Conformational Analysis of Acyclic Compounds with Oxygen–Sulphur Interactions. Part 3.[1] A Study of Some *erythro*-2-Thio-derivatives of 1,2-Diphenylethanol

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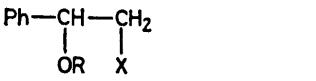
A conformational study of *erythro*-1,2-diphenyl-2-X-ethanol [X = SH, SCH_3, $SOCH_3$, SO_2CH_3, and $^+S(CH_3)_2$] and its *O*-acetyl derivatives is reported. The electrostatic interactions between the heteroatoms, when the sulphur atom supports a positive charge determine a preference for *gauche* conformations in spite of the fact that they are destabilized by steric factors. The synthesis of new compounds is described.

THE oxygen–sulphur interaction and its influence on conformational equilibria in acyclic compounds have previously been reported.[1,2] Some 2-thio-derivatives of 1-phenylethanol, with sulphur in different states of oxidation (Scheme 1), have been studied. The electrostatic interactions were claimed to account for the different populations in the conformational equilibria in these compounds. Nevertheless, the relative contribution of steric effects could not be determined.



R = H, Ac
X = SH, SCH_3, $SOCH_3$, SO_2CH_3, $\overset{+}{S}(CH_3)_2$

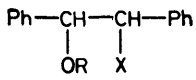
SCHEME 1

In the present paper, the conformational study of some derivatives of *erythro*-2-thio-1,2-diphenylethanol and its *O*-acetyl derivatives, shown in Scheme 2, is reported. In these compounds, the steric and electrostatic factors favour different conformations and so they are adequate models for evaluating the relative contribution of both effects in conformational equilibria.

RESULTS AND DISCUSSION

The syntheses of the different compounds were carried out according to Scheme 3. The *erythro*-configuration originated from the well documented stereospecific epoxidation of *trans*-stilbene and cleavage of the resulting epoxide, since other transformations were carried out on oxygen or sulphur without any change at the chiral centres.

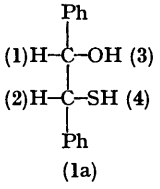
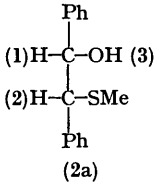
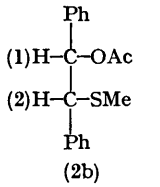
The three staggered conformations of these compounds are given in Figure 1. The different conformational

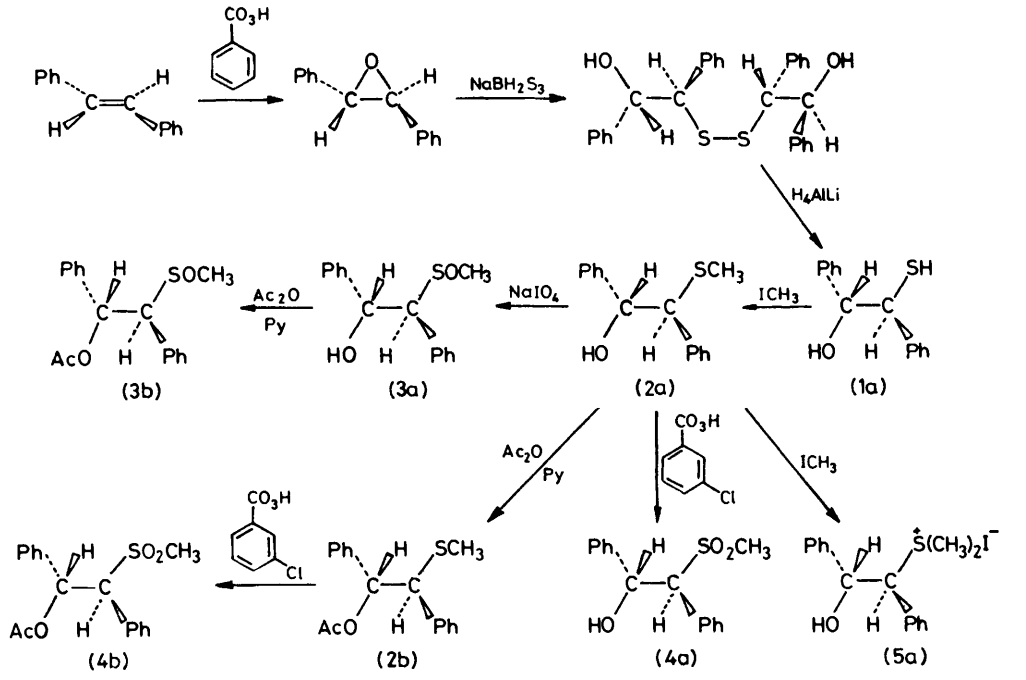


a; R = H
b; R = Ac
(1) X = SH
(2) X = SCH_3
(3) X = $SOCH_3$
(4) X = SO_2CH_3
(5) X = $\overset{+}{S}(CH_3)_2$

SCHEME 2

TABLE 1

Compound	Solvent	Concentration (% w/v)	Chemical shift (δ) H(1)	H(2)	H(3)	H(4)	Coupling constants (J/Hz) $J_{1,2}$	$J_{1,3}$	$J_{2,4}$
 (1a)	$CDCl_3$	10	4.803	4.135	2.206	1.652	7.76		5.05
		5	4.844	4.165	2.150	1.674	7.81		5.04
		1	4.958	4.267	2.055	1.768	7.83		4.96
	$[^2H_6]$DMSO	10	4.926	4.283	5.546	2.469	7.08		6.47
		5	4.886	4.248	5.546	2.300	6.95	4.78	6.14
		1	4.878	4.245	5.525		6.91	4.83	
 (2a)	$CDCl_3$	10	4.921	3.925	2.320		7.20		
		5	4.951	3.944	2.220		7.19		
		1	4.978	3.962	1.860		7.25		
	$[^2H_6]$DMSO	10	4.918	3.943	5.455		7.00	4.80	
		5	4.918	3.942	5.471		7.11	4.63	
		1	4.904	3.935	5.452		7.06	4.86	
 (2b)	$CDCl_3$	10	6.117	4.081			8.17		
		5	6.114	4.081			8.19		
		1	6.112	4.081			8.06		
	$[^2H_6]$DMSO	10	6.086	4.307			7.79		
		5	6.072	4.303			7.81		
		1	6.063	4.297			7.76		



SCHEME 3

populations were evaluated from the values of vicinal coupling constants in the ^1H n.m.r. spectra. The chemical shifts, as in Part 1,[2] were not used in the analysis due to the difficulty in predicting the substituent effect and the lack of comparable model systems. Because of the conformational mobility around the C–C bond, the observed coupling constants are weighted means between the different conformations [equation (1)

$$J^{obs}_{1.2} = \sum_i x_i J^i_{1.2} \qquad (1)$$

where x_i is the mole fraction of conformation i and $J^i_{1.2}$ the vicinal coupling coupling constant]. From the relative position of the protons in each rotamer the observed coupling constant is $J^{I}_{1.2} = J_{anti}$, and $J^{II}_{1.2} = J^{III}_{1.2} = J_{gauche}$,* and equation (1) becomes (2).

$$J^{obs}_{1.2} = x_I J_{anti} + (x_{II} + x_{III}) J_{gauche} \qquad (2)$$

The results obtained from the analysis of the spectra indicate very different behaviour for compounds (1a), (2a), and (2b) with respect to the others, and the conformational study has been carried out independently.

Table 1 gives the ^1H n.m.r. parameters used for the analysis of (1a), (2a), and (2b). In order to verify the effect of the polarity change and the relative role of the intermolecular–intramolecular interactions on conformational equilibria, the spectra were recorded using different solvents and several concentrations.

The values of the vicinal coupling constant $J_{1.2}$ found for (1a), (2a), and (2b) (7—8.2 Hz) suggest a marked preference for conformation I, where H(1) and H(2) are in an *anti*-relationship, but undoubtedly the contribution of II and III, where the protons are in a *gauche*-relationship, must also contribute to conformational equilibria.

On steric grounds the two *gauche*-forms II and III ought to be destabilized, since they have a Ph–Ph interaction, whereas the heteroatom polar interactions may stabilize them. In compounds (1a) and (2a) there is the possibility of intramolecular hydrogen bonding (O–H · · · S), whereas in (2b) the interactions between the two heteroatoms should be only destabilizing including the effect of orbital repulsion,[4] which may explain the preference for the *anti*-conformation in this

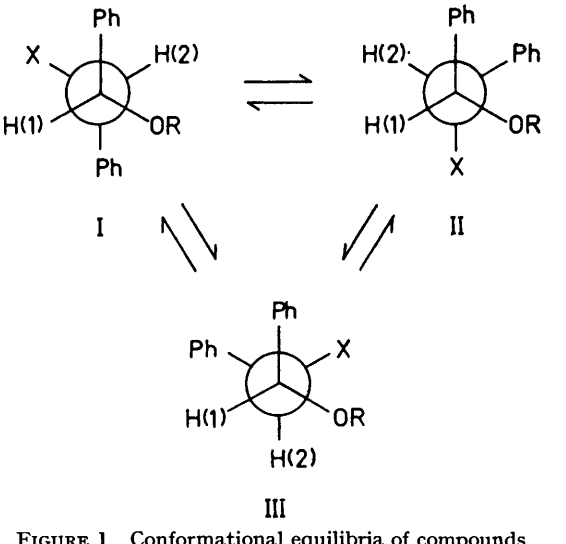


FIGURE 1 Conformational equilibria of compounds (1a)—(5a) and (1b)—(4b), around the C–C bond

* Due to the difference in electronegativity between oxygen and sulphur, the values of $J^{II}_{1.2}$ and $J^{III}_{1.2}$ are not expected to be exactly the same.[3] However, in order to establish the conformational preference in a qualitative way, the condition $J^{II}_{1.2} = J^{III}_{1.2}$ can be accepted.

compound. Nevertheless intramolecular hydrogen bonding is not the main factor in the stabilities of the *gauche*-forms of (1a) and (2a) as can be deduced from the following facts. (1) The influence of dilution on $J_{1.2}$ is negligible compared with the observed changes in 2-mercapto-(or 2-methylthio)-1-phenylethanol, previously studied. (2) When the spectra were recorded in [$^2H_6$]DMSO the $J_{1.2}$ values remain constant. (3) The i.r. spectra (Table 2) of compounds (1a) and (2a) in

TABLE 2

I.r. data for compounds (1a) and (2a)

Compound	Free O–H (cm^{-1})	Intramolecular bonded O–H (cm^{-1})	$\Delta\nu$ (cm^{-1})
(1a)	3 608	3 584	24
(2a)	3 605	3 582	23

carbon tetrachloride (10^{-2}—10^{-4}M) show that the intramolecular hydrogen bonds are weaker ($\Delta\nu$ 23—24 cm^{-1}) than in 2-mercapto- or 2-methylthio-1-phenylethanol ($\Delta\nu$ 70—95 cm^{-1}). From the relative intensity of the associated band with respect to the free OH band the predominance of the *anti*-form in the conformational equilibria may also be deduced.

In compounds (3a), (3b), (4a), (4b), and (5a) $J_{1.2}$ is small (3—4 Hz) (Table 3), which is consistent with the preference for the *gauche*-forms II and III. These results suggest a role for polar SR–OR interactions, which are capable of stabilizing these rotamers in spite of the fact that they are destabilized by steric interactions.

An i.r. study to demonstrate intramolecular associations could not be carried out due to problems of the solubility of these compounds in appropriate apolar solvents. Nevertheless, there is evidence which allows us to rule it out as a major factor. (1) The spectra of (3a) and (4a) recorded in [$^2H_6$]DMSO, in which an intramolecular hydrogen bond cannot be formed, reveal only a small decrease in the conformational preference. (2) In (5a), an analogous predominance of the *gauche*-forms is found. (3) In the acetyl derivatives a similar preference is observed in spite of the increase of destabilization by steric effects.

These facts indicate that electrostatic effects are the main stabilizing factors of the preferred conformations. Moreover, the long-range coupling constant between H(2) and the hydroxy protons ($^4J_{2.3}$) observed in the sulphoxide (3a) (1.1 Hz) suggests a preference for con-

TABLE 3

Compound	Solvent	Concentration (% w/v)	Chemical shift (δ) H(1)	H(2)	H(3)	Coupling constants (J/Hz) $J_{1.2}$	$J_{1.3}$	$J_{2.3}$
Ph (1)H–C–OH(3) (2)H–C–SOMe Ph (3a)	$CDCl_3$	0.5	5.741	3.830	2.580	2.66		
	[$^2H_6$]DMSO	5	5.470	4.000	6.016	2.99	4.43	1.07
		1	5.477	4.025	6.040	3.04	4.42	1.15
Ph (1)H–C–OH(3) (2)H–C–SO_2Me Ph (4a)	$CDCl_3$	5	5.985	4.156	2.550	2.72		
		1	5.987	4.154	2.420	2.70		
	[$^2H_6$]DMSO	10	5.694	4.594	6.126	3.35	4.73	0.50
		5	5.685	4.602	6.148	3.43	4.63	0.65
		1	5.675	4.589	6.112	3.44	4.81	0.82
Ph (1)H–C–OH(3) (2)H–C–$^+SMe_2$ Ph (5a)	[$^2H_6$]DMSO	10	5.576	5.414	6.685	4.00	4.52	0.45
		5	5.561	5.322	6.701	3.95	4.20	0.69
		1	5.537	5.191	6.704	4.03	4.33	
Ph (1)H–C–OAc (2)H–C–SOMe Ph (3b)	$CDCl_3$	10	6.565	3.853		3.23		
		5	6.565	3.855		3.25		
		1	6.560	3.851		3.49		
	[$^2H_6$]DMSO	10	6.422	4.416		3.54		
		5	6.410	4.414		3.49		
		1	6.392	4.405		3.51		
Ph (1)H–C–OAc (2)H–C–SO_2Me Ph (4b)	$CDCl_3$	10	6.846	4.359		4.99		
		5	6.842	4.329		4.97		
		1	6.848	4.318		4.95		
	[$^2H_6$]DMSO	10	6.724	5.102		4.05		
		5	6.724	5.100		4.09		
		1	6.691	5.078		4.03		

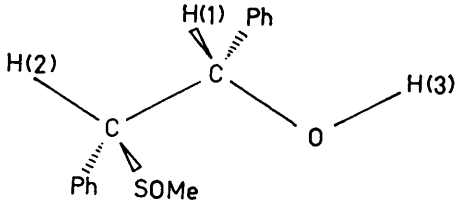
formation II, where both protons may adopt a W-like coplanar arrangement,[5] as shown in Figure 2.

The different stability of rotamers II and III derives from the fact that rotamer II has a Ph–OH interaction, by contrast with rotamer III, which has a Ph–SR one, which is possibly more destabilizing. The smaller values obtained for $^4J_{2,3}$ in (4a) and (5a) may be explained by a larger contribution from rotamer III, or by a slight change in the torsion angles due to different steric hindrance.

In the sulphinyl derivatives (3a) and (3b) the $J_{1,2}$ values are in accord with previous arguments, since they show a large preference for *gauche*- over *anti*-rotamers and this predominance slightly decreases in polar solvents, as expected.

The anomalous behaviour observed for the sulphonyl derivative (4a) under the same experimental conditions, might be produced by different associations with the solvent, although this has not been confirmed.

The fact that the spectra of (4a and b) do not show long-range coupling constants between H(2) and the



(II)

FIGURE 2 Spatial arrangement of H(1)—(3) in conformation II

protons of the methylsulphonyl group, in contrast with the reference compounds of Scheme 1, suggests that in these compounds the rotamer with the methyl group in an *anti*-relationship with H(2) makes little contribution to the equilibrium around the C–S bond. This behaviour is probably due to the steric interactions between the 2-phenyl and methyl groups. (This crowding can be easily visualized using Dreiding models.)

Finally, we conclude that in compounds (3a), (4a), (5a), (3b), and (4b), where the sulphur atom has a certain density of positive charge, electrostatic attraction between the heteroatoms is the main factor in conformational equilibria, even more relevant than Ph–Ph steric interactions, since it determines the main populations of the *gauche*-rotamers.

These results confirm our previous conclusions [1,2] on the importance of electrostatic interactions. On the other hand, in compounds (1a), (2a), and (2b), where the sulphur atom does not support any positive charge, steric effects determine the conformational populations.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a 100 MHz Varian XL100-15 spectrometer by the Fourier transform technique using 16 K of core in a Nicolet 1180 stored program computer The signal of the deuteriated solvent was employed as the deuterium field-frequency lock and tetramethylsilane as an internal reference. The analyses of the spectra were carried out using a LAOCOON III program [6,7] on a Nicolet 1180 computer. We estimate the reliability of all values as ± 0.1 Hz and the root mean square deviations for the calculated and the experimental lines were usually better than 0.05 Hz. I.r. spectra were recorded on a Pye–Unicam SP 1100 spectrometer. Studies on intramolecular hydrogen bonding were carried out on a Beckman IR-4240 spectrophotometer.

erythro-1,2-*Diphenyl*-2-*mercaptoethanol* (1a).—This was obtained from *trans*-stilbene oxide [8] by reaction with $NaBH_2S_3$ and reduction of the resulting disulphide with $LiAlH_4$.[9]

erythro-1,2-*Diphenyl*-2-*methylthioethanol* (2a).—A solution of *erythro*-1,2-diphenyl-2-mercaptoethanol (4 g, 17 mmol) in absolute ethanol (50 ml) was added dropwise to a solution of sodium (0.78 g, 17 mmol) in absolute ethanol (100 ml) and cooled at 0°. Methyl iodide (2.4 g, 17 mmol) was added and the mixture left overnight at room temperature. Water (100 ml) was added and the solution was extracted with chloroform (3 × 50 ml). The organic layer was dried and concentrated to yield compound (2a) (4.2 g, 98%). The solid was recrystallized from carbon tetrachloride, m.p. 74—75° (lit.,[10] 74°).

Acetyl Derivative (2b).—This was prepared by treatment of (2a) with acetic anhydride and pyridine (91%) and recrystallized from light petroleum, m.p. 62—63° (Found: C, 71.25; H, 6.6; S, 10.95. $C_{17}H_{18}O_2S$ requires C, 71.3; H, 6.35; S, 11.2%); $\nu_{max.}$ (Nujol) 1 745 and 1 230 cm^{-1}; δ($CDCl_3$) 1.73 (s, CH_3S), 1.83 (s, CH_3CO), 4.04 (d, J 8.17 Hz, CHSMe), 6.05 (d, J 8.17 Hz, CHOAc), and 7.22 (m, C_6H_5).

erythro-1,2-*Diphenyl*-2-*methylsulphinylethanol* (3a).—To an ice-cooled solution of sodium metaperiodate (1.5 g, 7 mmol) in water (20 ml) was added compound (2a) (1.7 g, 7 mmol). The mixture was maintained at 0° for 2 h and then left overnight at room temperature. Water (20 ml) was added and extracted with chloroform (3 × 20 ml). The chloroform extracts were dried ($MgSO_4$) and concentrated (rotary evaporator) to afford a solid. Crystallization from ethanol gave a crystalline solid (1.4 g, 78%), m.p. 207—209°. This method yielded only one diastereoisomer and its configuration has not yet been determined (Found: C, 69.05; H, 6.4; S, 12.55. $C_{15}H_{16}O_2S$ requires C, 69.2; H, 6.2; S, 12.3%), $\nu_{max.}$ (Nujol) 3 200 and 1 030 cm^{-1}; δ($CDCl_3$) 2.37 (s, CH_3SO), 2.58br (s, OH), 3.78 (d, J 2.66 Hz, CHSO), 5.78 (d, J 2.66 Hz, CHO), and 7.08 (m, C_6H_5).

Acetyl Derivative (3b).—This was crystallized from ethanol, m.p. 141—143° (Found: C, 67.6; H, 5.95; S, 10.85. $C_{17}H_{18}O_3S$ requires C, 67.55; H, 5.95; S, 10.6%); $\nu_{max.}$ (Nujol) 1 755, 1 235, and 1 050 cm^{-1}; δ($CDCl_3$) 2.14 (s, CH_3CO), 2.28 (s, CH_3SO), 3.82 (d, J 3.23 Hz, CHSO), 6.51 (d, J 3.23 Hz, CHOAc), and 7.08 (m, C_6H_5).

erythro-1,2-*Diphenyl*-1-*methylsulphonylethanol* (4a).—A solution of *erythro*-1,2-diphenyl-2-methylthioethanol (0.97 g, 3.5 mmol) and *m*-chloroperbenzoic acid (1.72 g, 10 mmol) in chloroform (120 ml) was stirred at room temperature for *ca.* 6 h. The solution was then washed with saturated aqueous sodium hydrogencarbonate (150 ml) and water (150 ml), dried ($MgSO_4$), and concentrated (rotary evaporator) to give, after recrystallization from benzene, compound (4a) (1.0 g, 91%), m.p. 179—181° (Found: C, 65.25; H, 5.55; S, 11.8. $C_{15}H_{16}O_3S$ requires C, 65.2; H, 5.85; S, 11.6%), $\nu_{max.}$ (Nujol) 3 455, 1 305, and 1 140 cm^{-1}; δ($CDCl_3$)

2.32br (s, OH), 2.67 (s, CH_3SO_2), 4.10 (d, J 2.70 Hz, $CHSO_2$), 5.92 (d, J 2.70 Hz, CHO), and 7.18 (m, C_6H_5).

Acetyl Derivative (4b).—This was recrystallized from benzene, m.p. 157—159° (Found: C, 63.95; H, 5.7; S, 10.3. $C_{17}H_{18}O_4S$ requires C, 64.15; H, 5.7; S, 10.05%); $\nu_{max.}$ (Nujol) 1 755, 1 310, 1 235, and 1 150 cm^{-1}; $\delta(CDCl_3)$ 2.00 (s, CH_3CO), 2.53 (s, CH_3SO_2), 4.31 (d, J 4.99 Hz, $CHSO_2$), 6.78 (d, J 4.99 Hz, CHOAc), and 7.24 (m, C_6H_5).

erythro-1,2-*Diphenyl*-2-*hydroxyethylsulphonium Iodide* (5a).—A solution of (2a) (0.97 g, 4 mmol) and methyl iodide (5 ml) in chloroform (40 ml) was stirred at room temperature for 3 h. The precipitate was collected by filtration and washed several times with ethyl ether to afford, after recrystallization from methanol, *compound* (5a) (1.0 g, 63%), m.p. 153—155° (Found: C, 49.5; H, 5.15; S, 8.4; I, 32.8. $C_{16}H_{19}IOS$ requires C, 49.75; H, 4.9; S, 8.3; I, 32.9%); $\nu_{max.}$ (Nujol) 3 190 and 800 cm^{-1}; $\delta([^2H_6]DMSO)$ 2.62 (s, CH_3S), 3.16 (s, CH_3S), 5.36 (d, J 4.00 Hz, CHS), 5.52 (dd, $J_{H,H}$ 4.00 Hz, $J_{H,OH}$ 4.52 Hz, CHO), 6.62 (d, J 4.52 Hz, OH), and 7.20 (m, C_6H_5).

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