The Conformational Analysis of Saturated Heterocycles. Part LVI.[1] Substituent Effects in the Conformational Equilibria of Spiro-oxazolines

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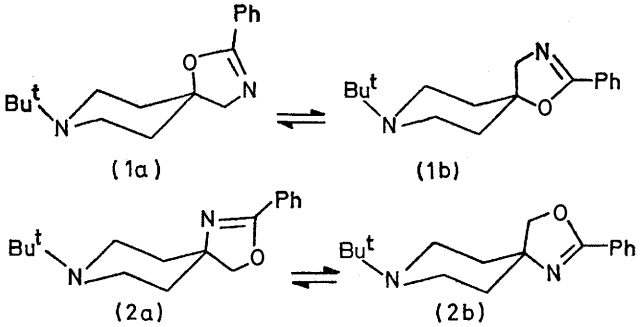
The effects on the conformational equilibria of cyclohexanespiro-4'-oxazolines of 2'-substituents of variable electronic effect and steric size has been examined: surprisingly all exist in the *N*-equatorial conformation. Possible explanations are given. 1,3-Dioxan-5-spiro-4'-oxazolines favour the *N*-equatorial conformation by a large factor, as expected.

WE recently suggested [2] the use of spiro-compounds as a general method for the investigation of intramolecular interactions in situations of defined geometry. In the piperidine-4-spiro-5'-oxazoline series, conformer (1a) was more stable than (1b) [3] by $\Delta G^\circ = 0{\cdot}40$ kcal mol^{-1}; the preference for (1a) is expected. However, it was also found [3] that in the piperidine-4-spiro-4'-oxazoline series conformer (2b) was preferred to (2a) by 0·17 kcal mol^{-1}, an unexpected result.

The present paper describes work designed to elucidate further the conformational equilibria of spiro-4-oxazolines. For a compound in which lone-pair interactions should dominate, we have investigated the equilibrium (3a) $\rightleftharpoons$ (3b); the two extra oxygen atoms should force the conformational equilibrium well towards the *N*-equatorial conformer (3b). We have also examined



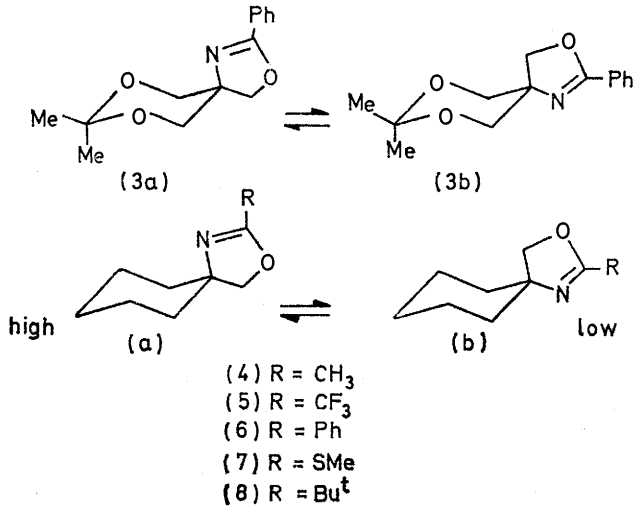
the effect of substituents in the oxazoline ring by studying compounds of the series (4)—(8).

[1] Part LV, I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, in preparation.

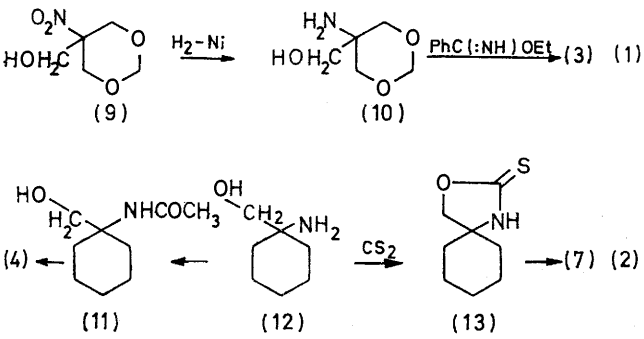
[2] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302.

[3] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1308.

Preparation of Compounds.—The dioxanspiro-oxazoline (3) was prepared by the route shown in equation



(1). 1-Amino-1-hydroxymethylcyclohexane (12) [4] was *N*-acetylated by heating under reflux with ethyl acetate; [5] this afforded a considerably better yield of



the amino-intermediate (11) than that previously obtained [6] by partial hydrolysis of the diacetyl derivative. The amido-alcohol was cyclised to (4). The phenyl (6) and trifluoromethyl analogues (5) were obtained by modifications of this route while the trimethylacetyl derivative was prepared by partial methanolysis of the diacyl derivative. Previous attempts [6,7] to prepare (4) were unsuccessful. Treatment of the amino-alcohol (12) with CS_2 gave the thione (13), converted by methyl iodide into (7). Attempts to prepare the t-butyl derivative (8) failed, as the pivaloyl compound corresponding to (11) could not be cyclised.

EXPERIMENTAL

5-Amino-5-hydroxymethyl-2,2-dimethyl-1,3-dioxan.— 5-Hydroxymethyl-2,2-dimethyl-5-nitro-1,3-dioxan [8] (29 g) in MeOH (290 ml) was stirred with Raney nickel (9 g) under hydrogen at 1400 lb in^{-2} for 2 h at 70°. MeOH was evaporated to give the amino-dioxan (18·5 g, 75%); it crystallised from ether, m.p. 54·5—55·5° (lit.,[9] 55°).

2,2-Dimethyl-1,3-dioxan-5-spiro-4'-(2'-phenyl-2'-oxazoline) (3).— 5-Amino-5-hydroxymethyl-2,2-dimethyl-1,3-dioxan (1·7 g) and ethyl benzimidate (1·7 g) [prepared by dissolution of the hydrochloride (5 g) in 30% aqueous $NaHCO_3$, extraction with ether (3 × 10 ml), and drying (Na_2SO_4) to give the free base (4 g)] were heated under reflux in xylene for 10 h. The solution was evaporated and the residue chromatographed on alumina and eluted with benzene to give the *oxazoline* (0·3 g); it crystallised from ether–light petroleum (b.p. 60—80°), m.p. 94—95° (Found: C, 68·2; H, 6·7; N, 5·7. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9; N, 5·7%).

1-Acetamido-1-hydroxymethylcyclohexane.— 1-Amino-1-hydroxymethylcyclohexane (2·58 g) and AnalaR ethyl acetate (3·52 g) were heated under reflux for 96 h. The solvent was evaporated and the residue crystallised from benzene–light petroleum (b.p. 60—80°) (1 : 10) to give the cyclohexane (1·15 g, 33·7%) as needles, m.p. 119—120° (lit.,[6] m.p. 121—123°); $\nu_{max.}$ (Nujol) 3420, 3320, and 1648 cm^{-1}.

Cyclohexanespiro-4'-(2'-methyl-2'-oxazoline) (4).—1-Acetamido-1-hydroxymethylcyclohexane (1·15 g) was added gradually to freshly distilled thionyl chloride at 0°. The solution was stirred for 24 h and then poured into ether (50 ml) at 0°. The precipitate was filtered off, dissolved in water (5 ml), the solution made strongly basic with NaOH, and extracted with ether (4 × 25 ml). The dried (Na_2SO_4) extracts were distilled to give the *oxazoline* (0·32 g, 31%) as an oil, b.p. 86° at 14 mmHg (Found: C, 70·6; H, 10·0; N, 9·4. $C_9H_{15}NO$ requires C, 70·6; H, 9·8; N, 9·2%); $\nu_{max.}$ (liquid film) 1670 cm^{-1}; τ (CCl_4) 6·24 (2H, s), 8·19 (3H, s), and 7·5—9·0 (10H).

1-Trifluoroacetamido-1-hydroxymethylcyclohexane.— Ethyl trifluoroacetate (0·71 g), 1-amino-1-hydroxymethylcyclohexane (0·65 g), and ether (4 ml) were stirred for 3 h. Light petroleum (b.p. 60—80°) (50 ml) was added. After 15 h at −5°, the *1-trifluoroacetamidocyclohexane* (0·80 g, 74%) separated; it crystallised from benzene–light petroleum (b.p. 60—80°) as needles, m.p. 85—86° (Found: C, 47·8; H, 6·6; N, 6·5. $C_9H_{14}F_3NO_2$ requires C, 48·0; H, 6·3; N, 6·3%); $\nu_{max.}$ ($CHBr_3$) 3465, 3280, and 1705 cm^{-1}.

1-Trifluoroacetamido-1-p-tolylsulphonyloxymethylcyclohexane.—Toluene-*p*-sulphonyl chloride (1·02 g) was added in portions to 1-trifluoroacetamido-1-hydroxymethylcyclohexane (1·2 g) in pyridine (1·68 g). The whole was stirred for 7 days, and the precipitate filtered off. Removal of the pyridine gave the *cyclohexane* (1·3 g, 64·5%) which crystallised from benzene–light petroleum (b.p. 60—80°) (1 : 10) as prisms, m.p. 103—104° (Found: C, 51·0; H, 5·5; N, 3·8. $C_{16}H_{20}NF_3O_4S$ requires C, 50·7; H, 5·3; N, 3·7%); $\nu_{max.}$ ($CHBr_3$) 3315 and 1725 cm^{-1}.

Cyclohexanespiro-4'-(2'-trifluoromethyl-2'-oxazoline) (5).—1-Trifluoroacetamido-1-*p*-tolylsulphonyloxymethylcyclohexane (1·3 g) was heated under reflux in pyridine (5 ml) for 2 h and then set aside for 7 days. The precipitate was filtered off and the filtrate distilled to give *cyclohexanespiro-4'-(2'-trifluoromethyl-2'-oxazoline)* (0·16 g, 24·5%) as an oil,

[4] M. S. Newman and W. M. Edwards, *J. Amer. Chem. Soc.*, 1954, **76**, 1840.
[5] *Cf.* G. R. Handrick, E. R. Atkinson, F. E. Granchelli, and R. J. Bruni, *J. Medicin. Chem.*, 1965, **8**, 762.
[6] W. E. Noland, J. F. Kneller, and D. E. Rice, *J. Org. Chem.*, 1957, **22**, 695.
[7] W. E. Noland and R. A. Johnson, *J. Org. Chem.*, 1964, **29**, 2760.
[8] G. B. Linden and M. H. Gold, *J. Org. Chem.*, 1956, **21**, 1175.
[9] M. Senkus, U.S.P. 2,370,586/1945 (*Chem. Abs.*, 1945, **39**, 4097 [9]).

b.p. 98° at 20 mmHg (Found: C, 49·3; H, 6·5; N, 7·1. $C_8H_{12}F_3NO$ requires C, 49·2; H, 6·2; N, 7·2%); $\nu_{max.}$ (liquid film) 1690 cm^{-1}.

1-*Benzamido*-1-*hydroxymethylcyclohexane*.—Freshly distilled benzoyl chloride (2·18 g) in benzene (5 ml) and NaOH (0·78 g) in water (6·4 ml) were added simultaneously with stirring to 1-amino-1-hydroxymethylcyclohexane (2 g) in water (30 ml) cooled in ice. After stirring for 4 h the solid was filtered off and crystallised from benzene to give the amide (2·90 g, 80%) as amorphous crystals, m.p. 118—120° (lit.,[10] m.p. 118—122°).

Cyclohexanespiro-4′-(2′-phenyl-2′-oxazoline) (6).—1-Benzamido-1-hydroxymethylcyclohexane [10] (2·85 g) was added gradually to freshly distilled thionyl chloride (24 g) at 0°. The solution was stirred for 24 h and poured into ice-cold ether. The white precipitate dissolved in water (25 ml), made strongly alkaline with NaOH, and extracted with ether (6 × 20 ml). The dry (KOH) extracts were distilled to give the *oxazoline* (1·63 g, 62%) as an oil, b.p. 145° at 0·4 mmHg (Found: C, 77·6; H, 6·5; N, 7·8. $C_{14}H_{17}NO$ requires C, 78·1; H, 6·5; N, 7·9%); $\nu_{max.}$ (liquid film) 1650 cm^{-1}; τ (CCl_4) 1·95—2·2 (2H, m), 2·5—2·8 (3H, m) 6·02 (2H, s), and 7·8—9·0 (10H).

TABLE 1

N.m.r. chemical shifts (τ) for cyclohexanespiro-4′-(2′-oxazolines) and 2,2-dimethyl-1,3-dioxan-5-spiro-5′-(2′-phenyl-2′-oxazoline) [a]

	Oxazoline ring				Cyclohexane or dioxan ring	
Compd.	5′-CH_2	2′-Me	2′-Ph	2′-Bu[t]	Ring	2-Me
(3)	5·78		2·1—2·9		6·32 (m)	8·60, 8·79
(4)	6·24	8·19			7·5—9·0	
(5)	5·91				7·5—9·0	
(6)	6·02		1·95—2·2 2·5—2·8		7·8—9·0	
(7)	6·07	7·63			7·9—9·0	
(8)	6·21			8·86	8·0—8·7	

[a] All measurements refer to 10% w/v solution in CCl_4 at 60 MHz and 34° with Me_4Si internal standard except that for (3) the solvent was toluene.

Cyclohexanespiro-4′-(oxazolidine-2′-thione).—Carbon disulphide (2·3 g) in benzene (9 ml) was added to 1-amino-1-hydroxymethylcyclohexane (3·87 g) in benzene (9 ml) at 0° over 15 min with vigorous stirring. After 30 min more, the solid was filtered off and heated at 120° for 4 h (evolution of hydrogen sulphide had then stopped). The residue was cooled in ice and the *thione* (1·35 g, 26%) separated; it crystallised from EtOH as needles, m.p. 190—191° (Found: C, 56·2; H, 7·4; N, 8·0. $C_8H_{13}NOS$ requires C, 56·2; H, 7·6; N, 8·2%); $\nu_{max.}$ (Nujol) 3170 and 1522 cm^{-1}; τ ($CDCl_3$) 5·68 (2H, s) and 8·0—8·9 (10H).

Cyclohexanespiro-4′-(2′-methylthio-2′-oxazoline) (7).—Cyclohexanespiro-4′-(oxazolidine-2′-thione) (1·2 g) in ethanolic NaOEt (from 0·16 g Na and 8 ml dry EtOH) was mixed with MeI (1·3 g) in EtOH (5 ml) and the solution stirred at 20° for 1·5 h. MeI (1 g) was added and the solution heated under reflux for 1 h. Volatile material was removed at 100° and 15 mmHg; the residue was dissolved in water and extracted with ether (3 × 10 ml). The dry ($MgSO_4$) extracts were evaporated and the residue chromatographed on silica and eluted with benzene–ether (1 : 19). The solvent was removed and the residue distilled to give the *methylthio-oxazoline* (106 mg, 8·2%) as an oil, b.p. 123° at 20 mmHg (Found: C, 58·7; H, 8·1; S, 17·5. $C_9H_{15}NOS$ requires C, 58·4; H, 8·1; S, 17·3%); $\nu_{max.}$ (liquid film) 1614 cm^{-1}; τ [$CFCl_3$–CS_2 (7 : 3)] 6·07 (2H, s), 7·63 (3H, s), and 7·9—8·9 (10H).

1-*Trimethylacetamido*-1-*trimethylacetoxymethylcyclohexane*.—1-Amino-1-hydroxymethylcyclohexane (1·35 g) and pyridine (4 ml) were dissolved in dry benzene (15 ml). To this was added with stirring during 20 min trimethylacetyl chloride [11] (4·0 g) in dry benzene (20 ml), followed by stirring for 2·5 h at room temperature. HCl (10%, 25 ml) and ether (25 ml) were added and the layers separated. The organic layer was extracted with Na_2CO_3 (3%, 4 × 15 ml) and water (2 × 15 ml), dried ($MgSO_4$), and removal of volatile material left the crude *amido-ester* (1·3 g, 42%), recrystallised from methanol–water, plates, m.p. 107·5—108° (Found: C, 68·4; H, 10·5; N, 4·6. $C_{17}H_{31}NO_3$ requires C, 68·7; H, 10·5; N, 4·7%); $\nu_{max.}$ (Nujol) 3407, 1710, and 1655 cm^{-1}.

1-*Trimethylacetamido*-1-*hydroxymethylcyclohexane*.—1-Trimethylacetamido-1-trimethylacetoxymethylcyclohexane (2·5 g) was dissolved in a solution of MeOH (50 ml) and NaOH (0·34 g) and allowed to stand for 72 h at room temperature. The MeOH was removed and ether (25 ml) and NaOH (10%, 25 ml) were added. The ether layer was dried ($MgSO_4$) and evaporated, leaving the *amido-alcohol* (1·8 g, 89%) which crystallised from CCl_4 as needles, m.p. 99—99·5° (Found: N, 6·4. $C_{12}H_{23}NO_2$ requires N, 6·6%); τ ($CDCl_3$) 4·4br (1H, s), 5·0br (1H, s), 6·4 (2H, s), 8·1—8·6 (10H, m), and 8·8 (9H, s); $\nu_{max.}$ (Nujol) 3350br and 1625 cm^{-1}.

TABLE 2

Low temperature n.m.r. measurements on chemical shifts of oxazoline methylene groups of individual conformers

				Ratio high to low field peaks [b]		
Compound	Concentration (w/v %)	T/°C	Chem. shifts [a] 5′-CH_2	Area	Height × width at 1/2 ht.	$\Delta G°$ [c] / kcal mol^{-1}
(4)	11·4	−82	3·834, 3·673	0·550 ± 0·002	0·558 ± 0·009	0·23
(5)	11·6	−82	4·214, 4·037	0·721 ± 0·003	0·779 ± 0·005	0·13
(6)	11·6	−83	4·056, 3·900	0·266 ± 0·002	0·274 ± 0·003	0·50
(7)	11·7	−82	4·021, 3·870	0·331 ± 0·002	0·350 ± 0·003	0·42
(8)	11·5	−95	3·820, 3·678	0·217 ± 0·002	0·232 ± 0·012	0·54

[a] In δ from Me_4Si standard (at 100 MHz). [b] Arithmetic means and standard deviations. [c] Calculated from peak area ratio. For all measurements the solvent was $CFCl_3$–CS_2 (7 : 3 v/v).

[10] W. E. Noland and R. A. Johnson, *J. Org. Chem.*, 1960, **25**, 1155.

[11] H. C. Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325.

Cyclohexanespiro-4'-(2'-t-butyl-2'-oxazoline) (8).—1-Trimethylacetamido-1-hydroxymethylcyclohexane (3·0 g) was added gradually to freshly distilled thionyl chloride (25 g) at 0°. The solution was stirred overnight and poured into ice-cold ether (50 ml). This solution was carefully poured onto ice (100 g) and made strongly basic by gradually adding KOH pellets while stirring and cooling. The ether layer was separated and the aqueous layer extracted with ether (2 × 50 ml). The combined ether extracts were dried (NaOH), and removal of ether left an oil (1·5 g) which was distilled to give the *product* (0·7 g, 26%), b.p. 80° at 6 mmHg (Found: C, 73·7; H, 11·0; N, 6·9. $C_{12}H_{21}NO$ requires C, 73·8; H, 10·8; N, 7·2%); $\nu_{max.}$ (liquid film) 1660 cm^{-1}.

TABLE 3

Dipole moment of 2,2-dimethyl-1,3-dioxan-5-spiro-4'-(2'-phenyl-2'-oxazoline) (3) [a]

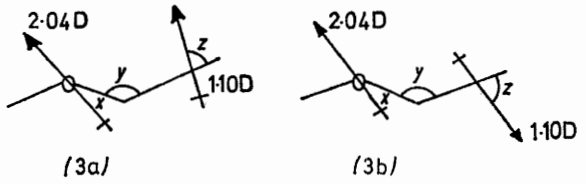
10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$		
1860	920	390		
3730	1690	753		
4040	1790	832		
5170	2230	1127		
$d\varepsilon/dw$	$-dv/dw$	$_{E}P$	$_{T}P_{2\infty}$	μ/D
0·43 ± 0·014	0·213 ± 0·014	64·25	88·55	1·09 ± 0·02

[a] At 25° in benzene. w = Weight fraction of solute, ε = dielectric constant, v = specific volume. The suffixes 1 and 12 refer to solvent and solution respectively.

Physical Methods.—The n.m.r. and dipole moment measurements were made as described in ref. 2 and data are recorded in Tables 1—3.

RESULTS AND DISCUSSION

1,3-*Dioxan-5-spiro-4'-oxazolines.*—The dipole moments of the two conformers (3a) and (3b) can be calculated by vector addition of constituent moments as illustrated in the Figure. The moments for the dioxan and oxazoline



FIGURE

moieties (2·04 and 1·1 D respectively) are those measured for 5,5-dimethyl-1,3-dioxan [12] and 4,4-dimethyl-2-phenyl-2-oxazoline.[3] The angles x, y, and z were taken as 23, 130, and 75° respectively.[2,3,13] The calculated moments are: $\mu_{(3a)}$ 3·04, $\mu_{(3b)}$ 0·93 D. The observed value of 1·09 D (Table 3) corresponds to 96·1% of conformer (3b), or to a $\Delta G°$ value of 1·9 kcal mol^{-1}. The result is insensitive to errors in the values of the angles x, y, and z; changes up to 10° either way lead to values of $n_{(3b)}$ (the mole fraction) between 0·96 and 0·97. The quantitative significance of this result is uncertain for reasons outlined in ref. 2, but the qualitative conclusion is clear, namely that the *N*-equatorial conformer predominates overwhelmingly.

Cyclohexanespiro-4-oxazolines.—The assignments in Table 2 are based on the assumption that the axial 5-methylene groups of the oxazoline ring in (4b)—(7b) occur at lower field than the equatorial 5-methylene groups in (4a)—(7a). This agrees with the conclusions of the survey of similar results previously reported [14] and reflects the deshielding due to steric crowding.

It follows from Table 2 that in all cases the *N*-equatorial conformers (4b)—(7b) are favoured, although the substituent at the 2'-position does have a considerable effect on the precise position of equilibrium. The fact that changing the substituent in the series Ph, SMe, Me, CF_3 increases the amount of *N*-axial conformer (4a)—(7a), may be rationalised by considering the effect of the substituent on the electron density at the nitrogen atom: the greater the electron density, the greater will be the interaction between the nitrogen lone pair and the axial hydrogen atoms of the cyclohexane ring. Phenyl and methylthio are both electron donating relative to methyl in this system; the trifluoromethyl group is electron withdrawing. Steric effects are also clearly significant as the $\Delta G°$ value for Bu^t is 0·54 kcal mol^{-1} compared with 0·23 for methyl: presumably the effect is relayed by buttressing of the t-butyl group against the nitrogen lone pair.

The difference between the piperidine (2) and cyclohexane compounds (6) with the *N*-axial conformer more favoured in the former may reflect greater dipole–dipole repulsions in the conformer (2a) than (2b).

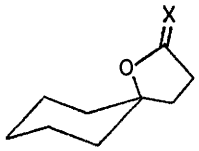
However, the predominance of the *N*-equatorial conformation for all the compounds (2) and (4)—(7) remains surprising and it is clear that subtle effects play a considerable part in determining the conformations of spiro-compounds of this type. These may include changes in bond lengths and angles (see ref. 15); the significant difference [16] between the conformational free-energies of 1·4 kcal mol^{-1} for both CH_2OH and CH_2OMe and of *ca.* 1·8 kcal mol^{-1} for CH_2OAc is relevant. Another possibility is that weak complex formation occurs between the oxazoline nitrogen atom and the $CFCl_3$ and/or CS_2 solvent used in this work: pyridine has been shown [17] to undergo weak complex formation with CCl_4.

Bushweller and O'Neil [18] have discussed the conformational preference of 'sp^2 hybridised lone pairs' by reference to N=C=NPh and other groups. They find a surprisingly large preference for the group to adopt the equatorial position ($\Delta G°$ 1·0 kcal mol^{-1}), far higher than

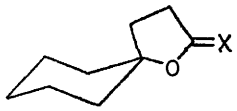
[12] K. A. F. Record, unpublished results.
[13] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.
[14] R. A. Y. Jones, A. R. Katritzky, and P. G. Lehman, *J. Chem. Soc.* (*B*), 1971, 1316.
[15] W. Vandenbroucke and M. Anteunis, *J.C.S. Perkin II*, 1972, 123.
[16] G. W. Buchanan and J. B. Stothers, *Chem. Comm.*, 1967, 1250.
[17] A. N. Sharpe and S. Walker, *J. Chem. Soc.*, 1961, 2974.
[18] C. H. Bushweller and J. W. O'Neil, *J. Org. Chem.*, 1970, **35**, 276.

that for the $N^{+}\equiv C^{-}$ group ($\Delta G°$ 0·21 kcal mol^{-1}). Moreover they observed a decreasing preference for the equatorial position for the groups N=C=X as X varied from NPh to O to S which they attributed to increasing contributions from $N^{+}\equiv C-X^{-}$. These results support the explanations outlined above.

In the cyclohexanespiro-2′-tetrahydrofuran series (14), the introduction of a 2-oxo-group [(14; X = O)] appears [19] to lessen the preference for the *O*-axial conformer (14a) compared to the non-oxo-compound [(14; X = H_2)]. However, the i.r. analytical method used [19]



(14a)



(14b)

involves assumptions regarding the ε_A values of ν(C–O–C) bands.

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[3/1095 *Received*, 30*th May*, 1973]

[19] P. Picard and J. Moulines, *Tetrahedron Letters*, 1970, 5133.