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# Compounds with Bridgehead Nitrogen

## 62*—NMR Spectra and Stereochemistry of Perhydropyrido[1,2-*c*][1,3]thiazepines and Related Systems

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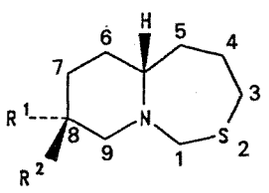
**Perhydropyrido[1,2-*c*][1,3] thiazepine adopts ($CDCl_3$ solution, 25 °C) an equilibrium containing > 98% *trans*-fused conformer, in contrast to perhydropyrido[1,2-*c*][1,3]oxazepine, which adopts a *ca.* 74% *trans*-fused ⇌ 26% *O*-inside-*cis*-fused conformational equilibrium. The *cis*-(H-5a, H-8)-8-ethyl-substituted derivatives of both systems show increased preference for the *S*/*O* inside *cis* conformations. The related 2-*tert*-butylperhydropyrido[1,2-*c*][1,3]diazepine adopts predominantly the *trans*-fused conformation.**

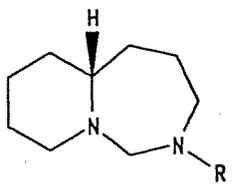
KEY WORDS $^1H$ and $^{13}C$ NMR Perhydropyrido[1,2-*c*][1,3]thiazepines

## INTRODUCTION

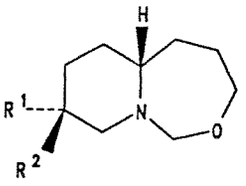
Since stereochemical studies on perhydropyrido[1,2-*c*]-[1,3]thiazepine (**1**) and the corresponding diazepine (**4**) have not been reported and work on perhydropyrido [1,2-*c*][1,3]oxazepine has been limited to a low-temperature $^{13}C$ NMR study of **6**[2] and to $^1H$ NMR studies[3] on some alkyl-substituted derivatives, it was decided to carry out a detailed study of these systems to assess the influence of heteroatom changes on conformational equilibria.



**1**: $R^1 = R^2 = H$
**2**: $R^1 = H$, $R^2 = Et$
**3**: $R^1 = Et$, $R^2 = H$



**4**: R = H
**5**: R = *t*-butyl



**6**: $R^1 = R^2 = H$
**7**: $R^1 = H$, $R^2 = Et$
**8**: $R^1 = Et$, $R^2 = H$

* For Part 61, See Ref. 1.
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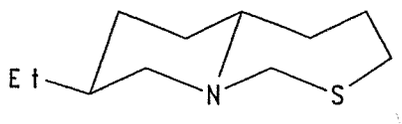
## RESULTS AND DISCUSSION

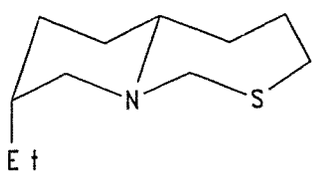
### Conformational equilibria for perhydropyrido[1,2-*c*][1,3]thiazepines

Examination of the $^1H$ NMR spectrum of **2** (Table 1) shows a triplet absorption for H-9ax [$J$(9eq, 9ax) = −11.0, $J$(9ax, 8ax) = 11.0 Hz] consistent with its expected existence in the *trans*-conformation **2**-*t*. The close correlation between the chemical shifts of C-8 and C-6 of *trans*-(H-6, H-8a)-6-ethylindolizidine[4] and **2** suggests that **2** exists exclusively in the *trans* conformation **2**-*t*.

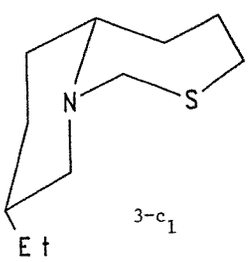


2-t

The equilibrium **3**-*t* ⇌ **3**-$c_1$ for the isomer **3**, however, is expected to shift towards the *S*-inside-*cis*-conformer **3**-$c_1$ relative to the equilibrium for **2**, since the *trans*-conformation **3**-*t* is destabilized by *gauche*-butane and *gauche*-propylamine interactions between the ethyl group and the C-6 methylene and nitrogen lone pair.



3-t



3-$c_1$

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**Table 1. $^1$H NMR spectra of perhydropyrido[1,2-*c*][1,3]thiazepines and related diazepines and oxazepines**

| | Chemical shifts, δ (ppm) | | | | | | | Coupling constants, J (Hz) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | H-1 | H-1′ | H-3 | H-3 | H-5a | H-9eq | H-9ax | 1,1′ | 3,3′ | 3,4 | 3′,4ax′ | 3′,4eq′ | 5a,5ax | 5a,6ax | 5a,5eq | 5ax,6eq | 9eq,9ax | 9eq,8ax | 9ax,8ax |
| **1**[a] | 4.43 | 4.1 | 2.75 | 2.5 | 2.5 | 2.75 | 2.5 | −14.75 | — | — | — | — | — | — | — | — | — | — | — |
| **2**[a] | 4.5 | 4.13 | 2.8 | 2.45 | 2.5 | 2.7 | 2.1 | −14.5 | −13.7 | 4.2/1.6 | — | — | 12.1 | 12.1 | — | 3.5 | −11.0 | 4.1 | 11.0 |
| **3**[a] | 4.25 | 4.18 | | | 2.5–2.8 | | | −13.9 | — | — | — | — | — | — | — | — | — | — | — |
| **3**[b] | 4.22 | 4.15 | | | | | | −13.9 | — | — | — | — | — | — | — | — | — | — | — |
| **3**-*t*[c] | 4.41 | 4.10 | | | | | | −13.3 | — | — | — | — | — | — | — | — | — | — | — |
| **3**-$c_1$[c] | 4.20 | 4.07 | | | | | | −13.6 | — | — | — | — | — | — | — | — | — | — | — |
| **5** | 3.5(s) | | 2.85 | 2.42 | 2.1 | 2.7 | 2.3 | — | −11.2 | 4.4/4.2 | 11.2 | 4.2 | — | — | — | — | — | — | 10.8 |
| **6**[a] | 4.38 | 4.26 | 3.9 | 3.6 | 2.5 | 2.9 | 2.5 | −11.4 | — | — | — | — | — | — | — | — | −11.7 | 4.6 | — |
| **7**[a] | 4.35 | 4.27 | 3.9 | 3.6 | 2.2 | 2.9 | 2.2 | −11.4 | −11.9 | 4.25 | — | — | — | — | — | — | −10.8 | — | 10.8 |
| **8**[a] | 4.83 | 4.47 | 3.8 | 3.8 | 3.0 | 2.7 | 2.55 | −11.5 | — | — | — | — | 5.5 | 11.0 | — | 3.0 | −11.9 | — | 10.0 |

[a] $CDCl_3$ at 298 K.
[b] $CD_2Cl_2$–$CFCl_3$ at 298 K.
[c] $CD_2Cl_2$–$CFCl_3$ at 183 K.

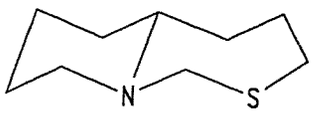
**Table 2. $^{13}$C NMR spectra of perhydropyrido[1,2-*c*][1,3]thiazepines and related diazepines and oxazepines**

| | | | Chemical shifts, δ (ppm) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | Solvent | Temperature (K) | C-1 | C-3 | C-4 | C-5 | C-5a | C-6 | C-7 | C-8 | C-9 | $CH_2$ | $CH_3$ |
| **1** | $CDCl_3$ | 298 | 64.1 | 34.75 | 31.7 | 34.6 | 62.6 | 32.4 | 24.65 | 26.2 | 54.7 | — | — |
| **2** | $CDCl_3$ | 298 | 63.9 | 34.9 | 31.8 | 34.55 | 62.6 | 32.2 | 31.4 | 38.3 | 61.0 | 27.1 | 11.4 |
| **3** | $CDCl_3$ | 298 | 64.9 | 33.5 | 32.1 | 29.7[a] | 60.7 | 29.5[a] | 26.6 | 37.1 | 54.2 | 26.0 | 11.7 |
| **3** | $CD_2Cl_2$–$CFCl_3$ | 298 | 64.7 | 34.1 | 32.3 | 30.3 | 61.4 | 30.5 | 27.4 | 37.5 | 55.1 | 26.25 | 12.0 |
| **3**-*t* | $CD_2Cl_2$–$CFCl_3$ | 183 | 65.0 | 35.2 | 32.3 | 33.5 | 63.7 | 30.4 | 28.7 | 35.55 | 58.7 | 24.2 | 12.7 |
| **3**-$c_1$ | $CD_2Cl_2$–$CFCl_3$ | 183 | 65.4 | 33.7 | 32.5 | 26.3[a] | 57.7 | 27.8 | 25.2 | 38.3 | 50.9 | 27.7[a] | 11 |
| **5** | $CDCl_3$ | 298 | 72.5 | 49.4 | 28.8 | 34.2 | 63.2 | 33.9 | 24.7 | 26.5 | 54.3 | (53.75)[b] | 27.45 |
| **7** | $CDCl_3$ | 298 | 87.5 | 70.2 | 29.3 | 33.3 | 62.3 | 31.45 | 23.15 | 26.4 | 50.9 | — | — |
| **6** | $CD_2Cl_2$–$CFCl_3$ | 298 | 87.8 | 70.3 | 29.6 | 33.5 | 62.5 | 31.5 | 23.3 | 26.7 | 51.1 | — | — |
| **6**-*t* | $CD_2Cl_2$–$CFCl_3$ | 193 | 88.1 | 70.8 | 29.2 | 34.0 | 63.8 | 32.2 | 24.9 | 26.3 | 53.9 | — | — |
| **6**-$c_1$ | $CD_2Cl_2$–$CFCl_3$ | 193 | 84.5 | 69.2 | 28.1 | 28.1 | 60.0 | 31.5 | 19.0 | 26.3 | 43.9 | — | — |
| **7** | $CDCl_3$ | 298 | 89.0 | 70.5 | 29.4 | 33.7 | 63.4 | 32.3 | 31.5 | 38.3 | 59.2 | 26.9 | 11.4 |
| **8** | $CDCl_3$ | 298 | 85.6 | 69.2 | 28.35 | 28.7 | 59.5 | 31.0 | 25.9 | 38.4 | 50.9 | 27.1 | 11.3 |

[a] Shifts may be interchanged.
[b] $C(CH_3)_3$.

The low temperature $^{13}C$ NMR spectrum of **3** at 183 K in $CD_2Cl_2$–$CFCl_3$ (1:1) solution (Table 2) showed two sets of signals corresponding to *ca.* 54% *trans*-fused conformer **3**-*t* and 46% *S*-inside-*cis*-conformer **3**-$c_1$. Assuming entropy effects are negligible, this gives an estimate for the equilibrium at 298 K of 52% *trans*-conformer **3**-*t* and 48% *cis*-conformer **3**-$c_1$. The position of the equilibrium at this temperature may also be estimated from chemical shift values, assuming that the temperature effects on these are negligible. Comparison of the observed $^{13}C$ shift of C-7 (in $CD_2Cl_2$–$CFCl_3$ at 298 K) of $\delta$ 27.4 for **3** with that obtained for **3**-*t* and **3**-$c_1$ at 183 K ($\delta$ 28.7 and 25.2, respectively) suggests that the equilibrium for **3** contains *ca.* 38% *cis*-conformer (in $CD_2Cl_2$–$CFCl_3$). The $^1H$ NMR spectrum of **3** in $CDCl_3$ at 183 K showed two AB quartets for the C-1 methylene protons corresponding to an equilibrium between 38% **3**-$c_1$ and 62% **3**-*t*, in line with the estimated position in $CD_2Cl_2$–$CFCl_3$. This estimate is considered more reliable than that from the integration of the $^{13}C$ signals.

Comparison of the $^1H$ NMR spectrum of perhydropyrido[1,2-*c*][1,3]thiazepine (**1**) and that of **2** shows very close correlation of chemical shifts for all the observed peaks except for H-9ax, which is shielded by the equatorial ethyl substituent (0.4 ppm).[5] This suggests that the parent compound **1** adopts predominantly (>98%) the *trans*-fused conformation **1**-*t*. This is confirmed by the close comparison of the observed $^{13}C$ chemical shifts of **1** with the calculated shifts for **1**-*t* based on the observed shifts for **2** and ethyl substituent effects ($\alpha$, +13, $\beta$eq +6.6 ppm) derived from the analogous indolizidine system.[4]

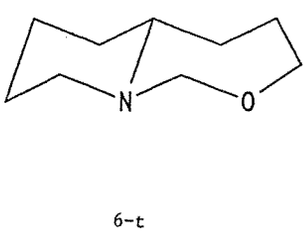



1-t

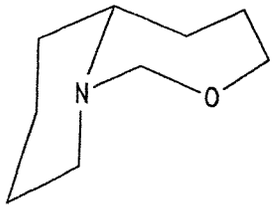
## Conformational equilibria for perhydropyrido[1,2-*c*][1,3]oxazepines

Perhydropyrido[1,2-*c*][1,3]oxazepine (**6**) has been shown[2] by low-temperature $^{13}C$ NMR spectroscopy to exist in $CDCl_3$–$CFCl_3$ solution at 193 K as 80% *trans*-(**6**-*t*) and 20% *cis*- (**6**-$c_1$) fused conformers, giving an estimate for the equilibrium at 298 K of *ca.* 74% **6**-*t* and 26% **6**-$c_1$. *trans*-(H-5a, H-8)-8-Ethylperhydropyrido[1, 2-*c*][1,3]oxazepine (**7**) is therefore expected to adopt exclusively the *trans*-conformation **7**-*t*, since the alternative *cis*-fused conformers suffer from unfavourable nonbonded interactions. In line with this, the $^1H$ NMR spectrum of **7** shows a triplet for H-9ax at $\delta$ 2.2 [$J$(9eq, 9ax) = −10.8 Hz, $J$(9ax, 8ax) = 10.8 Hz], typical of an equatorially ethyl-substituted piperidine ring.

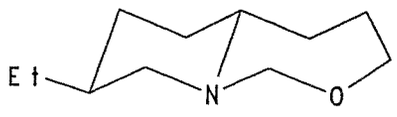
The similarity of the $^{13}C$ NMR shifts of **7** with the calculated shifts for **7**-*t* based on the observed shifts of **6**-*t* at 193 K[2] and the ethyl substituent effects mentioned above shows the extreme predominance of the




6-t



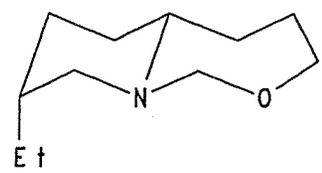

6-$c_1$



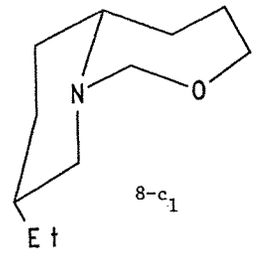

7-t

*trans*-fused conformer **7**-*t*. This is also indicated by the upfield absorptions of H-5a ($\delta$ 2.2) and H-9ax ($\delta$ 2.2).[6]

Examination of the $^1H$ NMR spectrum of isomer **8** shows a doublet of doublets for H-9ax with two large couplings [$J$(9ax, 9eq) = −11.9 Hz, $J$(9ax, 8) = 10.0 Hz]. The observed $J$(8, 9) of 10.0 Hz indicates an equatorial ethyl substituent in the piperidine ring, and suggests the predominance of the *O*-inside-*cis*-conformer **8**-$c_1$, possibly in equilibrium with a small amount of *trans*-conformer **8**-*t*. The similarity of the $^{13}C$ shifts of **8** with the calculated shifts for **8**-$c_1$ (obtained from the observed shifts of **6**-$c_1$ at 193 K) shows a close correlation, indicating the predominance of the *O*-inside-*cis*-conformation **8**-$c_1$. A comparison of the $^{13}C$ shift of C-7 in **8** ($\delta$ 25.9) with those calculated for **8**-*t* ($\delta$ 31.5) and **8**-$c_1$ ($\delta$ 25.6) allows the position of equilibrium to be estimated as between *ca.* 95% **8**-$c_1$ and 5% **8**-*t*. The downfield absorptions of H-5a ($\delta$ 3.0) and H-9ax ($\delta$ 2.55) relative to those of **7**-*t* are in line with this estimate.



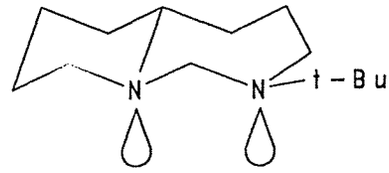

8-t




8-$c_1$

## Conformational equilibria for 2-*tert*-butylperhydropyrido[1,2-*c*][1,3]diazepine

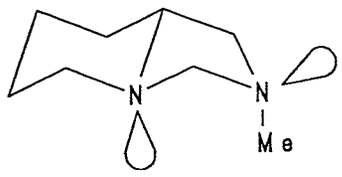
Examination of the $^1H$ NMR spectrum of 2-*tert*-butylperhydropyrido[1,2-*c*][1,3]diazepine (**5**) shows absorption at $\delta$ 2.10 for H-5a (cf. H-5a of $\delta$ 2.2 in **7**-*t*), showing the predominance of the *trans*-fused conformation **5**-*t*. This is confirmed by the similarity of the ring A $^{13}C$ NMR shifts of **5** with those of **1**-*t* and **6**-*t*.




5-t

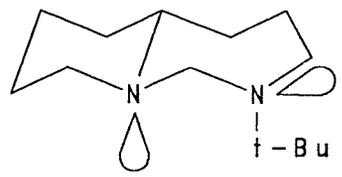
### Rationalization of conformational equilibria shifts with heteroatom changes in 6/7 bicyclic systems

The most striking aspect of this work is the shift in the position of equilibria of the systems studied with the change of heteroatom. Replacement of oxygen by sulphur in the seven-membered ring favours the *trans*-fused conformation **1**-*t*. This may be due to longer C—S bonds in the seven-membered ring, which reduce the magnitude of non-bonded interactions present in some conformations of *trans*-perhydropyrido[1,2-*c*][1,3] benzoxazepine (**6**-*t*), and to changes in anomeric effects[7] due to differing conformations of the seven-membered rings. The adoption of the *trans*-conformer for 2-*tert*-butylperhydropyrido[1,2-*c*][1,3]diazepine (**5**-*t*) is not unexpected, by analogy with the conformational equilibrium for 2-methylperhydroimidazo[3,4-*a*]pyridine (**17**),[8] which favours the *trans*-conformation with a

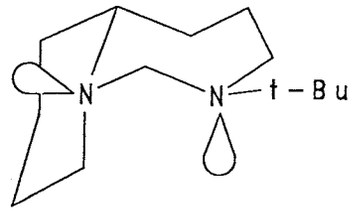



17

pseudo-axial methyl group.[8] Thus, in **5**-*t* the unfavourable anomeric effect which destabilizes the analogous conformation **6**-*t* may be reduced in **5**-*t'* by inverting at the 2-N, without going to **5**-$c_1$ by inversion at the 9-N (analogous to **6**-$c_1$). The *tert*-butyl group interactions are better accommodated in **5**-*t'* since this group is in the stereochemically less demanding situation of being 1,3-*syn*-axial to a lone pair.




5-t'




5-$c_1$

## EXPERIMENTAL

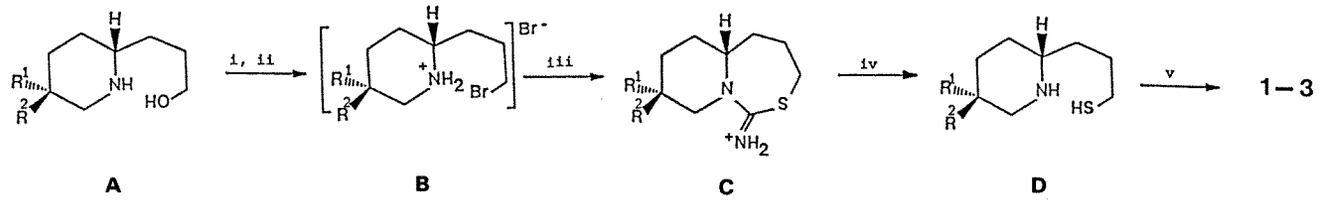
$^1$H and $^{13}$C NMR spectra were recorded at room temperature in $CDCl_3$ solution and at low temperature in $CD_2Cl_2$–$CFCl_3$ solution in 5-mm tubes on a JEOL GSX-270 ($^1$H, $^{13}$C) FT spectrometer at 270.16 ($^1$H) and 67.97 ($^{13}$C) MHz, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring 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 1–20K ($^{13}$C), computer memory 32K.

### General procedure for the preparation of perhydropyrido[1,2-*c*][1,3]oxazepines

The individual isomers of 2-(5-ethylpiperidin-2-yl)-propan-1-ol were treated with 40% aqueous formaldehyde solution and the mixture was left to stand overnight. The reaction mixture was then basified with 30% aqueous sodium hydroxide solution and extracted several times with dichloromethane (4 × 10 ml). The dichloromethane extracts were combined, dried (sodium sulphate) and evaporated to give an oily residue. Each ring-closed isomer was chromatographed over a small chromatographic column packed with Woelm grade IV alumina (*ca.* 10.0 g) and eluted with light petroleum (b.p. 40–60 °C). Evaporation of the light petroleum left in each case a colourless oil (0.0047 mol, 95%). The following compounds were obtained: *trans*-(H-5a, H-8)-8-ethylperhydropyrido[1,2-*c*][1,3]oxazepine (**7**), b.p. 96 °C at 4 mmHg (found, C 72.2, H 11.7, N 7.7; $C_{11}H_{21}NO$ requires C 72.1, H 11.55, N 7.6%), *cis*-(H-5a, H-8)-8-ethylperhydropyrido[1,2-*c*][1,3]oxazepine (**8**), b.p. 96 °C at 4 mmHg (found, C 72.2, H 11.7, N 7.7; $C_{11}H_{21}NO$ requires C 72.1, H 11.55, N 7.6%).

### General procedure for the preparation of perhydropyrido[1,2-*c*][1,3]thiazepines (Scheme 1)

A solution of the appropriate 2-(piperidin-2-yl)propanol (**A**) (0.025 mol) in carbon tetrachloride (50 ml) was saturated with hydrogen bromide gas. The hydrobromide formed was isolated by removing the solvent, giving white crystals which were treated slowly with phosphorus tribromide (10.0 g, 0.037 mol). After the completion of the ensuing vigorous exothermic reaction, the mixture was heated for 0.5 h on a steam-bath. The dark mixture was allowed to crystallize and the crude product recrystallized from absolute ethanol. The bromide hydrobromide salt (**B**) so formed was dissolved in absolute ethanol (50 ml) and the solution boiled under reflux in the presence of a small excess of thiourea (1.5 g, 0.025 mol) for 5 h. The isothiouronium salt (**C**) formed was decomposed to the thiol (**D**) by boiling under reflux for 1.5 h with 10% excess of tetraethylenepentamine (3.78 g, 0.02 mol). The solvent was removed rapidly and the residual viscous oil ring-closed with formaldehyde. The mixture of 8-ethylperhydropyrido[1,2-*c*][1,3]thiazepines (3.0 g, 60%) was separated by flash column chromatography over silica gel using 2–10% of a mixture of dichloromethane, ethanol and 40% aqueous ammonia (94:5:1) in light petroleum (b.p. 40–60 °C). The following compounds were obtained: perhydropyrido[1,2-*c*][1,3]thiazepine (**1**) (2.4 g, 58%), b.p. 80–86 °C at 0.6 mmHg (found, $M^+$,




Reagents: (i) HBr; (ii) $PBr_3$; (iii) thiourea; (iv) tetraethylenepentamine; (v) $CH_2O$

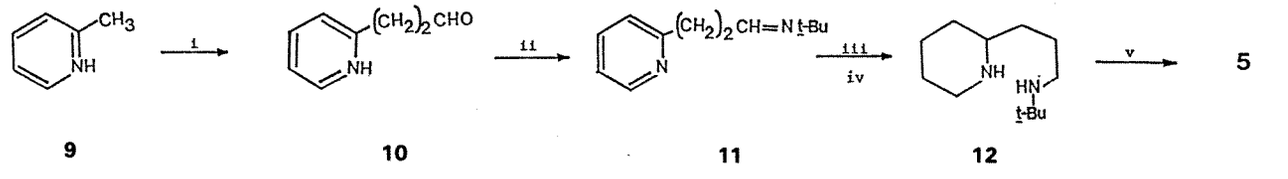
**Scheme 1.** Synthesis of perhydropyrido[1,2-*c*][1,3]thiazepines.

171.1074; $C_9H_{17}NS$ requires M, 1712.1082); *trans*-(H-5a, H-8)-8-ethylperhydropyrido[1,2-*c*][1,3]thiazepine (**2**), the first isomer to be eluted (*ca.* 60%), b.p. 98–101 °C at 0.6 mmHg (found, $M^+$, 199.1391; $C_{11}H_{21}NS$ requires M, 199.1391); and *cis*-(H-5a, H-8)-8-ethylperhydropyrido[1,2-*c*][1,3]thiazepine (**3**), the second isomer to be eluted (*ca.* 40%), b.p. 98–101 °C at 0.6 mmHg (found, $M^+$, 199.1391; $C_{11}H_{21}NS$ requires M, 199.1395).

## Synthesis of 2-*tert*-Butylperhydropyrido[1,2-*c*][1,3]-diazepine (5) (Scheme 2)

A solution of 2-pyridylmethyllithium (0.25 mol) (from **9** and phenyllithium) in dry diethyl ether was stirred under dry nitrogen while 2-chloroacetaldehyde diethylacetal (0.25 mol) was added. The mixture was boiled under reflux for 15 min after the addition without external heating; it was then stirred for 4 h under reflux, during which much white solid separated. The mixture was set aside overnight at room temperature, cooled, hydrolysed by the addition of dilute ammonia and ammonium chloride and the ethereal layer was separated. The aqueous layer was extracted with diethyl ether (3 × 100 ml) and the combined ethereal extracts were dried (sodium sulphate) and distilled. The acetal boiled at 81 °C at 0.125 mmHg (25.0 g, 51.5%). The acetal (20.0 g, 0.1 mol) so prepared was treated with dilute hydrochloric acid (50 ml) and allowed to stand for 0.5 h, during which time it was occasionally heated gently on a steam-bath. The solution was then basified with a saturated solution of sodium hydrogen-carbonate and extracted with diethyl ether (3 × 100 ml). The ethereal extracts were dried (sodium sulphate) and the ether removed. The residue was distilled to give the required aldehyde **10**, b.p. 64 °C at 0.5 mmHg (9.0 g, 73%).

A solution of **10** (5.0 g, 0.04 mol) and *tert*-butylamine in sodium-dried benzene (50 ml) was boiled under reflux using a Dean and Stark apparatus to separate the water produced (0.7 ml, 0.04 mol). The benzene was removed under reduced pressure and the residue **11** was dissolved in dried methanol (50 ml) and the solution placed in a conical flask containing a magnetic stirrer. Sodium borohydride (3.2 g, 0.08 mol) was added to the solution slowly while stirring, and this caused gentle reflux. The solution was stirred for 2 h, then neutralized by the dropwise addition of concentrated hydrochloric acid. The mixture was basified with sodium hydroxide solution (30%) and extracted with diethyl ether. The ether was removed under vacuum and the oily residue was passed through a column packed with Woelm (grade IV) alumina to give a colourless oil. This was hydrogenated catalytically and the *N*-*tert*-butyl-3-(2-piperidyl)propylamine (**12**) formed was treated with an aqueous solution of formaldehyde (40%) to give 2-*tert*-butylperhydropyrido[1,2-*c*][1,3]diazepine (**5**) (4.5 g, 95%), b.p. 72–75 °C at 0.08 mmHg (found, $M^+$, 210.3609; $C_{13}H_{26}N_2$ requires M, 210.3618).




Reagents: (i) PhLi, $ClCH_2CH(OEt)_2$; (ii) $H_2NC(CH_3)_3$; (iii) $NaBH_4$; (iv) $H_2/PtO_2$; (v) $CH_2O$

**Scheme 2.** Synthesis of 2-*t*-butylperhydropyrido[1,2-*c*][1,3]diazepine.

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