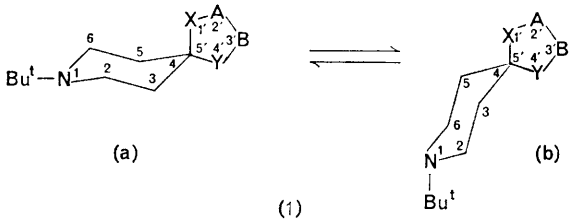
The Conformational Analysis of Saturated Heterocycles. Part XXXII.[1] 1-t-Butylpiperidine-4-spiro-4′- and -5′-oxazolines and -4′- and -5′-thiazolines

By **Richard A. Y. Jones, A. R. Katritzky, P. G. Lehman,** and (Mrs.) **B. B. Shapiro,** School of Chemical Sciences, University of East Anglia, Norwich

Compounds of the type mentioned in the title have been prepared and their dipole moments and low-temperature n.m.r. spectra investigated to provide evidence on the position of the conformational equilibria of type (1a) ⇌ (1b) and hence of the relative steric interactions involving sp^2-hybridised nitrogen, and of oxygen and sulphur attached to sp^2-carbon, compared in each case with a methylene group.

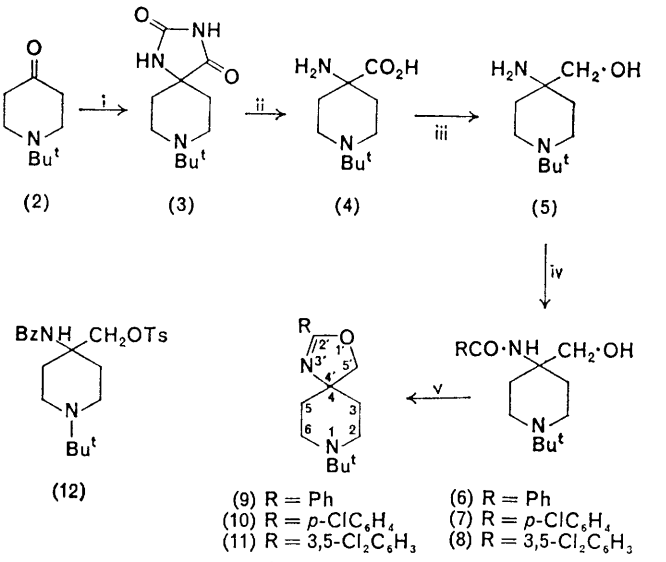
In the previous paper, we described a new general method for the comparison of intramolecular interaction across space in defined geometric situations. This involved the preparation of spiro-compounds of type (1) and the



determination of the position of the conformational equilibria (1a) ⇌ (1b) by dipole moment and n.m.r. techniques. The present paper describes the application of this method to a series of spiro-oxazolines and -thiazolines. In the systems presently under discussion, Y is CH_2 in all cases, whereas XAB is N=C–O, O–C=N, N=C–S, and S–C=N. The compounds were designed to allow comparison of the steric requirements of sp^2-hybridised nitrogen atoms, and of oxygen and sulphur atoms bonded to a sp^2-hybridised carbon with those of a methylene group, and hence with each other. Relatively little quantitative work is available regarding steric interactions involving sp^2-hybridised nitrogen: the dipole moments of 2-(pyridylmethylene)indan-3-ones indicated [2,3] that the steric requirements of an sp^2-lone pair were less than those of a hydrogen atom attached to sp^2-hybridised carbon when the probe was another hydrogen atom. This is supported by work on azabiphenyls [4] and on azametacyclophanes,[5] though not by some on 2-phenylpyridine.[6]

Preparation of Compounds.—The spiro-oxazolines were prepared as outlined in Schemes 1 and 3, the spiro-thiazolines as in Scheme 5, and various model compounds required for the dipole moment work as in Schemes 2 and 4.

Scheme 1 utilises the hydantoin synthesis of amino-acids:[7] the hydantoin (3) was prepared by a modification of a general method.[8] Hydrolysis (3) → (4) was conveniently effected by barium hydroxide. Attempts to esterify the amino-acid (4) failed; it was reduced by



Scheme 1

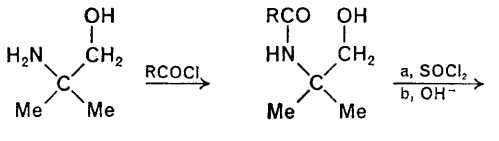
Reagents: i, $(NH_4)_2CO_3$—KCN; ii, $Ba(OH)_2$—H_2O, 160°; iii, $LiAlH_4$; iv, RCOCl, NaOH, PhH; va, $SOCl_2$; vb, OH^-.

the technique described in ref. 9. Selective *N*-benzoylation of (5) was, after difficulty, finally achieved by the method of Leffler and Adams.[10] The oxazoline cyclisation (6) → (9) caused difficulty (*cf.* ref. 11): with (6), toluene-*p*-sulphonyl chloride [12,13] produced a tar from which a small quantity of the ester (12) was isolated; thionyl chloride worked well under mild,[14] but not

[1] Part XXXI, R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), preceding paper.
[2] J. M. Bobbitt, A. R. Katritzky, P. D. Kennewell, and M. Snarey, *J. Chem. Soc.* (*B*), 1968, 550.
[3] A. R. Katritzky in 'Topics in Heterocyclic Chemistry,' ed. R. N. Castle, Wiley, New York, 1969, p. 35.
[4] P. H. Cureton, C. G. Le Fèvre, and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1963, 1736; S. Castellano, H. Günther, and S. Ebersole, *J. Phys. Chem.*, 1965, **69**, 4166; J. N. Murrell, V. M. S. Gill, and F. M. van Duijneveldte, *Rec. Trav. chim.*, 1965, **84**, 1399.
[5] I. Gault, B. J. Price, and I. O. Sutherland, *Chem. Comm.*, 1967, 540.
[6] H. H. Huang, *Chem. Comm.*, 1969, 815.
[7] H. Wheeler and C. Hoffman, *Amer. Chem. J.*, 1911, **45**, 368.
[8] H. Th. Bucherer and V. A. Libe, *J. prakt. Chem.*, 1934, **141**, 5.
[9] O. Vogel and M. Pöhm, *Monatsh.*, 1952, **83**, 541.
[10] M. T. Leffler and R. Adams, *J. Amer. Chem. Soc.*, 1937, **59**, 2252.
[11] R. H. Wiley and L. L. Bennett, jun., *Chem. Rev.*, 1949, **44**, 447.
[12] R. N. Boyd and R. H. Hansen, *J. Amer. Chem. Soc.*, 1953, **75**, 5896.
[13] R. N. Boyd and R. C. Rittner, *J. Amer. Chem. Soc.*, 1960, **82**, 2032.
[14] (*a*) R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, and A. C. Richards, to be published; (*b*) P. W. Collins and J. Andrako, *J. Het. Chem.*, 1966, **3**, 260.

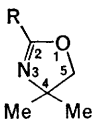
vigorous [10] conditions. The reactions of Scheme 2 follow the methods of Scheme 1.

The reduction of the cyanohydrin (22) [14a] (Scheme 3) was unsatisfactory in tetrahydrofuran [15] at room temperature but proceeded well in ether at 0°. [16] The amino-alcohol (23) was readily converted into the benzamido-alcohol (26), but attempts to cyclise this to the oxazoline (24) by the thionyl chloride method failed. This would not be surprising in view of the S_N2 mechanism demonstrated for this reaction [17] except that (*a*) both *erythro*- and *threo*-1-benzamido-1,2-diphenylpropan-2-ol have been cyclised [18] to the corresponding oxazolines and (*b*) the 5,5-dimethyloxazolines (Scheme 4) were successfully prepared by this method. Sulphuric acid, which has successfully cyclised tertiary amido-alcohols,[8] also failed with (26), this could be due to extra steric hindrance because of the six-membered ring and/or to the effect of the positive charge on the piperidine ring nitrogen.[19] The oxazolines (24) and (25) were finally prepared by the benzimidic ester method [20] in which the C–OH bond is not broken.[19] (This method gave only a poor yield in the conversion (5) ⟶ (9), as expected.)[19] The reduction (27) ⟶ (28) is best carried out at low temperature (*cf.* ref. 21). The cyclisations (29) ⟶ (31) and (30) ⟶ (32) succeed by the thionyl chloride method although we now consider better yields would probably be obtained by the benzimidic ester route.



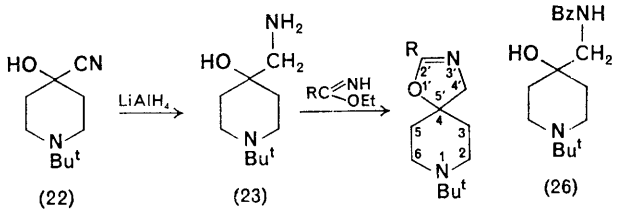
(13)

(14) R = Ph
(15) R = *p*-ClC$_6$H$_4$
(16) R = 3,5-Cl$_2$C$_6$H$_3$
(17) R = *p*-BrC$_6$H$_4$



(18) R = Ph
(19) R = *p*-ClC$_6$H$_4$
(20) R = 3,5-Cl$_2$C$_6$H$_3$
(21) R = *p*-BrC$_6$H$_4$

SCHEME 2

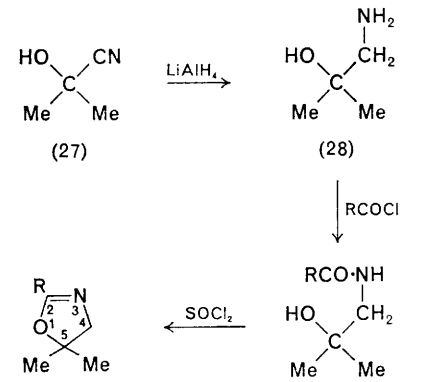


(22) (23) (26)

(24) R = Ph
(25) R = *p*-ClC$_6$H$_4$

SCHEME 3

1-Benzamido-2-methylpropan-2-ol (29) was also cyclised by phosphorus pentasulphide to 5,5-dimethyl-2-phenyl-2-thiazoline (37) by the published [22] method, but application of this method, or a modification [23] failed to effect the conversion (26) ⟶ (35), as did attempts to prepare (35) by fusion of 4-aminomethyl-4-bromo-1-t-butylpiperidine dihydrobromide with thiobenzamide.[24] A specimen of 4,4-dimethyl-2-phenyl-2-thiazoline (38) was prepared in low yield by treatment of 2,2-dimethylaziridine with thiobenzamide, after the method of Kuhn and Drawert.[25]

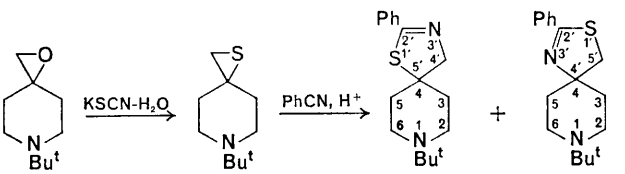


(27) (28)

(31) R = Ph
(32) R = *p*-ClC$_6$H$_4$

(29) R = Ph
(30) R = *p*-ClC$_6$H$_4$

SCHEME 4



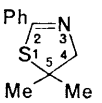
(33) (34) (35) (36)

SCHEME 5

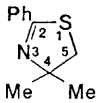
Oxirans have been reported to yield 2-oxazolines with amidines,[26] and 1-t-butylpiperidine-4-spiro-2-oxiran [2] (33) did yield the oxazoline (24) with benzamidine. However, the thiiran (34) [2] and benzamidine gave only traces of (35).[19]

[15] H. R. Nace and B. B. Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 1861.
[16] L. H. Amundsen and L. S. Nelson, *J. Amer. Chem. Soc.*, 1951, **73**, 242.
[17] W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, 1950, **72**, 2187.
[18] G. Drefahl, M. Hartmann, and H.-H. Hörhold, *Chem. Ber.*, 1958, **91**, 1092.
[19] For a full discussion see P. G. Lehman, Ph.D. Thesis, University of East Anglia, 1969.
[20] D. F. Elliott, *J. Chem. Soc.*, 1949, 589; J. Sicher and M. Svoboda, *Coll. Czech. Chem. Comm.*, 1958, **23**, 1252.
[21] R. M. Srivastava, K. Weissman, and L. B. Clapp, *J. Het. Chem.*, 1967, **4**, 114.
[22] J. C. Sheehan and G. D. Laubach, *J. Amer. Chem. Soc.*, 1951, **73**, 4376.
[23] C. Djerassi and C. R. Sholz, *J. Org. Chem.*, 1949, **14**, 660.
[24] S. Gabriel and C. F. von Hirsch, *Chem. Ber.*, 1896, **29**, 2609.
[25] R. Kuhn and F. Drawert, *Annalen*, 1954, **590**, 55.
[26] R. F. Lambert and C. E. Kristofferson, *J. Org. Chem.*, 1965, **30**, 3938.

Thiirans have been shown by Helmkamp *et al.*[27,28] to react with nitriles to yield 2-thiazolines. Most of the examples involved symmetrical thiirans, but they claimed [28] that the reaction was stereospecific because only 2,4-dimethyl-2-thiazoline was isolated (17% yield) from 2-methylthiiran and acetonitrile. We found that the thiiran (34) in this procedure gave both isomeric 2-thiazolines (35) and (36) the structures of which were assigned by comparison of the n.m.r. chemical shifts with model compounds (37) [22] and (38) [25] (*cf.* Tables 1



(37)



(38)

and 2). N.m.r. investigation of the *crude* reaction product (which was obtained in 45% total yield) indicated that compounds (35) and (36) are formed in the ratio *ca.* 1·4 : 1. Separation of (37) and (38) was tedious but they were finally obtained in yields of 12 and 4%; 1-t-butylpiperidine-4-spiro-4′-(2′-phenyl-2′-thiazoline) (36) was obtained isomerically pure but 1-t-butylpiperidine-4-spiro-5′-(2′-phenyl-2′-thiazoline) (35) was not. It contained *ca.* 25% of (36), but this did not interfere with the variable-temperature n.m.r. experiment as the methylene resonances were well separated. These findings necessitate modification of the mechanism proposed [28] for the reaction of thiirans with nitriles; the similar reaction of nitriles with unsymmetrical oxirans usually gives a mixture of products [29] although preferential attack was at the more substituted carbon atom (see also ref. 30). In our reaction (Scheme 5), a larger proportion of product is derived from attack at the *least* substituted carbon atom of the thiiran (34); possibly steric factors balance electronic effects in the present system.

EXPERIMENTAL

1-t-Butylpiperidine-4-spiro-5′-hydantoin.— 1-t-Butylpiperid-4-one (25·0 g.) in ethanol (81·0 ml.), ammonium carbonate (46·5 g.) in water (200 ml.), and potassium cyanide (12·9 g.) in water (42 ml.) were heated at 50—60° for 2 hr., and then kept at 20° for 16 hr. *1-t-Butylpiperidine-4-spiro-5′-hydantoin* (31·7 g., 88%) separated and was dried at 120°: it crystallised as prisms (from methanol–water) m.p. >300° (sublimed on further heating) (Found: C, 58·8; H, 8·7; N, 18·9. $C_{11}H_{19}N_3O_2$ requires C, 58·6; H, 8·5; N, 18·7%); $\nu_{max.}$ at 1775, 1730 (C=O), and 3260, 3180 cm.$^{-1}$ (NH).

4-Amino-1-t-butylpiperidine-4-carboxylic Acid.—1-t-Butylpiperidine-4-spiro-5′-hydantoin (8·0 g.) and barium hydroxide octahydrate (19·2 g.) in water (100 ml.) were heated at 160° for 3 hr. (sealed tube). The contents of three such tubes were combined and the precipitated barium carbonate was filtered off. The filtrate was treated with solid carbon dioxide, again filtered, and concentrated to a small volume from which *4-amino-1-t-butylpiperidine-4-carboxylic acid* (17·5 g., 82·2%) separated as large plates; it crystallised from water–dimethoxyethane as prisms which sublimed at 256—258° (sealed tube) (Found: C, 59·7; H, 10·3; N, 14·3. $C_{10}H_{20}N_2O_2$ requires C, 60·0; H, 10·1; N, 14·0%); $\nu_{max.}$ at 1667, 1590 cm.$^{-1}$.

4-Amino-4-hydroxymethyl-1-t-butyl Piperidine.—Lithium aluminium hydride (2·7 g.), in tetrahydrofuran (150 ml. previously distilled from $LiAlH_4$) was heated under reflux for 10 min. after which dry, finely powdered 4-amino-1-t-butylpiperidine-4-carboxylic acid (7·0 g.) was added in small portions with efficient stirring. After the addition was completed, the solution was heated under reflux for a further 4 hr. With external cooling the reaction mixture was worked up after the method of Mićović and Mihailović [31] and the inorganic solid which was filtered off was extracted with boiling tetrahydrofuran (3 × 25 ml.). The tetrahydrofuran filtrate and extracts were combined and the solvent removed at 20 mm. The residue crystallised from benzene–light petroleum (b.p. 60—80°) to give *4-amino-4-hydroxymethyl-1-t-butylpiperidine* (4·9 g., 75%) as needles, m.p. 75—75·5° (Found: C, 64·2; H, 11·7; N, 15·1. $C_{10}H_{22}N_2O$ requires C, 64·5; H, 11·9; N, 15·0%); $\nu_{max.}$ at 3365, 3330 (NH), 3120br (OH), 1578 cm.$^{-1}$ (NH_2).

4-Benzamido-4-hydroxymethyl-1-t-butylpiperidine.—Freshly distilled benzoyl chloride (1·35 g.) in benzene (2·0 ml.) was added to 4-amino-4-hydroxymethyl-1-t-butylpiperidine (1·9 g.) in water (15 ml.). With external cooling and vigorous stirring, a solution of sodium hydroxide (0·4 g.) in water (9·0 ml.) was added during 30 min. After further stirring at 20° for 1 hr., benzene (30 ml.) was added and the stirring was continued for 30 min. The benzene phase was separated and the aqueous phase was saturated with sodium chloride and extracted with benzene (3 × 20 ml.). The benzene phase and extracts were combined, dried (Na_2SO_4), and the solvent removed under reduced pressure to give *4-benzamido-4-hydroxymethyl-1-t-butylpiperidine* which crystallised from ethyl acetate as plates (1·4 g., 47%), m.p. 154—154·5° (Found: C, 70·8; H, 9·1; N, 9·9. $C_{17}H_{26}N_2O_2$ requires C, 70·3; H, 9·0; N, 9·7%); $\nu_{max.}$ 3330, 3270 (NH), 3200 (OH), 1638 (C=O), 1550 cm.$^{-1}$ (amide II).

The following were similarly prepared: *4-(p-chlorobenzamido)-4-hydroxymethyl-1-t-butylpiperidine* (42%) as prisms, m.p. 163—164° (decomp.) (from isopropyl alcohol) (Found: C, 62·6; H, 7·9; N, 8·2. $C_{17}H_{25}ClN_2O_2$ requires C, 62·9; H, 7·8; N, 8·6%); *4-(3,5-dichlorobenzamido)-4-hydroxymethyl-1-t-butylpiperidine* (49%) as rods, m.p. 184—186° (decomp.) (from ethyl acetate) (Found: C, 57·0; H, 6·8; N, 7·7. $C_{17}H_{24}Cl_2N_2O_2$ requires C, 56·8; H, 6·7; N, 7·8%).

4-Benzamido-1-t-butyl-4-toluene-p-sulphonyloxymethylpiperidine.—Toluene-*p*-sulphonyl chloride (0·93 g.) was added with stirring at 20° to 4-benzamido-4-hydroxymethyl-1-t-butylpiperidine (1·40 g.) in anhydrous pyridine (4·0 ml.). After being stirred for 3 hr., the mixture was poured onto ice (25 g.) and concentrated hydrochloric acid (8 ml.). The acid solution was made strongly alkaline with 20% sodium hydroxide and then extracted with benzene (4 × 20 ml.)

[27] G. K. Helmkamp, D. J. Pettitt, J. R. Lowell, jun., W. R. Mabey, and R. G. Wolcott, *J. Amer. Chem. Soc.*, 1966, **88**, 1030.
[28] J. R. Lowell, jun., and G. K. Helmkamp, *J. Amer. Chem. Soc.*, 1966, **88**, 768.
[29] R. Oda, M. Okano, S. Tokiura, and F. Misumi, *Bull. Soc. Chem. Japan*, 1962, **35**, 1219.
[30] F. Johnson and R. Madroñero, *Adv. Heterocyclic Chem.*, 1966, **6**, 95.
[31] V. M. Mićović and M. Lj. Mihailović, *J. Org. Chem.*, 1953, **18**, 1190.

and chloroform (2 × 20 ml.). The extracts were combined and evaporated. The red solid residue (1·95 g.) was chromatographed on silica gel (B.D.H.) with ethyl acetate–absolute ethanol (2·5 : 1) and 4 fractions were collected. The *toluene*-p-*sulphonate* from fraction 2 recrystallised from ethyl acetate as prisms (0·6 g.), m.p. 220—221° (Found: C, 64·4; H, 7·3; N, 6·4. $C_{24}H_{32}N_2O_4S$ requires C, 64·85; H, 7·3; N, 6·3%); $\nu_{max.}$ 3295 (NH), 1657 (C=O), 1555 (amide II), 1190, 1315 (–SO_2–O).

1-*t-Butylpiperidine-4-spiro-4′-(2′-phenyl-2′-oxazoline)*.— 4-Benzamido-4-hydroxymethyl-1-t-butylpiperidine (1·0 g.) was added to freshly distilled thionyl chloride (11·6 g.) stirred at 10°. The solution was kept at room temperature ($CaCl_2$-protected gas outlet) for 24 hr., and was then poured into dry ether (60 ml.). The separated solid was washed with ether by decantation, and then dissolved in cold water (10 ml.). This solution was made strongly alkaline with 20% sodium hydroxide. 1-*t-Butylpiperidine-4-spiro-4′-(2′-phenyl-2′-oxazoline*) separated and was dried at 15 mm.; it crystallised as plates (0·45 g., 48%), m.p. 157° (from ethyl acetate) (Found: C, 75·3; H, 8·9; N, 10·3. $C_{17}H_{24}N_2O$ requires C, 75·0; H, 8·9; N, 10·3%); $\nu_{max.}$ at 1650 $cm.^{-1}$ (C=N).

The following were similarly prepared: 1-*t-butylpiperidine-4-spiro-4′-(2′-p-chlorophenyl-2′-oxazoline*) (58%) as plates, m.p. 205—205·5° (from isopropyl alcohol) (Found: C, 66·7; H, 7·4; N, 9·2. $C_{17}H_{23}ClN_2O$ requires C, 66·6; H, 7·6; N, 9·1%); 1-*t-butylpiperidine-4-spiro-4′-*[*2′-(3,5-dichlorophenyl)-2′-oxazoline*] (58%) as plates, m.p. 135—135·5° [from isopropyl alcohol–ligroin (b.p. 60—80°)] (Found: C, 59·9; H, 6·5; N, 8·1. $C_{17}H_{22}Cl_2N_2O$ requires C, 59·8; H, 6·5; N, 8·2%).

2-*Benzamido-2-methylpropan-1-ol*.— 2-Benzamido-2-methylpropan-1-ol (60%) was obtained by a literature method [12] as prisms, m.p. 90—90·5° (lit.,[12] m.p. 90·2—91·2°) (from aqueous methanol) (Found: C, 68·5; H, 7·8; N, 7·4. Calc. for $C_{11}H_{15}NO_2$: C, 68·3; H, 7·8; N, 7·3%).

The following 2-methylpropan-1-ols were similarly prepared: 2-(*p*-chlorobenzamido)- (56%), m.p. 88—88·5° (lit.,[1] m.p. 88—89°) (from aqueous methanol) (Found: C, 58·0; H, 6·2; N, 6·2. Calc. for $C_{11}H_{14}ClNO_2$: C, 58·0; H, 6·2; N, 6·2%); 2-(*3,5-dichlorobenzamido*)- (78·5%) as prisms, m.p. 97—97·5° [from ethyl acetate–light petroleum (b.p. 60—80°)] (Found: C, 50·6; H, 5·0; N, 5·6. $C_{11}H_{13}Cl_2NO_2$ requires C, 50·4; H, 5·0; N, 5·4%); and 2-(p-*bromobenzamido*)- (52%) as prisms, m.p. 92—92·5° [from ethyl acetate–light petroleum (b.p. 40—60°)] (Found: C, 48·7; H, 5·1; N, 5·2. $C_{11}H_{14}BrNO_2$ requires C, 48·5; H, 5·2; N, 5·2%).

4,4-*Dimethyl-2-phenyl-2-oxazoline*.— 4,4-Dimethyl-2-phenyl-2-oxazoline was obtained by a literature method [12] as an oil, b.p. 70°/0·4 mm., which crystallised when set aside to give plates (72%), m.p. 24° (lit.,[13] m.p. 23—24°) (Found: C, 75·2; H, 7·8; N, 8·2. Calc. for $C_{11}H_{13}NO$: C, 75·4; H, 7·5; N, 8·0%).

The following was similarly prepared: 2-(p-*chlorophenyl*)-4,4-*dimethyl-2-oxazoline* as an oil, b.p. 88°/0·7 mm., which when set aside crystallised as needles (22%), m.p. 34—34·5° (lit.,[13] m.p. 33—34°) (Found: C, 62·7; H, 6·1; N, 6·5. Calc. for $C_{11}H_{12}ClNO$: C, 63·0; H, 5·8; N, 6·7%).

The following were prepared by the thionyl chloride ring-closure method described above: 2-(*3,5-dichlorophenyl*)-4,4-*dimethyl-2-oxazoline* (75%) as an oil, b.p. 87°/0·25 mm. (Found: C, 54·1; H, 4·7; N, 5·8. $C_{11}H_{11}Cl_2NO$ requires C, 54·1; H, 4·8; N, 5·7%); and 2-(p-*bromophenyl*)-4,4-*dimethyl-2-oxazoline* (71%) as an oil, b.p. 100°/0·3 mm., which crystallised as prisms, m.p. 36·5—37° (Found: C, 52·3; H, 5·0; N, 5·5. $C_{11}H_{12}BrNO$ requires C, 52·0; H, 4·8; N, 5·5%).

4-*Aminomethyl-4-hydroxy-1-t-butylpiperidine*.— 4-Cyano-4-hydroxy-1-t-butylpiperidine (3·64 g.) in tetrahydrofuran (20 ml.) and ether (20 ml.) was added dropwise, during 1 hr., to a stirred solution of lithium aluminium hydride (2·0 g.) in dry ether (100 ml.) at 0°. The whole was stirred for a further 3 hr. at 0° and then at 20° overnight. The reaction mixture was worked up [31] and the inorganic material was filtered off and extracted with ether (Soxhlet) for 3 hr. The ether solutions were combined and the ether removed under reduced pressure, to leave 4-aminomethyl-4-hydroxy-1-t-butylpiperidine which separated from light petroleum (b.p. 60—80°) as (hygroscopic) needles (2·95 g., 79%), m.p. 100—102°. It was characterised as the N-*benzoyl derivative* which was prepared as above as prisms (from isopropyl alcohol), m.p. 184—186° (Found: C, 70·4; H, 8·7; N, 9·6. $C_{17}H_{26}N_2O_2$ requires C, 70·3; H, 9·0; N, 9·7%).

1-*t-Butylpiperidine-4-spiro-5′-(2′-phenyl-2′-oxazoline)*.— 4-Aminomethyl-4-hydroxy-1-t-butylpiperidine (1·42 g.) and benzimidic ester [32] (1·36 g.) were heated at 180° (oil bath) for 1 hr. The solid obtained from the cool mixture crystallised from light petroleum (b.p. 60—80°) (1·25 g.), and was recrystallised from the same solvent to give 1-*t-butylpiperidine-4-spiro-5′-(2′-phenyl-2′-oxazoline*) (1·0 g., 48%) as plates, m.p. 130·5—131° (Found: C, 75·1; H, 9·2; N, 10·4. $C_{17}H_{24}N_2O$ requires C, 75·0; H, 8·9; N, 10·3%).

1-*t-Butylpiperidine-4-spiro-5′-(2′-p-chlorophenyl-2′-oxazoline)*.— 4-Aminomethyl-4-hydroxy-1-t-butylpiperidine (0·79 g.) and *p*-chlorobenzimidic ester (0·93 g.),[32] were heated at 140° for 1 hr. The mixture was cooled and the solid product was recrystallised from isopropyl alcohol to give 1-*t-butylpiperidine-4-spiro-5′-(2′-p-chlorophenyl-2′-oxazoline*) (1·15 g., 87%) which separated as plates, m.p. 171—172° [from light petroleum (b.p. 60—80°)–isopropyl alcohol] (Found: C, 66·6; H, 7·8; N, 9·1. $C_{17}H_{23}ClN_2O$ requires C, 66·6; H, 7·6; N, 9·4%).

1-*Amino-2-methylpropan-2-ol*.—Freshly distilled acetone cyanohydrin [25·5 g.; b.p. 74°/12 mm. (lit.,[33] b.p. 81°/15 mm.)] was added during 1 hr. to lithium aluminium hydride (25·0 g.) in dry ether (600 ml.) with stirring below −5°. Stirring was continued for a further 2 hr. and the reaction mixture was then kept for 12 hr. at 20°. After being stirred for a further 4 hr. the reaction mixture was worked up.[31] The inorganic material that had been precipitated was filtered off and extracted (Soxhlet) with ether. The ether solutions were combined, concentrated to *ca.* 100 ml. and dried ($MgSO_4$); the ether was removed at 20 mm., and the residue was distilled to give 1-amino-2-methylpropan-2-ol (11·2 g., 42%), b.p. 58°/12 mm. (lit.,[34] b.p. 145—155°).

1-*Benzamido-2-methylpropan-2-ols*.—The following were obtained by a modification of the method of Leffler and Adams: [10] 1-*benzamido-2-methylpropan-2-ol* (86%) as prisms, m.p. 104—105° (lit.,[35] m.p. 108°) [from ethyl acetate–light petroleum (b.p. 60—80°)] (Found: C, 68·5; H, 7·7; N, 7·4. Calc. for $C_{11}H_{15}NO_2$: C, 68·4; H, 7·8;

[32] A. W. Dox, *Org. Synth.*, Coll. Vol. 1, 1932, 5.
[33] K. N. Welch and G. R. Clemo, *J. Chem. Soc.*, 1928, 2629.
[34] T. L. Cairns and J. H. Fletcher, *J. Amer. Chem. Soc.*, 1941, **63**, 1034.
[35] Krassusky, *Compt. rend.*, 1908, **146**, 238; taken from 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1953.

N, 7·3%); 1-(p-*chlorobenzamido*)-2-*methylpropan*-2-*ol* (69·5%) as prisms, m.p. 132° [from ethyl acetate–light petroleum (b.p. 60—80°)] (Found: C, 58·1; H, 6·2; N, 6·3. $C_{11}H_{14}ClNO_2$ requires C, 58·0; H, 6·2; N, 6·2%).

1-*t-Butylpiperidine*-4-*spiro*-5′-(2′-*phenyl*-2′-*oxazoline*) (*By the Oxiran Method* [23]).—1-t-Butylpiperidine-4-spiro-2′-oxiran (0·68 g.) and benzamidine (0·85 g.), were heated at 135° (oil bath) for 12 hr. The resulting spiro-oxazoline (0·35 g.,

TABLE 1

N.m.r. chemical shifts (p.p.m. on τ scale) and coupling constants (Hz) for 4,4- and 5,5-dimethyl-2-phenyl-2-oxazolines and -thiazolines [a]

Compound			Ring-CH_2		Methyl		Phenyl ring			
Posn. of Me	Subst. on phenyl	Oxa or Thia	4	5	4	5	2′,6′-H	3′,5′-H	4′-H	*J*
4		O		5·86	8·62		1·98 [b]	2·53 [b]		
4	4′-Cl	O		5·87	8·62		2·09	2·58		9·0
4	4′-Br	O		5·88	8·62		2·12	2·40		9·0
4	3′,5′-Cl_2	O		5·86	8·61		2·15		2·56	1·8
5		O	6·20			8·52	2·00 [b]	2·56 [b]		
5	4′-Cl	O	6·19			8·50	2·08	2·54		8·1
4		S		6·76	8·53		2·10 [b]	2·53 [b]		
5		S	5·84			8·42	2·14 [b]	2·56 [b]		

[a] All measurements refer to a 20% w/v solution in $CDCl_3$ at 60 MHz and 34° with Me_4Si internal standard. [b] Centres of broad multiplets.

5,5-*Dimethyl*-2-*phenyl*-2-*oxazolines*.—The following were obtained by the method described above for 2-(3,5-dichlorophenyl)-4,4-dimethyl-2-oxazoline: 5,5-*dimethyl*-2-*phenyl*-2-*oxazoline* (36%) as an oil, b.p. 67—68°/0·3 mm., which when set aside solidified to needles, m.p. 36·5—37·5° (Found: C, 75·2; H, 7·6; N, 8·3. $C_{11}H_{13}NO$ requires C, 75·4; H, 7·5; N, 8·0%; 2-p-*chlorophenyl*-5,5-*dimethyl*-2-*oxazoline* (48%) as an oil, b.p. 90°/0·3 mm., which when set aside solidified to prisms, m.p. 38·5—39° (Found: C, 62·9; H, 5·7; N, 6·4. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; N, 6·7%).

TABLE 2

N.m.r. chemical shifts (p.p.m. on τ scale) and coupling constants (Hz) for 1-t-butylpiperidine-4-spiro-4′- and -5′-(2′-phenyl-2′-oxazolines) and -4′- and -5′-(2′-phenyl-2′-thiazolines) [a]

Five-membered rings					Five-membered ring CH_2		Phenyl ring			
Spiro posn.	Subst. on 2′-phenyl	Oxa or Thia	But^t	Piperidine ring [b]	4	5	2′,6′-H	3′,5′-H	4′-H	*J*
4		O	8·89	7·02, 7·49, 8·13		5·83	1·97	2·53 [b]		
4	4-Cl	O	8·89	7.14, 7·49, 8·19		5·86	2·06	2·59		8·4
4	3,5-Cl_2	O	8·88	7·11, 7·48, 8·19		5·83	2·11		2·51	1·8
5		O	8·88	7·28, 8·08	6·23		1·98	2·53 [b]		
5	4-Cl	O	8·89	7·30, 8·10	6·24		2·07	2·58		8·7
4		S	8·87	7·22, 8·02		6·78	2·09	2·55 [b]		
5		S	8·89	7·06, 8·00	5·79		2·11	2·55 [b]		

[a] All measurements refer to 20% w/v solutions in $CDCl_3$ at 60 MHz and 34° with Me_4Si internal standard. [b] Centres of broad multiplets.

1-*t-Butylpiperidine*-4-*spiro*-5′-(2′-*phenyl*-2′-*thiazoline*) *and* -4′-(2′-*phenyl*-2′-*thiazoline*).—Sulphuric acid (6·5 g.) was added dropwise with stirring to benzonitrile (5·3 ml.) at 0°. The solution was stirred at 0° for 30 min. and then at 20° for a further 30 min. 1-t-Butylpiperidine-4-spiro-(2′-thiiran) (1·0 g.) in benzonitrile (1·75 ml.) was then added during 75 min. after which stirring was continued for a

TABLE 3

Low-temperature n.m.r. measurements on chemical shift of oxazoline or thiazoline ring methylene groups of individual conformers (at 100 MHz)

					Ratio of high- to low-field peaks				
1-t-Butylpiperidine-4-spiro-	Solvent	Conc. w/v %	*T* [a]	Chem. shifts [b]	Area	Height	Width ½ ht.	Height × wdt. ½ ht.	$\Delta G°$ [d]
-4′-(2′-phenyl-2′-oxazoline)	$CDCl_3$—CCl_4 (4 : 1)	8·2	−72	424·4, 410·2	0·65 ±0·02	0·69 ±0·01	0·91 ±0·03	0·63 ±0·01	−0·17 ±0·01
-5′-(2′-phenyl-2′-oxazoline)	$CDCl_3$—$CFCl_3$ (1·33 : 1)	5·6	−72	384·9, 377·0	2·72 ±0·10	2·64 ±0·15	0·98 ±0·03	2·57 ±0·18	+0·40 ±0·01
-4′-(2′-phenyl-2′-thiazoline)	$CDCl_3$—CCl_4 (4 : 1)	6·8	−73	sepn. 9·4 Hz	2·01 ±0·07	2·00 ±0·07	0·94 ±0·01	1·87 ±0·06	+0·28 ±0·01
-5′-(2′-phenyl-2′-thiazoline)	$CDCl_3$—$CFCl_3$ (2·3 : 1)	7·6	−79	425·0, 413·0	(>4)				(>0·6)

[a] Temperature of measurement (°C). [b] In Hz from internal Me_4Si standard. [c] Arithmetic means and standard deviations (see Experimental section of ref. 19). [d] kcal./mole, calculated from the peak area ratio.

further 2 hr. at 20°. The reaction mixture was poured onto ice (200 g.), made strongly alkaline with sodium hydroxide, and extracted with ether (3 × 50 ml., 4 × 25 ml.). The ether solution was dried ($MgSO_4$), the ether removed under reduced pressure, and the residual oil taken up in n-pentane: benzamide precipitated from the cool mixture and was filtered off. The pentane was removed to leave an oil which, after being warmed under reduced pressure (0·1 mm.) to remove the residual benzonitrile, solidified. The crude product was chromatographed over alumina (B.D.H.) with benzene as eluant, and three fractions were collected. The resinous material from fraction 3 was discarded. The solid (0·3 g.) obtained from fraction 1 was recrystallised from n-pentane and then sublimed (110°/0·2 mm.) to give 1-*t-butylpiperidine-4-spiro-4'-(2'-phenyl-2'-thiazoline*) (0·19 g., 12·5%) as prisms, m.p. 115—116° (Found: C, 70·8; H, 8·4; N, 9·9. $C_{17}H_{24}N_2S$ requires C, 70·8; H, 8·4; N, 9·7%).

The yellow solid from fraction 2 was dissolved in n-pentane, treated with charcoal, filtered, and the solvent removed under reduced pressure to leave a colourless solid (0·4 g.) which was twice sublimed (65°/0·2 mm.) to give 1-t-butylpiperidine-4-spiro-5'-(2'-phenyl-2'-thiazoline) admixed with *ca.* 25% of the 4'-analogue (0·06 g., 3·9%), m.p. 74·5—76°, as prisms (Found: C, 71·0; H, 8·1; N, 10·1).

TABLE 4

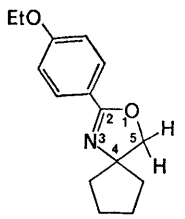
Dipole-moment measurements * at 25° in benzene

10^6w	$10^6(\varepsilon_{12}-\varepsilon_1)$	$10^6(v_1-v_{12})$	10^6w	$10^6(\varepsilon_{12}-\varepsilon_1)$	$10^6(v_1-v_{12})$
4,4-Dimethyl-2-phenyl-2-oxazoline			*m*-Dichlorobenzene		
7229		1291	3085	5423	1133
7349	6127		4922	8687	1812
8436	7051	1504	7673	13,550	2806
8780		1569			
8925	7454	1593			
11,612	9655				
4,4-Dimethyl-2-(3,5-dichlorophenyl)-2-oxazoline)			1-t-Butylpiperidine-4-spiro-4'-(2'-phenyl-2'-oxazoline)		
2439	6993	846	405	390	94
3219	9212	1133	506	442	118
3261	9391	1145	737	667	151
3672	10,541	1273	789	746	182

* w = Weight fraction of solute, ε = dielectric constant, v = specific volume. The suffixes 1 and 12 refer to solvent and solution respectively.

Physical Measurements.—N.m.r. spectra were obtained at room temperature (Tables 1 and 2) and at low temperatures (Table 3) under the conditions described in ref. 1. Dipole moments were measured and calculated as described elsewhere: [2] the results are recorded in Tables 4 and 5.

at 5·83—5·87 p.p.m., enabling a clear distinction to be drawn. These assignments are supported by the limited literature data available: in 2-methyl-2-oxazoline and its 4,4- and 5,5-dimethyl derivatives, a 4-methylene group occurs at 0·38—0·44 p.p.m. higher field than a 5-methylene group.[36] The spiro-compound (39) has the 5-methylene signal at 5·83 p.p.m., in excellent agreement with our spiro compound (9).[14]



(39)

The chemical shifts of the 4- and 5-methylene groups in the 2-thiazolines are at 5·84 and 6·76 p.p.m., respectively, and the assignment of structures to the spirothiazolines is based on comparisons with these. Again the literature data [36] support this assignment: 2-methyl-2-thiazoline and its 4,4- and 5,5-dimethyl derivatives show relative shifts for the methylene groups which are in line with the above.

Chemical shifts of the methyl groups at the 4- and 5-positions of 2-oxazoline rings of the model compounds (Table 1) show relative shifts of similar direction but smaller in magnitude to the methylene protons. Similar behaviour was earlier reported for 2,4,4- and 2,5,5-trimethyl-2-oxazoline.[36] Surprisingly, the chemical shifts of the 4- and 5-methyl groups in 2-thiazolines show a reversal; however, this is also as previously reported.[36]

The proton chemical shifts and coupling constants for the aryl substituents are as expected.

At low temperatures, the spectra of the spiro-compounds became considerably more complex: in particular the sharp singlets for the 4- or 5-methylene groups of the oxazoline or thiazoline ring broadened and finally split into two singlets of unequal intensity. The other changes were far less clear-cut, and a detailed study was made only of the 4- and 5-methylene groups. Equilibrium constants for the conformational equilibria of type (1a) ⇌ (1b) were calculated, both from peak

TABLE 5

Dipole moments in benzene

Compound	$d\varepsilon/dw$	$-dv/dw$	$P_{2\infty}$	P_E	μ(D)
4,4-Dimethyl-2-phenyl-2-oxazoline	0·83 ± 0·01	0·179 ± 0·003	77·74	52·55	1·11 ± 0·01
4,4-Dimethyl-2-(3,5-dichlorophenyl)-2-oxazoline	2·87 ± 0·01	0·349 ± 0·005	189·41	62·00	2·50 ± 0·01
m-Dichlorobenzene	1·77 ± 0·01	0·366 ± 0·003	82·98	34·57	1·54 ± 0·01
1-t-Butylpiperidine-4-spiro-4'-(2'-phenyl-2'-oxazoline)	0·91 ± 0·02	0·255 ± 0·006	120·86	81·47	1·39 ± 0·03

DISCUSSION

N.m.r. Spectroscopy.—Assignments for the room temperature spectra are shown in Table 1 for the model compounds and in Table 2 for the spiro-derivatives. For the 2-oxazoline ring, the 4-position methylene is at 6·19—6·24 p.p.m. whereas a 5-methylene group shows

area and peak height × peak width at half height measurements (*cf.* ref. 1); they are in good agreement (Table 3) but those from the area measurements are considered more accurate and were used to calculate the

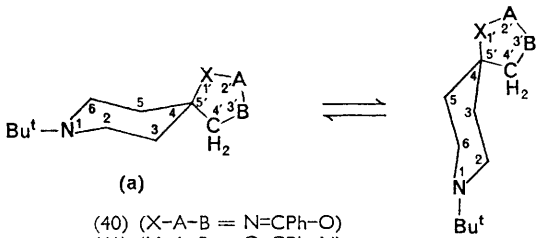
[36] M. A. Weinberger and R. Greenhalgh, *Canad. J. Chem.*, 1963, **41**, 1038.

$\Delta G°$ values of Table 3. In this way, clear-cut quantitative results were obtained for both the spiro-oxazolines and for the 4-spiro-4′-(2′-thiazoline). However, for the 5′-thiazoline, sharp methylene resonances were not obtained at the lowest temperature employed; although it appears clear that the upfield peak is of considerably greater area, no quantitative conclusion could be drawn.

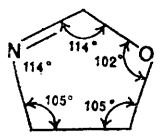
The assignments of the low temperature methylene signals to the individual conformers has been discussed in detail in ref. 37; for the reasons therein stated we believe that the upfield signal in each case should be assigned to the equatorial methylene, the steric compression occurring for the axial methylene causing significant deshielding.

Dipole Moments.—We originally intended to use dipole moment measurements (*cf.* ref. 1) to obtain independent estimates of the conformer populations, but uncertainties in the ring geometry lead to errors in these systems which are greater than we believe to be acceptable. We have, however, been able to use dipole moments to confirm the assignment of the n.m.r. signals which implies a preponderance of the *N*-equatorial conformer (40b) of 1-t-butylpiperidine-4-spiro-4′-(2′-phenyl-2′-oxazoline).

The precise geometry of the oxazoline ring is unknown; for our calculations we have assumed a planar ring with angles as shown in (46), which were obtained by supposing that all the angles are reduced in the same proportion from the corresponding values found [38] in acyclic systems. We have further assumed (*a*) that the direction of the moment in the piperidine ring [39] is as shown in (47); (*b*) that the bisector of the



(40) (X–A–B = N=CPh–O)
(41) (X–A–B = O–CPh=N)
(42) (X–A–B = O–CH_2–O)
(43) (X–A–B = O–CMe_2–NH)
(44) (X–A–B = S–CPh=N)
(45) (X–A–B = N=CPh–S)



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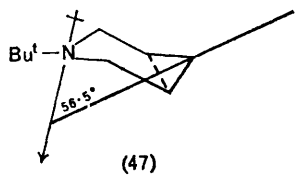
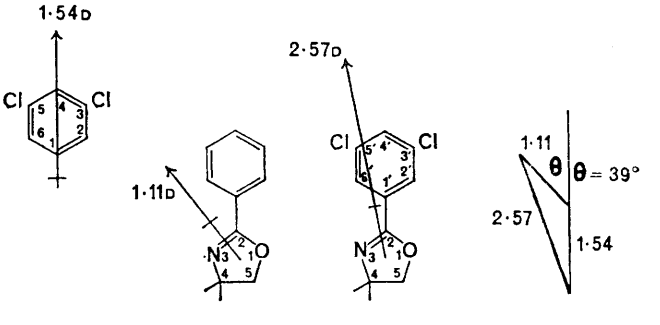


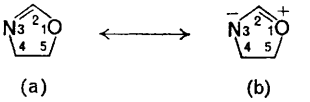
(47)

C(3)–C(4)–C(5) angle of the piperidine ring also bisects the 4′-angle of the oxazoline ring; (*c*) that the C(2′)–aryl bond bisects the NCO angle; (*d*) that the dipole moment of the spiro-compound is the vector sum of the moments of 1-t-butylpiperidine [39] (0·73 D in cyclohexane) and of 4,4-dimethyl-2-phenyl-2-oxazoline.

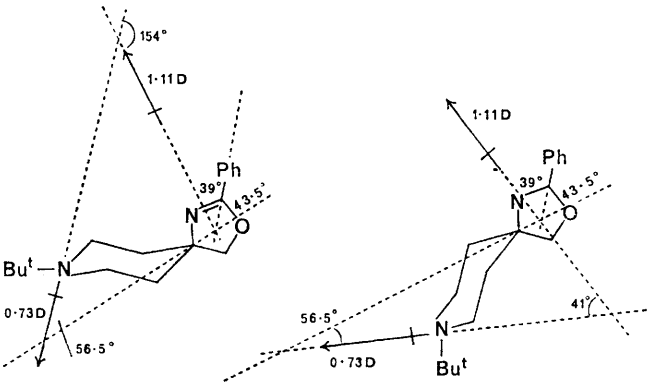
The direction of the moment of the 2-phenyloxazoline moiety was determined by vector triangulation (48) using as model compounds 4,4-dimethyl-2-phenyl-2-oxazoline, 4,4-dimethyl-2-(3′,5′-dichlorophenyl)-2-oxazoline, and *m*-dichlorobenzene. The *meta*-chloro-substituents were chosen to minimise mesomeric interactions



(48)



(49)



(50)

between the chlorine atoms and the oxazoline ring. The calculated direction for the moment of the 2-phenyl compound is thus shown to be at 39° to the C(2)-aryl bond. The calculations do not tell us on which side of this bond the dipole vector lies, although the contribution of the canonical form (49b) would lead us to expect the moment to lie on the nitrogen side, as shown in (48) and (50). We have, however, calculated our results both on this assumption and on the alternative assumption that the moment lies on the oxygen side.

We then calculate the moments of the two conformers, (40a) and (40b), as indicated in (50), and from them we can calculate the expected moment of the conformational mixture, from the relation:

$$\mu^2_{(40)} = N_{(40a)}\mu^2_{(40a)} + N_{(40b)}\mu^2_{(40b)}$$

[37] Part XXXIII, R. A. Y. Jones, A. R. Katritzky, and P. G. Lehman, *J. Chem. Soc.* (*B*), following paper.

[38] 'Interatomic Distances,' ed. L. E. Sutton, Chemical Society Special publications No. 11 and No. 18.

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

The n.m.r. assignment suggests that $N_{(40a)}$, the mole fraction of conformer (40a), is 0·375 and that $N_{(40b)}$ is 0·625. If the assignment is reversed then so would these values. Therefore we can calculate four different values for $\mu_{(40)}$, depending on the assumptions taken about the direction of the oxazoline vector and about the n.m.r. assignment. These values are recorded in Table 6.

TABLE 6

Calculated values of the dipole moment (D) of 1-t-butyl-piperidine-4-spiro-4′-(2′-phenyl-2′-oxazoline)

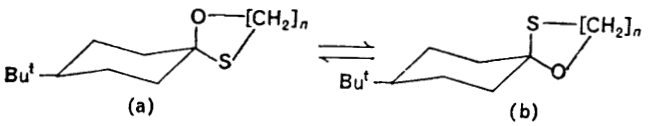
N.m.r. assignment [a]	Dipole direction [a] N-side	O-side
Correct	1·41	1·07
Incorrect	1·15	1·01

[a] See text.

It can be seen that only one of these values (1·41 D) is close to the observed value of 1·39 D, and that this is the value calculated by supposing that the oxazoline vector lies to the nitrogen side and that *the n.m.r. assignment described above is correct.*

Conformational Free Energies.—For the spiro-5-oxazoline (41), the conformational equilibrium favours (41a), with a free-energy difference between the conformers of +0·40 kcal./mole. This is in line with the equilibria for the corresponding spiro-dioxolan (42a) ⇌ (42b) [1] and the spiro-5-oxazolidine (43a) ⇌ (43b) [37] and gives additional support to our claim that the steric requirements of an oxygen atom are less than those of a methylene group where the probe is a hydrogen atom at a β-axial position of a six-membered ring. The $-\Delta G°$ value for (41) is, in fact, the largest of the three (41), (42), (43). This could be partly due to the particular geometry of the 5-membered ring in (41), but could also reflect a significant contribution from the canonical form (51) to the resonance hybrid of (41a).

(51)



(52) $n = 3$
(53) $n = 2$

The situation for the spiro-5-thiazoline (44) is qualitatively similar. Unfortunately, at the lowest temperature attained before freezing of the solvent occurred, the spectrum of (44) was not sufficiently well defined to allow a quantitative estimate of the equilibrium constant to be calculated. However, from the appearance of the spectrum it was concluded that the conformer with S axial, (44a), was probably preferred to an even greater extent than the conformer with O axial, (41a), in the analogous spiro-oxazoline system.

Previous work on sulphur-containing systems is conflicting. The substituents –S–Me,[40] –S–CD_3,[41] and –S–Ph [42] in cyclohexyl systems have been reported to show a strong preference for the equatorial position (0·7, 1·07, and 0·8 kcal./mole respectively). The –O–Me [42] and –O–CD_3 [41] groups also favour the equatorial position, but to a somewhat smaller extent (0·6 and 0·55 kcal./mole respectively). By comparison a sulphur atom appears to have slightly larger steric requirements than an oxygen atom. Similarly, a small preference for the isomer with the oxygen atom axial has been found in the spiro-thioxan series (52).[40] In this case (52a) is preferred by 75—100 cal./mole. However in the spiro-thioxolan series (53), the reverse situation is found and the isomer with sulphur axial (53b), is favoured [43,44] by *ca.* 0·2 kcal./mole. The so-called ' leverage effect ' has been proposed [43] to account for this reversal, *i.e.* the restricted geometry of the 5-membered ring may relieve the steric compression of the sulphur atom (with the *syn*-axial hydrogen atoms) to a greater extent than that of the oxygen atom. It is conceivable that such an effect could also operate in compound (44).

The preference of conformation (40b) in the spiro-4-oxazoline (40) is surprising in view of the previous work mentioned above which suggests that an sp^2 hybridised nitrogen atom has relatively small steric requirements. However the strong n.m.r. evidence is independently supported by the dipole-moment study. Although the free-energy difference between (40a) and (40b) is relatively small (—0·17 kcal./mole) we believe that it is significant. A possible explanation is that a significant contribution from the canonical form of type (49b) increases the effective size of the nitrogen atom and results in the preference for (40b).

For the spiro-4-thiazoline (45), the conformer with nitrogen axial, (45a), is preferred (+0·28 kcal./mole). Although the structure of (45) is superficially similar to that of (40) two important differences should be noted: (*a*) the ' long ' C(2)–S and C(5)–S bonds would alter the ring geometry considerably [*cf.* (40)]. The overall effect would be to force the C(5)–methylene group closer to the probe in (45b), thereby increasing the steric repulsion and increasing the preference for (45a); (*b*) less-efficient overlap of the $2p$–$3p$ orbitals in (45) probably results in a smaller contribution from the canonical form equivalent to (49b) (*cf.* ref. 36). These two differences could significantly reduce the relative stability of (45b).

Clearly, caution must be exercised in predicting conformational preferences, particularly when electronic and geometric effects can operate. Additional work in this area is necessary.

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[40] E. L. Eliel and B. P. Thill, *Chem. and Ind.*, 1963, 88.
[41] F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, 1969, **91**, 344.
[42] E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 1962, 97.
[43] E. L. Eliel, E. W. Della, and M. Rogić, *J. Org. Chem.*, 1965, **30**, 855.
[44] E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, 1962, **84**, 2377.