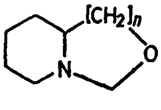
Novel Reversible Dimerisation of Perhydropyrido[1,2-c][1,3]oxazepines; *X*-Ray Analysis of a 14-Membered Macrocyclic Dimer

By D. A. Whiting*
(*Department of Chemistry, University of Nottingham, Nottingham* NG7 2RD)
and R. Cahill and T. A. Crabb*
(*Department of Chemistry, Portsmouth Polytechnic, Portsmouth*)

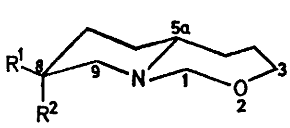
Summary *trans*-Isomers of the title oxazepines, *e.g.* (**2**) and (**6**), but not the *cis*-isomers, *e.g.* (**5**), undergo an unusual dimerisation from the liquid state; *X*-ray analysis shows that the crystalline dimer (**7**; R = Et) contains a 14-membered heterocyclic ring.

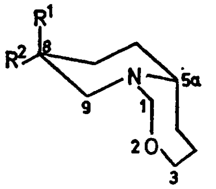
In extension of conformational studies with the heterocycles (**1**; $n = 1$)[1] and (**1**; $n = 2$)[2] some substituted 3-(2-piperidyl)propan-1-ols were condensed with formaldehyde to provide perhydropyrido-oxazepines (**1**; $n = 3$). Thus, the two diastereoisomeric 3-(5-methyl-2-piperidyl)propan-1-ols (*trans*-isomer predominant in the mixture) gave two cyclised products: a solid, m.p. 91—96° (major component), and a liquid (minor). By analogy with (**1**; n = 1 and 2) the major product (*trans*-5a-H,8-H) was expected to exist in solution predominantly as (**2**) and the minor product (*cis*-5a-H,8-H) predominantly as (**5**). However, the n.m.r. spectrum of the solid in $CDCl_3$ taken immediately showed an AB quartet (δ 4·61 and 3·91 p.p.m.) for the NCH_2O protons (J_{gem} −8·8 Hz), but in successive scans this quartet was replaced by another (δ 4·31 and 4·23 p.p.m., J_{gem} −11·1 Hz). Evaporation gave an oil which crystallised to the initial solid isomer. The n.m.r. spectrum of the solid isomer changed too rapidly for a 220 MHz spectrum to be obtained but such a spectrum was obtained for the ethyl substituted analogue. The ethyl group was shown to be equatorial from the vicinal coupling constants ($J_{8,9ax}$ 11·5, $J_{8,9eq}$ 4·0 Hz).

However, the spectrum showed features not in complete accord with the pyrido-oxazepine structure (**6**) with 5a-H and 8-H *trans*; in particular rather low-field absorption (δ 2·56 and 2·50 p.p.m.) for 9-H_{ax} and 5a-H_{ax} were observed. Accordingly, an *X*-ray study was undertaken.

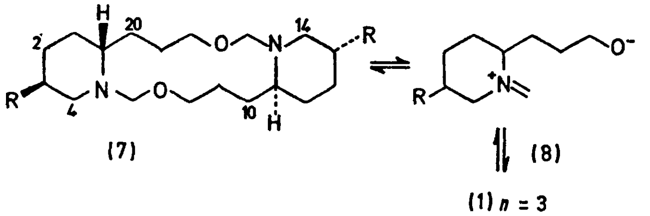


(1)

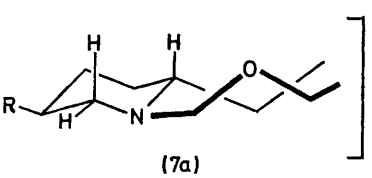




(2) R^1 = Me, R^2 = H $\rightleftharpoons$ (3) R^1 = Me, R^2 = H
(4) R^1 = H, R^2 = Me $\rightleftharpoons$ (5) R^1 = H, R^2 = Me
(6) R^1 = Et, R^2 = H
(9) R^1 = R^2 = H $\rightleftharpoons$ (10) R^1 = R^2 = H

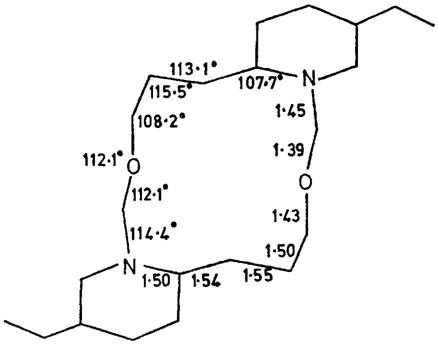


(7) (8) (1) n = 3



(7a)

The compound, m.p. 86—93°, crystallised in space group $P2_1/c$ with a = 5·08, b = 23·47, c = 9·43 Å, and β = 106·17°. 963 Observed intensity data were measured with an automatic four-circle diffractometer. The structure was solved by direct methods using symbolic addition[3] and revealed an asymmetric unit ($C_{11}NO$) which proved to be half the complete molecule. The full centrosymmetric dimeric structure (**7**; R = Et) ($C_{22}H_{42}N_2O_2$) (see Figure) contains a 14-membered heterocyclic ring, *trans*-fused with two perhydropyridine nuclei. Refinement by block-diagonal least-squares proceeded to R 0·099, with anisotropic temperature factors for non-hydrogen atoms, and including hydrogens.



FIGURE

Molecular-weight determinations (vapour pressure osmometer, CCl_4) showed that the dimer (**7**; R = Et), and analogues, *e.g.* (**7**; R = H or Me), rapidly dissociated to liquid monomers (**1**; n = 3). On evaporation, the residual oils crystallised to the original dimers. Interconversion presumably involves such an intermediate as (**8**).

In the light of the dimeric structure, the low field absorption of the axial protons (20a-H, 10a-H, 4-H, and 14-H) in the spectrum of (**7**; R = Et) were explicable in terms of a deshielding by the *cis*-C–O bonds (see **7a**).

The n.m.r. spectrum obtained on keeping a solution of (**7**; R = Me) was completely in accord with the *trans*-fused perhydropyrido[1,2-*c*][1,3]oxazepine structure (**2**; R^1 = Me); the difference in chemical shift between the C(9) methylene protons being 0·70 p.p.m., indicative of a C(9)–H_{ax} bond *trans* coplanar with the axial nitrogen lone pair[4] and the coupling constants involving these protons indicating equatorial methyl. Thus for the compounds (**7**; R = Me or Et) the equilibrium is between the *trans*-fused dimers (**7**) and the *trans*-fused monomers (**2**) and (**6**).

The second isomer obtained from cyclisation of 3-(5-methyl-2-piperidylpropan-1-ol (2-H and 5-H *cis*) with formaldehyde was then examined. The molecular weight of this liquid showed it to exist in solution as monomer and the n.m.r. spectrum indicated the predominance of the *cis*-fused ring conformation (**5**). In particular, whereas in the *trans*-fused (**2**) the chemical shift difference between the C(9) methylene protons was 0·70 p.p.m., the corresponding difference in (**5**) was only 0·11 p.p.m., as a result of deshielding of 9-H_{ax} by the *syn* axial C(5)–C(5a) bond.

Reaction of 3-(2-piperidyl)propan-1-ol with formaldehyde also gave a crystalline dimer (**7**; R = H) which showed an identical J_{gem} value to (**7**; R = Me) and (**7**; R = Et) and the monomer in equilibrium with this was shown to be the *cis*-fused ring conformation (**10**) by, *inter alia*, the very small chemical shift difference between the C(9) methylene protons. Perhydropyrido[1,2-*c*][1,3]oxazepine presumably adopts conformation (**10**) rather than (**9**) in order to relieve unfavourable dipolar interactions present in (**9**).

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