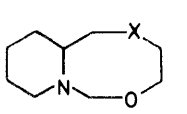
Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part 35.[1] The 5-t-Butylperhydropyrido[1,2-*c*][1,3,7]oxadiazonine ⇌ 10,22-Di-t-butylperhydrodipyrido[1,2-*c*:1,2-*l*]-1,10-dioxa-3,7,12,16-tetrazacyclodecine ⇌ 2-t-Butyl-2-β-hydroxyethylperhydropyrido[1,2-*c*]pyrimidinium Equilibrium

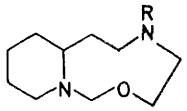
By **Trevor A. Crabb,*** Department of Chemistry, Portsmouth Polytechnic, Portsmouth PO1 2DT
Graham C. Jackson, Exposure Trials Station, Central Dockyard Laboratory, Portsmouth PO4 9LY

The reaction between 2-(*N*-β-hydroxyethyl-*N*-β-t-butylaminoethyl)piperidine and formaldehyde gives the crystalline dimeric 10,22-di-t-butylperhydrodipyrido[1,2-*c*:1,2-*l*]-1,10-dioxa-3,7,12,16-tetrazacyclodecine. In chloroform solution this compound rapidly comes into equilibrium with 5-t-butylperhydropyrido[1,2-*c*][1,3,7]oxadiazonine and the 2-t-butyl-2-β-hydroxyethylperhydropyrido[1,2-*c*]pyrimidinium ion. Evaporation of the chloroform followed by crystallisation of the residual oil gives the crystalline dimer.

As a development of our work on the eight-membered ring systems (1) and (2)[2] the 5-alkylperhydropyrido-[1,2-*c*][1,3,7]oxadiazonines (3) containing a nine-membered ring were chosen for study. Such systems should, in theory, be obtained by the reaction between 2-(*N*-β-hydroxyethyl-*N*-β-alkylaminoethyl)piperidine [*e.g.* (4)—(6)] and formaldehyde. Accordingly the *N*-methyl, *N*-ethyl, and *N*-t-butyl compounds (4)—(6) were prepared as shown in Scheme 1. The *N*-methyl and *N*-ethyl derivatives (4) and (5) were recovered unchanged after treatment with aqueous formaldehyde at room temperature and at 80° instead of the hoped-for oxadiazonine (3; R = Me or Et) the *N*(1)-methylated derivatives of (4) and (5) were obtained.



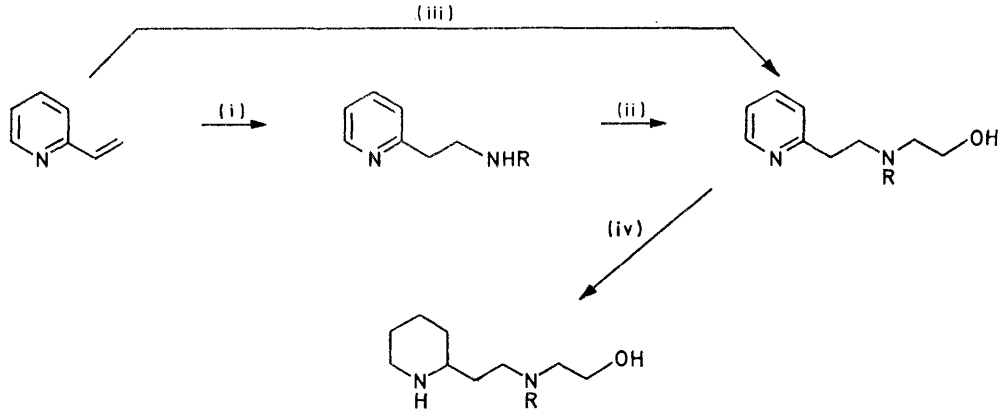
(1) X = O
(2) X = NR



(3)

In contrast the t-butyl derivative (6) readily underwent a cyclisation process with aqueous formaldehyde at room temperature to give a solid melting over the range 105—127°, the elemental analysis of which being in apparent agreement with the oxadiazonine structure (3; R = Bu^t). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this substance showed an AB quartet, δ 4.45 and 4.03 (J −10 Hz) characteristic of the NCH_2O protons but on re-running the spectrum after 5 min three AB quartets were seen in the region δ 3.9—5.1. In the light of our work on the reversible dimerisation (7) ⇌ (8) observed for the perhydropyrido[1,2-*c*]-oxazepine system[3] this observation suggested the occurrence of a similar, but more complicated, process involving three species with the crystalline product possessing the dimeric structure (9).

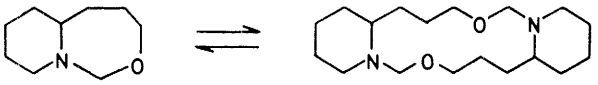
An attempt to determine the molecular weight of crystalline (9) in carbon tetrachloride solution at 37° using a vapour phase osmometer showed that an equilibrium had been established after 6 min (the time taken to obtain the first reading). The mean value of the molecular weight obtained was 289, *i.e.* between the



(4) R = Me
(5) R = Et
(6) R = Bu^t

SCHEME 1 Reagents: i, RNH_2; ii, $ClCH_2CH_2OH$; iii, $HOCH_2CH_2NHR$; iv, H_2–PtO_2

molecular weights of the monomer (3; R = Bu^t) and the dimer (9). In this respect the system appears to differ from that of (7) ⇌ (8) in which the dimer is completely converted to monomer in solution.



(7) (8)

The 220 MHz n.m.r. spectrum of (9) obtained at −45° in $CDCl_3$–$CFCl_3$ solution showed a single low field AB quartet, δ 4.10 and 4.45 (J −9.2 Hz), and re-running the spectrum after storage of the solution for one week at this temperature showed no change to have taken place. The temperature of the solution was then allowed to rise and at −23° a second AB quartet, δ 4.08 and 4.43 (J −9.2 Hz) appeared with a third AB quartet, δ 4.48 and 5.10 (J −9.5 Hz) appearing at −2°.

The spectrum at −45° corresponds to only one compound, and it is not unreasonable therefore to assume that this is the spectrum of the dimeric compound (9). Accordingly the AB quartet at δ 4.08 and 4.43 may be assigned to the NCH_2O protons in the monomeric structure (3; R = Bu^t). The relatively downfield position of the third AB quartet, δ 4.48 and 5.10, indicates a compound possessing the NCH_2N^+ moiety and a consideration of a possible mechanism for conversion of the dimer to the monomer (Scheme 2) suggests that this may be the perhydropyrimidinium ion (11) obtained *via* the ring-opened species (10). Evidence for the existence of (11) in the equilibrium mixture was obtained by recording the spectrum of equimolar quantities of perhydropyrido[1,2-*c*]pyrimidine and ethylene bromohydrin in deuteriopyridine solution, when an AB quartet at δ 4.34 and 5.25 (J_{gem} −9.8 Hz) was observed similar to that assigned to (11) in the spectrum of the equilibrium mixture.

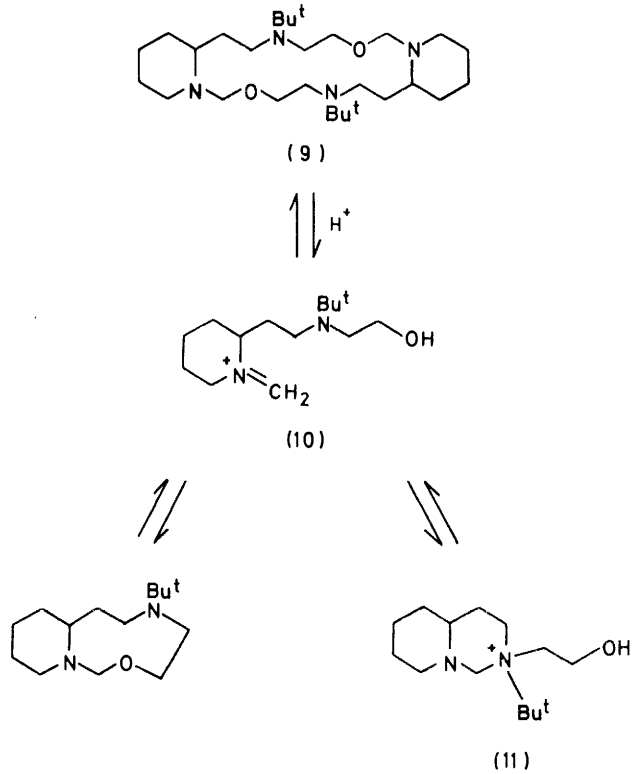
Intensity measurements on the n.m.r. spectrum of a $CDCl_3$ solution of (9) at 19° indicated the presence of 45% of perhydropyrido[1,2-*c*]pyrimidinium ion, 27% of the dimer and 28% of the monomer in the resulting equilibrium mixture. In the spectrum of a solution of (9) in deuteriopyridine at 97° only the pyrimidinium ion was detected.

EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. The n.m.r. spectra were determined on Varian T60 and HR 220 spectrometers as 10% solutions with tetramethylsilane as internal reference.

General Procedure for the Preparation of 2-(N-β-*Hydroxyethyl*-N-β-*alkylaminoethyl*)*pyridines.—Method A*.[4-6] To 2-vinylpyridine (1.0M) in glacial acetic acid (60 g) and methanol (300 ml) was added the alkylamine (1.1M), and this was heated under reflux for 4 days. The solvents were removed at reduced pressure, the residue basified with aqueous sodium hydroxide solution, and ether extracted. The combined extracts were dried (Na_2SO_4), the ether removed under reduced pressure, and the residue distilled. The resulting 2-(β-alkylaminoethyl)pyridine (0.25M) in ethanol (250 ml) was heated under reflux for 24 h with ethylene bromohydrin (0.3M). The solvents were then removed at reduced pressure, the residue basified with aqueous sodium hydroxide solution, and extracted with ether. The combined extracts were dried (Na_2SO_4), concentrated, and distilled.

Method B.[7] The ethanolamine (0.5M) was dissolved in methanol (125 ml) and concentrated hydrochloric acid (44.0 ml) added dropwise with cooling, followed by the addition of 2-vinylpyridine (0.5M). The solution was boiled for 4 h on a water-bath and left overnight at room temperature. The solvents were removed under reduced pressure, and the residue basified with aqueous sodium hydroxide solution and ether extracted. The combined extracts were dried (Na_2SO_4), concentrated, and distilled.



(9) (10) (11)

SCHEME 2

2-(N-β-*Hydroxyethyl*-N-β-*t-butylaminoethyl*)*pyridine* (method A) was obtained from 2-(β-t-butylaminoethyl)-pyridine (5) (44.5 g) as a mobile oil, b.p. 120—122° at 0.80 mmHg (Found: C, 70.0; H, 10.2; N, 12.6. $C_{13}H_{22}N_2O$ requires C, 70.3; H, 9.9; N, 12.6%).

2-(N-β-*Hydroxyethyl*-N-β-*methylaminoethyl*)*pyridine* (method B) (13.9 g, 15.4%) was obtained from 2-methylaminoethanol (37.5 g) as a mobile oil, b.p. 112° at 0.10 mmHg (Found: C, 66.5; H, 9.0; N, 15.1. $C_{10}H_{16}N_2O$ requires C, 66.7; H, 8.9; N, 15.6%).

2-(N-β-*Hydroxyethyl*-N-β-*ethylaminoethyl*)*pyridine* (method B) (28.9 g, 28%) was obtained from 2-ethylaminoethanol (44.5 g) as a mobile oil, b.p. 120—123° at 0.20 mmHg (Found: C, 68.5; H, 9.4; N, 14.5. $C_{11}H_{18}N_2O$ requires C, 68.4; H, 9.3; N, 14.4%).

General Procedure for the Preparation of 2-(N-β-

Hydroxyethyl-N-β-alkylaminoethyl)piperidines.—The 2-(*N*-β-hydroxyethyl-*N*-β-alkylaminoethyl)pyridines (0.1M) were dissolved in ethanol–glacial acetic acid (1 : 1), and reduced with hydrogen at 60 lb in^{-2} in a Parr hydrogenator in the presence of platinum oxide catalyst (1.0 g). When the reduction was complete the catalyst was filtered off, the filtrate concentrated at reduced pressure, and the residue basified with aqueous sodium hydroxide solution. This was extracted with ether, the combined extracts dried (Na_2SO_4), concentrated and the residue distilled.

2-(N-β-*Hydroxyethyl*-N-β-*methylaminoethyl*)*piperidine* (17.2 g, 92.3%) was obtained from 2-(*N*-β-hydroxyethyl-*N*-β-methylaminoethyl)pyridine (18.0 g) as a viscous oil, b.p. 107—108° at 0.50 mmHg (Found: C, 64.3; H, 12.0; N, 14.8. $C_{10}H_{22}N_2O$ requires C, 64.5; H, 11.8; N, 15.0%).

2-(N-β-*Hydroxyethyl*-N-β-*ethylaminoethyl*)*piperidine* (15.6 g, 78.0%) was obtained from 2-(*N*-β-hydroxyethyl-*N*-β-ethylaminoethyl)pyridine (19.4 g) as a viscous oil, b.p. 115—117° at 0.20 mmHg (Found: C, 65.9; H, 12.2; N, 14.0. $C_{11}H_{24}N_2O$ requires C, 66.0; H, 12.0; N, 14.0%).

2-(N-β-*Hydroxyethyl*-N-β-*t-butylaminoethyl*)*piperidine* (15.0 g, 65.8%) was obtained from 2-(*N*-β-hydroxyethyl-*N*-β-t-butylaminoethyl)pyridine (22.2 g) as a viscous oil, b.p. 118° at 0.35 mmHg (Found: C, 68.5; H, 12.6; N, 12.5. $C_{13}H_{28}N_2O$ requires C, 68.4; H, 12.3; N, 12.3%).

General Procedure for the Preparation of 5-Alkylperhydropyrido[1,2-c][1,3,7]*dioxazonines*.—The 2-(*N*-β-hydroxyethyl-*N*-β-alkylaminoethyl)piperidines (0.025M) were shaken with excess 40% aqueous formaldehyde solution at room temperature for 30 min, and then basified with ice cold sodium hydroxide solution. This was extracted with ether, the combined extracts dried (Na_2SO_4), concentrated, and the residue distilled.

5-*t-Butylperhydropyrido*[1,2-c][1,3,7]*oxadiazonine* (2.0 g, 31.3%) was obtained from 2-(*N*-β-hydroxyethyl-*N*-β-t-butylaminoethyl)piperidine (5.7 g) as a viscous oil, b.p. 140° at 0.50 mmHg, which solidified at room temperature, m.p. 105—127° [from petroleum spirit (b.p. 40—60°)] (Found: C, 70.1; H, 11.6; N, 11.4. $C_{14}H_{28}N_2$ Orequires C, 70.0; H, 11.8; N, 11.8%).

General Procedure for the Preparation of 1-*Methyl*-2-(N-β-*hydroxyethyl*-N-β-*alkylaminoethyl*)*piperidine*.—The 2-(*N*-β-hydroxyethyl-*N*-β-alkylaminoethyl)piperidines where the alkyl group was methyl (or ethyl) did not react with formaldehyde at room temperature, and so were heated on a water-bath with 40% aqueous formaldehyde solution for 3 h. The solution was then cooled, basified with aqueous sodium hydroxide solution, and ether extracted. The combined extracts were dried (Na_2SO_4), concentrated, and the residue distilled.

1-*Methyl*-2-(N-β-*hydroxyethyl*-N-β-*methylaminoethyl*)-*piperidine* (3.4 g, 43.9%) was obtained from 2-(*N*-β-hydroxyethyl-*N*-β-methylaminoethyl)piperidine (7.2 g) as a mobile oil, b.p. 129—131° at 0.06 mmHg (Found: C, 66.4; H, 13.6; N, 12.1. $C_{11}H_{24}N_2O$ requires C, 66.0; H, 14.0; N, 12.0%).

1-*Ethyl*-2-(N-β-*hydroxyethyl*-N-β-*ethylaminoethyl*)*piperidine* (1.3 g, 60.7%) was obtained from 2-(*N*-β-hydroxyethyl-*N*-β-ethylaminoethyl)piperidine (2.0 g) as a mobile oil, b.p. 88—92° at 0.20 mmHg (Found: C, 67.2; H, 12.4; N, 13.3. $C_{12}H_{26}N_2O$ requires C, 67.4; H, 12.15; N, 13.1%).

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