# STUDY OF THE STEREOSPECIFICITY

OF THE REACTION OF r-4-BENZAMIDO-t-3-

HYDROXY-c(OR t)-2-(4-METHOXYCARBONYL-

BUTYL)THIOPHAN WITH THIONYL CHLORIDE

S. D. Mikhno, T. M. Filippova,
N. S. Kulachkina, I. G. Suchkova,
and V. M. Berezovskii

It has been established that the presence of a substituent in the 2 position in trans-4-benza-mido-3-hydroxythiophan changes the mechanism of the reaction with thionyl chloride from S_N2 to S_N1. r-4 Benzamido-t-3-chloro-c(or t)-2-(4-methoxycarbonylbutyl)thiophan and 2-phenyl-cis(or trans)-6-(4-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxa-zoline are formed simultaneously from r-4-benzamido-t-3-hydroxy-c(or t)- 2-(4-methoxy-carbonylbutyl)thiophans on reaction with thionyl chloride. The configurations of the products were established by PMR spectroscopy by means of the temperature dependence of the vici-nal spin−spin coupling constants and the angular dependence of these constants.

Continuing our study of the stereospecificity of the reaction of thionyl chloride with substituted 3-hy-droxythiophans [1] we carried out this reaction with r-4-benzamido-t-3-hydroxy-c- and r-4-benzamido-t-3-hydroxy-t-2-(4-methoxycarbonylbutyl)thiophans (I, V). When thiophans I and V are added to thionyl chloride at −20° C, the signal of the proton attached to C_3 in the PMR spectra of the resulting compounds is shifted to weak field as compared with the spectra of the starting compounds, and this constitutes evidence for a change in the substituent attached to C_3. The parameters of the PMR spectra of these compounds are similar to those of the spectra of the spectra of 4-amino-substituted 3-chlorosulfitothiophans [1]. Thus chlorosulfites II and VI, re-spectively, are formed from thiophans I and V.
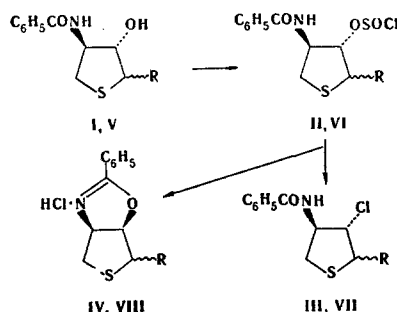
$R = (CH_2)_4COOCH_3$; in I-IV the substituents in the 2 and 4 positions of the thiophan ring are in the cis con-figuration, whereas in V-VIII they are in the trans configuration.

The sum of the vicinal constants ($\Sigma J_{4,5} = 11.2$ Hz) in the PMR spectrum of VI is of relatively small mag-nitude, whereas the chemical shifts of the geminal protons attached to C_5 do not coincide (Table 1). Proton magnetic resonance spectral peculiarities of this sort are characteristic for the r-4-t-3-t-2 substituent configuration [2]. In the case of II the sum of the vicinal constants along the 4−5 bond is substantially larger (15.6 Hz), and in this case one observes larger $J_{2,3}$ and $J_{3,4}$ values (7.6 Hz, Table 1); this is characteristic for

TABLE 1. Parameters of the PMR Spectra of II–IV and VI–VIII*

Com-pound	Solvent	Temper-ature	δ, ppm						J, Hz					
			2-H	3-H	4-H	5-H'	5-H''	NH	$J_{2,3}$	$J_{3,4}$	$J_{4,5'}$	$J_{4,5''}$	$J_{5',5''}$	$J_{4,NH}$
II	SOCl$_2$	−15	3,35—3,75	5,46	4,88	3,12	3,12	9,18	7,6	7,6	ΣJ_{4-5}=15,6			7,2
VI	SOCl$_2$ (82%) C$_5$D$_5$N (18%)	0	3,35—3,75	5,68	4,93	2,75—3,60†	2,75—3,60†	9,19	5,6	5,6	5,6	5,6		7,2
III	CD$_3$COOD	50	3,13—3,58	4,14	4,75	3,22	2,88		9,6	9,6	7,4	9,4	10,4	
VII	CD$_3$COOD	71,5	3,61—3,85	4,68	4,87	3,52	2,88		4,0	4,6	5,8	3,0	11,7	
			3a-H	4-H'	4-H''	6-H	6a-H		$J_{3a,4'}$	$J_{3a,4''}$	$J_{4',4''}$	$J_{6,6a}$	$J_{3a,6a}$	
IV	CD$_3$COOD	52	5,52	3,28	3,28	3,35—3,85	6,08		5,7	ΣJ_{3a-4}=5,3	12,2	3,8	7,4	
VIII	C$_5$D$_5$N	56	5,08	3,27	2,98	3,30—3,80	4,94			2,6		2,0	7,9	

*The corresponding AB systems were isolated and calculated in the determination of the chemical shifts of the geminal protons ($\Delta\delta$ gem $\neq$0) and the protons attached to C$_{3a}$ and C$_{6a}$ in VIII. The chemical shifts of the remaining protons were determined as the centers of the multiplets. The spin–spin coupling constants presented in the table correspond to the distances between definite lines in the spectra.
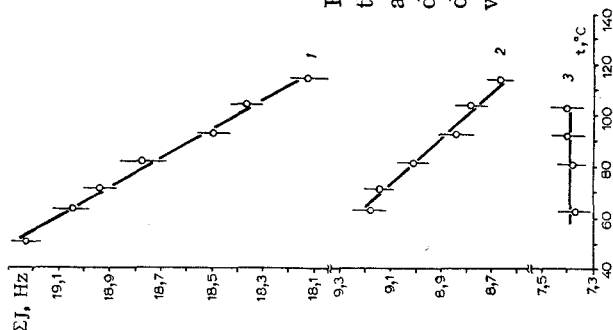†A broad poorly resolved multiplet.

Fig. 1. Temperature dependences of the sum of $J_{2,3}$ and $J_{3,4}$ (1), $J_{4,5''}$ (2), and $J_{4,5'}$ (3) for a solution of III in deuteroacetic acid (the mean-square deviations are shown by means of the vertical lines near each point).
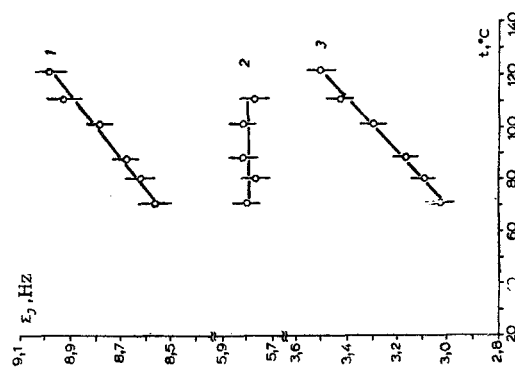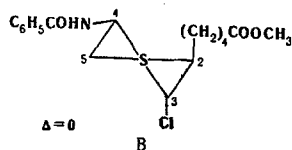

Fig. 2. Temperature dependences of the sum of $J_{2,3}$ and $J_{3,4}$ (1), $J_{4,5'}$ (2), and $J_{4,5''}$ (3) for a solution of II in deuteroacetic acid.

TABLE 2. Torsion and Dihedral Angles and Ranges of the Theoretical Values of the Vicinal Spin–Spin Coupling Constants for the 20 Possible Conformations of VII in the B Configuration*

C_6H_5COHN—(4)⟨ ⟩(CH$_2$)$_4$COOCH$_3$ (2) ; S (5,1); Cl (3)

$\Delta = 0$

B

No.	$\Delta_{(1)}$, °	$\Delta_{(2)}$, °	$\varphi_{2H,3H'}$, °	$J_{2,3}$, Hz	$\psi_{3-4'}$, °	$J_{3,4'}$, Hz	$\psi_{4-5'}$, °	$J_{4,5'}$, Hz	$\varphi_{4H-5H''}$, °	$J_{4,5}''$, Hz
1	0		79	0,3—0,4	49	3,3—5,2	41	4,5—6,9	161	9,6—14,5
2		360	161	9,6—14,5					79	0,3—0,4
3	36		90	0	49	3,3—5,2	49	3,3—5,2	169	10,4—15,6
4		396	150	8,1—12,2					71	0,8—1,3
5	72		105	0,7—1,1	41	4,5—6,9	49	3,3—5,2	169	10,4—15,6
6		432	135	5,4—8,0					71	0,8—1,3
7	108		120	2,7—4,0	30	6,0—9,0	49	3,3—5,2	169	10,4—15,6
8		468							71	0,8—1,3
9	144		135	5,4—8,0	15	7,4—11,2	41	4,5—6,9	161	9,6—14,5
10		504	105	0,7—1,1					79	0,3—0,4
11	180		150	8,1—12,2	0	8,0—12,0	30	6,0—9,0	150	8,1—12,2
12		540	90	0					90	0
13	216		161	9,6—14,5	15	7,4—11,2	15	7,4—11,2	135	5,4—8,0
14		576	79	0,3—0,4					105	0,7—1,1
15	252		169	10,4—15,6	30	6,0—9,0	0	8,0—12,0	120	2,7—4,0
16		612	71	0,8—1,3						
17	288		169	10,4—15,6	41	4,5—6,9	15	7,4—11,2	105	0,7—1,1
18		648	71	0,8—1,3					135	5,4—8,0
19	324		169	10,4—15,6	49	3,3—5,2	30	6,0—9,0	90	0
20		684	71	0,8—1,3					150	8,1—12,2

* The phase angle of pseudorotation (Δ) was varied for the ring of pseudorotation from 0 to 720° (through 36°) [10, 11]. The maximum torsion angle (ψ) was assumed to be 49° (the typical maximum torsion angle for a five-membered ring [12]). The remaining torsion (ψ) and dihedral (φ) angles were brought into conformity with the maximum values [13].

TABLE 3. Calculated and Experimental Values of the Vicinal Spin–Spin Coupling Constants for the 1,2 Conformations and the 1⇌2 Conformational Equilibrium

	Conformation		
	1	2	$I(70\%) \rightleftharpoons 2(30\%)$
Ψ_{2-3}, ° $J_{2,3}$calc, Hz		49 / 3,3—5,2	($J^{exp} = 4,0$)
φ_{3H-4H}, ° $J_{3,4}$calc, Hz	71 / 0,8—1,3	169 / 10,4—15,6	3,6—5,6 ($J^{exp} = 4,6$)
Ψ_{4-5}, ° $J_{4,5}$calc, Hz		30 / 6,0—9,0	($J^{exp} = 5,8$)
φ_{4H-5H}, ° $J_{4,5'}$calc	90 / 0	150 / 8,1—12,2	2,4—3,7 ($J^{exp} = 3,0$)

an r-4-t-3-c-2 orientation of the substituents [2]. Thus the configuration of the substituents is retained during the formation of chlorosulfites II and VI.

The subsequent transformations of chlorosulfites II and VI in solution in thionyl chloride during thermal reaction were monitored by PMR spectroscopy.

Chlorosulfites II and VI are stable in thionyl chloride at temperatures up to 0°; when the temperature is raised to 20°, r-4-benzamido-t-3-chloro-c-2-(4-methoxycarbonylbutyl)thiophan (III) and 2-phenyl-cis-6-(4-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline (IV) are formed from II in a ratio of 1:2, whereas r-4-benzamido-t-3-chloro-t-2-(4-methoxycarbonylbutyl)thiophan (VII) and 2-phenyl-trans-6-(4-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline (VIII) are formed from VI in a ratio of 1:3.
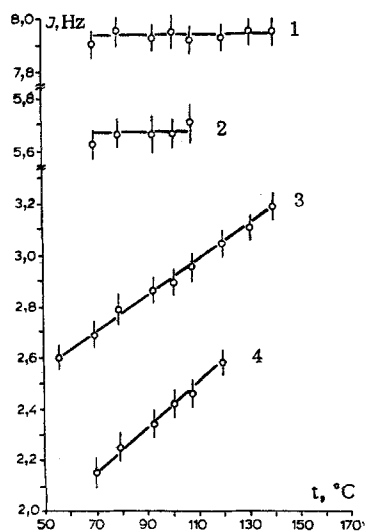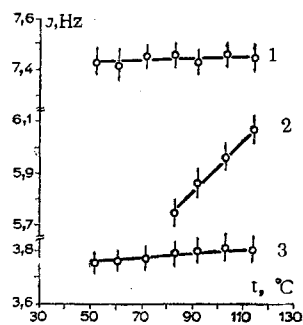
Fig. 3. Temperature dependences of $J_{3a,6a}$ (1), $J_{3a,4'}$ (2), $J_{3a4''}$ (3), and $J_{6,6a}$ (4) for a solution of VIII in deuteropyridine.

Fig. 4. Temperature dependences of $J_{3a,6a}$ (1), the sum of $J_{3a,4'}$ and $J_{3a,4''}$ (2), and $J_{6,6a}$ (3) for a solution of IV in deuteroacetic acid.

The configurations of III, IV, VII, and VIII were established by PMR spectroscopy (Table 1). It has previously been shown that the temperature dependences of the vicinal spin–spin coupling constants (SSCC) are characteristic in the determination of the configurations of saturated substituted five-membered rings [5]. The temperature dependences of the vicinal constants (Figs. 1 and 2) were therefore investigated to determine the mutual orientation of the substituents in III and VII.

In III and VII there are both cis and trans vicinal SSCC constants along the 4–5 bond. As expected, the magnitude of the trans-vicinal constant depends on the temperature ($J_{4,5''}$, Figs. 1 and 2, curves 2 and 3), whereas the magnitude of the cis constant is independent of the temperature ($J_{4,5'}$, Figs. 1 and 2, curves 3 and 2). The signal of the proton attached to C_3 is practically a triplet in the spectra of both compounds (Table 1). The temperature dependence of the sum of the vicinal constants along the 2–3 and 3–4 bonds (the sum of $J_{2,3}$ and $J_{3,4}$) was therefore measured for both compounds. In the case of III the change in the magnitude of this sum exceeds the change in the single trans-vicinal constant $J_{4,5''}$ by a factor of almost two (Fig. 1 at 63 to 114°, $\Delta\Sigma = -0.92$ Hz, curve 1; $\Delta J_{4,5''} = -0.51$ Hz, curve 2). Consequently, the measured sum of the constants consists of two trans-vicinal constants ($J_{2,3}^{trans}$, $J_{3,4}^{trans}$), and III is r-4-benzamido-t-3-chloro-c-2-(4-methoxycarbonylbutyl)thiophan.

In the case of VII the changes with temperature in the magnitude of the sum of $J_{2,3}$ and $J_{3,4}$ and of the trans-vicinal constant ($J_{4,5''}$) are practically identical (Fig. 2, at 71.5 to 122.5°, $\Delta\Sigma = 0.41$ Hz, curve 1; $\Delta J_{4,5''} = 0.48$ Hz, curve 3), i.e., one cis-and one trans-vicinal constant enter into the measured sum. Thus the two following configurations of substituents remain possible for VII:
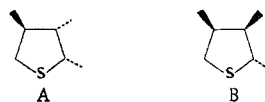

In order to choose between these configurations, for each of them we calculated the ranges of the vicinal constants of all 20 symmetrical conformations that make up the network of pseudorotation of the five-membered ring by means of angular dependence equations [6, 7]. In the calculation of the ranges of the vicinal constants, coefficient J^0 in the angular dependence equation was varied from 8 to 12 Hz, and the $J^{180°}$ coefficient was 1.35 J^0; this makes it possible to allow for the effect of different substituents on the magnitude of the constant [7]. The calculated constants were compared with the experimental values.

It was found that in the case of the B configuration (Table 2) none of the conformations can explain the vicinal constants observed for VII (Table 1). Moreover, the calculated vicinal constants cannot, with any satisfactory accuracy, approach the experimental values by consideration of the possible conformational equilibria with participation of two conformations, the phase angles of which differ by 360° [8]

$(\Delta_{(1)} \rightleftharpoons \Delta_{(2)}$, Table 2). The contribution to the conformational equilibrium of conformations that are adjacent, along the network of pseudorotation, to each of the conformations under consideration (the pseudolibration phenomenon [8]) also does not change the picture.

In a similar examination of the A configuration we were able to choose a conformational equilibrium that satisfactorily explains the observed values of the vicinal constants for VII (Table 3):
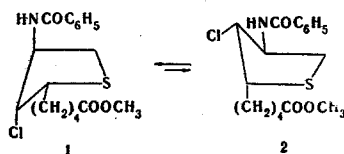

Thus VII is r-4-benzamido-t-3-chloro-t-2-(4-methoxycarbonylbutyl)thiophan.

It should be noted that the form of the conformational equilibrium and the primary conformation for VII are identical to those previously found for r-4-benzamido-t-3-acetoxythiophan [9], i.e., the introduction of a 4-methoxycarbonylbutyl substituent in the 2 position oriented trans to the substituent attached to C_4 practically does not change the conformational state of the molecule. This evidently also explains the above-noted retention of the characteristic peculiarities of the spectra of the cis and trans isomers of disubstituted thiophans for the corresponding isomers of the trisubstituted compounds for a trans configuration of the substituents in the 2 and 4 positions [2].

The parameters of the PMR spectra of solutions of IV in deuteroacetic acid and of VIII in deuteropyridine are presented in Table 1. The configuration of VIII was previously proved by an examination of the magnitudes of the vicinal spin–spin coupling constants [2]. A study of the temperature dependences of the vicinal constants confirms the correctness of the choice of configuration. As seen from Fig. 3, two of the constants for it [$J_{3a,4''}$ (curve 3) and $J_{6,6a}$ (curve 4)] depend on the temperature, i.e., they are trans constants, whereas two other constants [$J_{3a,6a}$ (curve 1) and $J_{3aH,4H'}$ (curve 2)] do not depend on the temperature, i.e., they are cis-vicinal constants [5]. The $J_{3a,6a}$ constant is found among the cis constants, and this constitutes evidence for cis fusion of the oxazoline and thiophan rings in VIII; the $J_{6,6a}$ constant is found among the trans constants, and this corresponds to trans orientation of the substituent attached to C_6 relative to the oxazoline ring.

In the case of IV, the $J_{6,6a}$ constant is retained as the temperature changes (Fig. 4, curves 1 and 3). Consequently, this constant is a cis-vicinal constant if, of course, the energies of the conformers participating in the conformational equilibrium differ. The chemical shifts of the protons attached to C_4 are close or coincide in the spectra of this compound at various temperatures (Table 1). It therefore did not seem possible to make an individual study of the temperature dependences of the cis- and trans-vicinal constants with respect to the 3a–4 bond. However, the sum of these constants (ΣJ_{3a-4}) depends on the temperature (Fig. 4, curve 2), and this provides evidence for a difference in the energies of the conformers other than zero (otherwise the trans-vicinal constant should also be independent of the temperature). Thus the temperature experiments provide evidence for a cis orientation of the substituent attached to C_6 with respect to the oxazoline ring in IV.

An examination of the magnitudes of the vicinal SSCC constants by means of angular dependence equations performed as in [2-4] showed that, as in the case of VIII [2], cis fusion of the thiophan and oxazoline rings and the following conformational equilibrium, in which conformation 3 predominates, are characteristic for IV:
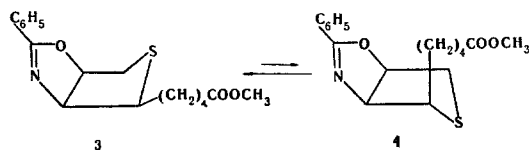
We have previously established that, whereas the reaction of trans-4-benzamido-3-hydroxythiophan is realized with thionyl chloride under the influence of heat, it proceeds with inversion of configuration (S_N2) to give 2-phenyl-cis-tetrahydrothieno[3,4-d]oxazoline [1].

In the present research we have shown that the introduction of a substituent in the 2 position in trans-4-benzamido-3-hydroxythiophan prevents reaction with thionyl chloride via an S_N2 mechanism and directs

it via an S_N1 mechanism inasmuch as oxazolines IV and VIII (the reaction proceeds with inversion of configuration) and chloro derivatives III and VII (retention of configuration) are formed simultaneously from II and VI.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Hitachi-20A spectrometer (60MHz) with tetramethylsilane as the internal standard. The assignment of the signals to definite protons in the investigated compounds was confirmed by the ratio of the integral intensities of the signals and double-resonance experiments. In the measurement of the temperature dependences the temperature was determined prior to and after recording of the spectra from the temperature dependence of the chemical shifts of the protons of ethylene glycol (with prior calibration of the ethylene glycol sample). Traces of oxygen were removed from the samples by blowing an inert gas through them. The vicinal constants were averaged over 12 to 20 measurements in order to raise the accuracy of the measurements. The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-10 spectrometer.

r-4-Benzamido-t-3-chloro-c-2-(4-methoxycarbonylbutyl)thiophan (III) and 2-Phenyl-cis-6-(4-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline Hydrochloride (IV). A 6-g (17 mmole) sample of thiophan I [2] was added at −30° to 18 ml of thionyl chloride, after which the mixture was stirred at −30° for 15 min and at 20° for 1 h. The thionyl chloride was then removed by vacuum distillation, 50 ml of methanol was added to the residue, and the mixture was allowed to stand at 0° for 10-12 h. The resulting precipitate was separated to give 1.4 g (22%) of colorless needles of III with mp 126-127° (from methanol). Found: C 57.8; H 6.3; Cl 10.0; N 3.7%. $C_{17}H_{22}ClNO_3S$. Calculated: C 57.4; H 6.2; Cl 10.0; N 4.2%. The filtrate was concentrated to a volume of 10 ml, and the concentrated solution was allowed to stand at 0° for 24 h. The resulting precipitate was separated to give 3.2 g (51%) of colorless prisms of IV with mp 77-78° (from methanol). Found: C 57.9; H 6.3; Cl 10.2; N 3.8%. $C_{17}H_{21}NO_3S \cdot HCl$. Calculated: C 57.9; H 6.3; Cl 10.1; N 4.2%.

r-4-Benzamido-t-3-chloro-t-2-(4-methoxycarbonylbutyl)thiophan (VII) and 2-Phenyl-trans-6-(4-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline Hydrochloride (VIII). These compounds were obtained from 6 g (17 mmole) of thiophan V [2] under conditions similar to those described for the preparation of III and IV. The yield of VII, which was obtained as colorless needles with mp 133-134° (from methanol), was 1.1 g (18%). Found: C 57.2; H 6.1; Cl 9.7; N 3.8%. $C_{17}H_{22}ClNO_3S$. Calculated: C 57.4; H 6.2; Cl 9.9; N 4.2%. The yield of VIII, which was obtained as colorless prisms with mp 135-136° (from methanol), was 3.5 g (57%). No melting-point depression was observed for a mixture of this product with a genuine sample [2].

LITERATURE CITED

1. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, I. G. Suchkova, V. A. Zamureenko, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 2, 183 (1975).
2. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, T. N. Polyanskaya, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 7, 897 (1972).
3. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, T. N. Polyanskaya, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 10, 1339 (1971).
4. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, T. N. Polyanskaya, I. K. Shmyrev, V. V. Mishchenko, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 6, 760 (1972).
5. T. M. Filippova, B. D. Lavrukhin, and I. K. Shmyrev, Org. Magn. Res., 6, 92 (1974).
6. M. Karplus, J. Chem. Phys., 30, 11 (1959).
7. S. Sternhell, Quart. Rev., 23, 236 (1969).
8. C. Altona, H. R. Buys, and E. Hovinga, Rec. Trav. Chim., 85, 973 (1966).
9. B. D. Lavrukhin, T. M. Filippova, and E. I. Fedin, Org. Magn. Res., 6, 368 (1974).
10. C. Altona, H. J. Geise, and C. Romers, Tetrahedron, 24, 8 (1968).
11. H. R. Buys, C. Altona, and E. Havinga, Tetrahedron, 24, 3019 (1968).
12. K. S. Pitrer and W. E. Donath, J. Amer. Chem. Soc., 81, 3213 (1959).
13. R. J. Abraham and K. A. McLaughlan, Mol. Phys., 5, 195 (1962).