The Conformational Analysis of Saturated Heterocycles. Part LI.[1] Spirodioxolans

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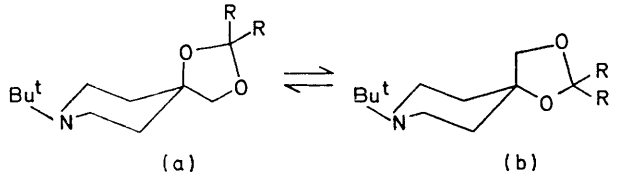
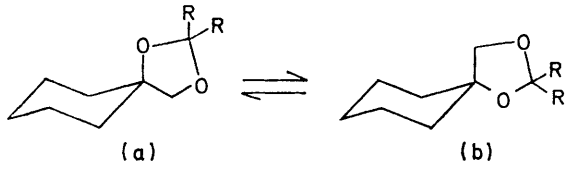
Cyclohexanespiro-4'-dioxolan exists in $CFCl_3$ preferentially in the *O*-axial conformation. The slight preference for *O*-axial is decreased in the geminally substituted 2',2'-dimethyl derivative and increased in the corresponding 1-t-butylpiperidine-4-spiro-4'-derivatives. These variations are discussed.

WE recently reported[2] that, in [$^2H_3$]toluene, the conformational equilibrium for the piperidinespirodioxolan (1a) ⇌ (1b) favours the *O*-axial conformer (1a), with ΔG°_{201} of 0·26 kcal mol^{-1}. We have now examined the corresponding equilibria for the dimethyl homologue (2) and for the two cyclohexanespirodioxolan analogues (3) and (4). Very recently, Uebel *et al.*[3] have published a



(a) (b)

(1) R = H
(2) R = Me



(a) (b)

(3) R = H
(4) R = Me

preliminary note on their study of these cyclohexanespirodioxolan equilibria (3a) ⇌ (3b) and (4a) ⇌ (4b); this work is discussed below. The compounds were all prepared from the corresponding 1,2-glycols with acetone or formaldehyde, and examined by low-temperature n.m.r. spectroscopy.

EXPERIMENTAL

2',2'-Dimethyl-1-t-butylpiperidine-4-spiro-4'-(1',3'-dioxolan).—Sulphuric acid (1·3 g, 98%) was added dropwise with shaking to 4-hydroxy-4-hydroxymethyl-1-t-butylpiperidine[2] (2·4 g) in acetone (50 ml). The mixture was stirred for 12 h at 20°. Saturated sodium carbonate was added until pH 8, and the solution ether-extracted (5 × 20 ml). The dry (Na_2SO_4) extracts were evaporated, and the residue (1·0 g) was dissolved in hexane (5 ml): at −30 °C the dioxolan (0·6 g, 25%) crystallised; it sublimed at 100°/0·35 mm, m.p. 52—54° (Found: C, 68·8; H, 11·3; N, 6·2. $C_{10}H_{18}O_2$ requires C, 68·6; H, 11·08; N, 6·1%).

1-t-Butylpiperidine-4-spiro-4'-(1',3'-dioxolan), b.p. 90—92°/1·1 mm (lit.,[2] b.p. 71—72°/0·4 mm), was prepared as previously described.[2]

[1] Part L, I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, preceding paper.

[2] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302.

[3] J. J. Uebel, E. L. Nickoloff, W. T. Cole, and C. B. Grant, *Tetrahedron Letters*, 1971, 2637.

1-Hydroxymethylcyclohexanol.—$LiAlH_4$ (3·0 g) in THF (100 ml previously distilled from $LiAlH_4$) was heated under reflux under nitrogen for 10 min, and 1-hydroxycyclohexanecarboxylic acid[4] (7·2 g) in THF (25 ml) was added dropwise to it. After being heated under reflux for 4 h, the solution was stirred for 12 h and then water (3 ml), 15% NaOH (3 ml), and water (9 ml) were added successively. The precipitate was filtered off and extracted with THF (2 × 50 ml). The solvent was removed from the dried, combined extracts to give the diol (6·5 g, 95%) which crystallised from benzene as plates, m.p. 75—76° (lit.,[5] m.p. 73—75°).

Cyclohexanespiro-4'-(1',3'-dioxolan).— 1-Hydroxymethylcyclohexanol, benzene (75 ml), toluene-*p*-sulphonic acid (0·05 g), and paraformaldehyde (1·5 g) were refluxed under a Dean and Stark head, with dried molecular sieve in the collecting limb for 1 h (t.l.c. then showed no starting material). Silver oxide (1 g) was added to the mixture and the benzene was distilled off at 100°/760 mm. The residue was distilled, and the fraction b.p. 65—70°/30 mm redistilled from sodium to give the *dioxolan* (0·65 g, 20%) as an oil, b.p. 180—182°/760 mm (Found: C, 69·2; H, 9·9. $C_8H_{14}O_2$ requires C, 69·5; H, 10·2%).

2',2'-Dimethylcyclohexanespiro-4'-(1',3'-dioxolan).— 1-Hydroxymethylcyclohexanol (3 g), acetone (18 ml, dried over molecular sieve type 4A), benzene (18 ml, dried over sodium wire), and toluene-*p*-sulphonic acid (0·05 g) were refluxed under a Dean and Stark head for 4 h. After 1 h, solvent (10 ml) was run off from the collecting limb of the Dean and Stark head (which was filled with dried molecular sieve). Silver oxide (1 g) was added and volatile material

TABLE 1

N.m.r. chemical shifts (p.p.m. on δ scale) for 1-t-butylpiperidine-4-spiro-4'-(1',3'-dioxolans) and cyclohexanespiro-4'-(1',3'-dioxolans) [a,b]

Compound	Dioxolan ring 2CH_2	Dioxolan ring 2Me	Dioxolan ring 5CH_2	Piperidine or cyclohexane ring	*N*-t-Butyl
1-t-Butylpiperidine-4-spiro-4'-(1',3'-dioxolan) (1)	4·89		3·50	2·57—1·57	1·04
2',2'-Dimethyl-1-t-butylpiperidine-4-spiro-4'-(1',3'-dioxolan) (2)		1·27	3·60	2·50—1·60	1·02
Cyclohexanespiro-4'-(1',3'-dioxolan) (3)	4·84		3·50	1·9—1·1	
2',2'-Dimethylcyclohexanespiro-4'-(1',3'-dioxolan) (4)		1·28	3·63	1·9—1·1	

[a] All measurements at 100 MHz and 34° with Me_4Si internal standard. [b] Measured in CCl_4.

[4] J. Rouzaud, G. Cauquil, and L. Giral, *Bull. Soc. chim. France*, 1964, 2908.

[5] H. E. Baumgarten, F. A. Bower, and T. T. Okamto, *J. Amer. Chem. Soc.*, 1957, **79**, 3145.

was distilled. The fraction b.p. 190—192°/760 mm was redistilled from sodium to give the *dioxolan* (1·3 g, 32%) as an oil, b.p. 191—192°/760 mm (Found: C, 71·9; H, 11·2. $C_{10}H_{18}O_2$ requires C, 72·2; H, 10·9%).

N.m.r. Spectroscopy.—Spectra, recorded in Tables 1 and 2, were obtained under the conditions described in ref. 2.

RESULTS AND DISCUSSION

The low-temperature n.m.r. results show (Table 2) that the spirodioxolans with the oxygen atom axial [*i.e.* (1)—(4a)] are favoured in each case with ΔG° values of 0·05—0·25 kcal mol^{-1}. The proportion of the *O*-axial conformer is greater for the piperidines (1) and (2) than for the cyclohexanes (3) and (4), and for the demethyl compounds (1) and (3) than for the 2′,2′-dimethyl derivatives (2) and (4), but these influences are not additive.

It appears unlikely that large solvent-interaction effects influence comparisons within the present results; we have studied the spiropiperidine (1) in $CFCl_3$ and mixed $CFCl_3$–$PhCD_3$ with results (Table 2) not significantly different from those obtained [2] for $PhCD_3$ solvent. However, other solvents may have a greater effect; the finding [3] that in CD_3OD–$CDCl_3$ the equilibrium for (4) favours the *O*-equatorial conformer (4b) by 0·13—0·28 kcal mol^{-1} depending on the proportion of CD_3OD present clearly indicates that hydrogen bonding of the oxygen atom is occurring in this solvent. The reported [3] results for (3) in acetone of 0·07 kcal mol^{-1} in favour of the *O*-axial conformer may also indicate some interactions with the acetone solvent.

The differences found for the equilibrium position between the piperidine and cyclohexane series could be due to dipole–dipole interactions. The dipole vectors associated with the nitrogen and 3′-position oxygen atoms in the *O*-equatorial conformers (1b) and (2b) are approximately parallel giving rise to repulsive interactions whereas in the *O*-axial conformers (1a) and (2a) the interaction is attractive. The interactions between the nitrogen and the 1-position oxygen atoms are negligible in both conformations. Quantitative assessment of these interactions is difficult; calculations based on point dipoles suggest repulsive interactions of *ca.* 0·2 kcal mol^{-1} in the *O*-equatorial conformers and slightly larger attractive interactions in the *O*-axial conformers. The combined effect would obviously be larger than the observed differences between the piperidine and cyclohexane systems; we place no reliance on the quantitative accuracy of these calculations but they serve to demonstate that dipole–dipole interactions can account for our observations of the difference between the piperidine and cyclohexane series. The considerable influence of a substituent at the 4-position on the conformation equilibrium position of a 1-substituent has been noted before.[6-9]

The most surprising feature of the present results is that the geminal 2′,2′-dimethyl group favours the *O*-equatorial conformation relative to the corresponding de-methyl compounds. On grounds of polar effect (*cf.* ref. 10), steric buttressing, or steric hindrance to solvation the opposite might have been expected.

We conclude that whereas the qualitative, and the grosser quantitative, aspects of the conformations of heterocycles can be rationalised, there remain subtler effects which require further investigation.

TABLE 2

Low-temperature n.m.r. measurements at 100 MHz on chemical shifts of the dioxolan ring 5-methylene protons of individual conformers

	Solvent	Conc. w/v %	T [a]	Chem. shifts (δ) (b)	(a)	Ratio of areas of high to low-field peaks [b] Hand planimetry	Height X width 1/2 ht.	ΔG° [c]
(1)	$C_6H_5CD_3$	22	−72	3·665	3·605	1·93 ± 0·01	1·83 ± 0·04	1·09 ± 0·04
	$CFCl_3$–$C_6H_5CD_3$ (1 : 1)	15	−85	(*J* 11 Hz) [d]		1·96 ± 0·01	1·93 ± 0·02	1·05 ± 0·04
	$CFCl_3$	15	−85	(*J* 9 Hz) [d]		2·04 ± 0·01	1·88 ± 0·02	1·13 ± 0·04
(2)	$CFCl_3$	8·25	−80	3·290	3·120	1·76 ± 0·01	1·69 ± 0·06	0·88 ± 0·13
(3)	$CFCl_3$	16·5	−80	3·578	3·430	1·55 ± 0·01	1·55 ± 0·05	0·71 ± 0·04
(4)	$CFCl_3$	16·5	−80	3·614	3·484	1·15 ± 0·03	1·13 ± 0·03	0·21 ± 0·04

[a] Temperature of measurement (°C). [b] Arithmetic means and standard deviations. [c] In kJ mol^{-1} at temperature T, calculated from peak area ratios, errors calculated from standard deviations of peak area ratios. [d] Coupling constant between axial and equatorial methylene peaks.

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[6] C. Ainsworth, R. E. Hackler, and H. E. Boaz, *J. Org. Chem.*, 1966, **31**, 3345.
[7] R. D. Stolow, T. Groom, and P. D. M'Master, *Tetrahedron Letters*, 1968, 5781.
[8] R. D. Stolow, T. W. Giants, and J. D. Roberts, *Tetrahedron Letters*, 1968, 5777.
[9] R. D. Stolow, D. I. Lewis, and P. A. D'Angelo, *Tetrahedron*, 1970, **26**, 5831.
[10] R. U. Lemieux and A. A. Pavia, *Canad. J. Chem.*, 1969, **47**, 4441.