Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen Atoms. Part XXII.[1] The Stereochemistry and ^{1}H Nuclear Magnetic Resonance Spectra of Some Perhydro-2-methylimidazo[1,5-*a*]-pyridin-1-ones and Perhydro-2-methylpyrido[1,2-*c*]pyrimidin-3-ones

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cis-Fused and *trans*-fused ring conformations have been assigned to a range of perhydro-2-methylimidazo[1,5-*a*]-pyridin-1-ones and perhydro-2-methylpyrido[1,2-*c*]pyrimidin-3-ones from a study of their i.r. and n.m.r. spectra. Unexpectedly the conformational preferences of these compounds and the values of the geminal coupling constants for the methylene group protons situated between the nitrogen atoms are similar to those observed for the corresponding compounds not substituted with a carbonyl function. An unusual long range coupling between 3*ax*'-H and 8a-H of *ca.* 2·5 Hz is shown by the perhydro-2-methylimidazo[1,5-*a*]pyridin-1-ones. *cis*(2-H,3-H)-3,*N*-Dimethyl-2-piperidylcarboxamide reacts with formaldehyde to give, instead of the expected *cis*(8-H,8a-H)-perhydro-8-methylimidazo[1,5-*a*]pyridin-1-one, *cis*(10-H,10a-H)-perhydro-2,10-dimethylpyrido[1,2-*c*][1,3,6]-oxadiazepin-1-one.

CONSIDERABLE interest has recently been shown in the conformational analysis of the hexahydropyrimidine system (1)[2-6] and in the related *trans*-perhydroquinazolines (2),[7] perhydropyrido[1,2-*c*]pyrimidines (3),[8] and perhydrodipyrido[1,2-*c*,2',1'-*f*]pyrimidines (4).[9] Low temperature n.m.r. studies have established[3] conformation (5) for 1-methylhexahydropyrimidine (1; R^1 = H, R^2 = Me) and similar axial NH conformations have been determined for the *trans*-perhydroquinazolines (2; R^1 = Me, R^2 = H) and (2; R^1 = H, R^2 = Me).[7] 1,3-Dimethylhexahydropyrimidine (1; $R^1 = R^2$ = Me),[2a] 1,3,5-trimethylhexahydropyrimidine,[4,5] and 1,3-dimethyl-*trans*-perhydroquinazoline (2; $R^1 = R^2$ = Me)[7] exist as equilibrium mixtures containing *ca.* 70% of the diequatorial methyl conformation [*e.g.* (6)] and 30% of the axial methyl–equatorial methyl conformation [*e.g.* (7)]. In contrast to these results 2-methylperhydropyrido[1,2-*c*]pyrimidine (3; R = Me)[8] appears to exist exclusively in the equatorial methyl conformation (8) and the existence of *syn*-perhydrodipyrido[1,2-*c*,2',1'-*f*]-pyrimidine in the *trans–syn–trans* conformation (9) has been demonstrated.[9] In all these systems the conformational preferences have been explained in terms of dipolar interactions arising from a 1,3-arrangement of the heteroatoms (generalised anomeric effect).[10]

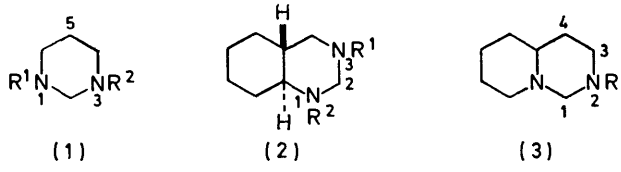
The importance of this effect in influencing the position of conformational equilibrium in systems incorporating a 1,3-hetero-five-membered ring is illustrated by the results obtained on 2-methylperhydroimidazo[1,5-*a*]-pyridine (10)[11] and perhydro-oxazolo[3,4-*a*]pyridine (11).[12] Whereas (11) exists as an equilibrium mixture of *ca.* 60% *trans*-fused (12) and 40% *cis*-fused conformations (13),[12] 2-methylperhydroimidazo[1,5-*a*]pyridine (10) exists predominantly in the *trans*-fused ring conformation [(14) and (15)] presumably because the destabilising influence present in (14) (evidenced by the presence of near parallel lone pairs) can be relieved without ring inversion by inversion at N-2 [conformation (15)].

Since it has been pointed out[13] that a considerable portion of the negative charge of the C–N–C dipole may reside in the area classically delineated by a nitrogen lone pair of electrons and that lone pair–lone pair interactions may be important[14] as part of the generalised anomeric effect it seemed worthwhile synthesising and examining for conformational preferences some perhydroimidazo[1,5-*a*]pyridin-1-ones (16) and perhydropyrido[1,2-*c*]pyrimidin-3-ones (17) in which *inter alia* the non-bridgehead nitrogen atom with its lone pair of electrons present in (10) and (3) has been replaced by a nitrogen atom with its lone pair of electrons incorporated in an amide group.

Synthesis of Compounds.—The series of methyl substituted perhydro-2-methylimidazo[1,5-*a*]pyridin-1-ones (16) were prepared starting from the appropriately methyl substituted 2-cyanopyridines which were converted to the corresponding ethyl pyridinecarboxylate. These were catalytically reduced to the ethyl piperidinecarboxylates and since catalytic hydrogenation normally produces that isomer expected by *cis*-addition of hydrogen the major isomer in each case was assigned that configuration in which the 2-ethoxycarbonyl group was *cis* to the methyl substituent. The correctness of these configurational assignments was confirmed by the results described below. Reaction of the substituted ethyl piperidinecarboxylate with methylamine in ethanol yielded the *N*-methyl-2-carboxamide which on treatment with formaldehyde gave the substituted perhydro-2-methylimidazo[1,5-*a*]pyridin-1-one. Similar sequences

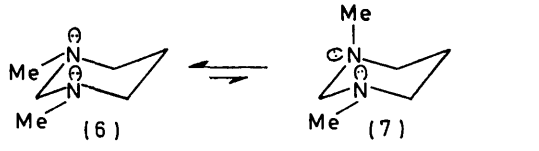
[1] Part XXI, R. Cahill and T. A. Crabb, *J.C.S. Perkin II*, 1972, 1374; Part XX, R. Cahill and T. A. Crabb, *Org. Magnetic Resonance*, 1972, in the press.
[2] (*a*) R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131; (*b*) P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *ibid.*, 1971, 1320.
[3] H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.
[4] F. G. Riddell and D. A. R. Williams, *Tetrahedron Letters*, 1971, 2073.
[5] E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, jun., *Tetrahedron Letters*, 1971, 3409.
[6] R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1968, **90**, 7174.
[7] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 2502.
[8] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 701.
[9] P. J. Chivers and T. A. Crabb, *Tetrahedron*, 1970, **26**, 3369.
[10] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.
[11] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 6327.
[12] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 1997.
[13] A. J. de Hoog, H. R. Buys, C. Altona, and E. Havinga, *Tetrahedron*, 1969, **25**, 3365.
[14] F. P. Chen and R. G. Jesaitis, *Chem. Comm.*, 1970, 1533.

of reactions were employed for the synthesis of the 7-t-butyl compound (16e) and of the perhydro-2-



(1) (2) (3)

(4) (5)



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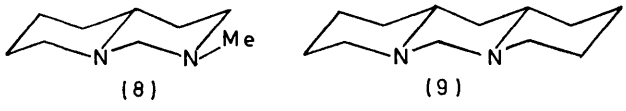

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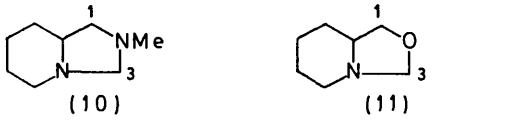

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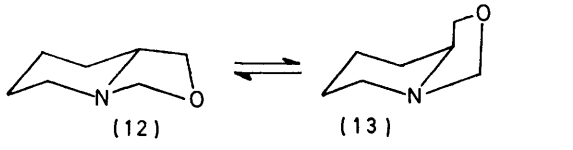
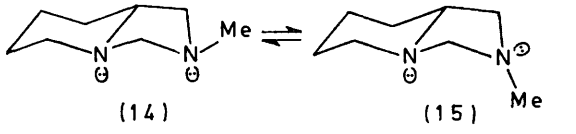
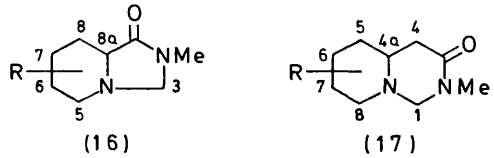


(12) (13)



(14) (15)

methylpyrido[1,2-*c*]pyrimidin-3-ones (17). The attempted synthesis of *cis*(8-H,8a-H)-perhydro-2,8-dimethylimidazo[1,5-*a*]pyridin-1-one gave instead *cis*-

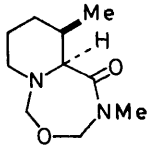


(16) (17)

a; R = H
b; *cis*(5-H,8a-H), R = 5-Me
c; *cis*(6-H,8a-H), R = 6-Me
d; *cis*(7-H,8a-H), R = 7-Me
e; *cis*(7-H,8a-H), R = 7-Bu^t
f; *trans*(8-H,8a-H), R = 8-Me

a; R = H
b; *cis*(4a-H,8-H), R = 8-Me
c; *trans*(4a-H,7-H), R = 7-Me
d; *cis*(4a-H,7-H), R = 7-Me
e; *trans*(4a-H,5-H), R = 5-Me
f; *cis*(4a-H,5-H), R = 5-Me

(10-H,10a-H)-2,10-dimethylperhydropyrido[1,2-*c*][1,3,6]-oxadiazepin-1-one (18). The evidence on which this

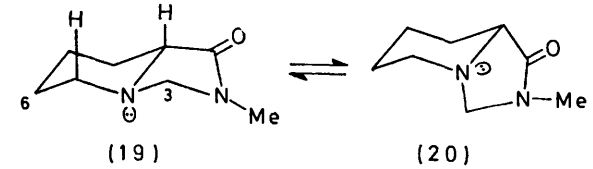


(18)

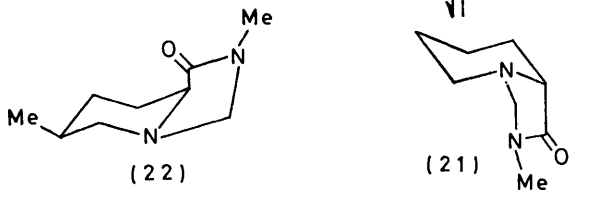
structure is used will be provided after the discussion of the conformational analysis of systems (16) and (17).

RESULTS AND DISCUSSION

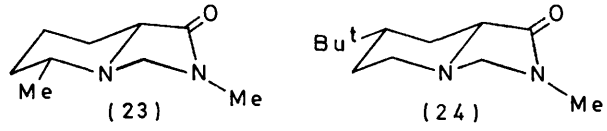
I. *Perhydro-2-methylimidazo*[1,5-a]*pyridin-1-ones* (16). —Perhydro-2-methylimidazo[1,5-*a*]pyridin-1-one can exist as an equilibrium mixture of one *trans*-fused (19) and two *cis*-fused [(20) and (21)] ring conformations inter-



(19) (20)



(22) (21)



(23) (24)

convertible by inversion at the nitrogen atom (19) ⇌ (20) or by ring inversion (20) ⇌ (21). In work on related systems [*e.g.* (11)] [12] the appearance of marked absorption (Bohlmann bands [15]) in the 2800—2600 cm^{-1} region of the i.r. spectrum has proved to be a reliable indication of the presence of *trans*-fused ring conformations since only this conformation possesses the two α-C–H bonds *trans* diaxial with the nitrogen lone pair necessary for band formation. This i.r. criterion was not as generally applicable to the 2-methylperhydroimidazo[1,5-*a*]pyridines (10) [11] because of Bohlmann absorption arising from the *N*-methyl and the C-1–H and C-3–H bonds. However in (16) [and (17)] incorporation of N-2 in the amide grouping inhibits Bohlmann band formation from C–H bonds α to the amide nitrogen atom so that any such absorption in the spectra of these compounds must arise from the bonds α to the bridgehead nitrogen atom.

[15] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.

With the exception of *cis*(6-H,8a-H)-perhydro-2,6-dimethylimidazo[1,5-*a*]pyridin-1-one (16c) all the derivatives of (16) described in this paper showed marked absorption in the 2800—2600 cm^{-1} region of their i.r. spectra showing their predominant existence in the *trans*-fused ring conformation.

cis(6-H,8a-H)-Perhydro-2,6-dimethylimidazo[1,5-*a*]-pyridin-1-one (16c) in which the 6-methyl group occupies an axial position when the ring fusion is *trans*, exhibited only weak absorption between 2850 and 2500 cm^{-1} and was accordingly assigned the equatorially methyl-substituted *cis*-fused ring conformation (22).

TABLE 1

N.m.r. parameters of C-3 methylene protons in compounds (16)

Compound	Solvent	Operating frequency (MHz)	Coupling constants (Hz) $J_{3eq,3ax}$	$J_{3ax,8a}$	Chemical shifts [δ (p.p.m.)] 3*eq*-H	3*ax*-H
(16a)	CCl_4	60	−4·9	2·1	4·06	3·81
	Benzene	60	−4·7	2·1	3·66	3·38
(16b)	CCl_4	60	−4·3	2·5	4·18	3·66
	Benzene	60	−4·4	2·5	3·81	3·21
(16c)	CCl_4	60	−7·1	1·8	3·83	4·13
	Benzene	220	−7·0	1·7	3·33	3·61
(16d)	CCl_4	60	−4·0	2·1	4·10	3·73
	Benzene	60	−4·2	2·1	3·71	3·30
(16e)	CCl_4	60	−4·2	2·1	4·05	3·70
	Benzene	220	−4·1	2·1	3·70	3·30
(16f)	CCl_4	60	−4·1	2·5	4·13	3·33
	Benzene	60	−4·0	2·5	3·70	3·17

The n.m.r. spectra (Table 1) of the perhydroimidazo-[1,5-*a*]pyridin-1-ones (16) provided confirmatory evidence for these conformational assignments. Those compounds (16a, b, d, e, and f) assigned *trans*-fused ring conformations on the basis of their i.r. spectra possessed a geminal coupling constant (J_{gem}, assumed negative) for the C-3 methylene protons of −4·0 to −4·9 Hz and (16c) (*cis*-fused) a J_{gem} value of −7·1 Hz. Surprisingly these J_{gem} values are close to those observed [11] for the *cis*- and *trans*-fused perhydroimidazo[1,5-*a*]pyridines (10) and it would appear that in the amides the reduced transfer of the N-2 lone pair into the antisymmetric methylene molecular orbital is almost exactly compensated for by the increased inductive withdrawal of electrons from the symmetric methylene molecular orbital.[16]

The slightly more negative J_{gem} (C-3 methylene) observed in the spectrum of the unsubstituted parent compound (16a) over that observed for the other *trans*-fused ring conformers suggests the existence of this compound as a conformational mixture containing appreciable amounts of the *cis*-fused ring conformation. If the *cis*(7-H,8a-H)-7-t-butyl compound (16e) is assumed to exist completely in the *trans*-fused ring conformation (J_{gem} −4·1 Hz) and the *cis*(6-H,8a-H)-6-methyl compound (16c) completely in the *cis*-fused ring conformation (J_{gem} −7·1 Hz) then (16a) (J_{gem} −4·9 Hz) must exist as a conformational mixture containing *ca.* 27% *cis*- and 63% *trans*-fused ring conformers at room temperature.

In the spectra of the *trans*-fused compounds the high field half of the C-3 methylene AB quartet showed a further 'splitting' of 2·1—2·5 Hz. It was possible to assign the high field signals to 3*ax*-H since on going from (19) [(16a)] to (23) [(16b)] the low-field 3-H is deshielded (0·12 p.p.m.) and the high-field 3-H shielded (0·15 p.p.m.). This suggests that the low-field proton is 3*eq*-H since many examples of deshielding of such a proton by a similarly situated methyl group are known.[11] Thus it is 3*ax*-H which is further coupled but it was not possible to determine the location of the coupled proton at 60 MHz.

To investigate the origin of this long range coupling and to provide more detailed evidence regarding the stereochemistry of these compounds a 220 MHz spectrum of the *cis*(7-H,8a-H)-7-t-butyl compound (16e) was obtained (Table 2). In this spectrum the angular

TABLE 2

220 MHz N.m.r. spectrum (C_6D_6) of compound (16e)

Chemical shifts [δ (p.p.m.)]		Coupling constants (Hz) J_{gem} and $J_{ax,ax}$		^4J, $J_{aa,eq}$ and $J_{eq,eq}$	
3*eq*-H	3·70	$J_{3eq,3ax}$	−4·1	$J_{3ax,8a}$	2·1
3*ax*-H	3·30				
5*eq*-H	2·45	$J_{5eq,5ax}$	−11·5	$J_{5eq,6eq}$	3·0
5*ax*-H	1·99			$J_{5eq,6ax}$	3·0
		$J_{5ax,6ax}$	11·5		
6*eq*-H	1·40			$J_{5ax,6eq}$	3·3
6*ax*-H	1·22	$J_{6eq,6ax}$	−12·5	$J_{6eq,7ax}$	3·0
7*ax*-H	0·88	$J_{6ax,7ax}$	12·0		
8*eq*-H	2·17	$J_{7ax,8ax}$	12·0	$J_{7ax,8eq}$	3·0
8*ax*-H	1·22	$J_{8eq,8ax}$	−12·5		
8*a*-H	2·70	$J_{8a,8ax}$	11·0	$J_{8a,8eq}$	4·5

(8a-H) proton was seen to absorb as a doublet of quartets (δ 2·70 p.p.m.) and analysis of the multiplet showed 3*ax*-H to be coupled (^4J 2·1 Hz) to this proton. Analysis of the rest of the n.m.r. spectrum gave the coupling constants shown in Table 2, demonstrating beyond doubt the existence of *cis*(7-H,8a-H)-perhydro-2-methyl-7-t-butylimidazo[1,5-*a*]pyridine-1-one (16e) in the *trans*-fused ring conformation (24) with a chair piperidine ring.

Analysis of the 220 MHz spectrum (Table 3) of *cis*-(6H,8a-H)-perhydro-2,6-dimethylimidazo[1,5-*a*]pyridine

TABLE 3

220 MHz N.m.r. spectrum (C_6D_6) of compound (16c)

Chemical shifts [δ (p.p.m.)]		Coupling constants (Hz) J_{gem} and $J_{ax,ax}$		^4J, $J_{ax,eq}$ and $J_{eq,eq}$	
3*eq*-H	3·33	$J_{3eq,3ax}$	−7·0	$J_{3eq,8a}$	1·7
3*ax*-H	3·61			$J_{5eq,7eq}$	1·5
5*eq*-H	2·42	$J_{5eq,5ax}$	−10·5	$J_{5eq,6ax}$	3·8
		$J_{5ax,6ax}$	8·5		
5*ax*-H	2·03	$J_{7eq,7ax}$	−11·5	$J_{6ax,7eq}$	5·5
6*ax*-H	1·54	$J_{6ax,7ax}$	9·5	$J_{7eq,8eq}$	5·5
7*eq*-H	2·23				
		$J_{7ax,8ax}$	10·5	$J_{7eq,8ax}$	4·8
7*ax*-H	1·75				
8*eq*-H	1·34	$J_{8eq,8xa}$	−9·5	$J_{7ax,8eq}$	5·1
8*ax*-H	1·05			$J_{8eq,8a}$	5·0
8*a*-H	2·90			$J_{8a,8ax}$	5·0

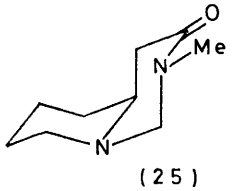
1-one (16c) provided confirmation of the *cis*-fused ring conformation (20). The C-3 methylene protons absorbed as an AB quartet (δ 3·61, 3·33 p.p.m., J_{gem} −7·0 Hz) with the low-field half of the quartet split

[16] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 1965, **42**, 1339.

again (J 1·6 Hz). Since in (24) this ^4J value arose from coupling with 8a-H, the signals arising from 8a-H were examined and found to be a broadened triplet (δ 2·90 p.p.m., J 5·0 and 5·0 Hz). The additional splitting (with 3-H) evidenced by the broadening of the signals was not resolved but values of the peak widths at half height were consonant with a ^4J value of 1·6 Hz. From the result for (24) [(16e)] it would appear that the preferred pathway for ^4J in the system C(O)N–C*H*–N·C*H* is a diaxial one. Assuming this to be applicable to (22), the long-range coupling may be tentatively attributed to coupling between 3*ax*′- and 8a-H and 3*ax*′-H must then absorb at lower field than 3*eq*′-H. The values of the vicinal couplings with 8a-H were of the magnitude expected for $J_{eq,eq}$ or $J_{eq,ax}$ in a chair conformation and were consistent with the *cis*-fused ring conformation (22). In the alternative *cis*-conformation [(20) with axial Me at C-6] and *trans*-conformation [(19) with axial Me at C-6] 8a-H is axial with respect to the six-membered ring and would thus absorb as a doublet of doublets (J *ca.* 11 and 4 Hz).

The 5*eq*-H signals showed a ^4J value of 1·5 Hz the origin of which could not be determined but might have been assigned as arising as a result of coupling of 3-H with 5*eq*-H instead of with 8a-H. However, similar long range couplings of 5*eq*-H in *cis*(6-H,8a-H)-perhydro-6-methyloxazolo[3,4-*a*]pyridine [12] and in *trans*(6-H,8a-H)-perhydro-6-methylindolizin-2-one [17] have been observed and attributed to $J_{5eq,7eq}$ (planar W pathway).[18] $J_{5eq,5ax}$ In *cis*-fused (22) is larger (−10·5 Hz) than in *trans*-fused (19) (−11·5 Hz) in line with a previously observed trend.[19]

II. *Perhydro-2-methylpyrido*[1,2-c]*pyrimidin-3-ones* (17).—On the basis of weak Bohlmann bands in their i.r. spectra (Experimental section) *cis*-fused ring conformations (25) were assigned to (17d) and (17f).



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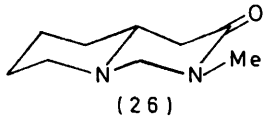


(26)

The remaining compounds showed marked Bohlmann bands and were assigned the *trans*-fused ring conformation (26). The n.m.r. data (Tables 4 and 5) was in agreement with these assignments, the *cis*-compounds showing more negative J_{gem} values (−10·8 to −11·7 Hz) for the C-1 methylene protons than the *trans*-compounds (−8·5 to −9·0 Hz). The parent unsubstituted compound (17a) (J_{gem} −9·0 Hz) appears to exist as *ca.* 16% *cis*-fused ring conformation in equilibrium with the *trans*-fused ring conformation and the *cis*(4a-H,7-H)-perhydro-2,7-dimethylpyrido[1,2-*c*]pyrimidin-3-one (17c) (J_{gem} −10·8 Hz) as 28% *trans*-fused conformation in equilibrium with 72% *cis*-fused conformation (assuming J_{trans} −8·5 Hz, J_{cis} −11·7 Hz). As in the case of the perhydroimidazo[1,5-*a*]pyridin-1-ones (16) these J_{gem}

TABLE 4

N.m.r. spectra (60 MHz) of compounds (17)

Compound	Solvent	Coupling constants (MHz) $J_{1ax,1eq}$	Chemical shifts [δ (p.p.m.)] 1*eq*	1*ax*	*N*-Me	*C*-Me
(17a)	CCl_4	−9·0	3·88	3·61	2·81	
	Benzene	−9·1	3·45	3·16	2·70	
(17b)	CCl_4	−8·7	4·25	3·45	2·81	1·08
	Benzene	−8·7	3·90	3·00	2·69	0·90
(17c)	CCl_4	−8·5	3·83	3·47	2·83	0·91
	Benzene	−8·5	3·48	3·08	2·73	0·73
(17d)	CCl_4	−10·8	3·75	4·15	2·81	0·96
	Benzene	−10·8	3·41	3·76	2·68	0·83
(17e)	CCl_4	−8·7	3·81	3·51	2·81	0·90
	Benzene					
(17f)	CCl_4	−11·7	3·78	4·31	2·78	0·85
	Benzene	−11·6	3·40	3·97	2·68	0·61

TABLE 5

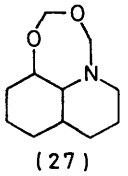
220 MHz N.m.r. spectrum (CCl_4) of compound (17f)

Chemical shifts [δ (p.p.m.)]		Coupling constants (Hz)			
1*eq*-H	3·78	$J_{1eq,1ax}$	−11·7	$J_{4eq,4a}$	6·0
1*ax*-H	4·31	$J_{4eq,4ax}$	−18·2	$J_{5ax,4a}$	5·0
4*eq*-H	1·93	$J_{4ax,4a}$	13·0	$J_{8eq,7eq}$	3·8
4*ax*-H	2·36	$J_{8eq,8ax}$	−11·6	$J_{8eq,7ax}$	3·8
4*a*-H	3·20	$J_{8ax,7ax}$	11·6	$J_{8ax,7eq}$	4·0
8*eq*-H	2·50	$J_{7ax,7eq}$	−11·6	$J_{7ax,6eq}$	4·8
8*ax*-H	2·85	$J_{7ax,6ax}$	11·6		

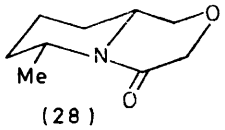
values are close to those observed for *trans*-fused (−8·5 Hz) and *cis*-fused (−11·3 Hz) perhydropyrido[1,2-*c*]-pyrimidines (3). The J_{gem} values of the C-4 methylene protons (−18·2 Hz) indicates a conformation such that the nodal plane of the amide carbonyl bisects the 4-H–4-H internuclear axis.[20]

The conformational preferences of the substituted derivatives of (16) and (17) being very similar to those of the analogously substituted derivatives of (3) and (10), clearly show the very small effect on the position of conformational equilibrium resulting from replacement of the tertiary nitrogen atom in (3) and (10) by an amide function.

III. *The Reaction of* cis(2-H,3-H)-3,N-*Dimethyl-2-piperidylcarboxamide with Formaldehyde*.—The piperidylcarboxamide reacted with formaldehyde to give a crystalline compound which analysed for $C_{10}H_{18}N_2O_2$.



(27)



(28)

Its n.m.r. spectrum (benzene solution) showed the presence of one *N*-methyl group (δ 2·78 p.p.m.) and a CH–Me group (δ 1·3 p.p.m.). Two AB quartets centred

[17] R. Cahill and T. A. Crabb, *Org. Magnetic Resonance*, 1972, **4**, 259.
[18] M. Barfield and B. Chakrabarti, *Chem. Rev.*, 1969, **69**, 757.
[19] R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magnetic Resonance*, 1971, **3**, 263.
[20] M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, 1963, **85**, 1899.

at δ 4·37 (J_{gem} −11·2 Hz) and 4·33 p.p.m. (J_{gem} −12·4 Hz) were clearly assignable to N–CH_2–O methylene group protons and the combined evidence suggested the *cis*(10-H,10a-H)-perhydro-2,10-dimethylpyrido[1,2-*c*]-[1,3,6]oxadiazepin-1-one structure (18). A similar reaction has been observed [21] between *cis*(4a-H,8-H)-*trans*-decahydroquinolin-8-ol and formaldehyde when the dioxazepine (27) was obtained.

cis(6-H,9a-H)-6-Methylperhydropyrido[2,1-*c*][1,4]-oxazin-4-one (28) has been shown [22] to exist in a conformation with a deformed piperidine ring presumably as a result of unfavourable interaction between the carbonyl function and the methyl group. A similar unfavourable interaction would be present in *cis*- and *trans*-fused conformations of *cis*(8-H,8a-H)-perhydro-2,8-dimethylimidazo[1,5-*a*]pyridin-1-one but this eclipsing relationship can be relieved in (18) by small changes in the conformation of the seven-membered ring.

trans(2-H,3-H)-3,*N*-Dimethylpiperidine-2-carboxamide reacted normally with formaldehyde to give the imidazo-[1,5-*a*]pyridin-1-one but this compound, unlike the others in the series, proved to be rather unstable and this instability must again be a result of an unfavourable carbonyl–methyl interaction.

EXPERIMENTAL

Elemental analyses were carried out by Drs. F. Pascher and E. Pascher. I.r. spectra were recorded on a Perkin-Elmer 457 spectrometer for 0·2M solutions in carbon tetrachloride using 0·2 mm matched cells. The n.m.r. spectra were recorded on Varian T60 and H220 spectrometers for 10% solutions in carbon tetrachloride and benzene with tetramethylsilane as internal standard.

General Procedure for Preparation of Methyl-substituted N-Methylpiperidine-2-carboxamides.—A cooled solution of the methyl-substituted ethyl piperidinecarboxylate in absolute ethanol was saturated with dry methylamine gas over a period of 4 h. The solution was kept at room temperature for 24 h after which the ethanol was removed *in vacuo*. The crude *N*-methylpiperidine-2-carboxamide so obtained was distilled and/or recrystallised from light petroleum. *N-Methylpiperidine-2-carboxamide* (11·2 g) was obtained from ethyl piperidine-2-carboxylate (15 g) as white felted needles, m.p. 153—155° (Found: C, 59·6; H, 9·7; N, 19·65. $C_7H_{14}N_2O$ requires C, 59·1; H, 9·9; N, 19·7%). cis(2-H,6-H)-6,N-*Dimethyl-2-piperidylcarboxamide* (5·7 g) was obtained from the corresponding ester (10 g) as a mobile oil, b.p. 117—119° at 0·1 mmHg (Found: C, 61·0; H, 10·1; N, 17·95. $C_8H_{16}N_2O$ requires C, 61·5; H, 10·3; N, 17·95%). cis(2-H,5-H)-5,N-*Dimethylpiperidine-2-carboxamide* (7·8 g) was obtained from the corresponding ester (10 g) as white felted needles, m.p. 106—107° (Found: C, 61·8; H, 10·15; N, 17·9%). cis(2-H,4-H)-4,N-*Dimethyl piperidine-2-carboxamide* (4·4 g) was obtained from the corresponding ester (4·3 g) as white needles, m.p. 121—123° (Found: C, 61·7; H, 10·35; N, 18·35%). cis(2-H,4-H)-N-*Methyl-4-t-butylpiperidine-2-carboxamide* (6·1 g) was obtained from the corresponding ester (7·1 g) as white plates, m.p. 112—114° (Found: C, 66·65; H, 11·2; N, 14·45. $C_{11}H_{22}N_2O$ requires C, 66·6; H, 11·2; N, 14·15%).

cis- and *trans*-3,*N*-Dimethylpiperidine-2-carboxamide (10·1 g) was obtained from an epimeric mixture of ethyl 3-methylpiperidine-2-carboxylate (16 g) as a viscous oil, b.p. 119—121° at 0·9 mmHg, which solidified on standing to give white felted needles, m.p. 109—111° (from light petroleum) (Found: C, 62·85; H, 10·35; N, 17·35. Calc. for $C_8H_{16}N_2O$: C, 61·5; H, 10·3; N, 17·95%).

General Procedure for the Preparation of Perhydro-2-methylimidazo[1,5-a]*pyridin-1-ones.*—The appropriately substituted piperidinecarboxamide and excess of 40% aqueous formaldehyde were heated together on a steam bath for 2 h. The mixture was basified with aqueous sodium hydroxide and ether-extracted three times. The extracts were dried (Na_2SO_4), concentrated, and the crude product was distilled. *Perhydro-2-methylimidazo*[1,5-a]*pyridin-1-one* (1·7 g) was obtained from the amide (2·5 g) as an oil, b.p. 80—82° at 0·15 mmHg, $n_D^{17·0}$ 1·5015. This compound was unstable and accurate analysis could not be obtained, $\nu_{max.}$ 2785 (ε 63), 2755 (48), 2718 (35), and 2650 cm^{-1} (15). cis(5-H,8a-H)-*Perhydro-2,5-dimethylimidazo*[1,5-a]*pyridin-1-one* (2·8 g) was obtained from the amide (4·0 g) as an oil, b.p. 92—94° at 0·5 mmHg, $n_D^{20·0}$ 1·4950 (Found: C, 64·5; H, 9·9; N, 16·75. $C_9H_{16}N_2O$ requires C, 64·25; H, 9·6; N, 16·65%), $\nu_{max.}$ 2787 (ε 75), 2742 (52), 2695 (35), 2655 (20), and 2587 cm^{-1} (12). cis(6-H,8a-H)-*Perhydro-2,6-dimethylimidazo*[1,5-a]*pyridin-1-one* (3·0 g) was obtained from the amide (5·0 g) as an oil, b.p. 95—96° at 0·05 mmHg which solidified on standing to give white rhombs, m.p. 86—88° (from light petroleum) (Found: C, 64·3; H, 9·85; N, 16·4%), $\nu_{max.}$ 2830 (ε 37), 2800 (40), 2790 (40), and 2750 cm^{-1} (30). cis(7-H,8a-H)-*Perhydro-2,7-dimethylimidazo*[1,5-a]*pyridin-1-one* (1·2 g) was obtained from the amide (4·0 g) as an oil, b.p. 112—114° at 1·2 mmHg which solidified on standing to give white plates, m.p. 87—88° (from light petroleum) (Found: C, 63·8; H, 9·4; N, 16·65%), $\nu_{max.}$ 2790 (ε 67), 2758 (55), 2710 (35), and 2642 cm^{-1} (12). cis(7-H,8a-H)-*Perhydro-2-methyl-7-t-butylimidazo*[1,5-a]*pyridin-1-one* (1·4 g) was obtained from the amide (4·0 g) as a viscous oil, b.p. 126—130° at 0·35 mmHg, $n_D^{20·5}$ 1·4924 (Found: C, 67·95; H, 10·65; N, 13·0. $C_{12}H_{22}N_2O$ requires C, 68·55; H, 10·55; N, 13·3%), $\nu_{max.}$ 2782 (ε 70), 2750 (52), 2718 (37), and 2650 cm^{-1} (15).

Reaction of cis- *and* trans-3,N-*Dimethylpiperidine-2-carboxamide with Formaldehyde.*—A mixture of *cis*- and *trans*-3,*N*-dimethylpiperidine-2-carboxamide (9·0 g) was treated with formaldehyde as described above to give an oil (3·25 g), b.p. 93—101° at 0·9 mmHg, which, on standing, deposited a white solid. This was recrystallised from light petroleum as white needles, m.p. 98—99°, and shown to be *cis*(10-H,-10a-H)-2,10-*dimethylperhydro*[1,2-c][1,3,6]*oxadiazepin-1-one* (Found: C, 60·7; H, 9·4; N, 14·1. $C_{10}H_{18}N_2O_2$ requires C, 60·6; H, 9·25; N, 14·15%).

A solution of the remaining liquid product (3·05 g) in benzene was chromatographed over grade III neutral Woelm alumina (280 g) to give trans(8-H,8a-H)-*perhydro-2,8-dimethylimidazo*[1,5-a]*pyridin-1-one* as a mobile oil, b.p. 106—108° at 0·9 mmHg, $\nu_{max.}$ 2785 (ε 63), 2762 (63), 2748 (50), and 2700 cm^{-1} (30). This compound decomposed to a thick brown oil after several days even when stored below 0° under N_2 and no analysis figures could be obtained.

General Procedure for the Preparation of N-Methyl-2-piperidylacetamides.—A cooled solution of the appropriate ethyl 2-piperidylacetate in absolute ethanol was saturated with dry methylamine gas over a period of 4 h. After standing at room temperature for an additional 24 h the

[21] T. A. Crabb and R. F. Newton, *Chem. Comm.*, 1970, 1123.
[22] R. Cahill and T. A. Crabb, *Org. Magnetic Resonance*, 1972, **4**, 283.

ethanol was removed *in vacuo* and the crude *N*-methyl-2-piperidylacetamide was either distilled or recrystallised from light petroleum. *N-Methyl-2-piperidylacetamide* (8·7 g) was obtained from the acetate (12·0 g) as white needles, m.p. 89—91° (Found: C, 61·6; H, 10·35; N, 18·2. $C_8H_{16}N_2O$ requires C, 61·5; H, 10·3; N, 17·95%). cis(2-H,6-H)-6,N-*Dimethyl-2-piperidylacetamide* (3·2 g) was obtained from the acetate (12 g) as a viscous oil, b.p. 124—127° at 0·15 mmHg, which solidified on standing. Recrystallisation gave felted needles, m.p. 83—84° (Found: C, 63·5; H, 10·9; N, 16·45. $C_9H_{18}N_2O$ requires C, 63·5; H, 10·65; N, 16·45%). cis- *and* trans-5,N-*Dimethyl-2-piperidylacetamide* (3·9 g) was obtained from a mixture of *cis*- and *trans*-acetate (8·0 g) as a viscous oil, b.p. 131—133° at 0·6 mmHg (Found: C, 64·0; H, 11·1; N, 16·3%).

General Procedure for the Preparation of Substituted Perhydro-2-methylpyrido[1,2-c]*pyrimidin-3-ones.*—The appropriately substituted *N*-methyl-2-piperidylacetamide was shaken with excess of 40% aqueous formaldehyde solution for 30 min. The mixture was heated on a steam bath for 30 min, then basified with sodium hydroxide solution, and ether-extracted three times. The extracts were dried (Na_2SO_4), concentrated, and the crude product was distilled. *Perhydro-2-methylpyrido*[1,2-c]*pyrimidin-3-one* (4·1 g) was obtained from the amide (5·0 g) as a viscous oil, b.p. 101—103° at 0·15 mmHg which solidified on standing. Recrystallisation from light petroleum afforded white needles, m.p. 64—66° (Found: C, 64·8; H, 9·6; N, 16·7. $C_9H_{16}N_2O$ requires: C, 64·25; H, 9·6; N, 16·65%) $\nu_{max.}$ 2792 (ε 77), 2758 (60), 2732 (60), 2670 (30), and 2620 cm^{-1} (10). cis-(4a-H,8-H)-*Perhydro-2,8-dimethylpyrido*[1,2-c]*pyrimidin-3-one* (1·2 g) was obtained from the amide (1·4 g) as a viscous oil, b.p. 103—104° at 0·25 mmHg, $n_D^{17·0}$ 1·5027 (Found: C, 66·15; H, 9·95; N, 15·65. $C_{10}H_{18}N_2O$ requires C, 65·9; H, 9·95; N, 15·35%), $\nu_{max.}$ 2795 (ε 67), 2737 (43), 2718 (43), and 2621 cm^{-1} (12). cis- and trans-*Perhydro-2,7-dimethylpyrido*[1,2-c]*pyrimidin-3-one* (3·6 g) was obtained from a mixture of the *cis*- and *trans*-amides (3·9 g) as a viscous oil, b.p. 104—105° at 0·06 mmHg (Found: C, 66·05; H, 9·95; N, 15·55. Calc. for $C_9H_{18}ON_2$: C, 65·9; H, 9·95; N, 15·35%). Separation was achieved by passing a solution of the mixture (4·8 g) in benzene down a grade III neutral Woelm alumina column (350 g). *cis*(4a-H,7-H)-Perhydro-2,7-dimethylpyrido[1,2-*c*]pyrimidin-3-one (1·5 g) was the first isomer off the column and was obtained as a viscous oil, b.p. 120—122° at 0·25 mmHg, $\nu_{max.}$ 2818 (ε 40), 2768 (25), and 2730 cm^{-1} (20). *trans*(4a-H,7-H)-Perhydro-2,7-dimethylpyrido[1,2-*c*]pyrimidin-3-one (1·3 g) the second fraction off the column, was obtained as a viscous oil, b.p. 112—114° at 0·23 mmHg, which solidified on standing to give white needles, m.p. 69—71° (from light petroleum), $\nu_{max.}$ 2790 (ε 58), 2755 (47), 2735 (50), and 2667 cm^{-1} (15). trans(4a-H,5-H)-*Perhydro-2,5-dimethylpyrido*[1,2-c]*pyrimidin-3-one* (0·65 g) was obtained from the amide as a viscous oil, b.p. 122—124° at 0·1 mmHg, $\nu_{max.}$ 2790 (ε 57), 2753 (55), 2660 (20), and 2600 cm^{-1} (10). cis(4a-H,5-H)-*Perhydro-2,5-dimethylpyrido*[1,2-c]*pyrimidin-3-one* (1·45 g) was obtained from the amide (1·75 g) as a viscous oil, b.p. 121—124° at 0·35 mmHg, $n_D^{17·0}$ 1·4937, which solidified on standing to give white rhombs, m.p. 54—55° (from light petroleum) (Found: C, 66·05; H, 9·8; N, 15·65. $C_{10}H_{18}N_2O$ requires C, 65·9; H, 9·95; N, 15·35%), $\nu_{max.}$ 2830 (ε 45), 2790 (25), and 2720 cm^{-1} (15).

[2/865 *Received*, 19*th April*, 1972]