Conformational Analysis of Acyclic Compounds with Oxygen–Sulphur Interactions. Some 2-Thio-derivatives of 1-Phenylethanol

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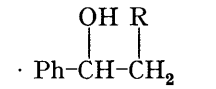
A conformational study of 1-phenyl-2-X-ethanol [X = SH, SCH_3, $SOCH_3$, SO_2CH_3, and $\overset{+}{S}(CH_3)_2$] is reported. The values of the vicinal and long-range (H–O–C–C–H and H–C–S–C–H) coupling constants obtained from n.m.r. spectra recorded in several solvents indicate that in most cases only one of the possible conformations around the C–C bond is preferred. This conformation, in which the sulphur function has a *gauche*-relationship with the hydroxy-group and an *anti*-relationship with the phenyl group, is probably stabilized more by polar interactions between the heteroatoms than by other factors.

THE influence of polar interactions in conformational analysis has previously been reported for X–C–C–Y systems.[1-3] The O–C–C–S system, with sulphur in different oxidation states, is useful for evaluating the contribution of polar effects to the relative populations of conformers. The literature on this subject is scarce and chiefly deals with sulphur compounds derived from 1,3-dioxan.[4]

This paper presents a conformational study of 1-phenyl-2-mercaptoethanol and derivatives (I)—(V).



(I) R = SH
(II) R = SCH_3
(III) R = $SOCH_3$
(IV) R = SO_2CH_3
(V) R = $\overset{+}{S}(CH_3)_2$

^1H N.m.r. spectral evidence was used to determine conformational preferences, as in the case of other acyclic molecules.[5-7]

RESULTS AND DISCUSSION

Possible conformations of compounds (I)—(V) are given in Figure 1. Conformational analysis of compounds (I)—(V) was carried out by studying the n.m.r. parameters of the protons on C-1 and -2. The chemical shifts are of little use in this analysis owing to the difficulty in predicting substituent effects and the lack of comparable model systems. Thus, the analysis was made on the basis of the coupling constants, using as a reference the value J 2.4 Hz (obtained from studies on *cis*-2-isopropyl-5-methylthio-1,3-dioxan [4]) for the coupling constant between vicinal protons in a *gauche*-arrangement.

From the equilibrium in Figure 1 and equations (1) and (2),† it may be deduced that very different values of the vicinal coupling constants are only compatible with a marked preference for conformations (A) and (B).

$$J_{1,2} = x_A J_{trans} + (x_B + x_C)\, J_{gauche} \quad (1)$$

$$J_{1,3} = x_B J_{trans} + (x_A + x_C)\, J_{gauche} \quad (2)$$

The δ and J values obtained from computer analysis of the ^1H n.m.r. spectra for compounds (I)—(V) are given in Tables 1 and 2. In order to verify the effect of changes in polarity and the relative role of inter- and intra-molecular interactions on conformational equilibria, the spectra were recorded using different solvents and several concentrations.

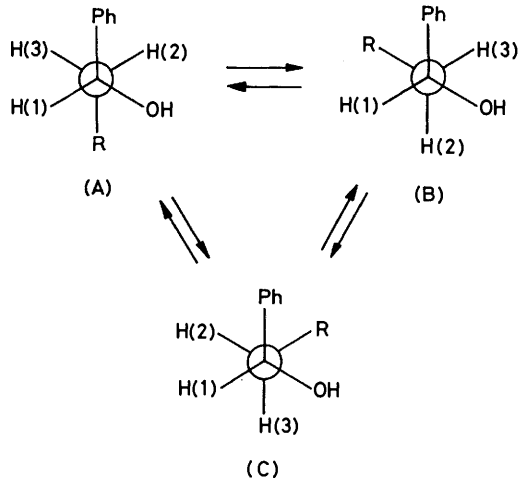


FIGURE 1 Conformational equilibria of compounds (I)—(V), around the C–C bond

The $J_{1,2}$ and $J_{1,3}$ values for compounds (III)—(V) show a marked conformational preference for (A) or (B). This preference is not so marked for compounds (I) and (II). Moreover in compounds (I) and (II) vicinal coupling constants were dependent on solvent and concentration whilst smaller and non-systematic variations were observed in compounds (III)—(V).

† These equations assume that J_{gauche} and J_{trans} are constant in all conformations.

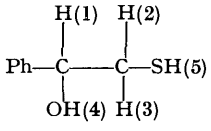
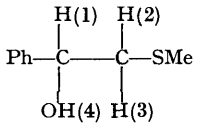
[1] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Interscience–Wiley, New York, 1965.
[2] M. Hanack, 'Conformational Theory,' Academic Press, New York, 1965.
[3] E. L. Eliel, *Angew. Chem. Internat. Edn.*, 1972, **11**, 739.
[4] M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1976, **98**, 956.
[5] H. S. Gutowsky, G. G. Belford, and P. E. MacMahon, *J. Chem. Phys.*, 1962, **36**, 3353.
[6] A. A. Bothner and C. N. Colin, *J. Amer. Chem. Soc.*, 1962, **84**, 743.
[7] H. Finegold, *J. Chem. Phys.*, 1964, **41**, 1808.

Owing to these differences of behaviour, independent studies of both types of compounds were undertaken.

When the spectra of compounds (III)—(V) were recorded using [$^2H_6$]DMSO, two long-range coupling hydroxy proton and 3-H. Since this proton is considered to be *gauche* with respect to 1-H, it can be seen from Figure 2 that this arrangement is only possible in conformation (A).

TABLE 1

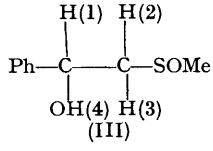
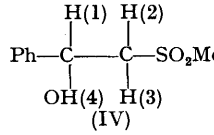
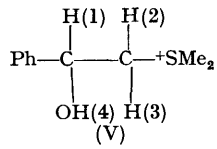
Chemical shifts and coupling constants of compounds (I) and (II)

Compound	Solvent	Concentration (% w/v)	Chemical shifts (δ) 1-H	2-H	3-H	4-H	5-H	Coupling constant (J/Hz) $J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,5}$	$J_{3,5}$
	CCl_4	20 [a]	4.476	2.671	2,719		1.269	6.39	5.61		−13.51	8.42	8.57
		15	4.545	2.640	2.674		1.310	7.22	5.32		−13.70	8.33	8.69
		10	4.585	2.643	2.673		1.283	7.50	4.85		−13.54	8.23	8.80
		2	4.594	2.687	2.741		1.256	7.96	4.03		−13.51	8.35	8.82
	$CDCl_3$	30 [a]	4.585	2.675	2.710		1.396	6.96	5.33		−13.62	8.51	8.38
		20	4.611	2.712	2.754		1.398	7.67	4.70		−13.58	8.64	8.45
		15	4.659	2.745	2.804		1.392	7.87	4.35		−13.66	8.60	8.47
		5	4.715	2.785	2.865		1.402	7.89	4.27		−13.59	8.54	8.48
		2	4.722	2.802	2.885		1.385	7.91	4.11		−13.46	8.58	8.67
	$CDCl_3$–2% DMSO	5	4.705	2.794	2.833		1.459	7.94	4.21		−13.66	8.59	8.30
(I)	$CDCl_3$–5% DMSO [c]	5	4.706	2.801	2.817		1.493	7.02	5.22		−13.38	8.70	8·30
	[$^2H_6$]DMSO	20	4.622	2.737	2.737	5.494	2.020	*b*	*b*	4.6			
	CCl_4	30 [a]	4.594	2.594	2.635			7.52	5.30		−13.54		
		20	4.606	2.609	2.653			8.70	4.09		−13.75		
		15	4.607	2.591	2.691			8.82	4.01		−13.68		
		5	4.640	2.500	2.653			9.14	3.74		−13.78		
		2	4.627	2.603	2.780			9.16	3.66		−13.82		
	$CDCl_3$	15	4.723	2.604	2.808			9.05	3.83		−13.78		
		5	4.752	2.722	2.849			9.24	3.67		−13.73		
		2	4.765	2.732	2.866			9.18	3.72		−13.68		
(II)	[$^2H_6$]DMSO	15	4.688	2.745	2.689	5.377		6.53	6.15	4.59	−13.30		
		3	4.675	2.734	2.662	5.367		7.23	5.51	4.63	−13.26		

[a] At greater concentrations deceptively simple spectra are obtained. [b] $J_{1,2} + J_{1,3}$ 12.08 Hz. [c] In this case the parameters obtained from the analysis are only accurate to 0.6 Hz or better due to the fact that the spectrum is very close to a deceptively simple spectrum.

TABLE 2

Chemical shifts and coupling constants of compounds (III)—(V)

Compound	Solvent	Concentrations (% w/v)	Chemical shifts (δ) 1-H	2-H	3-H	4-H	Me	Coupling constant (J/Hz) $J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{Me,2}$	$J_{Me,3}$
 (III)	$CDCl_3$	10	5.254	2.991	2.870	4.909		10.71	2.19	3.67	−12.91				
		5	5.286	3.010	2.879	4.741		10.94	1.87	3.25	−12.95				
		1.25	5.372	3.094	2.890			10.41	2.10		−13.13				
	[$^2H_6$]DMSO	12	4.985	3.036	2.854	5.779		10.88	2.47	4.81	−12.82	−0.16	1.34		
		3	4.976	3.034	2.853	5.760		11.02	2.58	4.66	−12.86	−0.16	1.34		
	D_2O	3	5.157	3.287	3.167			10.57	2.89		−13.48				
		1.6	5.160	3.298	3.298			10.58	2.89		−13.45				
 (IV)	$CDCl_3$	4	5.299	3.418	3.137		3.010	9.45	2.03		−14.60			0.50	0.97
		1	5.348	3.444	3.201		3.010	10.28	1.96		−14.55			0.53	0.83
	[$^2H_6$]DMSO	15	5.073	3.574	3.166	5.887	3.025	10.05	2.86	4.86	−14.73	−0.05	1.03	0.33	1.01
		4	5.063	3.566	3.162	5.877	3.025	20.05	2.86	4.70	−14.73	−0.05	1.18	0.45	1.08
	D_2O	4	5.256	3.773	3.494		3.100	9.33	4.22		−14.90			0.46	0.95
 (V)		16	5.178	3.698	3.792	6.272		10.21	3.22	4.61	−12.78		0.93		
	[$^2H_6$]DMSO	4	5.138	3.650	3.710	6.036		10.28	3.06	4.42	−12.83		1.01		
	D_2O	4	5.300	3.754	3.717			10.31	2.50		−13.25				

constants ($^4J_{2,4}$ *ca.* 0 and $^4J_{3,4}$ *ca.* 1 Hz) were observable between the hydroxy and the methylene protons. This suggests, by analogy with the value obtained in a similar system,[8] a W planar arrangement between the

Although long-range coupling may also be possible in conformation (C), the latter may be discarded because

[8] J. C. Jochims, G. Taigel, A. Seeliger, P. Lutz, and H. E. Driesen, *Tetrahedron Letters*, 1967, 4363.

of the relative values of $J_{1,2}$ and $J_{1,3}$. Owing to OH proton exchange, no long-range coupling was observed using other solvents ($CDCl_3$ and D_2O). However, the

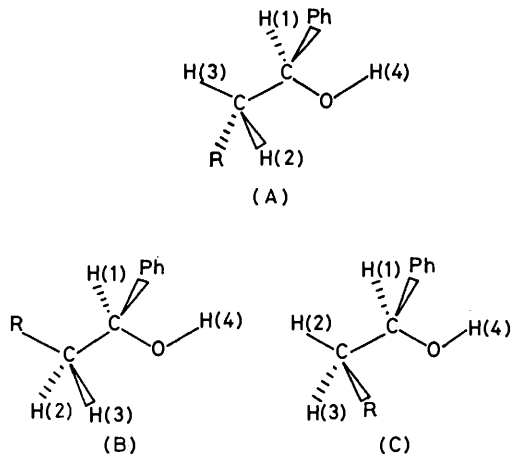
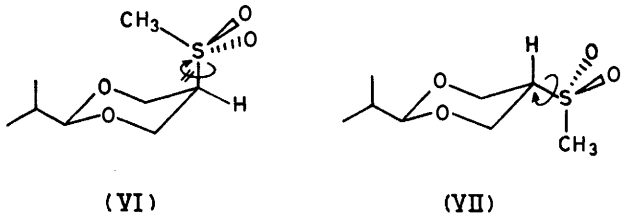


FIGURE 2 Spatial arrangement of the H-2, -3, and -4, in conformations (A)—(C)

vicinal coupling constants remained practically unchanged. This fact together with the results obtained for sulphone (IV) (see below), suggests that conformation (A) is preferred in these solvents also.

In sulphone (IV) other long-range coupling constants ($J_{H-C-S-C-H}$) were observed ($^4J_{Me,3}$ *ca.* 1 and $^4J_{Me,2}$ *ca.* 0.5). These values were very similar in all solvents used indicating that the possibility of total inversion between populations (A) and (B) with change in solvent has to be rejected. Similar $^4J_{H-C-S-C-H}$ values have been found in *cis*- and *trans*-2-isopropyl-5-methylsulphonyl-1,3-dioxan [4] (VI) and (VII) (Scheme). In the *cis*-isomer (VI) $^4J = 1.14$ Hz and in the *trans*-isomer (VII) $^4J = 0.39$ Hz. Eliel attributes this disparity to the different conformational mobility around the C–S bond of the two compounds.

Conformations (A) and (B) for sulphone (IV) have similar spatial arrangements to the *cis*- (VI) and *trans*-isomer (VII), respectively. The rotamers around the C–S bond in conformations (A) and (B) are shown in Figure 3. In view of the small contribution of conformation (B), the results can be rationalized considering only



SCHEME

the equilibrium $(A_1) \rightleftharpoons (A_2) \rightleftharpoons (A_3)$. Although conformations (A_2) and (A_3) are destabilized by one electrostatic repulsive interaction between the oxygen atoms (in the dioxan model, the comparable conformations have two of these interactions), their contribution to the equilibrium must be important, since they allow the formation of hydrogen bonds. It may reasonably be anticipated that the value of ^4J will be the same for

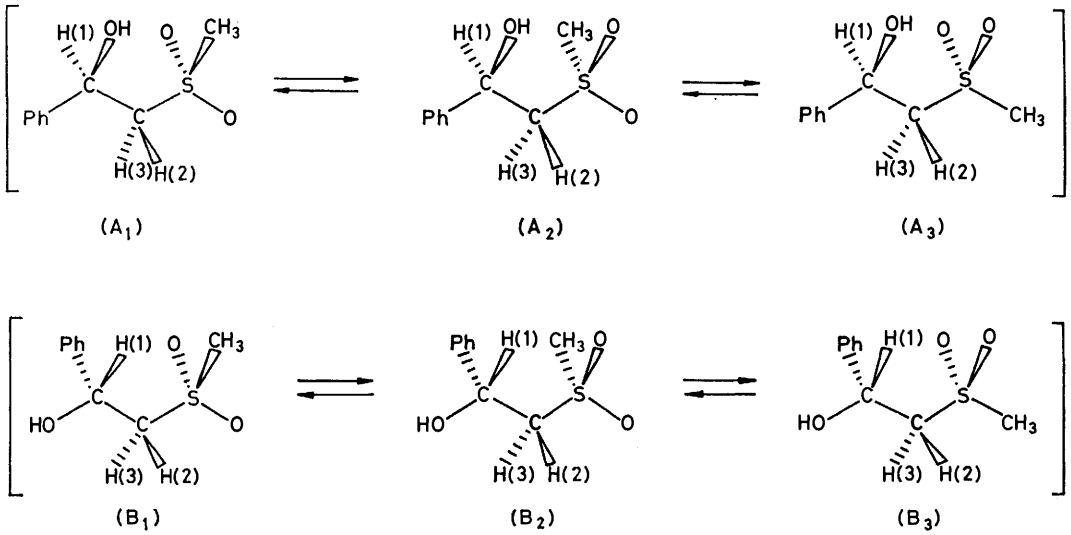


FIGURE 3 Rotamers around the C–S bond for the conformations (A) and (B)

the Me–H(3) and –H(2) couplings and consequently expressions (3) and (4) are obtained where $x_{(A_1)} =$

$$(J_{Me,3})_{obs} = x_{(A_1)}{}^4J \quad (3)$$

$$(J_{Me,2})_{obs} = x_{(A_1)}{}^4J \quad (4)$$

$(1 - x_{(A_1)})/2$, because rotamers (A_2) and (A_3) are approximately equally stabilized. When these equations are applied to the different values obtained for $J_{Me,2}$ and $J_{Me,3}$ (Table 2), it may be deduced that the contribution of (A_1) to the equilibrium is 44—60%. Therefore, the contributions of (A_2) and (A_3), are not negligible but less important than that of (A_1).

The preference of compounds (III)—(V) for conform-

ation (A) may be rationalized by considering electrostatic interactions between heteroatoms, hydrogen bonding, and steric effects. Electrostatic interactions and hydrogen bonding will basically stabilize conformations (A) and (C), while steric effects can explain the absence of, or small, contribution of conformation (C) to the equilibrium.

With regard to the relative weight of the above mentioned factors, it was impossible to carry out a satisfactory study of hydrogen bonding from i.r. spectra owing to problems in the solubility of these compounds in adequate apolar solvents. However, there are two pieces of evidence which allow us to rule out hydrogen bonding as a major factor. (1) The spectra of sulphoxide (III) and sulphone (IV) in DMSO and the salt (V) in all solvents, where an intramolecular hydrogen bond cannot be formed, reveal the same preference for conformation (A). (2) In compound (IV), conformational equilibrium around the C–S bond is shifted towards rotamer (A_1), which has not an adequate spacial arrangement to form intramolecular bonds. Quantitative data on the mutual steric interactions between the groups in question are not available. However, one may expect that Ph–R interactions, although larger than the OH–R ones, are not strong enough to explain the marked preference for conformation (A). The further discussion below for compounds (I) and (II) reinforces this point. The density of positive charge on the sulphur atom in compounds (III)—(V) suggests strong electrostatic interactions with the hydroxylic oxygen, and these stabilizing factors must be responsible for the conformational preference. Similar attractive forces have been used to explain the preference for the *gauche*-form in acetylcholine.[9,10] Furthermore, the observed equilibrium shift to rotamer (A_1) on sulphone (IV) may also be explained by assuming an O–Me attractive interaction due to the delocalization of the sulphur positive charge on the methyl group as previously postulated for acetylcholine.[11]

In the case of the thiol (I) and sulphide (II) the situation is clearly different, since changes in concentration and in solvent polarity affect conformational equilibrium (see Table 1). Thus, in CCl_4 and $CDCl_3$ it can be seen that, as the concentration increases, the chemical shifts for 1- and 2-H become more and more similar until they are identical. A deceptively simple spectrum is then observed which precludes evaluation of the equilibrium composition, since only the value $J_{1.2} + J_{1.3}$ can be determined from the spectrum. Before the deceptively simple spectrum stage, a conformational preference can still be seen. However, it is not possible to establish which of the two conformations predominates, since no long range coupling, $^4J_{H-O-C-C-H}$, is observable in the spectra.

On the other hand, i.r. spectra have shown the existence of intramolecular hydrogen bonds in compounds (I) and (II) (see Table 3). Although these i.r. results are not conclusive either, they suggest that conformations (A) must be preferred, since it can be stabilized by intramolecular hydrogen bonding. In addition the conformational preference deduced from n.m.r. spectra is greater in cases where conditions favour the formation of intramolecular hydrogen bonding. Thus, as the concentration increases in low polarity solvents the preference decreases as a result of competition between inter- and intra-molecular associations. In the case of compound (II) the predominance almost disappears when DMSO is used as solvent. [Compound (I) shows a deceptively simple spectrum in DMSO at any concentration.]

On the other hand, it may be deduced from the n.m.r. spectra that there is a greater predominance of the preferred conformation in the sulphide (II) than in the thiol (I). This agrees with the fact that the intramolecular hydrogen bond is stronger in compound (II), as can be deduced from the i.r. spectra on the basis of the $\Delta\nu$ values and the relative intensities of the free and associated OH bands (see Table 3).

TABLE 3

O–H Stretching frequency of compounds (I) and (II) ($<10^{-2}$M) in CCl_4

Compound	Free O–H(cm^{-1})	Intramolecular bonded O–H(cm^{-1})	$\Delta\nu$ (cm^{-1}
(I)	3 635	3 565 (0.4) [a]	70
(II)	3 635	3 540 (0.7) [a]	95

[a] Relative intensity of associated with respect to free O–H band.

In view of the values of the vicinal coupling constants in low polarity solvents and, above all, the value of the sum $J_{1.2} + J_{1.3}$, which is fairly constant in all cases, the possibility of a significant contribution by conformation (C) to the equilibrium may be rejected.

Steric interactions are probably responsible for the absence of conformation (C), but the possibility of its playing a major role in determining the relative populations of the other conformations may be rejected owing to the dependence of conformational equilibrium on changes in the polarity of the solvent and in the concentration of the compounds. This point reinforces the arguments above for the negligible importance of steric effects on the conformational equilibrium in compounds (III)—(V). As steric interactions in sulphide (II) are probably not much different from those in sulphoxide (III),[12] since substituents in the latter compound can be orientated so as to minimize these interactions, the conformational preference observed in this case cannot be explained by assuming a predominant role for steric factors.

We may therefore conclude that in all compounds where the sulphur atom has some positive charge [(III)—(V)], electrostatic interactions with the oxygen

[9] F. G. Canepa, P. Pauling, and H. Sörum, *Nature*, 1966, **210**, 907.

[10] P. Partington, J. Feeney, and A. S. V. Burgen, *Mol. Pharmacol.*, 1972, **8**, 269.

[11] B. Pullman, P. Courriere, and J. L. Coubeils, *Mol. Pharmacol.*, 1971, **7**, 397.

[12] E. L. Eliel and D. Kandasamy, *J. Org. Chem.*, 1976, **41**, 3899.

atom are the main factor determining the conformational population. On the other hand, where this positive charge is absent [(I) and (II)] other factors, such as hydrogen bonding, become more important.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 100 MHz on a Varian XL-100-15 spectrometer using tetramethylsilane as internal reference. Analyses of the spectra were carried out using a LAOCOON III program [13,14] on an I.B.M. 360/44 computer. Because of the linewidths encountered in all the spectra, the parameters obtained from the analysis are only accurate to 0.2 Hz or better, although the average agreement between observed and calculated transitions was 0.02 Hz or better. I.r. spectra were recorded on a Pye–Unicam SP 1100 spectrometer.

2-*Mercapto*-1-*phenylethanol* (I) was prepared from styrene epoxide by reaction with $NaBH_2S_3$ and reduction of the resulting disulphide with $LiAlH_4$.[15]

2-Methylthio-1-phenylethanol (II) was obtained by reaction of compound (I) with methyl iodide and sodium ethoxide following the procedure reported by Kondo [16] for similar compounds, b.p. 93—95 °C at 1 mmHg (lit.,[17] 92—95 °C at 1 mmHg).

2-Methylsulphinyl-1-phenylethanol (III) was prepared by reaction of compound (II) with sodium metaperiodate according to the general method for oxidising sulphides reported by Leonard and Johnson.[18] Compound (III) was obtained as a mixture of two diastereoisomers (two n.m.r. signals for the methyl group), m.p. 78—123 °C. Russell *et al.*[17] and Corey *et al.*[19] obtained the same mixture by different methods. The isolation of one of the diastereoisomers was carried out by repeated recrystallization from benzene,* m.p. 126—127.5 °C (Found: C, 58.6; H, 6.55; S, 17.35. Calc. for $C_9H_{12}O_2S$: C, 58.7; H, 6.5; S, 17.4%).

2-Methylsulphonyl-1-phenylethanol (IV) was obtained by oxidation of the sulphide (II) with *m*-chloroperbenzoic acid, as reported by Eliel [4] for similar compounds, m.p. 105—106 °C (lit.,[20] 106—106.5 °C).

(2-Hydroxy-2-phenylethyl)dimethylsulphonium iodide (V) was obtained in quantitative yield by reaction of compound (II) with methyl iodide in chloroform, m.p. 137—138 °C (lit.,[17] 137—139 °C).

[7/549 *Received*, 28*th March*, 1977]

* In this paper only this diastereoisomer has been studied. Although its configuration has not yet been determined, the results of conformational analysis may be expected not to differ significantly from those of the other diastereoisomer.

[13] A. A. Bothner-By and S. M. Castellano, *J. Chem. Phys*, 1964, **41**, 3863.
[14] S. M. Castellano, 'LAOCN3 in Computer Programs for Chemistry', ed. Detar, Benjamin, New York, 1968, vol. 1, p. 10.
[15] J. M. Lalancette and A. Frêche, *Canad. J. Chem.*, 1971, **49**, 4047.
[16] K. Kondo, A. Negishi, and I. Ojima, *J. Amer. Chem. Soc.*, 1972, **94**, 5786.
[17] G. A. Russell, E. Sabourin, and G. J. Mikol, *J. Org. Chem.*, 1966, **31**, 2854.
[18] N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 1962, **27**, 282; *J. Amer. Chem. Soc.*, 1962, **84**, 3701.
[19] E. J. Corey and M. Chaykosky, *J. Amer. Chem. Soc.*, 1965, **87**, 1345.
[20] W. E. Truce and K. R. Buser, *J. Amer. Chem. Soc.*, 1954, **76**, 3577.