Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part XXVII.[1] Configurational and Conformational Studies with Derivatives of Perhydro-oxazolo[3,4-*d*][1,4]oxazine

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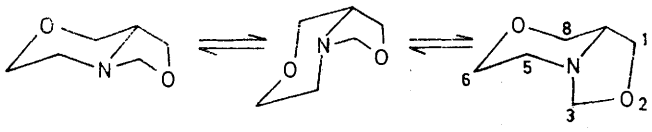
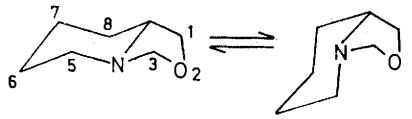
Replacement of the 7-methylene group in perhydro-oxazolo[3,4-*a*]pyridine by an oxygen atom markedly increases the proportion of *cis*-fused conformer in the cis ⇌ *trans*-fused ring conformational equilibrium from *ca.* 30% to *ca.* 86%. This result is interpreted largely in terms of differences in non-bonded interactions, but changes in ring-fusion strain also appear to be important.

PERHYDRO-OXAZOLO[3,4-*d*][1,4]OXAZINE may exist in solution as an equilibrium mixture of the *trans*-fused conformer (1) and the two *cis*-fused conformers (2) and (3), interconvertible by nitrogen inversion and/or ring reversal. Dominant among the interactions influencing the position of conformational equilibrium is that arising from the 1,3-arrangement of the heteroatoms in the oxazolidine ring [unfavourable in (1) and (3) as evidenced by, but not necessarily due to, the nearly parallel arrangement of lone pairs [2]]. This interaction is minimised in



(1) (2) (3)



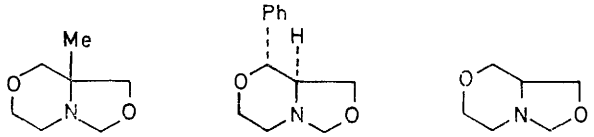
(4) (5)

(2) at the expense of introducing one *gauche* butane interaction and two new *syn*-axial interactions between the oxygen atoms and methylene groups [C(5)–O(2) and C(1)–O(7)]. Conformation (3) may be neglected since this suffers from additional non-bonded interactions and still retains the unfavourable 1,3-heteroatom interaction. Thus, *a priori*, perhydro-oxazolo[3,4-*d*][1,4]oxazine might be expected to exist as an equilibrium (1) ⇌ (2) with perhaps more of the *cis* conformation than in the related (4) ⇌ (5) equilibrium [3,4] since the C(1)–O(7) interaction in (2) is considered [5] to be less than the C(1)–C(7) interaction in (5). However, a number of other factors such as changes in ring-fusion strain (*cf. cis* ⇌ *trans* hydrindan equilibrium [6]) in (1) compared with that in (4) might also affect the position of conformational equilibrium, and it was with the intention of obtaining, albeit indirect, evidence for these more subtle effects that this work was undertaken.

Synthesis of Compounds.—8a-Methylperhydro-oxazolo[3,4-*d*][1,4]oxazine (6) has been previously prepared,[7] but no stereochemical studies on the compound have been reported. Reaction between 2-amino-2-methylpropane-1,3-diol and ethyl chloroacetate in basic medium produced 3-hydroxymethyl-3-methylmorpholin-5-one. This was reduced with lithium aluminium hydride and the resulting carbinol ring-closed with formaldehyde to form the required oxazolo-oxazine (6). The same procedure was repeated starting from *threo*-2-amino-1-phenylpropane-1,3-diol when only one product was obtained. N.m.r. spectral data described below were consistent with it being *c*-8-phenyl-*r*-8a*H*-perhydro-oxazolo[3,4-*d*][1,4]-oxazine (7).

Synthesis of the unsubstituted oxazolo-oxazine (8) was achieved by following the same synthetic path starting from crude 2-aminopropane-1,3-diol.[8]

Assignment of Configuration and Preferred Conformations to the Perhydro-oxazolo[3,4-d][1,4]*oxazines.*—(i) *I.r. spectra.* The phenyl perhydro-oxazolo[3,4-*d*][1,4]oxazine, which must be either the *c*-8-phenyl-*r*-8a*H* or the *c*-1-phenyl-*r*-8a*H* compound, having been prepared from *threo*-2-amino-1-phenylpropane-1,3-diol, showed marked absorption in the Bohlmann region of its i.r. spectrum (2800—2600 cm^{-1}). In contrast, the 8a-methyl compound (6) showed only very weak bands in this region. Since strong Bohlmann bands are shown only by compounds which exist predominantly in conformations in

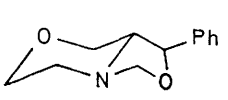


(6) (7) (8)

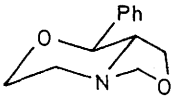
which there are two axial C–H bonds adjacent and *trans* to a nitrogen lone pair of electrons,[9] then the i.r. spectral evidence shows the phenyl compound to exist predominantly as (9) or (10) and the 8a-methyl compound as (11) or (12). *A priori* considerations suggest that (11) is more probably the preferred conformation of the 8a-methyl compound since this suffers less from non-bonded

[1] Part XXVI, T. A. Crabb, M. J. Hall, and R. O. Williams, *Tetrahedron*, 1973, **29**, 3389.
[2] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136; H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.
[3] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 1997.
[4] Y. Takeuchi, P. J. Chivers, and T. A. Crabb, *J.C.S. Chem. Comm.*, 1974, 210.
[5] E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.
[6] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1967.
[7] M. Rink and H. Jakobiedess, *Arch. Pharm.*, 1964, **297**, 632.
[8] H. Schlenk and B. W. deHaas, *J. Amer. Chem. Soc.*, 1951, **73**, 3921.
[9] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.

interactions than does (12), and is favoured by the generalised anomeric effect.[2] The unsubstituted perhydro-oxazolo-oxazine (8) also shows only weak absorption in the Bohlmann region of the i.r. suggesting that this too exists predominantly in a *cis*-fused conformation.



(9)



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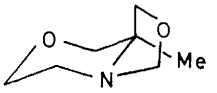

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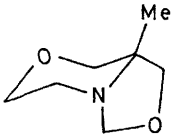
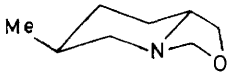


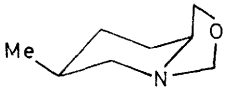
(12)

(ii) *N.m.r. spectra.* (*a*) Perhydro-oxazolo[3,4-*d*][1,4]-oxazine (8). The n.m.r. spectrum of (8) (Table) showed an AB quartet for the C(3) protons with a J_{gem}* value of −5·3 Hz. The J_{gem} values for the NCH_2O protons in the related compounds (13),[3] (14),[3] and (15),[10] which correspond to the three possible conformations (1), (2), and (3), of (8) are shown beneath their structures. Clearly the value of $J_{3ax',3eq'}$ in (8) suggests that it exists predominantly in conformation (2), a result which agrees with the i.r. evidence for a *cis*-fused conformation.



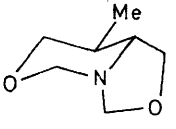
$J_{3ax',3eq'}$ −0.8 Hz

(13)



$J_{3ax',3eq'}$ −5.0 Hz

(14)



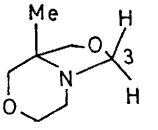
$J_{3ax',3eq'}$ −0.9 Hz

(15)

The only other signals which permit analysis are those at δ 4·08 and 4·21 due to the C(5) protons. Coupling constant data show that the former signals are attributable to 5*eq*-H and the latter to 5*ax*-H. This reversal from the usual relative chemical shift positions of geminal protons β to a ring oxygen atom has been previously encountered in certain 1,3-dioxans [11] and for the C(8) protons in perhydro-oxazolo[3,4-*c*][1,3]oxazines.[10] The value of J_{gem} (−10·9 Hz) for the C(5) methylene protons favours conformer (2) rather than (3) since the bisecting lone pair—C(5)-methylene geometry present in the latter conformation would be characterised by a more negative value of J_{gem}.[12]

(*b*) 8a-Methylperhydro-oxazolo[3,4-*d*][1,4]oxazine (6). The value of J_{gem} (−5·8 Hz) for the C(3) methylene protons in the spectrum of (6) confirms the *a priori* suggestion that the preferred *cis*-fused conformation is (11). This assignation is supported by the chemical shift of 8*ax*-H (δ 3·25), at somewhat higher field than for C(2)-H_{ax} in previously studied morpholines (δ 3·55).[13] This must be due to an equatorial orientation of the vicinal methyl group since this leads [14] to shielding of 8*ax*-H, and, to a far lesser extent to some deshielding of this proton by the vicinal axial C(1) methylene group. Hence the overall effect in (11) is, as observed, a shielding of 8*ax*-H. These effects [with the C(1) methylene now shielding and the C(8) methyl deshielding] will also operate in (12) but in this conformation there will be an additional deshielding due to the *syn*-axial C(3) methylene group, the overall consequence, therefore, being a deshielding of 8*ax*-H, which is not observed. 6*ax*-H also appears at higher field than expected in a simple morpholine derivative and this rules out conformation (12) since here 6*ax*-H would be deshielded by the axial C(3) methylene.

A Dreiding model of (11) shows that, with respect to the pseudoaxial C(3)-methylene proton, the methyl group at C(8a) is almost *syn*-axial (16) suggesting that deshielding should be experienced by this proton. Deshielding



(16)

220 MHz N.m.r. spectra (CCl_4 solution) of the perhydro-oxazolo[3,4-*d*][1,4]oxazines

Coupling constants (Hz)

Compound	$J_{1ax',1eq'}$	$J_{3ax',3eq'}$	$J_{5ax,5eq}$	$J_{6ax,6eq}$	$J_{8ax,8eq}$	$J_{5ax,6ax}$	$J_{5ax,6eq}$	$J_{5eq,6ax}$	$J_{5eq,6eq}$	$J_{8a,1ax'}$	$J_{8a,1eq'}$	$J_{8a,8ax}$	$^4J_{6eq,8eq}$
(8)		−5·3	−10·9			10·7	3·6	2·7	2·7				
(6)	−6·9	−5·8	−11·4	−11·4	−12·1	11·4	3·8	2·3	2·1				1·1
(7)	−7·1	−1·2	−10·8	−11·0		10·9	3·6	2·8	1·9	9·8	5·6	8·6	

Chemical shifts (δ)

Compound	1*eq'*-H	1*ax'*-H	3*ax'*-H	3*eq'*-H	5*ax*-H	5*eq*-H	6*ax*-H	6*eq*-H	8*ax*-H	8*eq*-H	(8a)-H	(8a)-Me
(8)			4·21	4·08	2·63	2·29						
(6)	3·81	3·21	4·49	4·12	2·62	2·23	3·30	3·50	3·25	3·41		0·73
(7)	3·54	3·46	4·53	3·80	2·43	2·85	3·70	3·91	4·25		2·36	

* Throughout this paper J_{gem} is assumed to be negative.

[10] T. A. Crabb and M. J. Hall, *J.C.S. Perkin II*, 1973, 1379.

[11] K. Pihlaja and P. Äyräs, *Acta Chem. Scand.*, 1970, **24**, 531, and references cited therein.

[12] P. J. Chivers and T. A. Crabb, *Tetrahedron*, 1970, **26**, 3389.

[13] W. Brügel, *Org. Magnetic Resonance*, 1969, **1**, 425.

[14] H. Booth, *Tetrahedron*, 1966, **22**, 615.

compared with the unsubstituted parent compound is indeed observed for the lower field C(3) proton of this compound (Table). Both C(3) protons in (12) however, are far from the vicinity of the methyl group, implying that little change in the chemical shifts from those observed in the unsubstituted compound would be expected, were this conformation preferred. Thus all the evidence points to (11) as the preferred conformation for the 8a-methyl compound.

A noteworthy feature of the n.m.r. spectrum of this compound was the extremely clear evidence of a long range coupling of |1·1| Hz involving the 6*eq*-H. This was shown to be a result of coupling between 6*eq*- and 8*eq*-H since the peak widths at half height of the broadened doublet (δ 3·41, J −12·1 Hz) arising from the latter proton were consistent with a ^4J value of |1·1| Hz. Long range couplings of this type are well known.[11,15] Like the unsubstituted perhydro-oxazolo[3,4-*d*][1,4]oxazine, the signals due to the C(5) protons in (6) are unusual in that 5*ax*-H absorbs at lower field (δ 2·62) than 5*eq*-H (δ 2·23).

(*c*) *c*-8-Phenyl-*r*-8a*H*-perhydro-oxazolo[3,4-*d*][1,4]-oxazine (7). Besides assigning the preferred conformation to the compound obtained from *threo*-2-amino-1-phenylpropane-1,3-diol the 1- or 8-location of the phenyl group must also be ascertained. The i.r. evidence presented above has already indicated a *trans*-fused conformation and this is confirmed by the value of J_{gem} for the C(3) protons (−1·2 Hz). Therefore the two possible stereochemistries for this compound are (9) and (10).

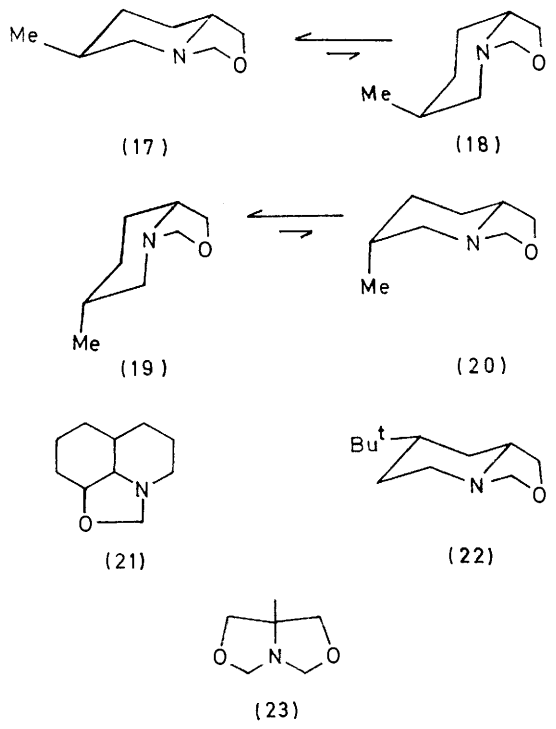
The 220 MHz n.m.r. spectrum of the phenyl substituted compound is summarised in the Table. The spectrum is almost completely analysable by first order methods, the exceptional portion being the two proton multiplet at δ 3·43—3·58 which approximates to the AB part of an ABX system, the X portion being those signals centred at δ 2·36.

The signals corresponding to the C(5) and C(6) protons were readily assigned from the values of the coupling constants and from the expected lower field absorption of the C(6) than the C(5) protons. The values obtained were of the order expected of a six-membered chair. Notably absent from the spectrum, however, was a ^4J involving 6*eq*-H. This was taken as a strong indication of the absence of an 8*eq*-H which would couple with 6*eq*-H (planar W stereochemistry) as was observed in the spectrum of the 8a-methyl compound. Thus the phenyl group must occupy the equatorial position at C(8).

Further evidence is given by analysis of the 'ABX' system referred to above. The AB portion yields J_{AB} |7·1| Hz, and this is of the order expected of $J_{1ax',1eq'}$ in (9). In addition, J_{AX} and J_{BX} (9·8 and 5·6 Hz respectively) approximately correspond to values of $J_{(8a)ax,1ax'}$ and $J_{(8a)ax,1eq'}$ in *trans*-fused perhydro-oxazolo[3,4-*a*] pyridines [*e.g.* (13)].[3] Analysis of the 'X' signals show X to be coupled to the proton giving rise to the doublet (J 8·7 Hz) centred at δ 4·25. Thus X is the proton on C(8a) and the signal at δ 4·25 is due to 8*ax*-H. The value of $J_{8ax,(8a)ax}$ (8·7 Hz) is typical of an axial–axial coupling in this type of structure.

The accumulated evidence thus shows the phenyl substituted compound to be *c*-8-phenyl-*r*-8a*H*-perhydro-oxazolo[3,4-*d*][1,4]oxazine existing predominantly as its *trans*-fused conformer (10).

Discussion of Results and Detailed Conformational Analysis.—The position of equilibrium (4) ⇌ (5) for perhydro-oxazolo[3,4-*a*]pyridine has been estimated by ^{1}H and ^{13}C n.m.r. spectroscopy as favouring 62—65% (4) [3] and 76% (4) [4] respectively. The estimate from ^{1}H n.m.r. work was originally based on a comparison of the J_{gem} and $\delta_{ax} - \delta_{eq}$ ($\Delta_{ax,eq}$) values for the NCH_2O protons

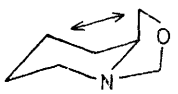


in (17) and (19), on the assumption that these are anancomeric derivatives, with the corresponding parameters in perhydro-oxazolo[3,4-*a*]pyridine (J_{gem} −2·4 Hz, $\Delta_{ax,eq}$ 0·58 p.p.m.). The weakness of this approach lies in the assumption regarding the percentage of (17) and of (19) in their respective equilibria. The value of −0·8 Hz, however, does seem reasonable for a *trans*-fused derivative since both the *trans*-locked derivative (21) and the anancomeric t-butyl compound (22) show J_{gem} values of −0·8 Hz identical with that observed for (17) ⇌ (18). The position of equilibrium (19) ⇌ (20) is more difficult to estimate in the absence of suitable locked compounds. Recent work on perhydro-oxazolo[3,4-*c*]oxazoles (23) [1] shows J_{gem} values for the C(3) methylene protons ranging from −6·0 to −7·8 Hz and the J_{gem} C(3) values for (6) and (8) (−5·8 and −5·3 Hz respectively) are also more negative than that in the 'model' compound (14) suggesting that there is a substantial amount of (20) in the (19) ⇌ (20) equilibrium mixture. In an attempt

[15] M. Barfield and B. Chakrabarti, *Chem. Rev.*, 1969, **69**, 757.

to obtain the value of J_{gem} for (19) its spectrum was recorded at 220 MHz and at −90° but even under these conditions the equilibrium was not ' frozen out.' However, the J_{gem} value had decreased to −6·0 Hz and if this is taken as the value for (19) then ΔG_{298}^0 for the (19) ⇌ (20) equilibrium may be estimated as +0·82 kcal mol^{-1} (80% *cis*) and ΔG_{298}^0 for the (5) ⇌ (4) equilibrium as −0·44 kcal mol^{-1} (32% *cis*). An examination of non-bonded interactions in these four structures shows that the difference in the ΔG^0 values should approximate to the sum of one *gauche* butane interaction (*ca.* 0·85 kcal mol^{-1}) and one 1,3-*syn*-axial methyl–nitrogen lone pair interaction (*ca.* 0·40 kcal mol^{-1}). The difference in the estimated values of ΔG^0 of 0·82 − (−0·44) = 1·26 kcal mol^{-1} then appears reasonable.

Using the value of −6·0 Hz for J_{gem} in (19), the position of equilibrium in the parent perhydro-oxazolo[3,4-*d*][1,4]-oxazine (8) may be estimated from its J_{gem} value of −5·3 Hz as 86% *cis* conformation (ΔG_{298}^0 for the *cis* ⇌ *trans* equilibrium of +1·07 kcal mol^{-1}). Again, examination of Dreiding models suggests that the difference in ΔG^0 for the latter equilibrium and for the (5) ⇌ (4) equilibrium (*viz.* 1·07 − (−0·44) = +1·51 kcal mol^{-1}) should be approximately equivalent to the difference between the *gauche* butane interaction and the *syn*-axial C(1) methylene–oxygen atom interaction shown in (24) and (25). In the absence of other data the value of +1·51 kcal mol^{-1} would indicate an attractive interaction between the C(1) methylene and the 7-oxygen atom in (25). However, the total interaction in axial 5-methyl-1,3-dioxan is *ca.* 0·8 kcal mol^{-1} which has been ascribed [5] to the interactions of the methyl group with the two oxygen atoms There would appear therefore to be an additional effect operating to destabilise (1) relative to



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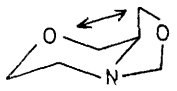

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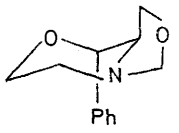

(26)

(2) and this may arise from ring-fusion strain present in *trans*-fused ring conformations.[6] The *trans*-fused ring conformations (1) and (4) must both be subject to some ring-fusion strain and the smaller oxazine ring in (1) compared with the piperidine ring in (4) may have greater resistance to *trans*-fusion with the oxazolidine ring.

The J_{gem} value of −1·2 Hz for the C(3) methylene protons in the 8-phenyl compound (7) indicates its existence in solution as *ca.* 8% *cis*-fused ring conformer (26) in equilibrium with the *trans*-fused conformer (10). On the basis of the estimated ΔG^0 of 1·07 kcal mol^{-1} for the *cis* ⇌ *trans* equilibrium (2) ⇌ (1) a higher percentage of (26) might have been expected. Trans-annular interatomic distances in the 1,3-oxazine ring, however, are different from those in cyclohexane so that the *syn*-axial phenyl–C(6)-H interaction in (26) may be much greater than the 1—1·5 kcal mol^{-1} for a similar interaction in an axially substituted phenyl cyclohexane.

EXPERIMENTAL

Elemental analyses were carried out by Drs. F. and E. Pascher, Microanalytical Laboratory, Bonn, Germany, and also by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. I.r. spectra were recorded on a Perkin-Elmer 457 grating instrument for 0·2M solutions using 0·2 mm matched cells. The n.m.r. spectra were determined on Varian T60 and HR-220 MHz spectrometers as 10% solutions with Me_4Si as internal reference.

2-Aminopropane-1,3-diols.— 2-Amino-2-methylpropane-1,3-diol and *threo*-2-amino-1-phenylpropane-1,3-diol were obtained commercially. 2-Aminopropane-1,3-diol was prepared by treating commercial nitromethane with paraformaldehyde in the presence of a catalytic amount of sodium hydroxide.[8] When solution was complete, sodium methoxide solution was added to precipitate the sodium salt of 2-nitropropane-1,3-diol. After cooling to 0 °C for 24 h the solid was filtered off and dried. Treatment of the sodium salt in water with oxalic acid, followed by removal of the oxalates formed and then the solvent, yielded 2-nitropropane-1,3-diol which was hydrogenated in the presence of Raney nickel at 50 lb in^{-2} in glacial acetic acid until the theoretical amount of hydrogen had been absorbed. Removal of catalyst and solvent gave a yellow, hygroscopic oil which was used immediately.

General Procedure for Preparation of 3-Hydroxymethylmorpholin-5-ones.—The appropriate 2-aminopropane-1,3-diol (0·3 mol) was dissolved in absolute ethanol (1 l) and sodium metal (0·65 g atom) was added to the solution. When all the metal had reacted the mixture was vigorously stirred while ethyl chloracetate (0·66 mol) was added dropwise over 2 h. The mixture was refluxed for 5 h and then allowed to cool. The resulting sodium chloride was filtered off and the solvent removed leaving the products as viscous yellow syrups.

3-Hydroxymethyl-3-methylmorpholin-5-one was obtained from 2-amino-2-methylpropane-1,3-diol. The syrup, on trituration with a trace of ethanol-ether, gave a solid which was recrystallised from toluene–tetrahydrofuran to give fine white granular crystals (35·4 g, 81%), m.p. 127·5—129° (lit.,[7] 129°) (Found: C, 49·6; H, 7·9; N, 9·8. Calc. for $C_6H_{11}NO_3$: C, 49·6; H, 7·6; N, 9·65%).

3-(α-Hydroxybenzyl)morpholin-5-one was prepared from racemic *threo*-2-amino-1-phenylpropane-1,3-diol. On trituration with ether the orange-yellow oil solidified rapidly. Recrystallisation from tetrahydrofuran gave white granular crystals (39·7 g, 64%), m.p. 184—185° (Found: C, 63·8; H, 6·2; N, 7·0. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%).

3-Hydroxymethylmorpholin-5-one was obtained from crude 2-aminopropane-1,3-diol as an orange oil which could not be crystallised and so was reduced directly.

General Procedure for Preparation of 3-Hydroxymethylmorpholines.—The hydroxymorpholin-5-one (0·1 mol) dissolved in dry tetrahydrofuran (300 ml) was added dropwise to a cooled slurry of lithium aluminium hydride (0·05 mol) in dry tetrahydrofuran (500 ml) at such a rate that steady reflux was maintained. The mixture was refluxed overnight and then allowed to cool. Water (30 ml) was added dropwise

and the grey mixture stirred for 24 h by which time the solids had turned white. These were filtered off and washed with ether. The combined liquids were dried (Na_2SO_4) and concentrated to give the products as pale yellow oils.

3-Hydroxymethyl-3-methylmorpholine was obtained from 3-hydroxymethyl-3-methylmorpholin-5-one as a pale yellow liquid which distilled at 132—134° at 15 mmHg as a syrup (9·8 g, 75%) (lit.,[7] 114—115° at 10 mmHg) (Found: C, 55·15; H, 10·1; N, 10·5. Calc. for $C_6H_{13}NO_2$: C, 54·9; H, 10·0; N, 10·7%).

3-(α-Hydroxybenzyl)morpholine was prepared from 3-(α-hydroxybenzyl)morpholin-5-one as a pale yellow oil. Distillation at 127—129° and 0·05 mmHg gave a highly viscous syrup (13·7 g, 71%) (Found: C, 68·1; H, 7·8; N, 7·3. $C_{11}H_{15}NO_2$ requires C, 68·4; H, 7·8; N, 7·25%).

3-Hydroxymethylmorpholine was obtained from the crude 3-hydroxymethylmorpholin-5-one as a pale yellow oil. The fraction of b.p. 103—120° at 5 mmHg was collected as an oil. Analytical g.l.c. showed two major components, so ring closure was carried out without further purification.

General Procedure for Preparation of Perhydro-oxazolo[3,4-d][1,4]*oxazines*.—The hydroxymorpholine (0·05 mol) was mixed with a slight excess of 37% aqueous formaldehyde solution and shaken. Initially the mixture became very warm and was cooled under the tap. Shaking was continued for 15 min. The mixture was then basified with concentrated aqueous NaOH and immediately extracted three times with ether. The combined extracts were dried (Na_2SO_4) and concentrated.

8a-Methylperhydro-oxazolo[3,4-*d*][1,4]oxazine was prepared from 3-hydroxymethyl-3-methylmorpholine as a pale yellow oil. Distillation gave pure product, b.p. 82·5—83·5° at 12·5 mmHg (5·9 g, 82%), n_{25}^{D} 1·4702 (lit.,[7] b.p. 82—83° at 12 mmHg) (Found: C, 58·9; H, 9·4; N, 9·75. Calc. for $C_7H_{13}NO_2$: C, 58·7; H, 9·15; N, 9·8%).

1-*Phenylperhydro-oxazolo*[3,4-d][1,4]*oxazine* was prepared from 3-(α-hydroxybenzyl)morpholine as a liquid. Distillation gave a fraction, b.p. 115·5° at 0·5 mmHg, n_{25}^{D} 1·5457, which solidified, m.p. 40—41° (Found: C 70·1; H, 7·6; N, 6·7. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%).

Perhydro-oxazolo[3,4-*d*][1,4]oxazine was obtained from the crude 3-hydroxymethylmorpholine as a yellow oil. Analytical g.l.c. on a polypropylene glycol column showed two major components in the ratio *ca.* 3 : 1. Preparative g.l.c. (using a 15 ft column of 15% Ucon 50 HB 2000 on JJ ' C ' 60—70 BSS mesh support in a Pye series 105 instrument at 150 °C) was used to separate these components: the required product was the minor of the two (shorter retention time). Only enough material to allow the recording of the n.m.r. and i.r. spectra was obtained by this method.

[4/443 *Received, 7th March,* 1974]