The Conformational Analysis of Perhydropyrido[1,2-*c*][1,3]oxazines, Perhydropyrido[1,2-*c*][1,3]thiazines, and Perhydropyrido[1,2-*c*]pyrimidines [1,2]

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Dipole moments of perhydropyrido[1,2-*c*][1,3]oxazine, 2-t-butylperhydropyrido[1,2-*c*]pyrimidine, and *syn*-perhydrodipyrido[1,2-*c* : 2',1'-*f*] pyrimidine indicate their exclusive existence in the *trans*-fused conformation. Perhydropyrido[1,2-*c*][1,3]thiazine and 2-methylperhydropyrido[1,2-*c*]pyrimidine also exist to a significant extent in this conformation. The effects of *cis*(4a-H,5-H)-5-methyl, *cis*(4a-H, 6-H)-6-methyl and *cis* and *trans*-(4a-H, 7-H)-7-ethyl groups in the perhydropyrido[1,2-*c*][1,3]oxazine system are discussed, and the conformational behaviour of this series is rationalized. These results are compared with estimates of the positions of conformational equilibria based on n.m.r. data.

CONSIDERABLE work on six-membered saturated heterocycles with additional heteroatoms [3,4] and on bicyclic and polycyclic analogues [5,6] reveals that interactions engendered by the heteroatoms are of prime importance in determining the preferred conformations of such systems. The conformational preferences of 1,3-diheterosystems have been explored by dipole moment measurements [4] and by a study of n.m.r. data.[6] In several instances however small variations in n.m.r. parameters correspond to appreciable shifts in the position of conformational equilibrium and it therefore seemed important to assess the preferred conformations of certain bicyclic and tricyclic 1,3-dihetero-systems from dipole moment data for comparison with the results based on n.m.r. data.

EXPERIMENTAL

Elemental analyses were carried out by Drs. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany, and also by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic.

Published methods were used for the synthesis of 2-methyl- and 2-t-butyl-perhydropyrido[1,2-*c*]pyrimidine,[7] *syn*-perhydrodipyrido[1,2-*c* : 2',1'-*f*]pyrimidine,[8] perhydropyrido[1,2-*c*][1,3] oxazine,[9] *cis*(4a-H, 5-H)-5-methyl-perhydropyrido[1,2-*c*][1,3]oxazine,[10] and perhydropyrido-[1,2-*c*][1,3]thiazine.[10]

cis(4a-H,6-H)-6-*Methylperhydropyrido*[1,2-c][1,3]*oxazine*.—A solution of the 2-(2-hydroxyethyl)-4-methylpyridine [11] (20 g) in glacial acetic acid (150 ml) was hydrogenated over Adams platinum oxide catalyst (1 g) at 60 lb in^{-2}. After absorption of the calculated amount of hydrogen (3 days) the catalyst was filtered off and the filtrate evaporated, made basic with sodium hydroxide solution, and extracted with ether (4 × 200 ml). The ether extracts were dried, evaporated, and the residual oil distilled to give 2-(2-hydroxyethyl)-4-methylpiperidine as a colourless oil (14.1 g), b.p. 105—106° at 0.3 mmHg.

2-(2-Hydroxyethyl)-4-methylpiperidine (10 g) was shaken for 5 min with 40% aqueous formaldehyde solution (10 ml). The solution was basified with sodium hydroxide solution and extracted with ether (4 × 150 ml). The extracts were dried, evaporated, and distilled to give cis(4a-H,6-H)-6-*methylperhydropyrido*[1,2-c][1,3]*oxazine* (7 g) as a liquid, b.p. 62—63° at 0.5 mmHg, $n_D^{15.5}$ 1.4741 (Found: C, 69.65; H, 11.1; N, 9.2. $C_9H_{17}ON$ requires C, 69.65; H, 11.05; N, 9.0%).

cis *and* trans(4a-H,7-H)-7-*Ethylperhydropyrido*[1,2-c][1,3]-

[1] Part LXXIII in the series 'Conformational Analysis of Saturated Heterocycles.' Part LXXII, I. J. Ferguson, A. R. Katritzky, and D. M. Read, submitted to *J.C.S. Perkin II*.

[2] Part XXX in the series 'Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen Atoms.' Part XXIX, T. A. Crabb and M. J. Hall, *J.C.S. Perkin II*, 1976, 203.

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[4] See ref. 1 for previous parts of this series.

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[6] See ref. 2 for previous parts of this series.

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[10] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 3941.

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oxazines.—A solution of 5-ethyl-2-(2-hydroxyethyl)pyridine (20 g) prepared from 5-ethyl-2-methylpyridine by an adaptation of the method of Finkelstein and Elderfield [12] in glacial acetic acid (150 ml) was hydrogenated at 60 lb in^{-2} and 50° over Adams platinum oxide catalyst (1 g). After the calculated amount of hydrogen had been taken up the solution was filtered, evaporated, and made basic with sodium hydroxide. The solution was extracted with ether (4 × 150 ml), the extracts were dried, evaporated, and the residual oil distilled to give 5-ethyl-2-(2-hydroxyethyl)piperidine (14 g) as an oil, b.p. 125—126° at 0.8 mmHg, which solidified and was recrystallised from light petroleum (40—60°) to give a mixture of *cis*- and *trans*-5-ethyl-2-(2-hydroxyethyl)-piperidine as a solid, m.p. 52—54° (Found: C, 68.6; H, 12.2; N, 8.85. Calc. for $C_9H_{19}NO$: C, 68.75; H, 12.2; N, 8.9%).

40% Aqueous formaldehyde solution (10 ml) was added to 5-ethyl-2-(2-hydroxyethyl)piperidine (10 g) and the solution was shaken for 5 min. The solution was made strongly alkaline and extracted with ether (3 × 200 ml). The ether solution was dried, evaporated, and the residue was distilled to give an epimeric mixture of *cis* and *trans*(4a-*H*,7-*H*)-7-ethylperhydropyrido[1,2-*c*][1,3]oxazines (8 g) as a liquid, b.p. 113—115° at 30 mmHg.

The mixture was separated by preparative g.l.c. on a 15 ft × 3/8 in 12½% Carbowax column at 160° with H_2 as carrier gas using a 0.1 ml sample size. The samples were rechromatographed to ensure purity. The compounds in order of increasing retention time were: cis(4a-H,7-H)-7-*ethylperhydro*[1,2-c][1,3]*oxazine*, b.p. 76—77° at 3 mmHg, $n_D^{15.5}$ 1.4713 (Found: C, 70.8; H, 11.15; N, 8.3. $C_{10}H_{19}NO$ requires C, 70.95; H, 11.3; N, 8.3%) and the trans-*isomers*, b.p. 84—85° at 3.7 mmHg, $n_D^{15.5}$ 1.4784 (Found: C, 70.9; H, 11.3; N, 8.3%).

Dipole Moments.—Dipole moments were calculated as described previously from measurements in benzene at 25°. The results are given in Table 1. Additional information is given in Supplementary Publication No. SUP 21517 (3 pp.).†

Results obtained for cyclohexane solutions were in general agreement but the present compounds possess unusually small magnitudes of ($\varepsilon_{solution} - \varepsilon_{cyclohexane}$) at the usual concentrations. The ' inherent mathematical sensitivity ' of such results, especially for highly favoured equilibria, make them less reliable.

Predicted dipole moments were calculated assuming for the dihetero-rings of the polycyclic derivatives the geometries of the corresponding monocyclic analogues.[13] Component dipole moments at oxygen and suphur were considered to act in the plane of the C–X–C system and the dipole moments at non-bridgehead nitrogen atoms in the same direction as the corresponding piperidines.[14,15] For bridgehead nitrogen atoms the dipole moment was treated as acting at 56.5° to the C–N–C plane of the diheterane ring (*cf.* results in ref. 14). Contributions from *C*-alkyl groups and ring residues were neglected.

Geometry of the Tetrahydro-1,3-thiazine Ring.—The energy-minimised geometry of tetrahydro-1,3-thiazine was obtained using the conjugate gradient programme GEOMIN and molecular parameters previously described,[15] with the exception of the C–S–C torsional barrier for which a value of 2.5 kcal mol^{-1} is used, as in other work.[16] The bond and torsional angles and Cartesian co-ordinates, calculated with the ICL 1905E computer at the University of East Anglia, are given in Table 2. N.m.r. and i.r. data have previously indicated [10] that the tetrahydro-1,3-thiazine ring of (8) shows a marked deviation from a normal chair conformation.

TABLE 1

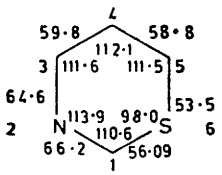
Dipole moments in benzene at 25°

Compound	$d\varepsilon/dw$ [a]	$-dv/dw$ [a]	$_TP_{2\infty}$	$_EP$	μ(D) [b]
(3)	3.22 ± 0.02	0.153 ± 0.003	127.1	39.5	2.07 ± 0.01
(4)	2.03 ± 0.02	0.158 ± 0.006	104.94	44.0	1.73 ± 0.01
(5)	2.98 ± 0.05	0.232 ± 0.009	129.3	44.0	2.04 ± 0.02
(7)	2.67 ± 0.03	0.113 ± 0.001	137.0	48.6	2.08 ± 0.01
(8)	3.02 ± 0.01	0.210 ± 0.002	133.1	45.3	2.07 ± 0.01
(9)	1.26 ± 0.02	0.072 ± 0.001	85.9	45.9	1.40 ± 0.01
(10)	1.07 ± 0.02	0.053 ± 0.003	103.4	59.5	1.47 ± 0.01
(11)	1.17 ± 0.04	0.114 ± 0.003	102.5	57.4	1.48 ± 0.03

[a] Range shown is ± one standard deviation. [b] Range shown is ± one standard deviation or 0.01 D, whichever is the greater.

TABLE 2

Bond and torsional angles and cartesian co-ordinates of tetrahydro-1,3-thiazine *



	Cartesian co-ordinates of atoms (Å)		
	X	*Y*	*Z*
1	0·0000	0.0000	0.0000
2	−0.9724	0.8428	−0.7107
3	−1.2494	2.1180	−0.0448
4	0.0000	3.0172	0.0000
5	1.1642	2.3522	0.7577
6	1.6348	0.7769	0.0000

* Convergence to 0.1° variation in bond angles (at apices). Dihedral (torsional) angles are given midway along relevant bonds.

RESULTS AND DISCUSSION

Decalin (1) *and Quinolizidine* (2).—The compounds investigated are all derivatives of quinolizidine (2) and hence of decalin (1). The best available [17] (*cf.* also ref. 18) value for ΔH°_{586} for the decalin equilibrium (1*A*) ⇌ (1*B*) is 2.72 ± 0.2 kcal mol^{-1} in favour of the

† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue. Items less than 10 pp. are supplied as full-size copies.

[12] J. Finkelstein and R. C. Elderfield, *J. Org. Chem.*, 1939, **4**, 365.

[13] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

[14] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.

[15] M. J. Cook, R. A. Y. Jones, A. R. Katritzky, M. Moreno-Mañas, A. C. Richards, A. J. Sparrow, and D. L. Trepanier, *J.C.S. Perkin II*, 1973, 325.

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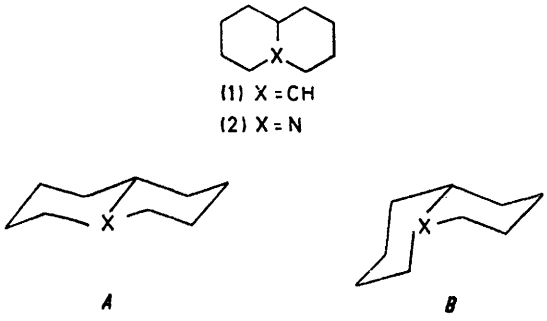
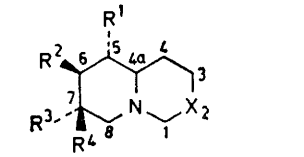
trans-isomer (1*A*). This value is in good agreement with the value expected in view of the three *gauche*-butane interactions which exist in the *cis*-isomer (1*B*) but are absent in the *trans*. We assume that all the compounds studied exist in all-chair forms only; for decalin, boat forms are of high energy.



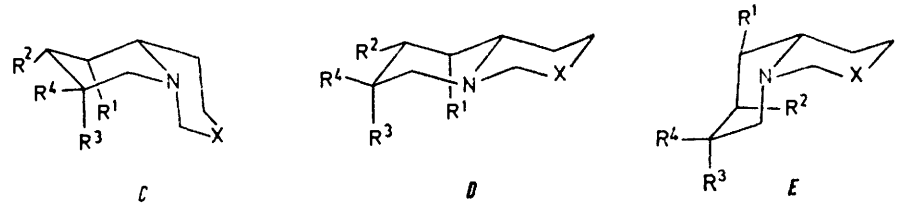
SCHEME 1

Quinolizidine (2) similarly exists in *cis*-(2*B*) and *trans*-(2*A*) conformers. To a first approximation the energy difference between them is again three extra *gauche*-butane interactions existing in the *cis*-conformer (2*B*); however, this picture is modified by at least two factors. First, the shortened C–N bond lengths (1.47 Å) compared with C–C (1.54 Å) will increase the H–H repulsion in the *gauche*-butane interactions. Second, ease of distortion of the C–N–C valency angles will decrease these H–H repulsions. For monocyclic *N*-alkylpiperidines it was thought that the second factor was the more important [14] although recent work [19] has cast doubt on this. In any case, in the more rigid bicyclic systems the influence of the two factors should be more balanced. Indeed ΔG° 2.6 kcal mol^{-1} has been deduced [20] in favour of the *trans*-isomer for quinolizidine by i.r. measurements on a hydroxy-derivative. We now believe this value to be more reliable than that of 4.4 kcal mol^{-1} reported earlier from this laboratory [21] and based on *N*-methylation rates, a technique now known to be very sensitive to minor structural changes.[22]

Perhydropyrido[1,2-c][1,3]*oxazine* (3).—This compound can exist in three all-chair (*cf.* ref. 9) conformations (3*C*—*E*). The dipole moments for the individual conformers (Table 3) were estimated from the measured moments of tetrahydropyran (1.55 in benzene [23,24] and 1.56 D in cyclohexane [15]) and quinolizidine (0.74 D in benzene [25]). The energy-minimised geometry of the tetrahydro-1,3-oxazine ring [13] was assumed to apply in the bicyclic system. Conformers (3*C* and *D*) possess identical calculated dipole moments; hence the mole proportions of conformers (3*C* + *D*) and of (3*E*) could be calculated from the measured moment in the usual manner [14,26] (Table 3). The *O*-outside *cis*-conformer (3*C*) should be higher in energy than the *trans*-conformer (3*D*) by approximately the amount of the *cis-trans*-quinolizidine ΔG°, and should therefore contribute only *ca.* 1%



	X	R^1	R^2	R^3	R^4
(3)	O	H	H	H	H
(4)	O	Me	H	H	H
(5)	O	H	Me	H	H
(6)	O	H	H	Et	H
(7)	O	H	H	H	Et
(8)	S	H	H	H	H



SCHEME 2

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to the equilibrium at 25°. Rather more of the *O*-inside *cis*-conformer (3*E*) could occur since replacement of CH_2 at the 2-position by an oxygen atom appreciably lowers interaction with the 8-methylene group. This recalls the diminished *N*-alkyl-equatorial preferences in the tetrahydro-1,3-oxazine system compared with piperidines. The effect of the additional heteroatom may be greater in the bicyclic system where the 8-methylene group is analogous to those for the demethyl derivative (3) previously discussed. The mole proportions of conformers (*C* + *D*) and of *E* for the two methyl derivatives were calculated as above (Table 3).

For the 5-methyl compound (4), the *O*-outside *cis*-conformation (4*C*) is of high energy because of *syn*-diaxial alkyl interaction and can be neglected. However, compared to the demethyl derivative (3), the extra methyl

TABLE 3

Calculated conformational equilibria

Compound	Observed moment (D)	Conformer	Predicted moment	Conformer of high energy (see text)	Equilibrium determined	% Preferred conformers	ΔG^0/ kcal mol^{-1}
(3)	2.07	*C* and *D*	2.08	*C*	*D* ⇌ *E*	⩾95	⩾1.5
		E	1.30				
(4)	1.73	*C* and *D*	2.08	*C*	*D* ⇌ *E*	50	0.0
		E	1.30				
(5)	2.04	*C* and *D*	2.08	*C*	*D* ⇌ *E*	⩾90	⩾1.3
		E	1.30				
(7)	2.08	*C* and *D*	2.08	*C*	*D* ⇌ *E*	~100	⩾1.5
		E	1.30				
(8)	2.07	*C* and *D*	2.21	*C*	*D* ⇌ *E*	80	0.8
		E	1.42				
(9)	1.40	*F* and *G*	1.54	*F*, *I*, *K*	*G* ⇌ [*H* + *J*]	75	0.6
		H, *I*, and *J*	0.88				
		K	0.93				
(10)	1.47	*F* and *G*	1.46	*F*, *H*, *I*, *J*, *K*	(*G*) only	~100	⩾1.5
		H	0.88				
		I and *J*	0.76				
		K	0.92				
(11)	1.48	*L* and *O*	1.48	*N*, *O*			
		M	0.85		*L* ⇌ *M*	~100	⩾1.5
		N	0.89				

TABLE 4

220 MHz (HR 220) N.m.r. spectra

(*a*) Perhydropyrido[1,2-*c*]pyrimidine and *syn*-perhydrodipyrido[1,2-*c*;2′,1′-*f*]pyrimidine

Compound	Solvent	Chemical shifts (δ) 1-*eq*	1-*ax*	Coupling constants *J*/Hz 1-*ax*, 1-*eq*
(9) R = Me	CCl_4	3.30	2.33	−9.2 [a]
(10) R = Bu^t	CCl_4	3.60	2.39	−8.8 [a]
		6-*eq*	6-*ax*	
(11)	CCl_4	3.24	2.26	

(*b*) Perhydropyrido[1,2-*c*][1,3]oxazines

Compound	Solvent	Temp. (°C)	Chemical shifts (δ) 1-*eq*	1-*ax*	Coupling constants *J*/Hz 1-*ax*, 1-*eq*
(3) R = R′ = H	CCl_4	20	4.10	3.48	−8.0
(3) R = R′ = H	$CDCl_3$–$CFCl_3$	18	4.30	3.60	−8.0
(6) R = Et, R′ = H	$CDCl_3$–$CFCl_3$	20	4.30	4.11	−9.6
(6) R = Et, R′ = H	$CDCl_3$–$CFCl_3$	−90	4.57	4.46	−11.0
			4.33	3.54	−8.0

[a] Average of ten measurements recorded on Varian T-60 spectrometer, 100 Hz sweep width charts.

held close to the 2-position by ring fusion. This reasoning indicates a ΔG° difference between (3*D*) and (3*E*) of 1.5–2.0 kcal mol^{-1}, equivalent to 3–10% of (3*E*). The results (Table 3) are consistent with this interpretation. This result is also consistent with previous spectroscopic studies [9] which give $J_{1\text{-}ax,1\text{-}eq}$ −8.0 Hz * indicating a predominantly *trans*-ring fusion, this value of J_{gem} is confirmed by the 220 MHz spectra (Table 4).

cis(4a-H,5-H)-5-*Methyl-* (4) *and* cis(4a-H, 6-H)-6-*Methyl-perhydropyrido*[1,2-c][1,3]*oxazine* (5).—These compounds both possess three all-chair conformations,

* For detailed discussion of J_{gem} values and further n.m.r. data of the compounds under investigation see refs. 7—10.

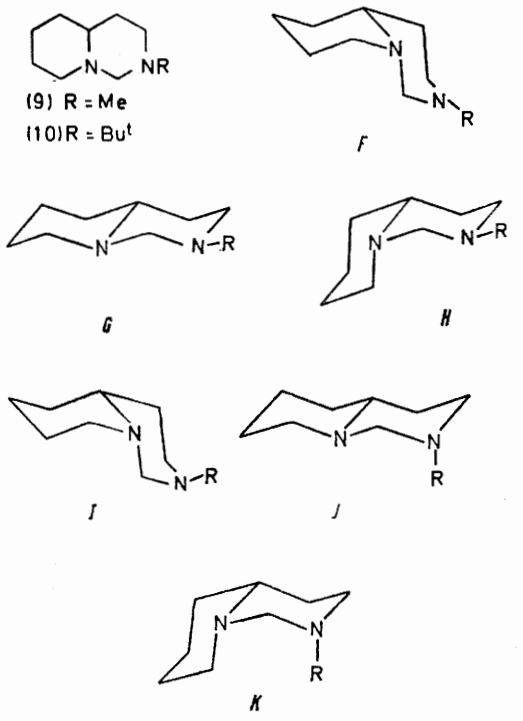
group destabilises the *O*-inside *cis*-conformation (3*E*) by only one *gauche*-butane interaction, compared with the destabilisation of the *trans*-conformation (3*D*) of two *gauche* butane and a *gauche* propylamine interaction. In classical energy terms the energy difference between (3*D*) and (3*E*) may be expressed as b + pa − 3p − e [22] (where b = *gauche*-butane, pa = *gauche*-propylamine, p = propane, and e = ethylamine interactions). This expression equates to b − 2p = 0.85 and pa− p − e = 0.35 kcal mol^{-1}, hence, ΔE is 1.2 kcal mol^{-1} and ΔG° between (4*D*) and (4*E*) should fall to the range 0.3—0.8 kcal mol^{-1}. The experimentally determined value (Table 3) is zero.

Further we have investigated the *cis*(4a-*H*,7-*H*)-7-ethyl analogue (6), for which the equilibrium should be similar to compound (4) by low temperature n.m.r. At −90° two AB quartets for the C-1 protons are observed (Table 4), the upfield quartet has $J_{1\text{-}ax,1\text{-}eq}$ −8.0 Hz (*cf.* J_{gem} −8.0 Hz for the parent unsubstituted compound) and is assigned to the *trans*-fused conformation (6*D*). The downfield quartet has $J_{1\text{-}ax,1\text{-}eq}$ −11.0 Hz and is assigned to the *cis*-fused conformation (6*E*). Planimeter measurements give *ca.* 70% *cis* and 30% *trans* with $\Delta G°$ 0.31 kcal mol^{-1} in favour of the *cis*-conformation. At 20° the spectrum shows one AB quartet for the protons at C-1 with $J_{1\text{-}ax,1\text{-}eq}$ −9.6 Hz. If J_{gem} of −8.0 Hz corresponds to 100% *trans* fused conformation and −11.0 Hz to 100% *cis* fused conformation then J_{gem} of −9.6 Hz indicates *ca.* 53% *cis* fused conformation in the equilibrium mixture [*cf.* 50% by dipole moment studies on the 5-methyl compound (4)]. The *trans*(4a-*H*,7-*H*)-7-ethyl analogue (7) was found by dipole moments to exist entirely in the *trans*-conformation.

For the 6-methyl compound (5), the *O*-inside conformer (5*E*) is of high energy and (5*C*) should contribute only *ca.* 1% to the equilibrium as discussed above for compound (3). Hence (5*D*) should be by far the most favoured conformer, in agreement with experiment (Table 3).

Perhydropyrido[1,2-c][1,3]*thiazine* (8).—The sulphur analogue (8) of the oxygen compound (3) possesses three analogous conformations (8*C*—*E*). Table 3 lists the predicted dipole moments for these conformations, determined from the measured moment of tetrahydrothiapyran (1.71 D in benzene).[23] The tetrahydro-1,3-thiazine geometry was assumed to apply in the bicyclic system. From the observed moment the mole proportions of (8C + *D*) and of (8*E*) were determined (Table 3). Puckering is revealed in the energy-minimised geometry of the tetrahydro-1,3-thiazine ring (Table 2) and this will affect the magnitudes of the *gauche*-butane-type interactions in the various conformations. However, more significant is the long C–S bond length (1.81 Å) compared with C–O (1.43 Å); while of little effect in (8*C* and *D*) since the sulphur atom is at maximum distance from the second ring, the longer bonds in (8*E*) result in even further diminution of interactions compared in turn with the oxygen analogue (3*E*) and *cis*-quinolizidine (2*B*). Approximately the same relationship between (8*C* and *D*) holds as for (3*C* and *D*) [and indeed (2*A* and *B*)], and (8*C*) should contribute only *ca.* 1% to the equilibrium. However conformer (8*E*) is expected to be appreciably populated in contrast to the oxygen analogue (3*E*) and this is observed (Table 3). Previous spectroscopic studies[10] of perhydropyrido[1,2-*c*][1,3]thiazine have deduced that the compound is predominantly in the *trans*-fused conformation (8*D*).

2-Methyl- (9) *and 2-t-Butyl-perhydropyrido*[1,2-*c*]*pyrimidine* (10).—These compounds possess six all-chair conformations (*F*—*K*). Predicted moments for *F*—*J* calculated using the hexahydropyrimidine ring geometry[13] and the moments of *N*-methylpiperidine[14] and quinolizidine, are given in Table 3. The conformers fall into two groups distinguishable by dipole moments, (*F*,*G*) and (*H*—*J*), and the mole proportions of the groups, calculated as before, are given in Table 3.



SCHEME 3

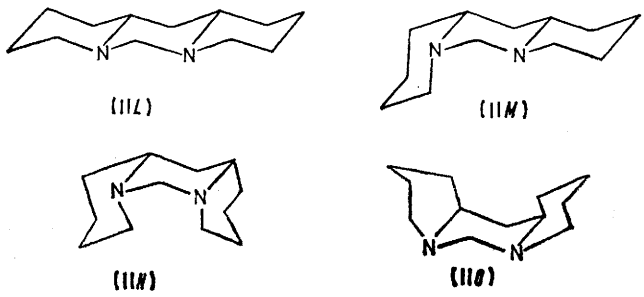
Of these conformations *K* possesses *syn*-diaxial and three *gauche*-butane interactions and *I* four *gauche*-butane interactions, and their contributions to the equilibrium will be negligible. The relationship between *F* and *G* is as in the previous systems and *F* should contribute only *ca.* 1% with respect to *G*. Hence we consider further only conformations *G*, *H*, and *J*.

For the *N*-methyl compound (9), the difference between between (9*H* and *J*) is approximately one *gauche*-butane interaction (*ca.* 0.9 kcal mol^{-1}) in favour of (9*J*) and they should be in equilibrium to the extent of *ca.* 4 : 1 at 25°. The equilibrium (9*G*) ⇌ (9*J*) should approximately equal that for the methyl group in 1-t-butyl-3-methylhexahydropyrimidine ($\Delta G°$ 0.43 kcal mol^{-1} in cyclohexane[13]). Hence the equilibrium $G \rightleftharpoons [J + H]$ should be of the order of 0.3 kcal mol.$^{-1}$ The observed value *ca.* 0.6 kcal mol^{-1} in benzene is in reasonable agreement. We conclude that the equilibrium proportions for the *N*-methyl compound (9) are *ca.* (9*G*) (75%), (9*J*) (20%), (9*H*) (5%). The previously[7] measured value of J_{gem} for the C-1 methylene group of compound (9) was $J_{1\text{-}ax,1\text{-}eq}$ −8.4 Hz; a more accurate determination from 220 MHz spectra (Table 4) gives a value of −9.2 Hz. If J_{gem} values of −8.5 (*cf.* 11) and −11.2 Hz[27] are representative of *trans*- and *cis*-fused conformations then the J_{gem} of −9.2 Hz corresponds to *ca.* 75% of the *trans*-fused conformation in agreement with the estimate based on dipole moment data.

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

For the t-butyl derivative (10), detailed consideration indicates that all conformations except (10*G*) are of high energy, in agreement with the experimental results (Table 3). J_{gem} for (10) is −8.8 Hz, a more negative value than expected (−8.5 Hz) for the *trans*-fused conformation. However the presence of the t-butyl group on the N-2 atom will produce some deformation at that nitrogen atom compared to the geometry present in the *N*-methyl analogue and this should affect the value of J_{gem}.

syn-*Perhydrodipyrido*[1,2-c, 2′,1′-f]*pyrimidine* (11).—Four possible all-chair conformations *L*—*O* are available of which (11*N* and *O*) may be excluded on the basis of the β-diaxial arrangement of the ring residues. The dipole moments for the individual conformations were estimated from the moment of quinolizidine, assuming the energy-minimised geometry of the hexahydropyrimidine ring to apply in the tricyclic system. The value for (11*G*) is just that expected from a 1,3-diaxial arrangement of two quinolizidine lone pairs, and agrees with the measured dipole moment (Table 3) indicating a large preference for conformation *L*. Previous spectroscopic studies [8] of



SCHEME 4

syn-perhydrodipyrido[1,2-*c*, 2′,1′-*f*]pyrimidine (11) have concluded that the compound adopts the *trans, syn, trans*-conformation *L*.

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