, 6.4. $C_{14}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.4%). Fractions 253–288 gave rel-(3R,7aR,10aS,11aR)-3-*ethylperhydrocyclopenta*[f]*pyrido*[1,2-c][1,3]*oxazepine* **7** (0.05 g) (Found: C, 73.7; H, 11.95; N, 6.45. $C_{14}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.4%). Intermediate 15 cm^3 fractions gave a mixture containing predominantly *rel*-(3*R*,7a*S*,10a*S*,11a*R*)-3-ethylperhydrocyclopenta[*f*]pyrido[1,2-*c*][1,3]oxazepine **14**, together with *rel*-(3*R*,7a*S*,10a*R*,11a*S*)-3-ethylperhydrocyclopenta[*f*]-pyrido[1,2-*c*][1,3]oxazepine **6** (0.05 g) (Found: C, 73.9; H, 11.7; N, 6.5. $C_{14}H_{25}NO$ requires C, 73.9; H, 11.9; N, 6.4%).

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