Organic Magnetic Resonance, 1975, Vol. 7, pp. 488 to 495.

Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen

XXVIII†—Stereochemical Studies with Perhydropyrido[1,2-*c*] [1,6,3]dioxazocines and 2-Alkylperhydropyrido[1,2-*c*] [1,3,6]Oxdiazocines

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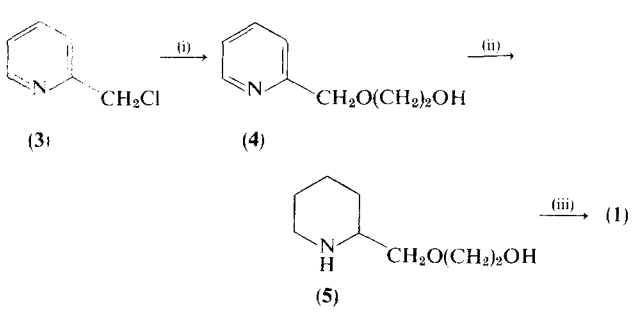
(Received 22 February 1975; accepted (revised) 27 April 1975)

Abstract—A series of perhydropyrido[1,2-*c*][1,6,3]dioxazocines and 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxdiazocines have been prepared. 6-*p*-Nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]-dioxazocine is shown to adopt the *cis* fused ring conformation in solution with the nitrogen lone pair axial with respect to the piperidine ring. The 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxdiazocines adopt a similar *cis* fused ring conformation and with increasing steric requirement of the 2-alkyl substituent the 8-membered ring increasingly favours the chair–chair conformation, rather than the chair–boat conformation favoured by the 2-methyl substituted compound.

NO STEREOCHEMICAL studies on bridgehead nitrogen systems containing an 8-membered ring have been described. Accordingly the perhydropyrido[1,2-*c*][1,6,3]dioxazocine (**1**) and 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxdiazocine (**2**) systems were selected for study, since these possess an 8-membered ring and the N—C—C—X moiety (X = O, N) present in many biologically active systems.[2]

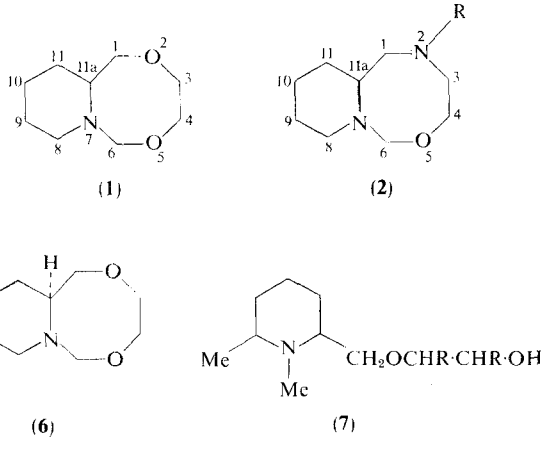
Synthesis of perhydropyrido[1,2-*c*][1,6,3]dioxazocines

Perhydropyrido[1,2-*c*][1,6,3]dioxazocine (**1**) was prepared by the route shown in Scheme 1.



SCHEME 1. Reagents: (i) $NaO(CH_2)_2OH$; (ii) H_2—PtO_2; (iii) 40% aqueous CH_2O.

A mixture of diastereoisomeric 9-ethylperhydropyrido-[1,2-*c*][1,6,3]dioxazocines was prepared by a similar route from 5-ethyl-2-chloromethylpyridine and the single pure isomer obtained was assigned (see below) the *cis*-(9H, 11aH) configuration (**6**). Attempts (see Experimental section) to prepare 8-methyl- and 3,4,8-trimethyl derivatives of **1** gave instead (**7**; R = H) and (**7**; R = Me).



A mixture of 3,4-dimethylperhydropyrido[1,2-*c*]-[1,6,3]dioxazocines (**9** and **10**) derived from *meso*-butane-2,3-diol resisted attempts at separation by a variety of techniques. However, the mixture of isomeric piperidyl alcohols (**11**; R^1, R^3 = H, R^2, R^4 = Me) condensed with *p*-nitrobenzaldehyde to give a single isomer of 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*]-[1,6,3]dioxazocine (**12**) and the amino alcohol which did not react in this manner ring closed with formaldehyde to yield a single isomer of 3,4-dimethylperhydropyrido-[1,2-*c*][1,6,3]dioxazocine. Other derivatives of **1** (see Experimental section) underwent very rapid polymerisation.

Synthesis of perhydropyrido[1,2-*c*][1,3,6]oxdiazocines

The 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxdiazocines (**2**) were synthesised by the route shown in Scheme 2.

Structural studies on perhydropyrido[1,2-*c*][1,6,3]dioxazocines

As described above, all the perhydropyrido[1,2-*c*]-[1,6,3]dioxazocines, with the exception of 3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine, were highly

† For Part XXVII, see Ref. 1.
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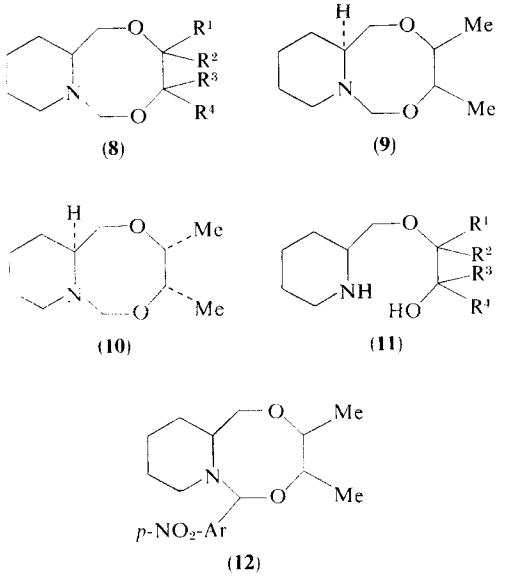


unstable and rapidly underwent polymerisation. However, it was possible to obtain the NMR spectrum of the parent unsubstituted compound, but before an expansion could be run polymerisation had occurred. The spectrum showed an AB quartet for the C-6 methylene protons (δ4·79 and 4·16 ppm and J_{gem} — 10·5 Hz), a six proton multiplet at δ3·5 to 4·0 ppm for the protons adjacent to the oxygen atoms and a three proton multiplet at δ2·6 to 3·1 ppm corresponding to the protons adjacent to the nitrogen atom. The absorption of the N—CH_2 protons below δ2·0 ppm suggests a *cis* fused ring conformation,[4] since an α-CH proton *trans* diaxial to the nitrogen lone pair would absorb to higher field of δ2·0 ppm. A *cis* fused ring conformation is also suggested by the absence of Bohlmann[5] bands in the IR spectrum.

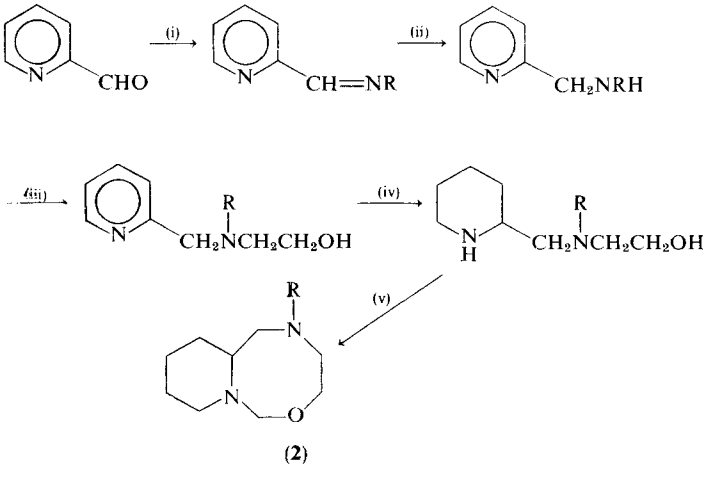
The NMR spectrum of the single isomer of 3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine showed a low field quartet for the N—CH_2—O protons (δ4·96 and 4·17 ppm, J_{gem} — 10 Hz), and absorptions for the four protons adjacent to oxygen at δ3·07 to 3·65 ppm and the three protons adjacent to nitrogen at δ2·43 to 2·83. This, and the lack of Bohlmann bands in the IR spectrum, indicates a similar conformation for this compound and perhydropyrido[1,2-*c*][1,6,3]dioxazocine.

To gain more information regarding the stereochemistry of this system the single isomer of 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine (**12**) was examined. Consideration of Dreiding models suggests three possible structures for **12** ignoring at present the configuration about C-3 and C-4. These are shown in Fig. 1, where the *trans* ring fused **13** is interconvertible by nitrogen inversion and ring inversion with the *cis* ring fused **14**. It is also possible to obtain the *cis* ring fused **15** which is a diastereoisomer of **13** and **14**. For each of the structures shown in Fig. 1,† the 8-membered ring can adopt a chair–chair conformation (shown by ———) or a boat–chair conformation (shown by · · · · ·), interconvertible by rotation about the C-3—C-4 bond. This interconversion does not affect the stereochemistry of the rest of the molecule. Both **13** and **15** are destabilised by the generalised anomeric effect,[6] whereas **14** is not. This is illustrated in Fig. 1 by bold arrows indicating the direction of the dipoles, interactions between these forming part of the generalised anomeric effect.

The 220 MHz NMR spectrum (Fig. 2) of **12** showed multiplets at δ2·76 and 2·34 corresponding to H-8ax and H-8eq, respectively, and analysis gave coupling constants characteristic of a chair piperidine ring (Table 1). The relatively high field absorption of H-8eq (δ2·34) compared to that normally observed in piperidine (δ2·8) must be a result of shielding by the aromatic ring. This is possible in all three structures shown in Fig. 1 if the plane of the aromatic ring is parallel to the H—C-8—H plane. Perhaps the most interesting feature of the spectrum is the very low field absorption of H-8ax (2·76 ppm). In quinolizidine[7] the corresponding axial proton absorbs 0·93 ppm to higher field than the equatorial proton, whereas in **12** H-8ax actually absorbs 0·42 ppm to lower field of H-8eq. This is not explicable in terms of structures **13** and **15**, but in **14** H-8ax should be deshielded by the *syn* axial C-1 methylene[8] and by the *syn* axial C—O-5 bond. A similar deshielding effect has been noted in **16** with chemical shifts of δ2·62 and 2·23 ppm for H-5ax and H-5eq, respectively.[1]

The C-1 methylene protons absorb as an AB part of an ABX multiplet at δ4·25 and 3·90 ppm, and if these were

† The compounds described in this paper exist as racemates and the structures in Fig. 1 are drawn for ease of representation; **13** and **14** do not represent the same enantiomer.



SCHEME 2. Reagents: (i) RNH_2; (ii) $NaBH_4$; (iii) $BrCH_2CH_2OH$; (iv) H_2—PtO_2; (v) C_2O.

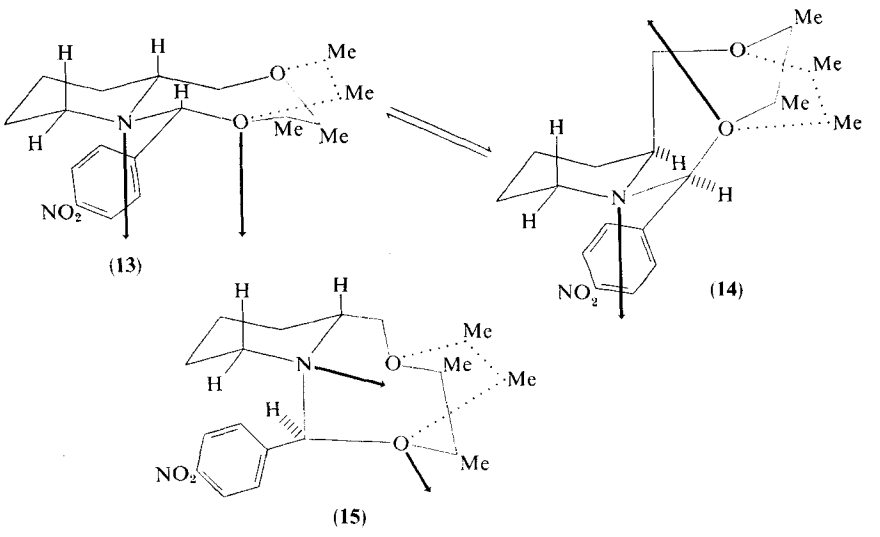


FIG. 1. Possible structures for 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine.

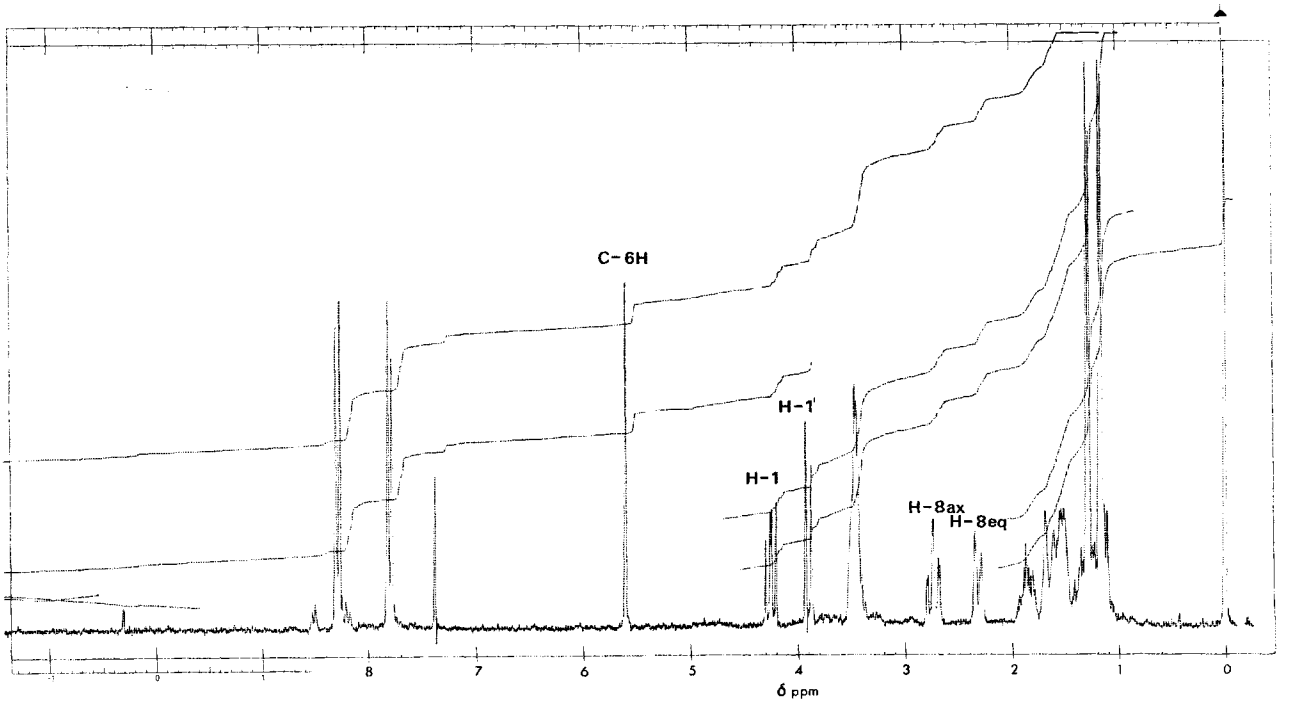


FIG. 2. 220 MHz spectrum of 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine (**12**). (Reference: TMS; Solvent: $CDCl_3$; Sweep rate (Hz/s)5).

TABLE 1. FIRST ORDER ANALYSIS OF THE 220 MHz NMR SPECTRUM OF 6-*p*-NITROPHENYL-3,4-DIMETHYL-PERHYDROPYRIDO[1,2-*c*][1,6,3]DIOXAZOCINE

	Coupling constants				Chemical shifts (δ ppm)	
J(H-8ax, H-8eq)	−12	*J*(H-8eq, H-9eq)	2·5	H-8eq	2·34
J(H-8ax, H-9ax)	12	*J*(H-1, H-1′)	−12	H-8ax	2·76
J(H-8ax, H-9eq)	3	*J*(H-1, H-11a)	9	H-1′	3·90
J(H-8eq, H-9ax)	3·5	*J*(H-1′, H-11a)	1·5	H-1	4·25
				H-3 and H-4	3·50

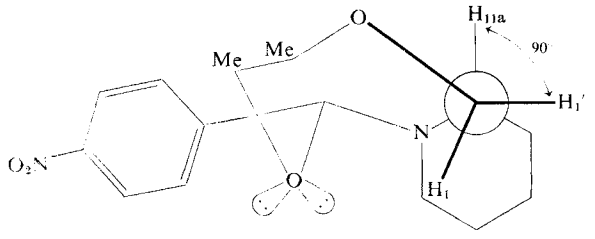


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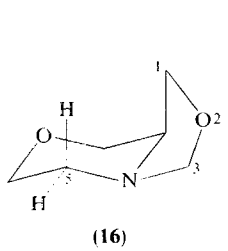
FIG. 3. Proposed structure (**14**) of 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine showing the dihedral angles between the C—H-11a bond and the C-1—H bonds, and the close approach of H-1 to the 5-oxygen atom.

strictly axial and equatorial with respect to H-11a, coupling constants of 11 and 5 Hz would be expected, but the observed values (Table 1) suggest dihedral angles of approximately 140° and 100°. Examination of the Dreiding model of **14** in fact shows (Fig. 3) dihedral angles of 90° and 150° between H-11a and H-1′ and between H-11a and H-1, respectively, consistent with the observed J_{vic} values. In addition, the H-1 proton absorbs 0·35 ppm to lower field of H-1′ and this too is in accord with structure **14** (Figure 3 shows H-1 close to the oxygen atom resulting in a deshielding of this proton.) Thus structure **14** is consistent with the NMR data, but assignment of the configuration of the methyl groups at C-3 and C-4 is not possible from an examination of the NMR spectrum.

The conformation, i.e. boat–chair or chair–chair, of the 8-membered ring in **14** cannot be deduced from the NMR spectrum, since alterations around C-3 and C-4 do not affect the relative disposition of the 5-oxygen atom with respect to H-8ax, or the dihedral angles between the C-11a and C-1 methylene protons.

The possible *cis* fused conformations with boat–chair and chair–chair conformations of the 8-membered ring of the 3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocines (**9** and **10**) obtained by the synthesis involving *meso*-butane-2,3-diol are conformations **17** and **18** for **9** and conformations **19** and **20** for **10**. The structure **19** has serious nonbonded interactions between the C-3 axial methyl group and the C-1 methylene and H-11a protons, and consequently the equilibrium favours **20**,



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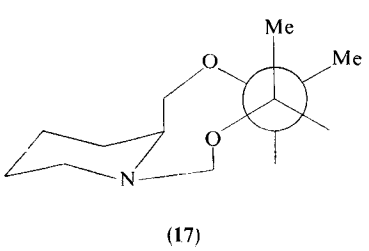

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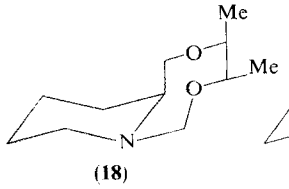

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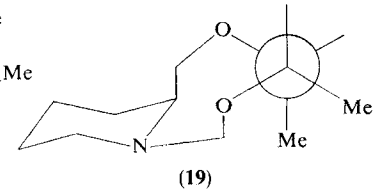

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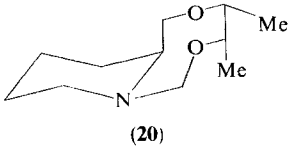
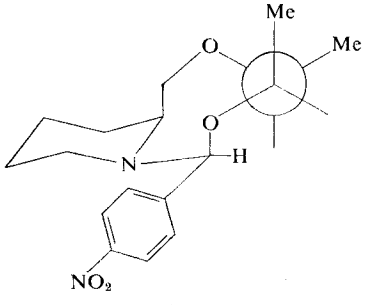


(20)

where nonbonded interactions between the C-4 axial methyl group and the C-6 methylene protons can be relieved by slight distortion of the 8-membered ring. The other possible conformations (**17** and **18**) for compounds derived from *meso*-butane-2,3-diol appear relatively free of nonbonded interactions, and from previous studies[9] on the conformations of 8-membered rings, the boat–chair conformation **17** is probably preferred.

Further studies of Dreiding models show that the single isomer of **12** prepared from the isomeric mixture of 1,2-dimethyl-2-(2-piperidylmethoxy)ethanols will have the structure **21**, where the C-3 and C-4 methyl groups have the same relative disposition as in **17**. It is seen from Dreiding models that the reaction of the precursor of **20** with *p*-nitrobenzaldehyde would yield a compound that was sterically crowded. Consequently the single



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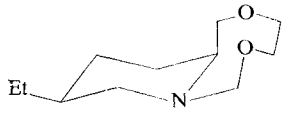

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isomer of 3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine synthesised from the 1,2-dimethyl-2-(2-piperidylmethoxy)ethanol that did not react with *p*-nitrobenzaldehyde was assigned structure **20**, slightly distorted so as to minimise the C-4—Me/C-6 methylene interaction. It was observed from Dreiding models that interconversion of the boat–chair and chair–chair conformations of the 8-membered ring did not seem to affect the N—CH_2—O geometry, as was shown by the constant J_{gem} of −10 Hz observed for these systems.

The 60 MHz NMR spectrum (in $CDCl_3$) of the single isomer of 9-ethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine obtained as described above showed a single AB quartet for the N—CH_2—O protons (δ4·77 and 4·16, J_{gem} — 11·2 Hz). A six proton multiplet was observed centred at δ3·60 and this was assigned to the protons adjacent to the oxygen atoms. A three proton multiplet centred at δ2·75 was assigned to the protons adjacent to the nitrogen atom, with a broad multiplet equivalent to ten protons at δ0·75 to 1·90. The spectrum was thus very similar to that obtained from the unsubstituted perhydropyrido[1,2-*c*][1,6,3]dioxazocine, indicating a similar stereochemistry for the two compounds. This suggests the equatorially substituted *cis* fused structure **22** for the 9-ethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine.

Structural studies of 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxdiazocines

This series of compounds were all obtained as colourless mobile liquids which were stable at room temperature. The use of Bohlmann bands to deduce the ring

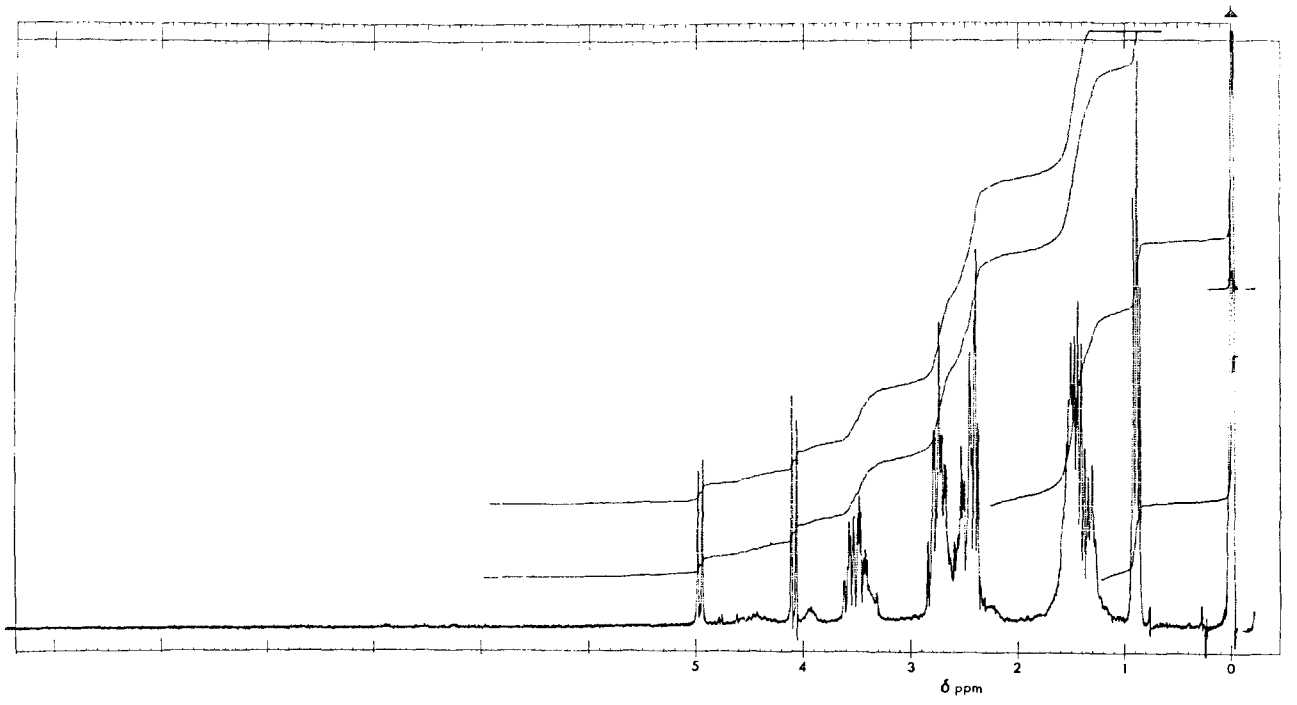


FIG. 4. 220 MHz spectrum of 2-isopropylperhydropyrido[1,2-*c*][1,3,6]oxdiazocine (**2**; R = iso-Pr). (Reference: TMS; Solvent: CCl_4; Sweep rate (Hz/s)5)

fusion of these compounds is complicated by absorption in this region from the alkyl substituent on the N-2 atom, but a *cis* ring fusion is indicated by the lack of Bohlmann bands in the IR spectrum of 2-*t*-butylperhydropyrido-[1,2-*c*][1,3,6]oxdiazocine.

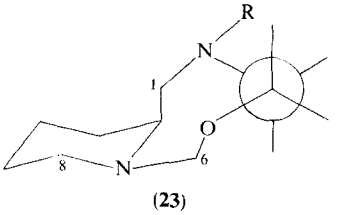
TABLE 2. CHEMICAL SHIFTS AND J_{gem} VALUES OBTAINED FROM THE 60 MHz NMR SPECTRA OF 2-ALKYLPERHYDROPYRIDO[1,2-*c*[]1,3,6]-OXDIAZOCINES IN CCl_4 SOLUTION

2-Alkyl group	δ 6ax′	δ 6eq′	J(6ax6eq)
Methyl	4·76	4·04	−10·0
Ethyl	4·87	4·07	−10·0
n-Propyl	4·90	4·07	−10·1
Isopropyl	4·91	4·08	−9·9
n-Butyl	4·91	4·07	−9·9
Isobutyl	4·95	4·15	−9·9
t-Butyl	5·09	4·13	−10·0

The NMR spectra of this series of compounds which showed similarities to those obtained for the perhydropyrido[1,2-*c*][1,6,3]dioxazocines are typified by that for 2-isopropylperhydropyrido[1,2-*c*][1,3,6]oxdiazocine (Fig. 4). As seen in Table 2, the chemical shifts of the AB quartets for the C-6 methylene protons are all very similar as is the value of J_{gem} for these protons (i.e. −9·9 to −10·1 Hz). The chemical shifts of the multiplets for protons adjacent to oxygen (δ3·30 to 3·77 ppm) and to nitrogen (δ2·20 to 3·07) are very similar to those observed for the oxygen analogues, as is the value of J_{gem} for the N—CH_2—O protons. The 220 MHz NMR spectra of the 2-alkylperhydropyrido[1,2-*c*][1,3,6]oxdiazocines are not analysable, as the region that would yield detailed information on the structure, i.e. δ2·2 to 3·1 ppm for the absorption of protons adjacent to nitrogen, contains many overlapping multiplets.

From the similarities between the 60 MHz NMR spectra of these compounds (Table 2) and those of the perhydropyrido[1,2-*c*][1,6,3]dioxazocines, it may be assumed that the nitrogen analogues possess a similar *cis* fused ring structure. The 8-membered ring may adopt the boat–chair conformation as shown in **23** or the chair–chair conformation **24**. Evidence for these 8-membered ring conformations comes from an examination of the chemical shifts of the low field 6-proton (designated 6ax′ in Table 2). This proton becomes increasingly deshielded as the 2-alkyl substituent increases in bulk from δ4·76 for 2-methyl to δ5·09 for 2-*t*-butyl. Dreiding models show that for the 2-methyl compound both **23** and **24** with R in a pseudo equatorial orientation are possible, whereas for the 2-*t*-butyl compound only (**24**; R = *t*-butyl) is relatively free of nonbonded interactions. In **24** H-6ax′ is close to the nitrogen lone pair and so should be deshielded, but this is not the situation for **23**. Thus the trend in the chemical shifts of H-6ax′ is explicable in terms of the existence of the 2-methyl compound as an equilibrium between **23** and **24** with **23** predominant, and as the steric requirements of the alkyl group increase so does the proportion of **24** until with the 2-*t*-butyl compound the equilibrium lies almost exclusively in favour of **24**.

The results of the biological testing of these compounds will be reported elsewhere.



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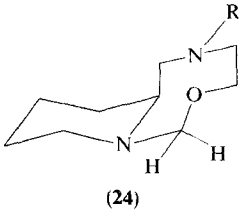

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EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Portsmouth Polytechnic. IR spectra were recorded on a Perkin-Elmer 457 grating instrument for 0·2 M solutions using 0·2 mm matched cells. NMR spectra were determined on Varian T-60 and HR-220 MHz spectrometers as 10% solutions with Me_4Si as internal reference.

Preparation of 5-ethyl-2-pyridylcarbinol

5-Ethyl-2-methylpyridine (180 g) was heated under reflux with 30% v/v hydrogen peroxide (255 ml) in glacial acetic acid (900 ml) at 70 °C for 12 h, then the excess acetic acid was removed at reduced pressure. The residue was reacted with acetic anhydride (500 g) on a water bath until the exothermic reaction had taken place and the solution then boiled under reflux with 10% aqueous sodium hydroxide solution (1:1) in methanol (400 ml) for 2 to 3 h. The mixture was then ether extracted, the combined extracts dried (Na_2SO_4), concentrated and distilled to give 5-ethyl-2-pyridylcarbinol (127 g, 62·3%) as a colourless mobile oil, b.p. 90 to 93 °C at 0·50 mmHg (Lit.[10] 140 to 142 °C at 18 mmHg).

General procedure for the synthesis of 6-methyl- and 5-ethyl-2-picolyl chlorides

To 5-ethyl- or 6-methyl-2-pyridylcarbinol (1·0 M) in ice cold ethyl acetate (700 ml) was added, with stirring, phosphorus oxychloride (165 g). The solution was heated for 1 h on a water bath, and then solvents and excess phosphorus oxychloride removed at reduced pressure. The residue was basified with aqueous sodium hydroxide solution, ether extracted, and the combined extracts dried (Na_2SO_4), concentrated and the residue distilled. *5-Ethyl-2-monochloromethylpyridine* (97 g, 61·2%) was obtained from 5-ethyl-2-pyridylcarbinol (131 g) as a colourless mobile oil, b.p. 60 to 64 °C at 0·60 mmHg (Lit.[11,12] 90 °C at 3·0 mmHg).

6-Methyl-2-monochloromethylpyridine (113 g, 80·0%) was obtained from 6-methyl-2-pyridylcarbinol (123 g) as a colourless mobile oil, b.p. 42 to 44 °C at 0·45 mmHg (Lit.[11,12] 81 °C at 12·0 mmHg).

General procedure for the synthesis of 2-(2-piperidylmethoxy)-ethanol

A solution of the required 1,2-diol (1·0 M) and sodium (0·5 M) in absolute ethanol (150 ml) was boiled under reflux for 30 min and then the ethanol was removed at reduced pressure. The monosodium 1,2-diol isolated was reacted with the appropriate 2-picolyl chloride (0·5 M) in toluene by heating under reflux for 2 to 3 h.[13,14] The toluene was then removed at reduced pressure, and the residue basified with aqueous sodium hydroxide solution and chloroform extracted. The combined extracts were dried (Na_2SO_4), concentrated and distilled (Table 3). The 2-(2-pyridylmethoxy)ethanols (0·1 M) were then dissolved in glacial acetic acid (50 ml) and ethanol (150 ml), platinum oxide catalyst (1·0 g) added, and reduced with hydrogen at 60 p.s.i. in a Parr hydrogenator. The catalyst was filtered off after completion of the reduction, the solvents removed at reduced pressure and the residue basified with aqueous sodium hydroxide solution. The solution was extracted with ether, the extracts combined, dried (Na_2SO_4) and the residue distilled (Table 4).

General procedure for the reaction of 2-(2-piperidylmethoxy)-ethanols with formaldehyde

The 2-(2-piperidylmethoxy)ethanols were reacted with excess 40% aqueous formaldehyde at room temperature for 30 min and the solution then basified with ice cold sodium hydroxide solution. The solution was ether extracted, and the combined extracts dried (Na_2SO_4) and the residue distilled.

Perhydropyrido[1,2-c][1,6,3]dioxazocine (1·0 g, 19·4%) was obtained from 2-(2-piperidylmethoxy)ethanol (4·58 g) as a colourless mobile oil, b.p. 99 to 102 °C at 0·50 mmHg.

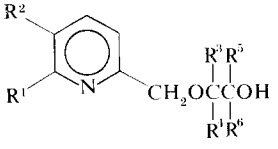

TABLE 3. SYNTHESIS OF 2-(2-PYRIDYLMETHOXY)ETHANOLS

									Analysis					
									% Found			% Required		
R^1	R^2	R^3	R^4	R^5	R^6	1:2 diol used in synthesis	Yield %	b.p. °C at mmHg	C	H	N	C	H	N
H	H	H	H	H	H	Ethylene glycol	37·4	106–110 at 0·10	62·58	7·12	9·07	62·72	7·24	9·14
H	H	H	H	Me	H	1,2 Propanediol	33·5	92–96 at 1·0	64·79	3·02	7·95	64·65	7·84	8·38
H	H	Me	H	Me	H	2,3 Butanediol	35·1	110–111 at 0·60	66·03	8·00	8·19	66·27	8·34	7·73
H	H	Me	Me	Me	Me	2,3-Dimethyl-2,3-butanediol	90·0	42 at 0·10	68·99	8·93	7·33	68·66	9·15	6·69
Me	H	H	H	H	H	Ethylene glycol	36·7	120–122 at 3·0	64·30	8·05	8·39	64·68	7·78	8·39
Me	H	Me	H	Me	H	2,3 Butanediol	33·4	93 at 0·10	67·45	8·73	7·19	67·68	8·73	7·19
H	Et	H	H	H	H	Ethylene glycol	32·4	124–127 at 0·70	66·02	8·06	8·33	66·30	8·29	7·73

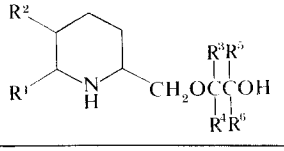

TABLE 4. SYNTHESIS OF 2-(2-PIPERIDYLMETHOXY)ETHANOLS

									Analysis					
									% Found			% Required		
R^1	R^2	R^3	R^4	R^5	R^6	Yield %	b.p. °C at mmHg	C	H	N	C	H	N
H	H	H	H	H	H	64·8	115 at 0·80	60·31	11·23	9·12	60·34	10·76	8·80
H	H	H	H	Me	H	69·4	91 at 0·20	62·13	11·08	8·24	62·39	11·05	8·09
H	H	Me	H	Me	H	82·9	103–106 at 0·15	63·89	11·19	7·18	64·13	11·30	7·48
H	H	Me	Me	Me	Me	64·1	43–45 at 0·25	67·05	11·89	6·02	66·93	11·70	6·51
Me	H	H	H	H	H	66·8	110 at 0·20	62·12	11·33	8·10	62·43	10·98	8·08
Me	H	Me	H	Me	H	72·7	90 at 0·30	65·63	11·36	7·55	65·73	11·40	6·97
H	Et	H	H	H	H	82·0	115–117 at 1·0	64·22	11·70	7·49	64·17	11·25	7·64

3-(or 4-)Methylperhydropyrido[1,2-c][1,6,3]dioxazocine (1·0 g, 22·9%) was obtained from 1-(or 2-)2-(2-piperidylmethoxy)ethanol 4·95 g) as a colourless mobile oil, b.p. 85 to 87 °C at 0·45 mmHg. *3,3,4,4-Tetramethylperhydropyrido[1,2-c][1,6,3]dioxazocine* (3·9 g, 50%) was obtained from 1,1,2,2-tetramethyl-2-(2-piperidylmethoxy)ethanol (5·91 g) as a colourless mobile oil, b.p. 80 °C at 0·40 mmHg).

Elemental analyses for these compounds were not obtainable, as the compounds were unstable.

3,4-Dimethylperhydropyrido[1,2-c][1,6,3]dioxazocine as a mixture of two isomers (3·7 g, 57·4%) was obtained from 1,2-dimethyl-2(2-piperidylmethoxy)ethanol (5·25 g) as a colourless mobile oil, b.p. 91 °C at 0·90 mmHg (Found: C, 66·14; H, 10·94; N, 7·02. $C_{11}H_{21}NO_2$ requires: C, 66·29; H, 10·62; N, 7·03%).

9-Ethylperhydropyrido[1,2-c][1,6,3]dioxazocine (2·8 g, 70·4%) was obtained from 2-(5-ethyl-2-piperidylmethoxy)ethanol (3·7 g) as a colourless mobile oil, b.p. 108 to 110 °C at 0·03 mmHg (Found: C, 66·02; H, 10·69; N, 6·81. $C_{11}H_{20}NO_2$ requires: C, 66·63; H, 10·55; N, 7·03%).

The 2-(6-methyl-2-piperidylmethoxy)ethanols did not react with aqueous formaldehyde solution at room temperature, but when refluxed for 48 h on a water bath yielded the *N*-methyl derivatives.

2-(1,6-Dimethyl-2-piperidylmethoxy)ethanol (4·2 g, 44·7%) was obtained from 2-(6-methyl-2-piperidylmethoxy)ethanol (8·7 g) as a yellow mobile oil, b.p. 121 °C at 0·80 mmHg (Found: C, 64·30; H, 8·05; N, 8·44. $C_{10}H_{21}NO_2$ requires: C, 64·68; H, 7·78; N, 8·39%).

1,2-Dimethyl-2-(1,6-dimethyl-2-piperidylmethoxy)ethanol (4·5 g, 41·9%) was obtained from 1,2-dimethyl-2-(6-methyl-2-piperidylmethoxy)ethanol (10 g) as a colourless viscous oil, b.p. 102 °C at 0·45 mmHg (Found: C, 67·53; H, 12·50; N, 6·50. $C_{12}H_{25}NO_2$ requires: C, 66·99; H, 11·62; N, 6·52%).

Preparation of 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido-[1,2-*c*][1,6,3]dioxazocine

1,2-Dimethyl-2-(2-piperidylmethoxy) ethanol (0·3 M) was dissolved in benzene (500 ml) and heated under reflux with *p*-nitrobenzaldehyde (0·35 M) and a trace of *p*-toluene sulphonic acid as a catalyst using a Dean and Stark water separator. When the calculated amount of water had been separated, the benzene was removed at reduced pressure and the residue recrystallised from ethanol. cis *Fused* 8-p-*nitrophenyl-3,4-dimethylperhydropyrido-[1,2-c][1,6,3]dioxazocine* (30·0 g, 31·3%) was obtained (52·5 g) as pale yellow needles, m.p. 134 °C (from ethanol) (Found: C, 63·98; H, 7·82; N, 8·68. $C_{17}H_{24}N_2O_4$ requires: C, 63·73; H, 7·55; N, 8·74%).

3,4-Dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine

6-*p*-Nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine was stirred with excess 10% aqueous hydrochloric acid at room temperature for 1 h and the precipitated *p*-nitrobenzaldehyde filtered off. The filtrate was ether extracted after basification with aqueous sodium hydroxide solution, and the crude 1,2-dimethyl-2-(2-piperidylmethoxy)ethanol shaken with aqueous formaldehyde solution at room temperature for ½ h. The 3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine (b.p. 78 to 80 °C at 1·0 mmHg) was isolated as a mixture of isomers as before.

The unreacted 1,2-dimethyl-2-(2-piperidylmethoxy)ethanol contained in the ethanol filtrate from the above described synthesis of 6-*p*-nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine was isolated after basification with aqueous sodium hydroxide and ether extraction. The product (b.p. 108 °C at 0·80 mmHg) was reacted with aqueous formaldehyde solution at room temperature for ½ h, and the product isolated after basification with aqueous sodium hydroxide solution was a single isomer of 3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine (b.p. 96 to 100 °C at 0·70 mmHg).

1,2-Dimethyl (*N*-methyl-2-piperidylmethoxy)ethanol

6-*p*-Nitrophenyl-3,4-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine (10 g) was stirred with an excess of 40% aqueous formaldehyde solution (225 ml) for 10 days at room temperature. The formaldehyde was removed at reduced pressure, and the residue basified with aqueous sodium hydroxide solution, ether extracted, and the combined extracts dried (Na_2SO_4), concentrated and the residue distilled. The product was not the expected formal but 1,2-dimethyl(*N*-methyl-2-piperidylmethoxy)ethanol (5·2 g, 48·4%) as a yellow mobile oil, b.p. 89 °C at 0·15 mmHg (Found: C, 64·92; H, 11·88; N, 5·55. $C_{11}H_{23}NO_2$ requires: C, 65·63; H, 11·52; N, 6·96%).

meso-2,3-Butanediol[15] was prepared by adding a solution of biacetyl (34·4 g) in water (50 ml) and methanol (25 ml) slowly to sodium borohydride (10 g) and sodium hydroxide (0·6 g) in water (100 ml). When the mixture became colourless, it was heated on a water bath for an hour and the solution concentrated until crystallisation of the complex began. The *meso*-2,3-butanediol was extracted with chloroform as a colourless viscous oil, b.p. 58 to 60 °C at 0·40 mmHg, n_D^{24} 1·4372. This was reacted as before to give 2,3-dimethylperhydropyrido[1,2-*c*][1,6,3]dioxazocine, b.p. 108 °C at 1·0 mmHg.

General procedure for the preparation of 2-alkyliminomethylpyridines[3]

Pyridine-2-aldehyde (0·40 M) was added to a solution of the alkylamine (0·50 M) in benzene (200 ml) and the mixture boiled under reflux until the calculated amount of water had been separated by a Dean and Stark apparatus. The benzene was then removed at reduced pressure and the residue distilled. Details regarding the individual preparations are given in Table 5.

TABLE 5. SYNTHESIS OF 2-ALKYLIMINOMETHYLPYRIDINES

2-Alkyl group	Yield (%)	b.p. °C	Analysis C	H	N
Et	93·3	44 at 0·15 mmHg	71·66	7·57	20·76[a]
n-Pr	81·6	75 at 0·30 mmHg	73·09	8·21	19·18[b]
iso-Pr	80·8	45 at 0·30 mmHg	72·95	7·90	18·96[b]
n-Bu	88·7	89 at 0·40 mmHg	73·97	8·79	17·11[c]
sec-Bu	93·8	74 at 0·50 mmHg	73·72	8·97	17·01[c]
t-Bu	85·6	73 at 0·45 mmHg	73·99	8·77	17·29[c]

[a] $C_8H_{10}N_2$ requires: C, 71·61; H, 7·51; N, 20·88%.
[b] $C_9H_{12}N_2$ requires: C, 72·94; H, 8·16; N, 18·90%.
[c] $C_{10}H_{14}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%.

General procedure for the preparation of 2-alkylaminomethylpyridines[3]

The 2-alkyliminomethylpyridine (0·25 M) was dissolved in dry methanol (500 ml) and sodium borohydride (0·5 M) added with vigorous stirring. When the reaction ceased, the solution was acidified with dilute aqueous hydrochloric acid, basified with aqueous sodium hydroxide solution and ether extracted. The ether was dried (Na_2SO_4), concentrated and the residue distilled to give the required products. Details concerning these are summarised in Table 6.

TABLE 6. SYNTHESIS OF 2-ALKYLAMINOMETHYLPYRIDINES

2-Alkyl group	Yield (%)	b.p. °C	Analysis C	H	N
Et	63·4	80–82 at 1·0 mmHg	70·03	9·13	21·05[a]
n-Pr	66·0	83 at 0·30 mmHg	71·69	9·41	19·10[b]
iso-Pr	70·3	79 at 0·45 mmHg	72·10	9·03	19·18[b]
n-Bu	63·7	93–5 at 2·0 mmHg	73·20	10·12	16·81[c]
sec-Bu	73·9	114–6 at 1·0 mmHg	72·93	10·16	17·29[c]
t-Bu	94·1	72–74 at 0·45 mmHg	73·27	10·29	17·13[c]

[a] $C_8H_{12}N_2$ requires: C, 70·55; H, 8·88; N, 20·75%.
[b] $C_9H_{14}N_2$ requires: C, 71·95; H, 9·39; N, 18·65%.
[c] $C_{10}H_{16}N_2$ requires: C, 73·12; H, 9·82; N, 17·06%.

General procedure for the preparation of 2-(*N*-β-hydroxyethyl-*N*-alkylaminomethyl)pyridines

To absolute ethanol (100 ml) was added 2-alkylaminomethylpyridine (0·15 M) and ethylene bromohydrin (0·20 M), and the reaction mixture heated at 60 °C for 24 h. The ethanol was removed at reduced pressure, and the residue basified with aqueous sodium hydroxide solution and ether extracted. The extracts were dried

(Na_2SO_4), concentrated and the residue distilled to give the products shown in Table 7.

TABLE 7. SYNTHESIS OF 2-(*N*-β-HYDROXYETHYL-*N*-ALKYLAMINOMETHYL)PYRIDINE

Alkyl group	Yield (%)	b.p. °C	Analysis C	H	N
Me	70·4	120 at 0·60 mmHg	64·09	8·67	17·10[a]
Et	36·0	105–107 at 0·80 mmHg	67·03	8·87	15·45[b]
n-Pr	57·0	120–122 at 0·40 mmHg	67·74	9·30	14·89[c]
iso-Pr	51·5	132 at 1·50 mmHg	68·00	9·48	14·70[c]
n-Bu	54·0	120–122 at 1·0 mmHg	69·54	9·91	14·14[d]
sec-Bu	50·7	75 at 0·50 mmHg	69·26	9·98	13·01[d]
t-Bu	55·0	73 at 0·50 mmHg	69·03	10·13	12·75[d]

[a] $C_9H_{14}N_2O$ requires: C, 65·06; H, 8·43; N, 16·88%.
[b] $C_{10}H_{16}N_2O$ requires: C, 66·63; H, 8·95; N, 15·54%.
[c] $C_{11}H_{18}N_2O$ requires: C, 68·00; H, 9·34; N, 14·42%.
[d] $C_{12}H_{20}N_2O$ requires: C, 69·19; H, 9·68; N, 13·45%.

General procedure for the preparation of 2-(*N*-β-hydroxyethyl-*N*-alkylaminomethyl)piperidine

The 2-(*N*-β-hydroxyethyl-*N*-alkylaminomethyl)pyridine (0·1 M) was dissolved in glacial acetic acid (50 ml) and absolute ethanol (150 ml), and shaken with hydrogen at 60 p.s.i. in a Parr hydrogenator using platinum oxide platinum oxide catalyst (1·0 g). When the reduction was complete, the catalyst was filtered off, the solvents removed 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 distilled. Details concerning the products are shown in Table 8.

General procedure for the preparation of 2-alkyl-perhydropyrido-[1,2-c][1,3,6]dioxazocine

To the 2-(*N*-β-hydroxyethyl-*N*-alkylaminomethyl)piperidine (0·04 M) was added an excess of 40% aqueous formaldehyde

TABLE 8. SYNTHESIS OF 2-(*N*-β-HYDROXYETHYL-*N*-ALKYLAMINOMETHYL)PIPERIDINES

Alkyl group	Yield (%)	b.p. °C	Analysis C	H	N
Me	75.2	102 at 0·20 mmHg	62·80	11·61	16·28[a]
Et	72·3	107 at 1·0 mmHg	63·50	11·83	15·11[b]
n-Pr	65·2	120 at 0·60 mmHg	66·18	11·50	14·52[c]
iso-Pr	70·3	118–20 at 0·20 mmHg	66·01	11·93	14·22[c]
n-Bu	61·1	88 at 0·30 mmHg	67·13	12·31	13·20[d]
sec-Bu	65·0	110 at 0·90 mmHg	66·97	12·00	13·03[d]
t-Bu	55·2	55 at 0·70 mmHg	67·07	11·89	13·12[a]

[a] $C_9H_{20}N_2O$ requires: C, 62·80; H, 11·61; N, 16·28%.
[b] $C_{10}H_{22}N_2O$ requires: C, 64·47; H, 11·90; N, 15·04%.
[c] $C_{11}H_{24}N_2O$ requires: C, 65·95; H, 12·08; N, 13·99%.
[d] $C_{12}H_{26}N_2O$ requires: C, 67·24; H, 12·23; N, 13·07%.

TABLE 9. SYNTHESIS OF 2-ALKYLPERHYDROPYRIDO[1,2-*c*][1,3,6]-DIOXAZOCINE

Alkyl group	Yield (%)	b.p. °C	Analysis C	H	N
Me	63·7	73 at 0·20 mmHg	64·91	11·00	14·89[a]
Et	41·8	84–86 at 0·80 mmHg	67·02	11·12	13·84[b]
n-Pr	47·2	101 at 1·5 mmHg	67·95	11·23	12·90[c]
iso-Pr	42·4	96–98 at 0·80 mmHg	68·07	11·41	13·08[c]
n-Bu	33·8	133 at 3·0 mmHg	69·36	12·17	12·02[d]
sec-Bu	41·2	121 at 0·70 mmHg	69·12	12·19	11·89[d]
t-Bu	37·0	110 at 0·35 mmHg	68·27	12·04	12·30[d]

[a] $C_{10}H_{20}N_2O$ requires: C, 65·22; H, 10·86; N, 15·22%.
[b] $C_{11}H_{22}N_2O$ requires: C, 66·62; H, 11·18; N, 14·13%.
[c] $C_{12}H_{24}N_2O$ requires: C, 67·88; H, 11·39; N, 13·19%.
[d] $C_{13}H_{26}N_2O$ requires: C, 69·88; H, 11·58; N, 12·38%.

solution and the mixture shaken for 30 min at room temperature. This was then basified with ice cold aqueous sodium hydroxide solution and ether extracted. The extract was dried (Na_2SO_4), concentrated and distilled. Products are shown in Table 9.

Acknowledgement—This work has been carried out with the support of Procurement Executive, Ministry of Defence.

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