ISOMERIZATION OF β-HALO DISULFIDES (ALKYL 2-HALOETHYL DISULFIDES)

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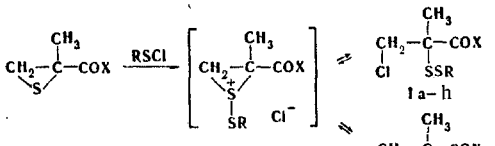
The methyl ester, amide, dimethylamide, and anilide of α-methylthioglycidic acid are readily cleaved by methane- and acetylsulfenyl chlorides to give mixtures of the corresponding isomeric cleavage products – vicinal chlorodithio derivatives of isobutyric acid. It is shown that the ratio of isomers obtained depends both on the character of the substituent in the carboxyl group of the isobutyric acid and on the character of the substituent attached to the sulfur atom in the sulfenyl chloride (sulfomonochloride) used. It was found that β-halo disulfides, like β-halo sulfides, are capable of isomerization.

It is known that sulfides that contain halogen in the β position are capable of isomerization. It is presently established that isomerization proceeds only in those cases in which the formation of an intermediate episulfonium ion is possible [1-3]. In later investigations, it was shown that the rate of isomerization and the resistance to isomerization of β-halo sulfides depend principally on the nucleophilicity of the sulfur atom. Thus no derivatives of 3-chloro-2-acetylthiobutyric acid isomerize, since the electron-acceptor substituent attached to the sulfur atom – the $COCH_3$ group – markedly lowers its nucleophilicity [4]. At the same time, derivatives of 3-chloro-2-methylthioisobutyric acid are readily isomerized to more stable isomers – 2-chloro-3-methylthioisobutyric acid derivatives. In this case, an electron-donor substituent – the CH_3 group – increases the nucleophilicity of the sulfur atom and promotes isomerization.

It should be noted that the rate of isomerization also depends on the character of the substituent in the carboxyl group of 3-chloro-2-methylthioisobutyric acid. The amides isomerized most readily, the anilide isomerized with somewhat greater difficulty, the esters isomerized considerably more slowly, and, finally, the acid chloride and nitrile were not isomerized [5].

In the cleavage of the methyl ester, amide, dimethylamide, and anilide of α-methylthioglycidic acid (2,3-epithioisobutyric acid) with methane- and acetylsulfenyl chlorides, we obtained the corresponding disulfides containing halogen in the β position. Since the cleavage of thioepoxides with electrophilic reagents occurs through the formation of an intermediate episulfonium ion [4-6], it was natural to expect the formation of isomeric cleavage products as a result of subsequent attack by chloride ion of both carbon atoms in the episulfonium ion.



I, II a X = NH_2, R = CH_3; b X = NH_2, R = $COCH_3$; c X = $N(CH_3)_2$, R = CH_3; d X = $N(CH_3)_2$, R = $COCH_3$; e X = NHC_6H_5, R = CH_3; f X = NHC_6H_5, R = $COCH_3$; g X = OCH_3, R = CH_3; h X = OCH_3, R = $COCH_3$

I a–h

II a–b

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TABLE 1. Isomerization of β-Halo Disulfides

Compound	X	R	Isomer ratio, I:II, %		mp, °C (from hexane)	bp, °C (mm)	n_D^{20}	Empirical formula	Found, %					Calc., %					Yield, %
			in reaction mixture at −20 to −40°	after heating					C	H	Cl	N	S	C	H	Cl	N	S	
a*	NH_2	CH_3	80 : 20	40 : 60	Undistillable oil			$C_5H_{10}ClNOS_2$											89
b†	NH_2	$COCH_3$			94	—	—	$C_6H_{10}ClNO_2S_2$	31,7	4,4	15,6	6,2	28,2	31,6	4,4	15,6	6,2	28,2	94
c*	$N(CH_3)_2$	CH_3	65 : 35	20 : 80	Undistillable oil			$C_7H_{14}ClNOS_2$											85
d	$N(CH_3)_2$	$COCH_3$	63 : 37	63 : 37	Undistillable oil			$C_8H_{14}ClNO_2S_2$	37,9	5,5			24,1	37,6	5,5			25,0	92
e	NHC_6H_5	CH_3	100 : 0	80 : 20	64			$C_{11}H_{14}ClNOS_2$	47,8	5,1	13,0	5,1	23,1	47,9	5,1	12,9	5,1	23,0	93
f	NHC_6H_5	$COCH_3$	100 : 0	100 : 0	74,5			$C_{12}H_{14}ClNO_2S_2$	48,0	4,6	11,8	5,0	21,2	47,5	4,6	11,7	4,6	21,1	96
g‡	OCH_3	CH_3	55 : 45			78 (4)	1,5216												63
h**	OCH_3	$COCH_3$	83 : 17			118 (3)	1,5340												95

*The compound could not be analyzed because of very facile disproportionation to the symmetrical disulfide.

†The isomer ratio could not be established by PMR spectroscopy because of the very low solubility of the compound in organic solvents.

‡In addition to the mixture of unsymmetrical disulfides, we also isolated a mixture of the corresponding symmetrical disulfides (V:VI = 30:70) in 37% yield; bp 160° (3 mm) and n_D^{20} 1.5245 (bp 154–155° (2 mm) and n_D^{25} 1.5225 [7]).

**See [4].

It was found that methane- and acetylsulfenyl chlorides reacted extremely readily with 2,3-epithioisobutyric acid derivatives. The reaction was complete in several minutes at −30 to −40°C in CCl_4 solution. When the reaction mass no longer gave a qualitative reaction for unchanged sulfenyl chloride, it was analyzed at the same temperature by recording the PMR spectra. It was found that a mixture of isomeric cleavage products – β-halo disulfides with different isomer ratios (I:II) – was obtained in almost quantitative yield; as in the case of the β-halo sulfides mentioned above, the isomer ratio depended on the character of the substituents attached to the sulfur atom in the sulfenyl chlorides and in the carboxyl group, of the α-methylthioglycidic acid (see Table 1).

Further investigations demonstrated that β-halo disulfides, like β-halo sulfides, are capable of isomerization and that the rate of isomerization and the resistance to isomerization depend mainly on the nucleophilicity of the sulfur atom in the investigated disulfides. Thus the isomer ratio (I:II) of the various derivatives of vicinal acetyldithiochloroisobutyric acid remained constant both after prolonged storage at room temperature and after prolonged heating at high temperatures (see Table 1, compounds d, f, and h). At the same time, the isomer ratio (I:II) of derivatives of vicinal methyldithiochloroisobutyric acid changed appreciably after heating at 100° for 10 h (see Table 1, compounds a, c, and e). However, in contrast to β-halo sulfides, the isomerization of β-halo sulfides proceeds considerably more slowly, although the effect of the character of the substituents attached to the sulfur atom and in the carboxyl group is precisely the same (see Table 2). For comparison, Table 2 also contains our isomer ratios (I:II) and isomer ratios (III:IV) reported in [2, 5] before and after isomerization of the analogous vicinal halo mono- and disulfide derivatives of isobutyric acid.

It should be noted that the ready disproportionation of the β-halo disulfides to symmetrical disulfides [7] interfered with observations of their isomerization and isolation in pure form.

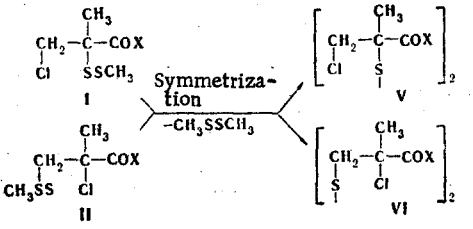
TABLE 2. Effect of Substituents of Vicinal Halo Mono- and Disulfide Derivatives of Isobutyric Acid on Isomerization

X	I : II		III : IV	
	before isomerization	after heating for 10 h at 100°C	before isomerization	after isomerization (time in h; temp. in °C)
NH_2	80 : 20	40 : 60	92 : 8	24 : 76 (a few; 20)
NHC_6H_5	100 : 0	80 : 20	100 : 0	0 : 100 (6; 70)
OCH_3	55 : 45	55 : 45	76 : 24	53 : 47 (24; 60; traces of H_2SO_4)

TABLE 3. PMR Spectra of β-Halo Disulfides

Compound	Chemical shifts δ, ppm					
	$-S-C-CH_3$	$Cl-C-CH_3$	$-SCH_3$	$-SCOCH_3$	$-CH_2-S-$	$-CH_2-Cl$
					AB system	
$ClCH_2(CH_3)C(SSCH_3)CONH_2$ [a]	1,58		2,45			3,56—4,18
$CH_3SSCH_2(Cl)C(CH_3)CONH_2$ [a]		1,83			3,12—3,65	
$ClCH_2(CH_3)C(SSCH_3)CON(CH_3)_2$ [b]	1,78		2,46			3,80—4,30
$CH_3SSCH_2(Cl)C(CH_3)CON(CH_3)_2$ [b]		2,03			3,26—3,80	
$ClCH_2(CH_3)C(SSCOCH_3)CON(CH_3)_2$ [c]	1,68			2,44		3,56—4,16
$CH_3COSSCH_2(Cl)C(CH_3)CON(CH_3)_2$ [c]		1,96			2,97—3,56	
$ClCH_2(CH_3)C(SSCH_3)CONHC_6H_5$ [d]	1,65		2,42			3,88 (A), 4,17 (B) $J_{AB}=12$ Hz
$CH_3SSCH_2(Cl)C(CH_3)CONHC_6H_5$ [d]		1,89			2,82—3,45	
$ClCH_2(CH_3)C(SSCOCH_3)CONHC_6H_5$ [e]	1,61			2,41		3,95 s [f]
$ClCH_2(CH_3)C(SSCH_3)COOCH_3$ [g]	1,54		2,38			3,67—4,29
$CH_3SSCH_2(Cl)C(CH_3)COOCH_3$ [g]		1,82			3,20—3,64	

[a] δ 7.2 ppm (d, J = 36 Hz, NH_2).
[b] δ 3.21 ppm [s, $N(CH_3)_2$].
[c] δ 3.15 ppm [s, $N(CH_3)_2$].
[d] δ 8.07 ppm (s, NH); δ 6.96-7.65 ppm (m, $N-C_6H_5$).
[e] δ 9.34 ppm (s, NH); δ 7.03-7.74 ppm (m, $N-C_6H_5$).
[f] The following abbreviations were used here and elsewhere: s is singlet, d is doublet, and m is multiplet.
[g] δ 3.75 ppm (s, OCH_3).



Disproportionation was inevitable in the case of methyldithiochloroisobutyric acid derivatives (see Table 1, compounds a, c, and e), since the capacity of the compounds for disproportionation and isomerization depends on the same reasons – namely, on the nucleophilicity of sulfur in the mixed disulfides.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were recorded with a Perkin-Elmer R-12 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

The methyl ester, amide, and dimethylamide of 2,3-epithioisobutyric acid were described in [8, 9]. The dimethylamide was previously [9] obtained by acylation of α-methylthioglycidic acid dimethylamide.* We synthesized it by a more practicable method from the β-thiolactone.

2,3-Epithioisobutryic Acid Dimethylamide. A solution of 13.65 g (0.1 mole) of α-chloro-α-methyl-β-thiolactone in 50 ml of absolute ether was added dropwise with vigorous stirring at −60° to a solution

*In the presence of 1,3-dicyclohexylcarbodiimide.

of 9.0 g (0.2 mole) of dimethylamine in 450 ml of absolute ether. The temperature of the reaction mixture was raised to 20°, and the precipitated dimethylamine hydrochloride [8.1 g (99.3%)] was removed by filtration. The solvent was evaporated, and the residue was distilled to give 2,3-epithioisobutyric acid dimethylamide in 89% yield with bp 67-68° (3 mm) and n_D^{20} 1.5130 [bp 75-78° (5 mm) and n_D^{25} 1.5110 [9]).

2,3-Epithioisobutyric Acid Anilide. A solution of 18.6 g (0.2 mole) of aniline in 50 ml of absolute ether was added dropwise with vigorous stirring at −40° to a solution of 13.6 g (0.1 mole) of 2,3-epithioisobutyryl chloride [9] in 150 ml of absolute ether. The temperature was raised to 20°, and the precipitate was removed by filtration. The filtrate was washed with water to remove aniline hydrochloride and evaporated, and the solid residue and the washed precipitate were recrystallized to give 2,3-epithioisobutyric acid anilide in 90% yield with mp 70-71° (from hexane). Found: C 61.9; H 5.8; N 7.2; S 16.4%. $C_{10}H_{11}NOS$. Calculated: C 62.2; H 5.7; N 7.2; S 16.4%.

Cleavage of 2,3-Epithioisobutyric Acid Derivatives with Methane- and Acetylsulfenyl Chlorides and Isomerization of the Cleavage Products. A solution of 0.1 mole of the sulfenyl chloride in 10 ml of CCl_4 was added with stirring at −30 to −40° to 0.1 mole of the appropriate 2,3-epithioisobutyric acid derivative in 10 ml of CCl_4, and the mixture was allowed to stand at this temperature until the reaction was complete (10-15 min) (the end of the reaction was established from a negative test for sulfenyl chloride with an aqueous KI solution). An aliquot of the solution was analyzed at low temperature by PMR spectroscopy to establish the isomer ratio. The temperature of the mixture was raised to 20°, and a portion of the solution was worked up by removing the solvent and isolating the unsymmetrical and, in some cases, symmetrical disulfides, usually in the form of mixtures of the isomers. Another portion of the solution was heated at 100° for 10 h, after which the changed isomer ratio was established. The isomer ratios, physical constants, yields, and analytical results are presented in Table 1, and the chemical shifts are given in Table 3.

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