Compounds with Bridgehead Nitrogen Part 71.[1] Stereochemistry of Protonated Perhydropyrido[1,2-*c*][1,3]benzoxazepines

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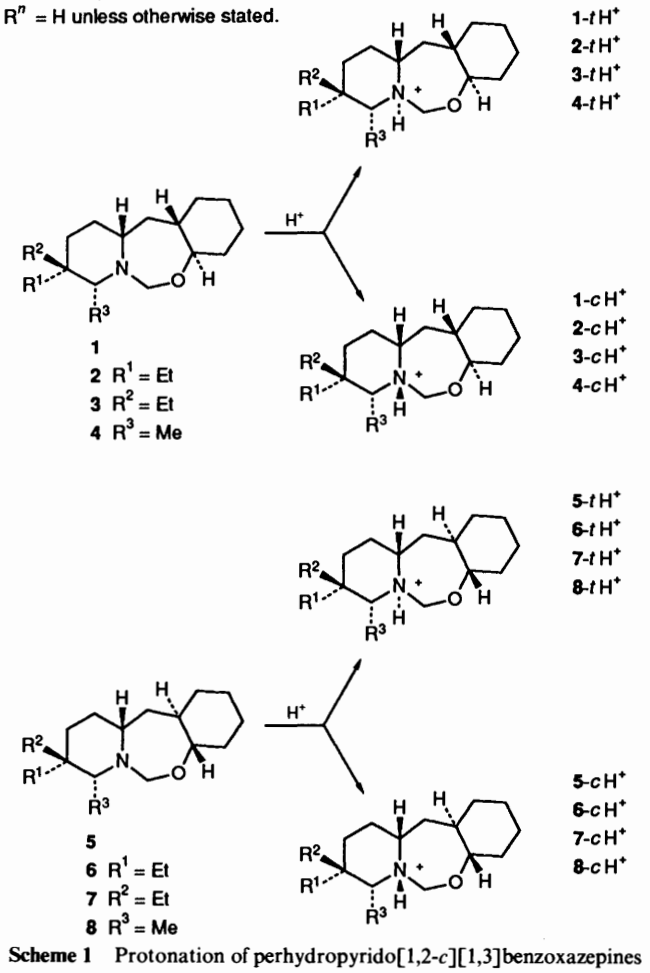
Protonation of *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepines in $CDCl_3$ solution by hydrogen chloride gas gives predominantly the *trans*-A/B ring fused hydrochloride salts. The corresponding *anti*-compounds give mixtures of hydrochlorides containing substantial amounts of the *cis*-salt. This latter compound prefers the *O*-outside *cis*-fused conformation.

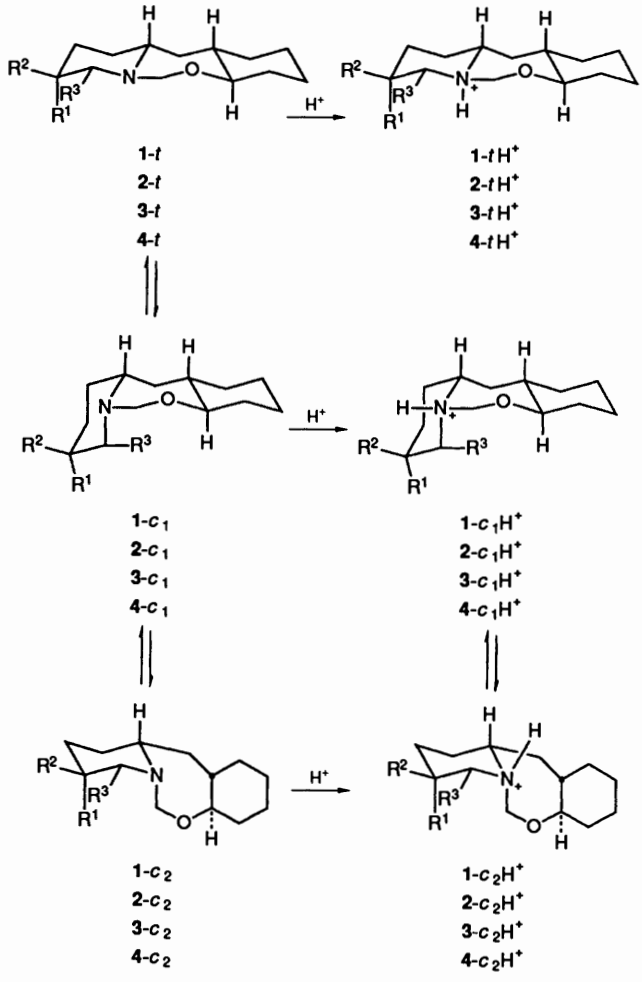
Protonation of *syn*- (**1**–**4**) and *anti*-perhydropyrido[1,2-*c*]-[1,3]benzoxazepines (**5**–**8**)[2] may give in each case *trans*- and/or *cis*-fused hydrochloride salts (Scheme 1). In the absence of proton exchange *trans* ⇌ *cis*-interconversion is prohibited but chair–chair interconversion permits an equilibrium for the *cis*-salt between *O*-inside and *O*-outside *cis*-conformations as shown in Schemes 2 and 3. This paper describes the stereochemistry of the protonated *syn*- and *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepines (**1**–**8**).



Scheme 1 Protonation of perhydropyrido[1,2-*c*][1,3]benzoxazepines

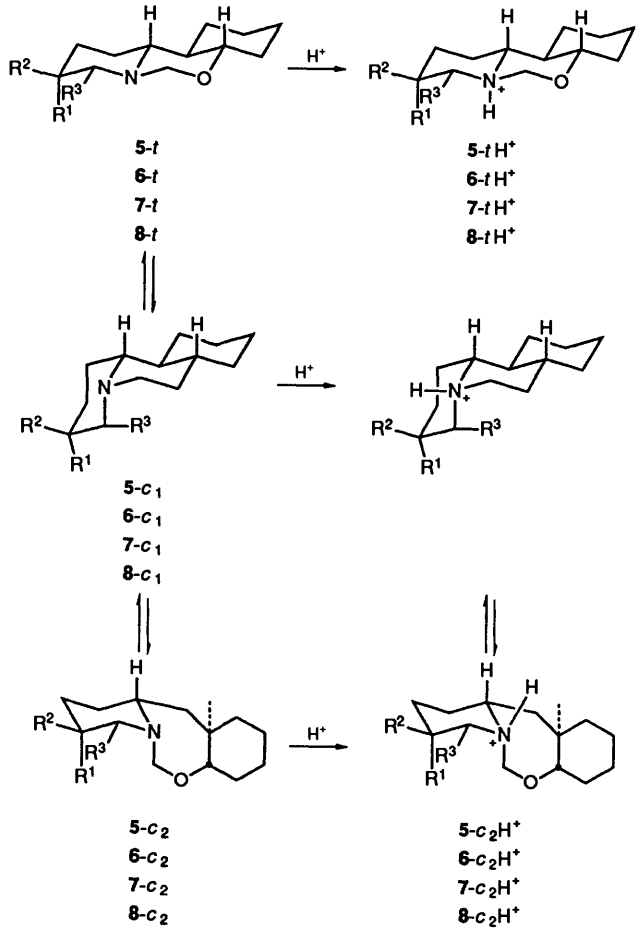
Results

Protonation of the perhydropyrido[1,2-*c*][1,3]benzoxazepines was carried out by passing a stream of hydrogen chloride gas through $CDCl_3$ solutions of the individual isomers and the ^1H and ^{13}C NMR spectra (see Tables 1 and 2) of the resultant hydrochlorides were recorded in this solution immediately. In general the *trans*-fused stereochemistry was assigned to that salt showing the largest Δae for C-6 methylene group protons (*cf.* Δae is 0.5 ppm for the C-4 methylene protons in *trans*-fused quinolizidine hydrochloride[3]).



Scheme 2 The protonation of *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine (for R^1, R^2, R^3 see Scheme 1)

Protonation of the syn-*Perhydropyrido*[1,2-*c*][1,3]*benzoxazepines.*—The ^1H NMR spectrum of the protonated ethyl substituted compound **3** shows only one set of signals for the expected *trans*-fused salt **3**-*t*H^+. Absorption of the C-6 methylene protons at δ 5.23 ($J_{6,6'} = -10.8$, $J_{6,^+NH} = 4.6$ Hz) and δ 4.67 ($J_{6,6'} = -10.8$, $J_{6',^+NH}$ = *ca.* 1.0 Hz) is



Scheme 3 The protonation of *anti*-perhydropyrido[1,2-*c*][1,3]benzoxazepines. (For R^1, R^2, R^3 see Scheme 1).

consistent with the *trans*-structure (**3**-*t*H$^+$). This is supported by absorption of 8-Hax as a quartet at δ 2.67 ($J_{8ax,^+NH}$ = 11.9 Hz).

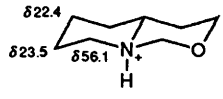
The ^{13}C NMR spectrum of protonated **3** (one set of signals) shows absorption at δ 89.0, δ 35.4 and δ 31.35 for C-6, C-9 and C-11 respectively, consistent with the *trans*-fused isomer **3**-*t*H$^+$ (C-6, C-9 and C-11 absorb at δ 88.7, δ 38.9 and δ 32.85 respectively in the corresponding free base **3**[2]).

The ^{1}H NMR spectrum of protonated **2** shows two sets of signals in the ratio of *ca.* 5:1 in favour of the *O*-inside *cis*-fused salt **2**-c_1H$^+$. The *trans*-fused salt is characterised by a large Δae value (0.84 ppm) for the C-6 methylene ($J_{6,6'}$ = −10.8 Hz) relative to that of the *cis*-fused salt (0.63 ppm). **2**-*t*H$^+$ is also characterised by the expected upfield shift of C-11 (δ 27.6) relative to that (δ 31.35) of **3**-*t*H$^+$ as a result of γax shielding by the ethyl group.

Absorption of 8-Hax as a quartet ($J_{8ax,8eq}$ = −11.8 Hz, $J_{8ax,9ax}$ = $J_{8ax,^+NH}$ = 11.8 Hz) in the spectrum of protonated **2** is consistent with equatorial ethyl substitution in the *O*-inside *cis*-fused salt **2**-c_1H$^+$. This absorption is almost identical to that observed for 8-Hax in the spectrum of **3**-*t*H$^+$ ($J_{8ax,9ax}$ = $J_{8ax,^+NH}$ = 11.9 Hz) indicating correct assignment of structure for **2**-c_1H$^+$. The presence of any *O*-outside *cis*-fused conformer in the **2**-c_1H$^+$ ⇌ **2**-c_2H$^+$ equilibrium is ruled out because of a severe interaction involving the C-6 methylene and the axial ethyl group. Upfield absorption of C-8 (δ 48.9) in the ^{13}C NMR spectrum of the protonated **2** relative to that (δ 58.15) in the *trans*-salt **2**-*t*H$^+$ and **3**-*t*H$^+$ (δ 59.8) is also consistent with the *O*-inside *cis*-fused conformer **2**-c_1H$^+$.

The ^{1}H NMR spectrum of protonated *cis* (8-H, 11a-H)-8-methyl-*syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine (**4**) showed one set of signals with the C-6 methylene absorbing as a singlet at δ 5.08. Examination of the corresponding ^{13}C NMR spectrum shows absorptions at δ 83.5, δ 32.1 and δ 31.2 for C-6, C-9 and C-11 respectively consistent with the *trans*-fused salt **4**-*t*H$^+$ (*cf.* C-6, C-9 and C-11 absorb at δ 80.9, δ 33.35 and δ 32.7 respectively in the corresponding free base[2]). The unexpected absorption of the C-6 methylene protons as a singlet may be due to change of conformation of the seven-membered ring on protonation [*cf.* Δae (C-6 methylene) 0.56 ppm in the *trans*-fused free base **4**[2]].

The ^{1}H NMR spectrum of protonated *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine **1** shows the presence of essentially one isomer with the $^+$NHCH$_2$O protons absorbing as a doublet of doublets at δ 5.27 ($J_{6',6''}$ = −10.5 Hz, $J_{6',^+NH}$ = 4.5 Hz) and a doublet at δ 4.62 ($J_{6',6''}$ = −10.5 Hz and $J_{6'',^+NH}$ = 0.0 Hz) consistent with the *trans*-fused structure **1**-*t*H$^+$. The ^{13}C NMR spectra of the protonated *syn*-perhydropyrido[1,2-*c*][1,3]benzoxazepine also showed only one set of signals. Comparison of some of the ^{13}C NMR chemical shifts of **1**-*t*H$^+$ (C-8 55.3, C-9 23.0, C-10 23.2) with corresponding shifts (δ 56.1, 23.5, 22.4) of *trans*-fused quinolizidine hydrochloride **9**[3] confirms the *trans*-fused isomer.



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Protonation of anti-*Perihydropyrido*[1,2-c][1,3]*benzoxazepines.*—The ^{1}H NMR spectrum of protonated *trans*(H-9, H-11a)-9-ethyl-*anti*-perhydropyrido[1,2-*c*][1,3] benzoxazepine **7** shows two sets of signals in the ratio of *ca.* 1:1. The *trans*-fused isomer **7**-*t*H$^+$ is characterised by a large Δae of 0.67 ppm for the C-6 methylene protons. Absorption of 8-Hax as a broad quartet at δ 2.65 ($J_{8ax,8eq}$ = −12.0 Hz, $J_{8ax,9ax}$ = $J_{8ax,^+NH}$ = 12.0 Hz) is also consistent with the *trans*-conformation (**7**-*t*H$^+$) in which 8-Hax has a large vicinal coupling with the axial $^+$N–H.

In the ^{1}H NMR spectrum of the *cis*-isomer **7**-*c*H$^+$ absorption of 8-Hax as a triplet of doublets at δ 2.9 ($J_{8ax,8eq}$ = −13.0 Hz, $J_{8ax,9ax}$ = 13.0 Hz and $J_{8ax,^+NH}$ = 3.0 Hz) is consistent with the *O*-outside *cis*-conformer **7**-c_2H$^+$ in which $J_{8ax,^+NH}$ is expected to be small (3.0 Hz). In the ^{1}H NMR spectrum of the *cis*-hydrochloride observation of a small Δae value (0.34 ppm) for the C-6 methylene protons is consistent only with the *O*-outside *cis*-conformer **7**-c_2H$^+$. This conformation was also characterised by upfield absorption of C-9 (δ 26.2) and C-11 (δ 25.4) relative to the shifts of corresponding nuclei of the *trans*-isomer (δ 34.9 and δ 28.2 respectively).

The ^{1}H NMR spectrum of protonated **6** shows only one set of signals corresponding to the *O*-inside *cis*-conformer **6**-c_1H$^+$. The *trans*-fused salt **6**-*t*H$^+$ and the *O*-outside *cis*-conformer **6**-c_2H$^+$ of the *cis*-salt are both destabilised by the presence of the axial ethyl group. Upfield absorption of C-8 (δ 51.05) and C-10 (δ 24.5) in the ^{13}C NMR spectrum of protonated **6** is consistent with **6**-c_1H$^+$ (*cf.* δ 57.4 and δ 31.5 in **7**-*t*H$^+$).

The ^{1}H NMR spectrum of protonated *anti*-8-methylperhydropyrido[1,2-*c*][1,3]benzoxazepine (**8**) showed the *trans*-isomer (**8**-*t*H$^+$) (Δ6,6' = 0.54 ppm) as the minor component (*ca.* 10%) with the *O*-outside *cis*-salt (**8**-c_2H$^+$) (Δ6,6' = 0.15 ppm) as the major component. The latter can only adopt the *O*-outside *cis*-conformer **8**-c_2H$^+$, since the *O*-inside *cis*-conformer **8**-c_1H$^+$ is destabilised by interactions involving the axial methyl group. The ^{13}C NMR spectrum of protonated **8** confirmed the presence of the *O*-outside *cis*-conformer **8**-c_2H$^+$

Table 1 1H NMR spectra of the perhydropyrido[1,2-*c*][1,3]benzoxazepine hydrochloride salts (in $CDCl_3$)

Compound	6-H	6'-H	4a-H	8-Heq	8-Hax	11a-H
1-*t*	5.27 $J_{6,6'} = -10.5$ Hz $J_{6,NH^+} = 4.5$ Hz	4.62	—	—	—	—
2-*t*H$^+$	5.42 $J_{6,6'} = -10.8$ Hz	4.58	—	—	—	—
2-c_1H$^+$	5.05 $J_{6,6'} = -10.0$ Hz	4.42	3.32	3.07 $J_{8ax,8eq} = -11.8$ Hz	2.75 $J_{8ax,9ax} = J_{8ax,^+NH} = 11.8$ Hz	3.73
3-*t*H$^+$	5.23 $J_{6,6'} = -10.8$ Hz $J_{6,^+NH} = 4.6$ Hz	4.67	3.22	3.36	2.67 $J_{8ax,9ax} = J_{8ax,^+NH} = 11.9$ Hz	3.06
4-*t*H$^+$	5.08	—	—		—	—
5-*t*	5.32 $J_{6,6'} = -9.6$ Hz $J_{6,^+NH} = 2.5$ Hz $J_{6',^+NH} = 2.5$ Hz	4.35	—	—	—	—
5-c_2	5.23 $J_{6,6'} = -10.5$ Hz $J_{6,^+NH} = 5.6$ Hz $J_{6,^+NH} = 3.75$ Hz	4.76	—	—	—	—
6-c_1H$^+$	4.75		—	—	—	—
7-*t*H$^+$	5.17 $J_{6,6'} = -10.0$ Hz $J_{6,^+NH} = 4.2$ Hz	4.5	—	3.45 $J_{8ax,8eq} = -12.0$ Hz	2.65 $J_{8ax,9ax} = J_{8ax,^+NH} = 12.0$ Hz	—
7-c_2H$^+$	5.17 $J_{6,6'} = -10.3$ Hz $J_{6,^+NH} = 3.7$ Hz	4.83	—	3.15 $J_{8ax,8eq} = -13.0$ Hz $J_{8ax,9ax} = 13.0$ Hz $J_{8ax,^+NH} = 3.0$ Hz	2.90	—
8-c_2H$^+$	5.03 $J_{6,6'} = -10.15$ Hz $J_{6,^+NH} = 5.7$ Hz $J_{6',^+NH} = 4.2$ Hz	4.88	—	—	—	—
8-*t*H$^+$	5.28	4.74	—	—	—	—

Table 2 ^{13}C NMR spectra of the perhydropyrido[1,2-*c*][1,3]benzoxazepine hydrochloride salts (in $CDCl_3$)

	Chemical shifts (δ)															
Compound	C-1	C-2	C-3	C-4	C-5a	C-6	C-8	C-9	C-10	C-11	C-11a	C-12	C-12a	$-CH_2$	$-CH_3$	Me
1-*t*$^+$	30.6	25.1	24.8	32.9	92.0	89.2	55.3	23.0	23.2	31.3	63.4	38.4	46.6	—	—	—
2-*t*H$^+$	31.1	24.65	26.1	31.95	91.8	89.55	58.15	33.9	29.4	27.6	63.7	37.9	46.5	22.7	12.3	—
2-c_1H$^+$	33.05	24.8	25.2	33.2	87.6	81.6	48.9	35.3	23.6	29.4	58.9	34.1	42.85	26.8	10.6	—
3-*t*H$^+$	31.4	24.7	25.1	32.8	91.7	89.0	59.8	35.4	28.95	31.35	63.6	38.0	46.15	26.2	10.7	—
4-*t*H$^+$	32.4	24.7	25.2	32.8	91.3	83.5	61.2	32.1	23.25	31.2	63.7	38.4	46.4	—	—	18.8
5-*t*H$^+$	32.9	24.45	26.0	33.4	90.35	85.5	54.3	24.7	23.0	31.7	60.7	38.0	40.5	—	—	—
5-c_2H$^+$	30.9	24.9	24.9	33.0	83.9	82.1	51.8	19.2	22.4	24.7	58.5	37.0	37.5	—	—	—
6-c_1H$^+$	29.7	24.5	25.5	34.0	84.5	87.9	51.05	35.0	24.5	27.0	54.9	34.2	41.75	26.5	11.4	—
7-*t*H$^+$	32.9	24.6	25.1	33.1	90.5	85.4	57.4	34.9	31.5[a]	28.2[a]	61.1	37.9	39.9	16.2	10.7	—
7-c_2H$^+$	31.8	24.55	24.9	32.85	85.4	84.7	57.0	26.2	29.2	25.4	59.4	37.2	39.1	26.2	10.9	—
8-c_2H$^+$	31.2	24.7	24.8	32.8	89.35	78.8	60.3	26.4	23.3	24.2	63.6	37.55	39.8	—	—	17.4
8-*t*H$^+$	31.9	24.45	24.5	32.65	91.0	83.2	60.9	32.6	23.0	31.0	63.5	38.2	46.1	—	—	18.65

[a] These shifts may be reversed

with upfield shifts of C-9 (δ 26.4) and C-11 (δ 24.2) relative to corresponding shifts for **8**-*t*H$^+$ of δ 32.6 and δ 31.0.

The ^{13}C NMR spectrum of protonated *anti*-perhydropyrido-[1,2-*c*][1,3]benzoxazepine (**5**) shows the presence of *trans*-fused (**5**-*t*H$^+$) and *cis*-fused (**5**-*c*H$^+$) (predominantly *O*-outside) isomers (*ca.* 55:45). The *trans*-fused isomer is indicated by the similar chemical shifts of C-9 (δ 24.7), C-10 (δ 23.0) and C-11 (δ 31.7) to the chemical shifts of the corresponding carbon nuclei in protonated quinolizidine. The unexpected upfield shift of C-8 (δ 51.5) relative to the corresponding carbon nucleus (δ 56.1) in protonated quinolizidine (**9**) and in the *syn*-compounds may be taken as an effect of the seven-membered ring.

The *cis*-fused isomer was assigned the *O*-outside *cis*-fused structure **5**-c_2H$^+$ on the grounds of the shielding of C-9 (δ 19.2) and C-11 (δ 24.7) relative to those (δ 24.7, 31.7 respectively) in the *trans*-fused isomer **5**-*t*H$^+$ due to γax effects. Absence of any significant shielding (two γax effects[4,5]) of C-6 (δ 82.1) relative to the *trans*-fused isomer (**5**-*t*H$^+$) may be taken as showing changes in the seven-membered ring conformation.

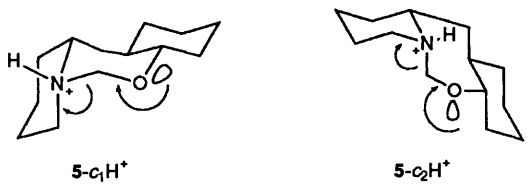


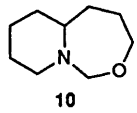
Fig. 1 Conformations of the *cis*-fused salt of **5**

Discussion

The results of the protonation of substituted *syn*- and *anti*-perhydro[1,2-*c*][1,3]benzoxazepines show that the *syn*-isomers have a very strong preference to form the *trans*-fused salt. This is shown by the presence of *ca.* 20% *trans*-fused salt in the mixture of salts obtained on protonation of **3** despite an axial ethyl group in the *trans*-salt **3**-*t*H$^+$. Thus the tendency for formation of the *trans*-salts of the *syn*-isomers parallel the preference of the *syn*-free bases for the *trans*-fused conformation.

On protonation of the *anti*-parent compound **5**, the *trans*-salt **5**-*t*H$^+$ and the *O*-outside *cis*-salts (**5**-c_2H$^+$) were formed in the ratio of *ca.* 45:55 respectively. Thus the *cis*-hydrochloride shows a marked preference for the *O*-outside *cis*-conformer whereas in the equilibrium (75% **5**-*t* $\rightleftharpoons$ 25% **5**-c_1) for the parent compound **5** only the *O*-inside *cis*-conformer **5**-c_1 is observed.[2] Examination of Dreiding models of the free base and of the protonated *anti*-parent compound show that the *O*-inside *cis*-conformer **5**-c_1, but not the *O*-outside *cis*-conformer **5**-c_2, is stabilised by a favourable $n_N \longrightarrow \sigma^*C{-}O$ anomeric effect.[6] Such an effect is lost on protonation and accordingly the *O*-outside *cis*-salt **5**-c_2H$^+$ increases in importance relative to the *O*-inside *cis*-salt **5**-c_1H$^+$.

Dreiding models (see Fig. 1) suggest a chair-type conformation of the B ring with C-6 as the prow and the C(11a)–C(12) bond as the stern as most favourable for the *O*-inside *cis*-salt **5**-c_1H$^+$. The conformation is stabilised by the anomeric effect involving the oxygen lone pair and the C(6)-N$^+$H bond but is destabilised by near eclipsing interactions about the C-(11a)–C(12) bond. The alternative *O*-outside *cis*-conformation **5**-c_2H$^+$ may adopt a rather more favourable chair-type conformation with C-12 as the prow and the O–C(6) bond as the stern. This conformation is stabilised by a similar anomeric effect to that present in **5**-c_1H$^+$ but the unfavourable eclipsing in **5**-c_1H$^+$ is replaced by the energetically more favourable O–C(6) eclipsing. This occurrence of the *O*-outside *cis*-conformation is unusual for these types of systems but must be due largely to the constraint on the conformations of the seven-membered ring caused by *trans*-fusion to the C-ring. In this connection protonation of perhydropyrido[1,2-*c*][1,3]oxazepine (**10**) in which the seven-membered ring is relatively unconstrained gives a mixture of the *trans*-fused hydrochloride and the *O*-inside *cis*-fused hydrochloride.[7]



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Experimental

Protonation of the perhydropyrido[1,2-*c*][1,3]benzoxazepines[2] was effected by passing a stream of dry hydrogen chloride gas through $CDCl_3$ solutions of the individual isomers. The ^{1}H and ^{13}C NMR spectra of the resultant hydrochlorides were recorded in these solutions immediately.

Attempts to isolate the individual hydrochlorides by recrystallisation from ethanol were unsuccessful due to ready interconversion between *trans*- and *cis*-salts accompanied by ring opening of the tetrahydro-1,3-oxazepine, presumably *via* cleavage of the C–O bond of the N–C–O moiety, to give the reactive iminium ion. Other solvents proved unsuitable for recrystallisation purposes. In addition the isolated solid hydrochlorides were hygroscopic. The corresponding methiodides were also unstable.

^{1}H 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 (^{1}H, ^{13}C) FT spectrometer at 270.16 (^{1}H) and 67.97 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and Me_4Si 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 (^{1}H) and 18 (^{13}C) kHz, pulse width 3 (^{1}H) 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 (^{1}H) and 1–20 K (^{13}C), computer memory 32 K.

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Paper 2/04079D
Received 29*th July* 1992
Accepted 29*th September* 1992