Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen Atoms. Part XXV.[1] The Stereochemistry and ^1H Nuclear Magnetic Resonance Spectra of Some Perhydro-oxazolo[3,4-*c*]oxazines and Perhydro[1,3]oxazino[3,4-*c*][1,3]oxazines

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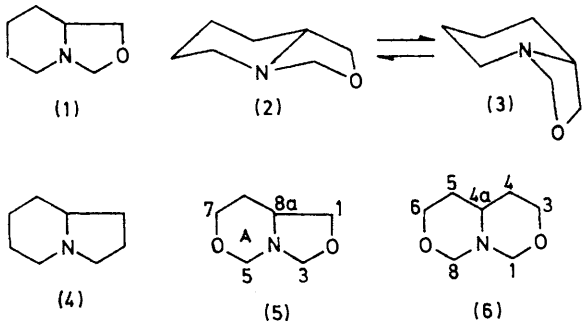
The configurations and preferred conformations of a number of perhydro-oxazolo[3,4-*c*]oxazines and perhydro-[1,3]oxazino[3,4-*c*][1,3]oxazines have been assigned on the basis of their n.m.r. spectra. The conformational preferences of these compounds have been interpreted in terms of the minimisation of dipolar type interactions arising from the 1,3 arrangements of the heteroatoms.

PREVIOUS work [2] has shown perhydro-oxazolo[3,4-*a*]-pyridine (1) to exist in solution at room temperature as an equilibrium mixture of the *trans*-fused (2) and the *cis*-fused (3) conformations with a ΔG^0 for the *cis* $\rightleftharpoons$ *trans* equilibrium of $-0{\cdot}24$ kcal mol^{-1}. This is in contrast to the situation for indolizidine (4) where $\Delta G^0 = -2{\cdot}4$ kcal mol^{-1} for the *cis* $\rightleftharpoons$ *trans* equilibrium [3] measured at 25°. This difference between the two systems as a result of the introduction of the oxygen atom must be due in part to unfavourable dipolar type interactions [4,5] present in (2) which are minimised in (3) and also to differences in non-bonded interactions and in the strain involved in the *trans*-fusion of a six- to a five-membered ring (*cf. cis* $\rightleftharpoons$ *trans*-hydrindane equilibrium).[6] In order to study these effects further some

[1] Part XXIV, T. A. Crabb, P. J. Chivers, and R. F. Newton, *Org. Magnetic Resonance*, in the press.
[2] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 1997.
[3] H. S. Aaron and C. Ferguson, *Tetrahedron Letters*, 1968, 6191.
[4] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.
[5] H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.
[6] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison. ' Conformational Analysis,' Interscience, New York, 1965, p. 228,

perhydro-oxazolo[3,4-*c*]oxazines (5) and perhydro[1,3]-oxazino[3,4-*c*][1,3]oxazines (6) were selected since in *trans*-fused (5) two unfavourable dipolar effects are



operative and in addition some of the non-bonded CH–CH interactions present in (1) have been replaced [in (5)] by oxygen lone pair–C–H interactions and there will be an increase in puckering of ring A in (5) resulting from the shorter C–O bond.[7] This latter effect should influence the strain arising from the six- to five-membered ring *trans*-fusion. System (6) was selected for comparative purposes.

Syntheses.—(a) *Perhydro-oxazolo*[3,4-c][1,3]*oxazines*. Aspartic acid was esterified with n-butanol and the hydrochloride of the resultant ester reduced [8] to provide racemic 2-aminobutane-1,4-diol. Condensation of this amino-diol with two molecular equivalents of 40% aqueous formaldehyde gave the required perhydro-oxazolo[3,4-*c*][1,3]oxazine (5).

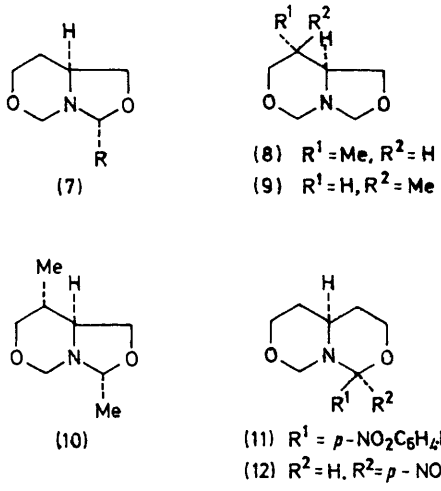
One isomer of 3-methylperhydro-oxazolo[3,4-*c*][1,3]-oxazine (7; R = Me) was prepared by treatment of racemic 2-aminobutane-1,4-diol with one mol. equiv. of acetaldehyde followed by the same molar amount of formaldehyde. This yielded a mixture of one of the 3-methyl isomers and unsubstituted perhydro-oxazolo-[3,4-*c*][1,3]oxazine which was separated by preparative g.l.c. to give the pure 3-methyl compound. Treatment of the diol with the aldehydes in the reverse order did not produce the 5-methyl isomer, however, but 3-methyl-perhydro-oxazolo[3,4-*c*][1,3]oxazine was again recovered from a mixture with the unsubstituted compound.

One of the 3-t-butylperhydro-oxazolo[3,4-*c*][1,3]-oxazines (7; R = Bu^t) was prepared in the same way using 2,2-dimethylpropanal in place of acetaldehyde. The pure product was again recovered from a mixture with the unsubstituted compound by preparative g.l.c.

Treatment of racemic 2-aminobutane-1,4-diol with an equimolar amount of *p*-nitrobenzaldehyde in benzene yielded an isomer of 2-(2-*p*-nitrophenyloxazolidin-4-yl)-ethanol as pale yellow crystals. Addition of formaldehyde (one mol. equiv.) to this compound, with warming, produced 3-*p*-nitrophenylperhydro-oxazolo-[3,4-*c*][1,3]oxazine (7; R = *p*-$NO_2C_6H_4$) together with *p*-nitrobenzaldehyde. The product was purified by fractional recrystallisation.

Two isomers of 8-methylperhydro-oxazolo[3,4-*c*][1,3]-oxazine (8) and (9) were prepared from α-methyl-aspartic acid which was itself prepared by reacting diethyl acetamidomalonate with ethyl α-bromopropionate in the presence of base followed by hydrolysis and decarboxylation of the product to give a mixture of the *threo*- and *erythro*-forms of the acid.[9] This was then esterified and reduced to give racemic 2-amino-3-methyl-butane-1,4-diol which was condensed as before with formaldehyde yielding an isomeric mixture of the 8-methylperhydro-oxazolo[3,4-*c*][1,3]oxazines. Analytical g.l.c. showed the mixture to consist of *ca.* 50% of each isomer and these were separated by preparative g.l.c.

Treatment of racemic 2-amino-3-methylbutane-1,4-diol with one mol. equiv. of acetaldehyde followed by the same molar amount of formaldehyde yielded a



mixture of two 3,8-dimethyl compounds and the two 8-methylperhydro-oxazolo[3,4-*c*][1,3]oxazines. Separation by preparative g.l.c. yielded only two pure fractions, the other two having very similar retention times. Those isolated pure were one of the 3,8-dimethyl-perhydro-oxazolo[3,4-*c*][1,3]oxazines (10) and one of the 8-methyl compounds.

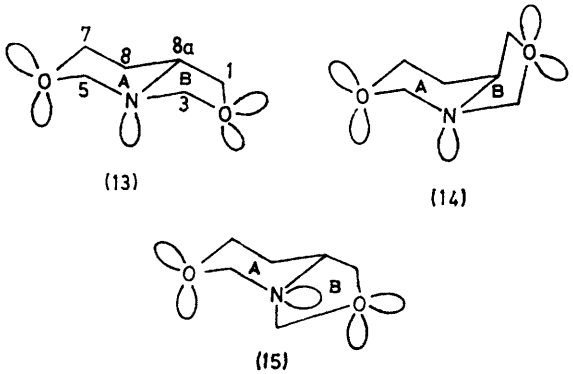
(b) *Perhydro*[1,3]*oxazino*[3,4-c][1,3]*oxazines*. The parent compound (6) was prepared *via* diethyl pent-3-enedioate [10] which was treated with ammoniacal ethyl alcohol [11] and the resulting ethyl β-aminopentanedioate was reduced with lithium aluminium hydride to give 3-aminopentane-1,5-diol. This diol was condensed with two mol. equiv. of formaldehyde to give the required perhydro-oxazino[3,4-*c*][1,3]oxazine.

3-Aminopentane-1,5-diol was condensed with one mol. equiv. of *p*-nitrobenzaldehyde to give 2-(2-*p*-nitrophenylperhydro[1,3]oxazin-4-yl)ethanol as pale yellow needles. This was treated with one mol. equiv.

[7] E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.
[8] G. R. Handrick and E. R. Atkinson, *J. Medicin. Chem.*, 1966, **9**, 558.
[9] G. A. Galegov, M. A. Sergeeva, and S. R. Mardashev, *Biokhimiya*, 1964, **29**, 497.
[10] E. P. Kohler and G. H. Reid, *J. Amer. Chem. Soc.*, 1925, **47**, 2807.
[11] H. Feuer and W. A. Swarts, *J. Amer. Chem. Soc.*, 1955, **77**, 5427.

of formaldehyde, with warming at length, to yield a yellow solid which was subjected to fractional recrystallisation. Three fractions resulted, two being isomers of 1-*p*-nitrophenylperhydro[1,3]oxazino[3,4-*c*]-[1,3]oxazine (11) and (12), the third being *p*-nitrobenzaldehyde.

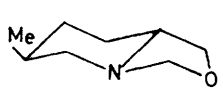
Configurational and Conformational Assignments.—(a) *Perhydro-oxazolo*[3,4-c][1,3]*oxazine.* The parent perhydro-oxazolo[3,4-*c*][1,3]oxazine (5) can exist in three conformations (13)—(15) all interconvertible by nitrogen inversion and ring inversion. An indication of the predominant conformation in solution at room temperature should readily be obtained from the magnitudes



(13)

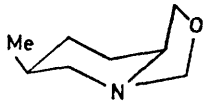
(14)

(15)



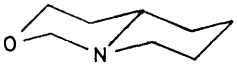
(16)

$J_{3ax-3eq}$ −0·8 Hz



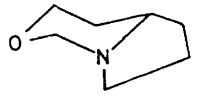
(17)

$J_{3ax-3eq}$ −5·0 Hz



(18)

$J_{1ax-1eq}$ −8·0 Hz



(19)

$J_{1ax-1eq}$ −10·0 Hz

of the geminal coupling constants of the 3- and 5-methylene protons since these are dependent upon the dihedral angles between the C–H bonds and the lone pairs of electrons on the heteroatoms.[12-14] J_{gem} Values for the N–CH_2–O protons in the related compounds (16)—(19) [2,15] range from *ca.* −0·8 to −10·5 Hz. No model compound possessing the correct lone pair–CH_2 geometry corresponding to (15) is available but a Dreiding model of (15) shows a rather similar heteroatom lone pair–methylene bond geometry to that in (16) and so in the absence of the operation of some special effect [*i.e.* rehybridisation of the nitrogen atom in (16) to accommodate strain involved in the *trans*-ring fusion] a J_{gem} value of −0·8 Hz for conformation (15) would be expected. Unfortunately, the 5-methylene signals in the n.m.r. spectrum of (5) appeared as a singlet in a wide variety of solvents but the J_{gem} value of −0·9 Hz for the 3-methylene protons clearly eliminated conformation (14). The remainder of the n.m.r. spectrum was then analysed by first-order methods to give the coupling constants shown in Table 1 and the chemical shifts shown in Table 2.

All the line separations involving the 7-, 8-, and 8a-protons are typical of a chair conformation for the six-membered ring and those between the 8- and 8a-protons (10·5 and 4·8 Hz) show the 8a-proton to be axially orientated with respect to this ring. The line separation of 10·5 Hz which approximates to an axial–axial coupling rules out (14) as a major component of the equilibrium mixture since in this conformation the 8a-proton is equatorial.

Having ruled out the presence of (14) on the basis of J_{gem} values and vicinal couplings between 8- and 8a-H the vicinal couplings between 8a-H and the 1-methylene protons were examined. In the related *trans*-fused perhydro-oxazolo[3,4-*a*]pyridines [2] [*e.g.* (16)], $J_{1\alpha,(8a)ax}$ averaged at *ca.* 6·1 Hz and $J_{1\beta,(8a)ax}$ at *ca.* 9·7 Hz, but in perhydro-oxazolo[3,4-*c*]oxazine (5) the corresponding couplings are 5·0 and 1·3 Hz. Since there is no reason for the vicinal couplings in (16) to be any different from those in the *trans*-fused conformation (13) this rules out conformation (13) and by elimination shows (15) to be the predominant conformation. Inspection of Dreiding models shows the dihedral angles between the 1-protons and 8a-H in (15) to be approximately 80 and 40°, which, according to the Karplus relationship [16] corresponds with values for J_{vic} of *ca.* 5 and 0 Hz respectively, a reasonable correlation confirming the existence of (5) in conformation (15).

The final piece of evidence required to provide unequivocal confirmation of conformation (15) was the J_{gem} value of the 5-methylene protons since in (13) and (14) this should be *ca.* −8 Hz [*cf.* (18)] and in (15) −10·5 Hz [*cf.* (19)]. As stated before, the 5-methylene protons absorbed as a singlet in a variety of solvents, so recourse to the n.m.r. shift reagent, tris(dipivaloylmethanato)europium Eu(dpm)$_3$, was made. This reagent was added in small (*ca.* 5 mg) portions to a carbon tetrachloride solution of (5) and allowed to dissolve completely. After ten such additions the 3β-proton was observed to be moving downfield from under the 5-methylene singlet. By the nineteenth addition, this singlet was itself seen to be slightly split and very small wings were observed. A further two portions of Eu(dpm)$_3$, and employment of different spin rates in order to avoid confusion with spinning sidebands, confirmed this observation, and the J_{gem} value was measured as −11·2 Hz. It is possible that complexing with the shift reagent may have altered both the J value and the position of conformational equilibrium. However the magnitudes of the other coupling constants

[12] G. F. Maciel, J. W. McIver, jun., N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 4151.
[13] P. J. Chivers and T. A. Crabb, *Tetrahedron*, 1970, **26**, 3389.
[14] R. Davies and J. Hudec, *J.C.S. Chem. Comm.*, 1972, 124.
[15] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 4423.
[16] M. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.

extracted from the spectrum of the complex do not differ significantly from those obtained from the uncomplexed material, so that it may be regarded as fairly certain that $J_{5ax,5eq}$ is indeed *ca.* −11·2 Hz.

The fact that only very weak bands occur in the 2800—2600 cm^{-1} region of the i.r. spectrum of this compound shows that the Bohlmann criterion [17] is not inapplicable to this system, but whether *trans*-fused derivatives show Bohlmann bands is not known.

(b) 3-*Monosubstituted perhydro-oxazolo*[3,4-c][1,3]-*oxazines* (7).—Only one isomer each of the monosubstituted perhydro-oxazolo[3,4-*c*][1,3]oxazines (with methyl, t-butyl, and *p*-nitrophenyl as substituents) was obtained from the synthetic sequence described above. In addition to establishing the preferred conformations of these compounds it was also necessary to assign the relative configuration of the substituent with respect to the bridgehead proton and to locate the position of the substituent [C(3) or C(5)].

The n.m.r. spectrum ($CDCl_3$) of the mono-*p*-nitrophenyl substituted derivative of (5) shows an AB quartet centred at δ 4·41 with J_{gem} −11·2 Hz which from the values of the chemical shifts must be due either to the 3- or the 5-methylene protons. The value of J_{gem} can only be reconciled with the presence of NCH_2O protons in a six-membered ring and so the *p*-nitrophenyl substituent must be located at C(3) (7; R = *p*-$NO_2C_6H_4$). Similarly the n.m.r. spectrum (CCl_4) of the t-butyl substituted compound shows an AB quartet centred at δ 4·46 with J_{gem} −11·4 Hz and, while the n.m.r. spectrum (CCl_4) of the methyl substituted compound displays only a singlet at *ca.* δ 4·42 without any discernible small wings, the similarity with the spectrum of the t-butyl compound shows it also to be C(3) substituted.

From the magnitude of J_{gem} of the 5-methylene protons of *ca.* −11·3 Hz and the small value (0·2—1·0 Hz) of $J_{(8a)ax,1\beta}$ in all the 3-substituted compounds, their preferred conformation must be as in (20) with the substituent (R) pseudoequatorial. The Bohlmann region of the i.r. spectra of all these compounds displays only weak bands similar to those of the parent compound, thus giving additional evidence for the *cis*-fused conformation.

TABLE 1

N.m.r. spectra [coupling constants (Hz)] of perhydro-oxazolo[3,4-*c*][1,3]oxazines

Compound	Solvent	$J_{5ax,5eq}$	$J_{3ax,3eq}$	$J_{7ax,7eq}$	$J_{8ax,8eq}$	$J_{1\alpha,1\beta}$	$J_{7ax,8ax}$	$J_{7ax,8eq}$	$J_{7eq,8ax}$	$J_{7eq,8eq}$	$J_{8ax,8a}$	$J_{8eq,8a}$	$J_{8a,1\alpha}$	$J_{8a,1\beta}$	$J_{Me,8ax}$	$J_{Me,3\beta}$
(5)	CCl_4 and C_6H_6	(−11·2) *	−0·9	−11·2	−13·4	−7·3	10·8	2·8	5·2	2·8	10·5	4·8	5·0	1·3		
(8)	CCl_4 and C_6H_6		−0·7	−10·9		−7·6	10·9		4·9		10·0		4·8	1·4	6·6	
(9)	CCl_4 and C_6H_6	−7·7	−5·2	−10·9		−7·2	10·0		4·9		0·8		10·2	5·7	7·0	
(7; R = Me)	CCl_4 and C_6H_6			−11·3	−13·2	−7·4	12·2	2·4	5·2	2·2	11·5	4·6	4·9	0·6		5·0
(7; R = But)	CCl_4	−11·4		−11·3	−13·2	−7·3	12·0	2·4	5·6	2·2	11·8	4·8	4·7	*ca.* 0·2		
(21)	C_6H_6	−11·5		−11·1		−7·6	11·2		4·8		10·8		4·9	*ca.* 1·0	6·5	5·1
(7; R = *p*-$NO_2C_6H_4$)	$CDCl_3$	−11·2			−14·5		12·8	2·2	5·6	2·1	12·8	4·2		*ca.* 1·0		

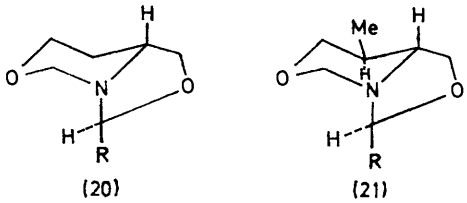
* This coupling constant was obtained by employing $Eu(dpm)_3$.

TABLE 2

N.m.r. spectra [chemical shifts (δ)] of perhydro-oxazolo[3,4-*c*][1,3]oxazines

Compound	Solvent	3α-H	3β-H	5*eq*-H	5*ax*-H	7*eq*-H	1α-H	1β-H	7*ax*-H	8a-H	8*ax*-H	8*eq*-H	8-Me	3-Me
(5)	Benzene	4·70	4·46	4·37	4·37	3·79	3·77	3·46	3·34	3·07	1·67	0·92		
	CCl_4	4·60	4·41	4·41	4·41	3·98	3·88	3·58	3·58	3·35	1·88	1·29		
(8)	Benzene	4·72	4·49	4·31	4·31	3·74	3·84	3·57	2·84	2·55	1·70		0·28	
	CCl_4	4·54	4·38	4·38	4·38		3·98	3·69	3·06	2·82	1·86		0·73	
(9)	Benzene	4·19	4·19	4·26	3·95						2·16		0·41	
	CCl_4	4·31	4·18	4·28	3·99				3·21	3·32	2·34		0·87	
(7; R = Me)	Benzene		5·07	4·42	4·42	3·87	3·88	3·35	3·31	3·08	1·79	0·70		1·19
	CCl_4		4·86	4·41	4·41	4·02	3·94	3·50	3·59		1·97	1·25		1·17
(7; R = But)	CCl_4		4·41	4·56	4·36	4·03	3·82	3·46	3·56		1·92	1·23		
(21)	Benzene		5·00	4·54	4·22	3·81	3·92	3·54	2·92	2·71	1·78		0·33	1·20
(7; R = *p*-$NO_2C_6H_4$)	$CDCl_3$		5·74	4·59	4·22						2·18	1·42		

(c) 8-*Methylperhydro-oxazolo*[3,4-c][1,3]*oxazines*. Two isomers of 8-methylperhydro-oxazolo[3,4-*c*][1,3]oxazine

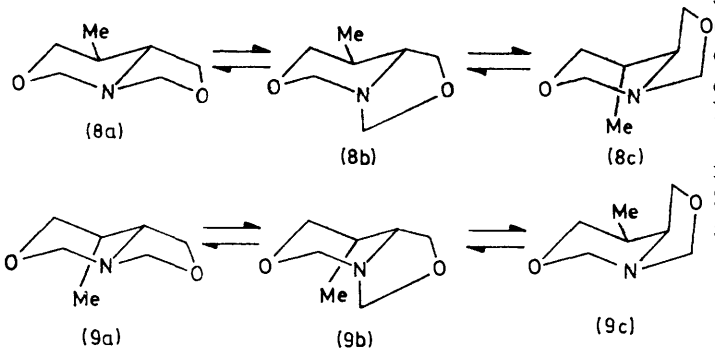


were obtained by the synthetic sequence outlined above, and the possible conformations of the two isomers are shown in Scheme 1. From the foregoing observations the isomer (8) might be expected to possess the stereochemistry (8b), and in fact the n.m.r. evidence (Tables 1 and 2) does permit the assignment of the *trans*(8-H,8a-H)-8-methyl configuration and conformation (8b) to the first fraction off the preparative g.l.c. column.

The second isomer off the column must therefore

[17] G. Bohlmann, *Angew. Chem.*, 1957, **69**, 641; *Chem. Ber.*, 1958, **91**, 2157.

be *cis*(8-H,8a-H)-8-methylperhydro-oxazolo[3,4-*c*][1,3]-oxazine (9) which may exist as an equilibrium mixture of conformations (9a)—(9c), but conformation (9b) may be excluded because of the serious *syn*-axial-Me–methylene interaction. The J_{gem} values for the 5- and



SCHEME 1 The possible conformations of *cis*(8-H,8a-H)- and *trans*-(8-H,8a-H)-8-methylperhydro[1,3]oxazolo[3,4-*c*][1,3]-oxazines

3-methylene protons of this isomer were —7·7 and —5·2 Hz respectively, which immediately (see Table 1) point to (9c) as the preferred conformation. This assignment is confirmed by the unusual (for this series of compounds) value of $J_{(8a),1a}$ of 10·2 Hz and by the lack of strong bands in the Bohlmann region of the i.r. spectrum.

constant (—8·1 Hz) between the 1-protons (and hence also the 8-protons) which is of the order expected [18] for N–CH_2–O protons in a chair tetrahydro[1,3]oxazine ring with the nitrogen lone pair axial and also by the presence of pronounced bands in the Bohlmann range of the i.r. spectrum. A conformational equilibrium between (22) ($J_{1ax,1eq} = J_{8ax,8eq}$ = *ca.* —8·0 Hz) and an appreciable quantity of the *cis*-fused conformation (23) ($J_{1ax,1eq}$ *ca.* —8·0, $J_{8ax,8eq}$ *ca.* —10·5 Hz) would be characterised by a J_{gem} value more negative than —8·0 Hz.

The three possible conformations of each of the two isomers of the 1-*p*-nitrophenyl compound are shown in Scheme 2. The J_{gem} value for the 8-protons of the less soluble isomer (—7·9 Hz) is compatible with (11a), (11c), (12a), and (12c) whereas that of the more soluble isomer (—10·6 Hz) suits (11b) and (12b). Conformation (11b) may be dismissed on the grounds of serious *syn*-axial non-bonded interactions involving the aromatic ring, which suggests that the more soluble isomer is (12b). For this reason the compound must be the *trans*(1-H,4a-H)-1-*p*-nitrophenyl isomer. Additional evidence for the absence of the *trans*-fused conformation is provided by the Bohlmann region of the i.r. where only very weak bands are visible.

By elimination the less soluble isomer must be the *cis*(1-H,4a-H)-1-*p*-nitrophenyl compound and as such

TABLE 3

N.m.r. spectra (benzene solution) of perhydro[1,3]oxazino[3,4-*c*][1,3]oxazines

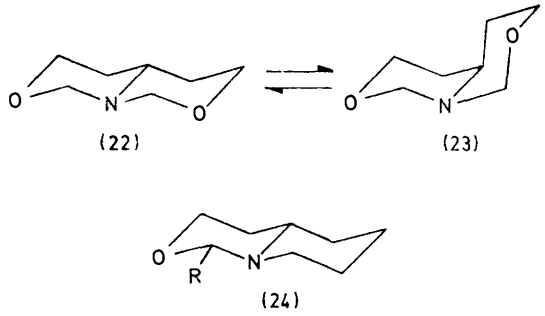
	Coupling constants (Hz)								
Compound	$J_{8ax,8eq}$	$J_{3ax,3eq}$	$J_{4ax,4eq}$	$J_{3ax,4ax}$	$J_{3ax,4eq}$	$J_{3eq,4ax}$	$J_{3eq,4eq}$	$J_{4ax,(4a)ax}$	$J_{4eq,(4a)ax}$
(6)	—8·1	—11·5	—12·8	10·0	3·4	3·9	3·7	9·3	3·6
(11)	—7·9	—11·7	—12·4	11·0	3·2	4·9	1·4		3·5
(12)	—10·6								

	Chemical shifts([δ(p.p.m.)]								
	8*eq*-H	8*ax*-H	3*eq*-H	3*ax*-H	(4a)*ax*-H	4*ax*-H	4*eq*-H	5*eq*-H	1*ax*-H
(6)	4·45	3·64	3·80	3·30	2·30	1·53	1·00	1·00	3·64
(11)	3·92	3·30	*ca.* 3·8	*ca.* 3·3	*ca.* 2·15	*ca.* 1·6	0·87	0·87	4·19
(12)	4·06	3·87	3·8—2·9		2·5—1·6		0·88	0·52	5·43

The only isomer of 3,8-dimethylperhydro-oxazolo-[3,4-*c*][1,3]oxazine obtained in the pure state was assigned the *trans*(8-H,8a-H), *trans*(3-H,8a-H)-configuration since its n.m.r. spectrum showed $J_{5ax,5eq}$ —11·5 Hz indicating the *cis*-fused conformation (21). The 8-methyl substituent in this conformation must be equatorially orientated.

(d) *Perhydro*[1,3]*oxazino*[3,4-c][1,3]*oxazines*. The data obtained from the n.m.r. spectra of these compounds are shown in Table 3. For the parent compound (6) the coupling constants between the 3- and 4-protons (identically situated to 6- and 5-protons) are of the order expected of a tetrahydro[1,3]oxazine ring in the chair conformation. The signal corresponding to the 4a-proton appears as a triplet (J 9·3 Hz, suggesting two axial–axial couplings) of triplets (J 3·6 Hz, suggesting two axial–equatorial couplings) showing that the symmetrical (22) is the preferred conformation. This assignation is confirmed by the geminal coupling

can only be (11a) or (11c). Since the chemical shift of the 1-proton (δ 4·19) is almost identical with that in the corresponding *cis*(1-H,4a-H)-1-*p*-nitrophenylperhydro-[1,3]oxazino[3,4-*a*]pyridine [19] (24) (δ 4·22), conformation



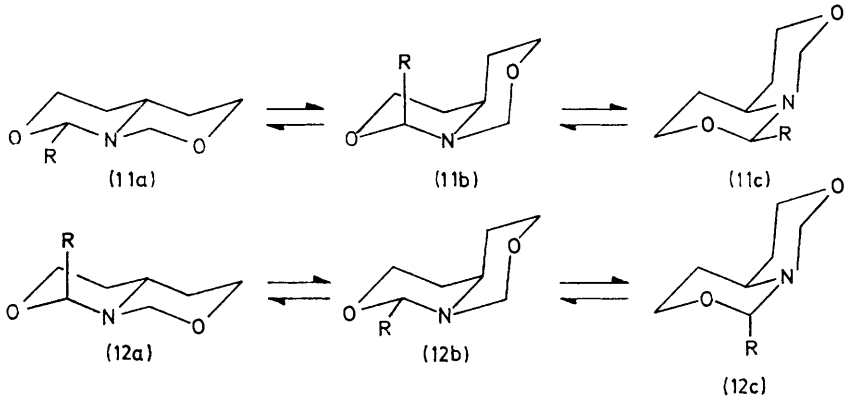
(11a) is assigned to the less soluble isomer. In addition, the chemical shift of the 4a-proton (δ 2·15) rules out (11c),

[18] T. A. Crabb and E. R. Jones, *Tetrahedron*, 1970, **26**, 1217.
[19] T. A. Crabb and J. S. Mitchell, unpublished work.

leaving (11a) as the predominant conformation. This is confirmed by the presence of strong bands in the Bohlmann region of the i.r. spectrum.

DISCUSSION

It is to be expected that the generalised anomeric effect [4,5] will greatly influence the adoption of a preferred conformation by the perhydro-oxazolo[3,4-*c*][1,3]oxazines. As discussed [5] the operation of an unfavourable interaction of this type is evidenced by, but not necessarily due in any great degree to, the presence of parallel lone pairs of electrons. In addition the unfavourable interaction is a complex one which may be considered to be the result of three distinct mechanisms.[20] With these reservations in mind the simple dipolar concept will be adopted in the following discussion since whatever the true nature of the interaction the results of the argument will be the same.



SCHEME 2 The possible conformations of 1-substituted *cis*(1-H,4a-H)- and *trans*(1-H,4a-H)-perhydro[1,3]oxazino[3,4-*c*]-[1,3]oxazines (R = *p*-$NO_2C_6H_4$)

In the *trans*-fused conformation (13) of the parent perhydro-oxazolo[3,4-*c*][1,3]oxazine (5) there are two sets of unfavourable dipolar interactions which may be termed ring A and ring B interactions. Ring A interaction may be relieved in conformation (15) and ring B interaction in (14). Inspection of Dreiding models suggests that the ring A interaction (*ca.* 60° between the directions of the resultant dipoles) is more severe than the ring B interaction (*ca.* 90°). Thus the existence of the parent compound in conformation (15) is explicable since in this conformation it is the more serious dipolar interaction which has been relieved. The *cis*(8-H,8a-H)-8-methyl isomer exists predominately in the alternative *cis*-fused conformation (9c) as it is only in this conformation that the methyl group adopts the energetically more favourable equatorial orientation.

In *trans*-fused perhydro-oxazolo[3,4-*a*]pyridines [*e.g.* (16)] J_{gem} for the 3-methylene protons is −0·8 Hz whereas in *cis*-fused derivatives [*e.g.* (17)] J_{gem} is −5·0 Hz. This is a consequence of the more efficient overlap of the nitrogen lone pair with the antisymmetric molecular orbitals of the methylene group in (16).[21,22] However, J_{gem} in (16) is unusually large being in the same region as that for the 2-methylene protons in 1,3-dioxolan in which the inductive effect on the methylene group must be greater than in (16) and in which there is back donation from four electron pairs rather than from three in (16). One possible explanation for this observation is a flattening of the bonds to nitrogen in (16) in order to accommodate the strain present in the *trans*-fusion (*cf.* *trans*-hydrindane) so that there is a more efficient overlap between the nitrogen lone pair and the adjacent CH bonds. This explanation has been discussed previously [23] but the conclusions were modified in a later publication.[24] Applying the arguments given in connection with *cis*- and *trans*-hydrindane [6] to (5) suggests that (15) should be strain free and yet J_{gem} is the same as in (16). In addition J_{gem} for the 5-methylene proton is −11·2 Hz, a 'normal' value for the lone pair–CH geometry shown in (15). Accordingly it is unnecessary to suggest rehybridisation of the nitrogen atom to account for the large J_{gem} value in (16). In (15) and in (16) there is very near eclipsing of both oxygen lone pair orbitals and the nitrogen lone pair with the adjacent CH bonds, the most favourable geometry for the observation of a large J_{gem} value, and it may simply be that since the nitrogen lone pair is not as tightly held as oxygen lone pairs then transfer of the nitrogen lone pair into the CH_2 antisymmetric orbital is more efficient than from oxygen, and the equality of J_{gem} in fully lone pair eclipsed oxazolidines and in 1,3-dioxolans is 'normal.'

The parent perhydro-oxazino[3,4-*c*][1,3]oxazine (6), like the parent perhydropyrido[1,2-*c*]oxazine (18) exists predominantly in the *trans*-fused conformation as does the *cis*(1-H,4a-H)-1-*p*-nitrophenylperhydro-oxazino-[3,4-*c*][1,3]oxazine, where the substituent is equatorial.

[20] A. J. de Hoog, H. R. Buys, C. Altona, and E. Havinga, *Tetrahedron*, 1969, **25**, 3365.
[21] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 1965, **42**, 1339.
[22] R. C. Cookson, J. J. Frankel, J. Hudec, and T. A. Crabb, *Tetrahedron*, Supplement No. 7, 1966, 355.
[23] T. A. Crabb and R. F. Newton, *Tetrahedron Letters*, 1970, 1551.
[24] R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magnetic Resonance*, 1971, **3**, 263.

Thus the insertion of the additional oxygen atom into (18) does not affect the conformational preferences of the system, whereas the same transposition [*i.e.* (1) to (5)] markedly affects the position of conformational equilibrium. These differences may be rationalised by considering the non-bonded interaction present in the various conformations. Thus alleviation of one of the unfavourable dipolar interactions in (22) by the adoption of the *cis*-fused conformation (23) results in the introduction of two *gauche*-butane and one *gauche*-propanol interaction relative to (22), whereas in the case of (5) relief of the ring A dipolar interaction in (13) was achieved in (15) only at the expense of one *gauche*-butane and one *gauche*-propanol interaction.

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher 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 as 0·2M solutions using 0·2 mm matched cells. The n.m.r. spectra were determined on Perkin-Elmer R10 and Varian T60 spectrometers as 10% solutions with tetramethylsilane as internal reference.

General Procedure for Preparation of the 3-Unsubstituted Perhydro-oxazolo[3,4-c][1,3]oxazines.—The appropriate 2-aminobutane-1,4-diol was shaken with an excess of 36% aqueous formaldehyde solution for 30 min. The mixture was then distilled to give the perhydro-oxazolo[3,4-*c*][1,3]-oxazine. *Perhydro-oxazolo*[3,4-c][1,3]*oxazine* (5·2 g) was obtained from racemic 2-aminobutane-1,4-diol (10·0 g) as an oil, b.p. 102° at 30 mmHg, n_D^{23} 1·4794 (Found: C, 55·7; H, 8·6; N, 11·0. $C_6H_{11}O_2N$ requires C, 55·8; H, 8·6; N, 10·9%), $\nu_{max.}$ 2760 (ε 31) and 2704 (21) cm^{-1}. cis- and trans-(8-H,8a-H)-8-*Methylperhydro-oxazolo*[3,4-c][1,3]*oxazine* (2·4 g) were obtained from racemic 2-amino-3-methylbutane-1,4-diol (4·0 g) as an oil, b.p. 61° at 0·2 mmHg. The epimeric mixture was separated by preparative g.l.c., using a Pye series 105 chromatograph with a 12½% Carbowax 6M column and nitrogen carrier gas. The isomer of shorter retention time was found to be the trans(8-H,8a-H)-8-*methyl compound*, n_D^{23} 1·4696 (Found: C, 58·5; H, 9·1; N, 9·7. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·15; N, 9·8%), $\nu_{max.}$ 2761 (ε 22), 2752 (21), and 2710 (12) cm^{-1}, while that of longer retention time was the cis(8-H,8a-H)-8-*methyl isomer*, n_D^{21} 1·4811 (Found: C, 58·8; H, 9·1; N, 10·0%), $\nu_{max.}$ 2789 (ε 24), 2768 (33), and 2739 (26) cm^{-1}.

Preparation of 3-Substituted Perhydro-oxazolo[3,4-c][1,3]-*oxazines.*— trans(3-H,8a-H)-3-*Methylperhydro-oxazolo*-[3,4-c][1,3]*oxazine*. Racemic 2-aminobutane-1,4-diol (18 g) was dissolved in dry benzene (150 ml) and treated with acetaldehyde (7·6 g). The mixture was first refluxed until the theoretical amount of water (3·1 g) had been removed using a Dean and Stark apparatus and the solvent was removed *in vacuo*, when the residual oil was distilled. The fraction boiling at 91—93° and 0·5 mmHg was collected as a pale yellow mobile oil (15·5 g) which slowly decomposed even when stored under nitrogen at 0 °C. This oil (13·2 g) was shaken with 37% aqueous formaldehyde solution (3·2 g) for 30 min and the resulting mixture was distilled. The pale yellow fraction collected at 127° and 100 mmHg (7·4 g) was redistilled at 50—86° and 0·5 mmHg to give a mobile liquid (6·7 g). Analytical g.l.c. using a Perkin-Elmer F11 instrument with a 12½% Carbowax 1540 column and nitrogen carrier gas showed that this product consisted of two major fractions which were separated on a Pye series 105 chromatograph with a 12½% Carbowax 6M column and nitrogen carrier gas. Comparison of the n.m.r. and i.r. spectra of the fraction of longer retention time with those of an authentic sample of perhydro-oxazolo[3,4-*c*][1,3]-oxazine showed them to be identical. The trans(3-H,8a-H)-3-*methyl compound* which was the fraction of shorter retention time, was collected as a mobile oil, n_D^{23} 1·6817 (Found: C, 58·4; H, 9·1; N, 10·05. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·15; N, 9·8%), $\nu_{max.}$ 2769 (ε 10), 2728 (9), and 2710 (9) cm^{-1}.

trans(3-H,8a-H)-3-*t-Butylperhydro-oxazolo*[3,4-c][1,3]*oxazine*. Racemic 2-aminobutane-1,4-diol (6·5 g) was dissolved in dry benzene (100 ml) and shaken with 2,2-dimethylpropanal (5·3 g) for 30 min. The mixture was refluxed until the theoretical amount of water (1·1 g) had been removed by Dean and Stark apparatus, when the solvent was removed *in vacuo*. The resulting oil (11·7 g) was shaken with a slight excess of 37% aqueous formaldehyde solution for 30 min. The reaction mixture was basified with concentrated aqueous sodium hydroxide solution and extracted with ether three times. The combined extracts were dried (Na_2SO_4), concentrated, and distilled. The fraction boiling at 49·6° and 0·2 mmHg was collected as a mobile oil (2·8 g). G.l.c. using a Perkin-Elmer F11 instrument as described above, showed the sample to consist of two major fractions. Separation was achieved using a Pye series 105 chromatograph as described above. Comparison of the n.m.r. and i.r. spectra of the fraction of shorter retention time with those of an authentic sample of perhydro-oxazolo[3,4-*c*][1,3]oxazine showed them to be identical. The trans(3-H,8a-H)-3-*t-butyl compound*, the fraction of longer retention time, was collected as a mobile oil, n_D^{23} 1·468 (Found: C, 64·7; H, 10·25; N, 7·6. $C_{10}H_{19}O_2N$ requires C, 64·9; H, 10·3; N, 7·6%), $\nu_{max.}$ 2767 (ε 20), 2706 (25), and 2661 (11) cm^{-1}.

trans(3-H,8a-H)-3-p-*Nitrophenylperhydro-oxazolo*[3,4-c]-[1,3]*oxazine*. Racemic 2-aminobutane-1,4-diol (10·5g) was dissolved in dry benzene (150 ml) and *p*-nitrobenzaldehyde (14·1 g) was added. The suspension was shaken, when the temperature rose sharply and the solid changed from discrete crystals into waxy, globular lumps. The mixture was shaken for several hours after which the solid was filtered off and dried *in vacuo*. Recrystallisation from benzene yielded 2-(2-p-*nitrophenyloxazolidin-4-yl*)*ethanol* as bright yellow needles, m.p. 113° (Found: C, 55·3; H, 5·8; N, 11·7. $C_{11}H_{14}O_4N_2$ requires C, 55·45; H, 5·9; N, 11·8%). A sample of these needles (3·0 g) was treated with a slight excess of 37% aqueous formaldehyde solution, when the temperature rose and two layers were observed. On cooling, the lower layer solidified. This was separated and recrystallised from ethanol to give trans(3-H,8a-H)-3-p-*nitrophenyl compound* as fine needles, m.p. 168—169° (Found: C, 57·4; H, 5·7; N, 11·25. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·6; N, 11·2%).

trans(8-H,8a-H),trans(3-H,8a-H)-3,8-*Dimethylperhydro-oxazolo*[3,4-c][1,3]*oxazine*. Racemic 2-amino-3-methylbutane-1,4-diol (2·94 g) was shaken with a mol. equiv. of 37% aqueous formaldehyde solution (2·0 g). The mixture was then shaken with a slight excess of acetaldehyde for 30 min and the resulting oil was distilled. The fraction boiling at 54° and 0·15 mmHg was collected (1·1 g) but analytical g.l.c. using a Perkin-Elmer F11 instrument with

a 20% Apiezon column showed that this fraction consisted of more than two major components. An attempt to separate these using a Pye series 105 chromatograph as described above was made but only two fractions could be obtained in a pure state. That of shorter retention time was collected as a pale yellow oil and identified as the trans-(8-H,8a-H),trans(3-H,8a-H)-3,8-*dimethyl compound* (Found: C, 61·1; H, 9·7; N, 9·1. $C_8H_{15}O_2N$ requires C, 61·1; H, 9·6; N, 8·9%). That of longer retention time was found to have n.m.r. and i.r. spectra identical with those of *trans*-(8-H,8a-H)-8-methylperhydro-oxazolo[3,4-*c*][1,3]oxazine.

Perhydro[1,3]*oxazino*[3,4-c][1,3]*oxazine*.— 3-Aminopentane-1,5-diol (2·7 g) was treated dropwise with 37% aqueous formaldehyde solution in slight excess of two mol. equiv. and shaken for 30 min. Following basification the mixture was extracted three times with ether and the combined extracts were dried (Na_2SO_4), and concentrated. Distillation of the residue gave an oil, b.p. 83° at 0·4 mmHg, which solidified and was recrystallised from light petroleum ether to give *plates* (2·5 g), m.p. 51—52° (Found: C, 58·6; H, 9·3; N, 9·9. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·15; N, 9·8%), $\nu_{max.}$ 2787 (ε 39), 2777 (44), 2758 (39), 2746 (41), 2728 (44), 2707 (36), and 2679 (38) cm^{-1}.

cis- *and* trans(1-H,4a-H)-p-*Nitrophenylperhydro*[1,3]*oxazino*[3,4-c][1,3]*oxazines*.—3-Aminopentane-1,5-diol (3·0 g) was dissolved in dried benzene (50 ml) and *p*-nitrobenzaldehyde (3·8 g) was added. The mixture was refluxed until the calculated amount of water had been collected in a Dean and Stark apparatus. The solution was cooled whereupon pale yellow needles (5·2 g) of 2-(2-*p*-nitrophenylperhydro[1,3]oxazin-4-yl)ethanol crystallised, m.p. 120·5—122°. A further crop (0·35 g) was obtained from the mother liquor. A sample (3·0 g) of this compound was heated on a steam-bath for 3 h with a slight excess of 37% aqueous formaldehyde solution. On cooling a solid separated which was dried *in vacuo*. A n.m.r. spectrum of the crude solid showed it to be a mixture of epimers. The isomers were separated by fractional recrystallisation from benzene–cyclohexane; the cis(1-H,4a-H)-1-p-*nitrophenyl* configuration was assigned to the less soluble isomer, m.p. 146—147·5° (Found: C, 59·3; H, 6·2; N, 10·5. $C_{13}H_{16}N_2O_4$ requires C, 59·1; H, 6·1; N, 10·6%), $\nu_{max.}$ 2791 (ε 49), 2752 (48), 2733 (46), and 2687 (24) cm^{-1} and the trans-(1-H,4a-H)-1-p-*nitrophenyl* configuration to the more soluble isomer, m.p. 115·5—117° (Found: C, 59·2; H, 6·2; N, 10·6%), $\nu_{max.}$ 2795 (ε 12), 2762 (12), and 2721 (13) cm^{-1}. An even less soluble fraction was also separated which was found to be *p*-nitrobenzaldehyde.

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