The Conformational Analysis of Saturated Heterocycles. Part XLIII.[1] 1-t-Butylpiperidine-4-spiro-2′-aziridine, -oxiran, and -thiiran

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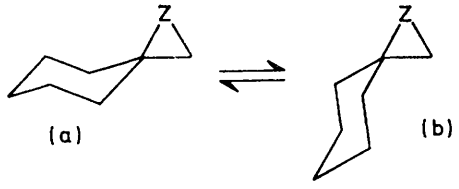
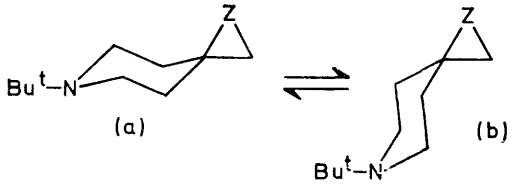
The title compounds have been prepared and the conformational equilibria for the oxiran and thiiran (4, 5 ; a ⇌ b) elucidated by electric dipole moment measurements. The relative steric requirements of CH_2-groups and of O- and S-atoms in three membered rings are discussed.

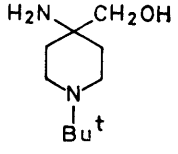
PART XXXI of this series [2] describes a general method for the elucidation of intramolecular interactions by investigation of suitable spiro-compounds. The present paper is concerned with the application of this method to spiro-aziridines, -oxirans, and -thiirans. The stereochemistry of spiro-oxirans in carbocyclic systems has been investigated [3] and the conformational preference of the oxiran group in cyclohexanespiro-oxirans has been determined by kinetic [4] and low-temperature n.m.r.[5] methods, but no previous work of this type is available on the corresponding sulphur and nitrogen compounds.



(1) Z = O
(2) Z = S
(3) Z = NH



(4) Z = O
(5) Z = S
(6) Z = NH



(7)

Preparation of Compounds.—Cyclohexanespiro-oxiran (1) and 1-t-butylpiperidine-4-spiro-2′-oxiran (4) were prepared from cyclohexanone and 1-t-butylpiperidin-4-one, respectively, by reaction with dimethyloxosulphonium methylide (*cf.* refs. 6 and 7). Each was converted into the corresponding thiiran [(2), (5)] by reaction with potassium thiocyanate.[8] Cyclohexanespirothiiran (2) has been prepared in low yield by Mousseron [9] but no physical properties have been published; in the present work difficulty was experienced because of low solubility of the oxiran (1) and in the separation of (1) and (2) which led to a poor yield. The thiirans were prepared immediately before the dipole moment measurements were made, because of their known [10] tendency to polymerise. The spiro-aziridine (6) was prepared by ring-closure of the amino-alcohol (7) according to the Wenker method.[11] Cyclohexanespiro-aziridine was prepared by the method of Talukdar and Fanta [12] from 1-amino-1-hydroxymethylcyclohexane.

Room-temperature n.m.r. spectra of the (rapidly inverting) compounds are recorded in Table 1; they confirm the structures and present no unusual features.

TABLE 1

Chemical shifts (p.p.m. on τ scale) of oxiran, thiiran, aziridine, and derivatives [a]

	Compound		CH_2-signals		
No.	3-Ring	Other ring or subs.	3-Ring [b]	6-Ring [c]	t-Bu [b]
(8)	Oxiran		7·40 [d]		
(1)	Oxiran	Cyclohexane	7·40	8·41	
(4)	Oxiran	*N*-t-Butylpiperidine	7·36	7·26, 8·30	8·89
(9)	Thiiran		7·61		
(2)	Thiiran	Cyclohexane	7·59	8·27	
(5)	Thiiran	*N*-t-Butylpiperidine	7·58	7·35, 8·19	8·89
(10)	Aziridine		8·39		
(3)	Aziridine	Cyclohexane	8·25—8·75 [e]		
(6)	Aziridine	*N*-t-Butylpiperidine	8·41	7·31, 8·41	8·89

[a] All *ca.* 20% w/v $CDCl_3$ solutions with internal Me_4Si measured at 60 MHz and 35°. [b] All singlets. [c] All centres of broad multiplets. [d] Taken from B. P. Dailey, A. Gawer, and W. C. Neikam, *Discuss. Faraday Soc.*, 1962, **34**, 18. [e] Broad band, not resolvable.

[1] Part XLII, R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, preceding paper.
[2] R. A. Y. Jones, A. R. Katritzky, P. H. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302.
[3] R. G. Carlson and N. S. Behn, *J. Org. Chem.*, 1967, **32**, 1363.
[4] J. J. Uebel, *Tetrahedron Letters*, 1967, 4751.
[5] R. G. Carlson and N. S. Behn, *Chem. Comm.*, 1968, 339.
[6] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.
[7] M. Fishman and P. A. Cruickshank, *J. Heterocyclic Chem.*, 1968, **5**, 467.
[8] H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, 1947, **69**, 2672.
[9] M. Mousseron, *Compt. rend.*, 1943, **216**, 812.
[10] D. D. Reynolds and D. L. Fields, ' Heterocyclic Compounds,' ed. A. Weissberger, Interscience Publishers, New York, 1964, p. 603.
[11] H. Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 2328.
[12] P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, 1959, **24**, 526.

The proximity of the methylene signals deriving from the three-membered rings to those of the piperidine ring prevents accurate area measurements of individual invertomers at low temperatures and therefore the n.m.r. method was not applied to the study of these conformational equilibria. Low-temperature n.m.r. studies were attempted with cyclohexanespirothiiran but in this case also the peaks for the heterocyclic ring CH_2-group were overlapped by the carbocyclic methylene signals sufficiently to preclude accurate area measurements.

(8) Z = O (9) Z = S (10) Z = NH

EXPERIMENTAL

1-t-Butylpiperidine-4-spiro-2'-oxiran.— Dimethyloxosulphonium methylide was prepared[6] in anhydrous dimethyl sulphoxide (93·0 g.) from trimethyloxosulphonium iodide (30·6 g.) and sodium hydride (50% in oil, 6·5 g.); the mixture was stirred at room temperature for 30 min. 1-t-Butylpiperidin-4-one (14·4 g.) was added during 30 min. and the stirring was continued for a further 10 hr. The mixture was kept overnight and then worked up after the method of Fishman and Cruikshank.[7] The yellow oil obtained was fractionally distilled to give the *spiro-2'-oxiran* (8·3 g., 53%) as an oil, b.p. 36°/0·25 mm. (Found: C, 71·2; H, 11·1; N, 8·0. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·3; N, 8·3%).

1-t-Butylpiperidine-4-spiro-2'-thiiran.— 1-t-Butylpiperidine-4-spiro-2'-oxiran (2·0 g.) and potassium thiocyanate (10·0 g.) in water (10 ml.) were shaken mechanically for 5 hr. and then extracted with ether (4 × 15 ml.). Solvent was removed from the dry ($MgSO_4$) extracts and the residue was treated with charcoal in n-pentane. Removal of solvent gave the *spiro-2'-thiiran* (2·05 g., 91·5%), which sublimed at 45—50°/0·2 mm. as needles, m.p. 51—52° (Found: C, 64·9; H, 10·6; N, 7·7. $C_{10}H_{19}NS$ requires C, 64·8; H, 10·3; N, 7·6%).

Cyclohexanespirothiiran.—Cyclohexanespiro-oxiran (6·15 g.) and potassium thiocyanate (40 g.) in water (40 ml.) were shaken for 5 hr. at 20° and then extracted with ether (1 × 60 ml., 3 × 30 ml.). Solvent was removed from the dry ($MgSO_4$) extracts at 20° and the residue was distilled to give unchanged oxiran (2·0 g.), b.p. 42—45°/13 mm. and crude *cyclohexanespirothiiran* (1·8 g., 24%), b.p. 61—63°/13 mm. After further fractional distillation, the b.p. was 63°/12 mm., but the compound still contained a trace (g.l.c.) of oxiran. It was then chromatographed over alumina (B.D.H.) using n-pentane as eluant. Fractional distillation of the recovered oil gave the pure (g.l.c.) thiiran (13·5%), b.p. 63°/12 mm. (Found: C, 65·8; H, 9·3. $C_7H_{12}S$ requires C, 65·6; H, 9·4%).

1-t-Butylpiperidine-4-spiro-2'-aziridine.—Sulphuric acid (5·9 g.) in water (12 ml.) was added slowly to 4-amino-4-hydroxymethyl-1-t-butylpiperidine (5·5 g.) in water (12 ml.) at 0° and the mixture was kept at 20° for 1 hr. Water was removed by heating the mixture (finally to 110°/0·1 mm. for 1 hr.). Sodium hydroxide (7·1 g.) in water (30 ml.) was added to the crude solid 4-amino-1-t-butylpiperidine-4-methyl hydrogen sulphate (10·9 g.) thus obtained. After mixing, the suspension was heated at 120—150° (oil-bath), and the distillate was collected and saturated with sodium hydroxide to give a white precipitate 'A' (0·9 g.). The aqueous alkaline distillate was extracted with ligroin (b.p. 40—60°) (4 × 15 ml.) and ether (2 × 15 ml.). The original alkaline reaction mixture was also extracted with ether (2 × 20 ml.). The combined extracts were evaporated and the residue (3·75 g.) was chromatographed over alumina (B.D.H.) with ether as eluant to give further product 'B' (1·8 g.) and unchanged amino-alcohol (0·95 g.). Sublimation of the combined products 'A' and 'B' at 50°/0·1 mm. gave *1-t-butylpiperidine-4-spiro-2'-aziridine* (2·3 g., 46%) as needles, m.p. 51·5—52·5° (Found: C, 71·3; H, 11·7; N, 16·8. $C_{10}H_{20}N_2$ requires C, 71·4; H, 12·0; N, 16·7%).

TABLE 2

Dielectric constant and specific volume measurements * at 25°

10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$	10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$
Thiiran			Cyclohexanespirothiiran		
3020	16,813	+378	2289	8932	+323
4071	22,660	+512	2918	11,367	408
5196	28,921	+653	3687	14,372	+516
7035	39,154	+887	4675	18,223	+654
1-t-Butylpiperidine-4-spiro-2'-thiiran			Oxiran		
2494	5654	313	2107	16,753	−38
2610	5917	+328	3790	30,130	−68
4780	10,836	+600	4650	36,967	−84
6834	15,497	+858	6912	—	−126
Cyclohexanespiro-oxiran			1-t-Butylpiperidine-4-spiro-2'-oxiran		
2072	8725	+157	2892	7300	+260
3249	13,674	+243	3918	9890	+352
3566	15,030	+275	3942	9932	+359
4263	17,951	+324	4290	10,848	+400
Aziridine			Cyclohexanespiroaziridine		
2876	16,050	−143	1033	2669	+175
3490	19,474	−171	1297	3008	+210
5106	28,490	−250	3062	7204	+548
5456	30,455	−267	4857	11,307	+875
12,243	—	−600			
1-t-Butylpiperidine-4-spiro-2'-aziridine					
1385	2981	276			
2080	4473	417			
3429	7370	687			
3872	8323	775			

* w = Weight fraction of solute, ε = dielectric constant, v = specific volume. The suffixes 1 and 12 refer to solvent and solution respectively. The oxiran and thiiran compounds were measured in benzene; the aziridines in cyclohexane.

Model Compounds.—The following were redistilled commercial products, checked by g.l.c.: oxiran (B.D.H.); thiiran (Fluka), b.p. 55—56° (lit.,[13] b.p. 55—56°) (Found: C, 40·2; H, 6·8. C_2H_4S requires C, 40·0; H, 6·7%); aziridine (Koch–Light), kept over NaOH for 1 week and fractionally distilled, b.p. 55° (lit.,[14] b.p. 56°) (Found: C, 56·0; H, 11·7. C_2H_5N requires C, 55·8; H, 11·7%).

The following were prepared by the method quoted: cyclohexanespiro-oxiran (66%, from cyclohexanone), b.p. 43°/12 mm. (lit.,[15] b.p. 62—63°/37 mm.) (Found: C, 74·7;

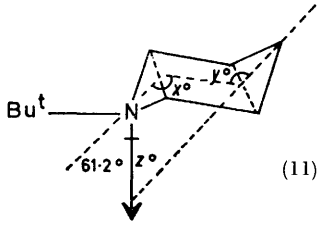
[13] D. D. Reynolds, *J. Amer. Chem. Soc.*, 1957, **79**, 4951.
[14] C. C. Howard and W. Marckwald, *Ber.*, 1899, **32**, 2036.
[15] J. G. Traynham and O. S. Pascual, *Tetrahedron*, 1959, **7**, 165.

H, 10·6. Calc. for $C_7H_{12}O$: C, 74·9; H, 10·8%); cyclohexanespiroaziridine (51%),[12] b.p. 160—161° (lit.,[12] b.p. 158—159°) (Found: C, 75·6; H, 11·5; N, 12·9. Calc. for $C_7H_{13}N$: C, 75·6; H, 11·7; N, 12·7%).

Physical Measurements.—N.m.r. spectra were measured on a Perkin-Elmer R 10 spectrometer. Dipole moments were measured and calculated as described elsewhere:[2] the results are recorded in Tables 2 and 3. The solvent for the oxiran and thiiran systems was benzene. Results for compounds containing NH groups are unreliable in this solvent[16] and for the aziridines the solvent used was cyclohexane. With the exception of oxiran, all the compounds were handled in a glove box containing phosphorus pentoxide and Carbosorb.

DISCUSSION

In the calculations the following assumptions were made. (*a*) That the geometry of the piperidine ring, and the angle at which its dipole moment acts, are as shown in (11). This geometry is based on the bond lengths and angles previously[17] used except for the C(3)–C(4)–C(5) bond angle. This is likely to be opened up from the normal piperidine value because of the moment in cyclohexanespirothiiran is found to be at 43·5° to the C–C–S bisector by assuming that the cyclohexane moiety contributes a group moment along the bisector and then applying the sine rule. Vector



(11)

	Oxiran aziridine	Thiiran
x	124·0	124·4
y	140·8	139·5
z	78·0	76·3

addition of the moments of 1-t-butylpiperidine and cyclohexanespirothiiran gives the following calculated moments for the two conformers: (5a), 1·60; (5b), 2·60 D. The observed value for 1-t-butylpiperidine-4-spirothiiran (μ_5) is 1·99 D, and by applying the equation $\mu_5^2 = Na\mu_{(5a)}^2 + (1\text{-}Na)\mu_{(5b)}^2$ we can deduce that *Na*, the mole fraction of conformer (5a) is 0·67, corresponding to $\Delta G°$ of 0·42 kcal. mole^{-1} in favour of the *S*-axial conformer. Similarly for the oxiran, the calculated moments are: $\mu_{(4a)}$, 1·55; $\mu_{(4b)}$, 2·64 D, corresponding to $Na = 0·61$ and $\Delta G° = 0·27$ kcal. mole^{-1} in favour of the *O*-axial conformer.

TABLE 3

Dipole moments of thiiran, oxiran, aziridine and derivatives [a]

Compound	dε/dw [b]	dv/dw	$_TP_{2\infty}$	$_EP$	μ(D) [c]
Thiiran	5·566 ± 0·002	−0·1257 ± 0·002	81·2	16·9	1·77 ± 0·01
Cyclohexanespirothiiran	3·898 ± 0·002	−0·140 ± 0·001	132·4	37·4	2·16 ± 0·01
1-t-Butylpiperidine-4-spiro-2′-thiiran	2·267 ± 0·002	−0·1256 ± 0·0003	135·3	54·7	1·99 ± 0·01
Oxiran	7·95 ± 0·01	+0·018 ± 0·001	81·1	11·00	1·85 ± 0·01
Cyclohexanespiro-oxiran	4·211 ± 0·002	−0·076 ± 0·001	124·5	31·3	2·14 ± 0·01
1-t-Butylpiperidine-4-spiro-2′-oxiran	2·524 ± 0·002	−0·090 ± 0·003	133·5	48·8	2·04 ± 0·01
Aziridine	5·580 ± 0·001	+0·0490 ± 0·0001	72·4	12·8	1·71 ± 0·01
Cyclohexanespiroaziridine	2·32 ± 0·03	−0·089 ± 0·003	92·9	33·3	1·71 ± 0·02
1-t-Butylpiperidine-4-spiro-2′-aziridine	2·1491 ± 0·0007	−0·2003 ± 0·0003	133·4	50·5	2·01 ± 0·01

[a] Oxiran and thiiran systems are measured in benzene, aziridines in cyclohexane. [b] Results are quoted as ± one standard deviation. [c] Results are quoted as ± one standard deviation or 0·01 D, whichever is the greater.

distorting influence of the spiro three-membered ring. We assume that all the C–C–C bond angles around the spiro-junction are identical except for the endocyclic angle of the three-membered ring (see below), leading to values for C(3)–C(4)–C(5) of 117·0° for the oxiran and aziridine systems and 116·3° for the thiiran. (*b*) That the C–C–O angles of the oxiran ring are 59·2°,[18] the C–C–S angles of the thiiran ring are 65·8°,[19] and the C–C–N angles of the aziridine ring are 60·2°.[20] (*c*) That the bisector of the C(3)–C(4)–C(5) angle of the piperidine ring also bisects the C–C–X angle of the three-membered ring. (*d*) That the dipole moments of the spiro-compounds are the vector sums of the moments of 1-t-butylpiperidine (0·73 D in benzene and 0·70 D in cyclohexane) and of one of the model compounds: cyclohexanespirothiiran, cyclohexanespiro-oxiran, or cyclohexanespiroaziridine.

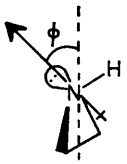
Thiiran and Oxiran Systems.—The direction of the

Uebel[4] found a preference for oxygen 'axial' of 0·15 ± 0·1 kcal. mole^{-1} at 25 °C. Carlson and Behn[5] found a preference for oxygen 'axial' of 0·27 ± 0·04 kcal. mole^{-1} at −99 °C.

Aziridine System.—The calculations here are complicated by the fact that the moment of the aziridine ring

[16] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 127.
[17] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 493.
[18] T. E. Turner and J. A. Howe, *J. Chem. Phys.*, 1956, **24**, 924.
[19] G. L. Cunningham, A. W. Boyd, R. J. Myers, W. D. Gwinn, and W. I. Le Van, *J. Chem. Phys.*, 1951, **19**, 676.
[20] T. E. Turner, V. C. Fiora, and W. M. Kendrick, *J. Chem. Phys.*, 1955, **23**, 1966.

does not lie in the plane of the ring but at an angle ϕ to it [*cf.* (12)]. We therefore attempted to calculate the



(12)

conformational preference of the system using a range of values for the angle ϕ. Unfortunately the variation with angle is not small and, unlike the calculations with the oxirans and thiirans, the result is also very sensitive to small errors in the measured dipole moment values. We are therefore not able to draw any conformational conclusions about the aziridine system.

[0/1034 *Received, July 26th,* 1971]