BIS(β -CHLOROETHYL) SULFIDES

COMMUNICATION 2. DERIVATIVES OF α -CHLORO- β -(β -CHLOROETHYLTHIO)-AND α -(β -CHLOROETHYLTHIO)- β -CHLOROISOBUTYRIC ACID

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The present paper is devoted to the synthesis of modified derivatives of yperite compounds of the (A) and (B) type and a study of their chemical and biological properties



Previously it had been reported that compounds of the (A) type can be obtained by the addition of β chloroethylsulfenyl chloride to methacrylic acid and its derivatives [1]. At the time this work was completed there appeared a similar investigation in the literature on the addition of methylsulfenyl chloride to derivatives of acrylic and methacrylic acids [2]. Steric factors play an important role in the opening of the intermediate cyclic episulfonium ion



At the same values of X, attack of the chloride anion on the α -carbon atom predominates in the case where Y = H, while attack on the β -carbon atom predominates in the case where Y = CH₃. In addition, the ratio of the isomers and their stability are both strongly dependent on the nature of X. The formation of the α -methylthio- β -chloro derivatives increases in the following order: COCl < COOCH₃ < CONH₂ < CN < SO₂CH₃. This rule is in good agreement with the activation of an α -halogen in carboxylic acids and their derivatives in nucleophilic substitution [2]. It was also observed that in some cases the presence of the hydrogen ion accelerates the isomerization of the initially obtained less stable adduct to the thermodynamically more stable isomer.

The studies performed by us on the addition of methyl-, phenyl-, and β -chloroethylsulfenyl chloride to derivatives of methacrylic acid are in good agreement with the data given in [2]. The addition of various sulfenyl chlorides to methacrylic acid derivatives also proceeded preferentially with the formation of the corresponding β -chloro- α -thio esters. The addition was run in CCl₄, CHCl₃, ether, or CH₂Cl₂ at either low or room temperatures.

The NMR spectra of the reaction mass were taken, and then after distillation or recrystallization of the substance, and finally, after long storage, at times for more than a year, at room temperature in CCl_4 solution in the same ampoule. As a rule, simple distillation failed to cause noticeable isomerization. The NMR spectra were compared with compounds of the (B) type and with model compounds [1]. All of the data are given in Tables 1-3. The addition of methyl-, phenyl-, and β -chloroethylsulfenyl chloride to the amides of methacrylic acid goes in a well-defined manner with the formation of only one isomer (I)

Institute of Heteroorganic Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2522-2529, November, 1971. Original article submitted February 20, 1970.

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x	Chemical shift, ppm					Spin-spin	Ratio of iso- mers, %	
	GH₃			(c) $(d)SCH2CH2Cl$		coupling con-	(B)	(A)
		(b) H		SCH.	CH2Cl	stant, HZ		(/
NHC ₆ H ₅	1,88	3,08	3,28	2,85	3,52	$J_{a, b} = 13, 1$	100	
$\rm NHCH_2C_6H_5$	1,73	3,02	3,16	2,76	3,50	$\begin{array}{c} J_{c,d} = 7,7\\ J_{a,b} = 13,1\\ r = 7,7 \end{array}$	100	1
OH	1,94	3,19	3,32	3,25	3,59	$J_{a, b} = 14.5$	100	40
Cl	1,94	3,33		3,04	3,70	$J_{c, d} = 0.8 \\ J_{c, d} = 7.8$	100	10
OCH3 (2)	1,32	3,01	3,23	2,82	3,60		100	- 1
OCH3 (b) Nitrile	1,99	3,15		3,04	3,53		76 67 67	24 33 33

TABLE 1. NMR Spectra and Ratio of (B) and (A) Isomers

TABLE 2. NMR Spectra and Ratio of (A) and (B) Isomers

	Chemical	shift, ppm	Spin-spin Ratio		of iso- %	
CH.		SCH ₂ CH ₂ CH ₃ Cl (c) (d)		coupling con-	(B)	(A)
0.125	(b) H	SCH2	CH2C1	stand 112		
1,60 1,53 1,59 1,73 1,56 1,70	3,65 3,96 3,56 4,02 3,53 3,96 3,72 4,09 3,54 3,87 3,60 3,99	2,88 2,86 3,02 2,99 2,96 3,17	3,48 3,39 3,58 3,71 4,01 3,76	$J_{a, b} = 11, 1$ $J_{c, d} = 7, 7$ $J_{a, b} = 11, 1$ $J_{c, d} = 7, 7$ $J_{a, b} = 11, 1$ $J_{c, d} = 7, 7$ $J_{a, b} = 12$ $J_{c, d} = 7, 7$	96 24 15 73 60 58 27 45 400	100 4 76 85 27 40 42 73* 55
4,10	0,00		0,10	Į	100	Į
	CH₃ 1,60 1,53 1,59 1,73 1,56 1,70	Chemical CH ₃ (a) H (b) H CCI (c) H 1,60 3,65 3,96 1,53 3,56 4,02 1,59 3,53 3,96 1,73 3,72 4,09 1,56 3,54 3,87 1,70 3,60 3,99	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c } \hline Chemical shift, ppm \\ \hline CH_3 & (a) H & CCI & SCH_3CH_4CI \\ (b) H & CCI & SCH_2 & CH_4CI \\ \hline (b) H & CCI & SCH_2 & CH_4CI \\ \hline 1,60 & 3,65 & 3,96 & 2,88 & 3,48 \\ 1,53 & 3,56 & 4,02 & 2,86 & 3,39 \\ 1,59 & 3,53 & 3,96 & 3,02 & 3,58 \\ 1,73 & 3,72 & 4,09 & 2,99 & 3,71 \\ 1,56 & 3,54 & 3,87 & 2,96 & 4,01 \\ 1,70 & 3,60 & 3,99 & 3,17 & 3,76 \\ \hline \end{tabular}$	Chemical shift, ppmSpin-spin coupling con- sch4CH.Cl (c) (d)CH_s(a) H (b) HSCH_4CH.Cl (c) (d)Sound CH_4Cl (d)coupling con- stant, Hz1,603,653,962,883,48 $J_{a,b} = 41.1$ $J_{c,d} = 7,7$ $J_{a,b} = 41.1$ $J_{c,d} = 7,7$ $J_{c,d} = 7,7$ $J_{c,d} = 7,7$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

* The amount of unreacted starting material was 16%.

$$\begin{array}{ccc} CH_3 & CH_3 & CH_3 & CH_3 \\ l \\ CH_2 = C - CONRR' \xrightarrow{R''SCl} CH_2 - C - CONRR' \xrightarrow{Rearrangement} CH_2 - C - CONRR' \\ \hline l & l \\ Cl & SR'' & (l) & SR'' & Cl & (l1) \\ R'' = CH_2, CH_2 CH_2 Cl, C_6 H_5 \end{array}$$

The obtained amides are crystalline compounds; they were all isolated in the pure state. However, in the case of methyl- and β -chloroethylsulfenyl chloride, when stored under normal conditions, depending on the character of the amide, they either isomerized at variable speeds or else did not isomerize to compounds of the (B) type (II). Isomerization was not observed after storage for a year in the case where $\mathbb{R}^n = C_6 H_5$. The same sulfenyl chlorides add with much greater difficulty to the nitrile of methacrylic acid, and even in the case of the most reactive methylsulfenyl chloride the addition is ended only after 5 days at ~20°C. The stable adducts ClCH₂C(CH₃)SRCN (III) are formed here. The addition of the sulfenyl chlorides to methacrylic acid was studied in greatest detail. The NMR spectra of the reaction mass disclosed that a mixture of isomers of the following composition is formed immediately



R	x	Chemical shift, ppm				Spin-spin	Ratio of iso- mers, %	
		СН3	SCH3	(a) H (b) H)cci	coupling constant, Hz	(B')	(A')
CH3	NHC ₆ H ₅	1,55	2,04	3,69	4,01	$J_{a, b} = 12^{-1}$	70	100 ·
CH3	ОН	1,59	2,22	3,54	4,06	$J_{a, b} = 12$	11	89 59
CH₃	OCH3	1,52	2,08	3,55	4,01		39 28 41	61 72: 59
C_6H_5	NHC ₆ H ₅	1,59		3,58	3,89	$J_{a, b} = 10, 3$	41	100
C_6H_5	он	1,62		3,59	3,93	$J_{a, b} = 11, 1$	32	68 67
C_6H_5	Nitrile	1,57		3,44	3,55		- 00	100-
CH3		1,63	2,31	3,55	3,85			100
C_6H_5	OCH3						30	70

TABLE 3. NMR Spectra and Ratio of Isomers $ClCH_2CCH_3(SR)COX$ (A') and $RSCH_2 - CCH_3(Cl)COX$ (B')

In the case of phenyl sulfenyl chloride the adduct, which was obtained as an oil, on the basis of the NMR spectra contained approximately equal amounts of the (A) and (B) isomers. After three recrystallizations from petroleum ether the ratio of the (B): (A) isomers was 1:2, and this ratio remained constant for a long time. In the case of β -chloroethyl sulfenyl chloride only the acid (V, R = CH₂CH₂Cl) was isolated in the pure state for the mixture of adducts (A) and (B).

The addition of β -chloroethylsulfenyl chloride to methyl methacrylate, $X = OCH_3$ in CCl_4 gave, within 10 min after mixing the reactants, 74% of the methyl ester of β -chloro- α -(β -chloroethylthio) isobutyric acid (VI), 26% of the methyl ester of α -chloro- β -(β -chloroethylthio) isobutyric acid (VII), and 27% of the starting methyl methacrylate. The ratio of the adducts remained constant for an hour, and only a decrease in the amount of the starting ester to 16% was observed. The ratio of the isomers remained practically constant when stored for two days and when distilled. Only after approximately three months did the ratio of the isomers become nearly equal (45-55%)



The same picture was also observed in the case of the addition of methylsulfenyl chloride. The addition of $CISCH_2CH_2CI$ to methacryloyl chloride goes much more slowly and is ended only after two days, in which connection the ratio of the isomers always remains constant, with a predominance of the (VIII) isomers (60%).

In order to synthesize compounds of the (B) type we used α -chloro- α -methyl- β -propiothiolactone, with a fixed position of the sulfur and chlorine atoms. The synthesis was accomplished by the following series of transformations shown in Scheme 1. α -Chloro- β -(β -chloroethylthio) isobutyric acid (V) and its amides (II) had been obtained previously [1]. The methyl ester of α -chloro- β -(β -chloroethylthio) isobutyric acid (VII) is easily formed by the reaction of acid chloride (VIII) with methanol in the presence of triethylamine. All of the compounds of this type are quite stable under ordinary conditions.

However, when acid chloride (VIII) was heated with methanol at 60° a mixture of isomers was obtained, which represented 76% of (VII) and 24% of the methyl ester of β -chloro- α -(β -chloroethylthio) isobutyric acid (VI). The preparation of the nitrile of α -chloro- β -(β -chloroethylthio) isobutyric acid (XIII) from





the corresponding amide using P_2O_5 also led to the formation of a mixture of isomers in the following proportions - 67% of (XIII) and 33% of the nitrile of β -chloro- α -(β -chloroethylthio) isobutyric acid (XIV)



In these cases the elevated temperature and acid catalysis could be the reason for the isomerization of the isomers, which are quite stable under ordinary conditions.

From what has been said it follows that in our case the addition of the same sulfenyl chloride to methacrylic acid and its derivatives goes in a variable manner and their subsequent behavior is also different. The addition is easiest to the amides, more slowly to the acid, and then to the ester and acid chloride. The nitrile of methacrylic acid reacts with the greatest difficulty. Of the compounds obtained in this manner the most stable is the nitrile of the α -alkthio- β -chloroisobutyric acid, which does not isomerize under ordinary conditions. The least stable are the amides of the α -alkthio- β -chloroisobutyric acid, which, depending on the substituent attached to the nitrogen, are isomerized at room temperature, either in CCl₄ solution or as the pure compound, to the corresponding amides of the β -alkthio- α -chloroisobutyric acid. During the spontaneous transition of one isomer to the other the isomerization does not always go to completion. For the acid and the methyl ester the equilibrium is reached at a different concentration of the isomers: 73/27 for the acid, and 45/55 for the ester.

The formation of only the α -phenylthio- β -chloro isomer was observed when phenylsulfenyl chloride was added to the nitrile and anilide of methacrylic acid. A mixture of isomers is formed when the same sulfenyl chloride is added to methacrylic acid and its methyl ester. But in both cases further isomerization is not observed under ordinary conditions.

As a result, the present investigation corroborates the mechanism previously proposed by Kharasch [3] for the addition of sulfenyl chlorides to unsaturated systems via the intermediate cyclic episulfonium ion



It is entirely probable that the subsequent isomerization of the β -chloro sulfides proceeds via the same intermediate ion. The fact that the more stable pure isomers of the (B) type were available to us greatly facilitated a study of this fairly complex problem.

EXPERIMENTAL METHOD

Methyl Ester of α-Chloro-β-(β-chloroethylthio) isobutyric Acid (VII). To 20 g of (VIII) in 150 ml of absolute ether, with cooling in ice water, were added in drops 3.4 ml of absolute methanol in 20 ml of absolute ether and 12 ml of triethylamine in 30 ml of absolute ether. The triethylamine hydrochloride was filtered, the solvent was removed in vacuo, and the residue was vacuum distilled. We obtained (VII) in 89% yield, bp 110° (5 mm); n_D^{22} 1.5040; d_4^{20} 1.2571. Found: C 35.75; H 4.95; Cl 30.73; S 13.19%; MR 54.40. C₇H₁₂Cl₂O₂S. Calculated: C 36.10; H 5.15; Cl 30.73; S 13.85%; MR 53.77 (Method a).

To 20 g of (I), with stirring, was added 30 ml of absolute methanol, in which connection the evolution of heat was observed. The mixture was heated under reflux for 2 h at 60°, after which the excess methanol was vacuum distilled. We obtained a mixture of (VII) and (VI) (74 and 26%, respectively) in 95% yield, bp 105° (4 mm) (Method b).

To 20 g of methyl methacrylate in 50 ml of anhydrous $CHCl_3$ at -20° was added in drops 26.2 g of $ClCH_2CH_2SCl$ in 50 ml of anhydrous $CHCl_3$. The mixture was allowed to stand overnight, the solvent was vacuum distilled, and the residue was distilled. We obtained a mixture of (VI) and (VII) (74 and 26%, respectively) in 72% yield, bp 85-86° (1 mm); n_D^{22} 1.5070; d_4^{20} 1.2888. Found: C 35.45; H 5.11; Cl 31.15; S 13.94%; MR 53.34. $C_7H_{12}Cl_2O_2S$. Calculated: C 36.10; H 5.15; Cl 30.73; S 13.83%; MR 53.77.

Nitriles of α -Chloro- β -(β -chloroethylthio) (XIII) and β -Chloro- α -(β -chloroethylthio) isobutyric Acid (XIV). To 16 g of (I) in 50 ml of anhydrous CHCl₃ at -20° was added in drops 2.3 g of NH₃ in 40 ml of anhydrous CHCl₃, after which the mixture was allowed to stand at room temperature for 3 h. The NH₄Cl was filtered (98%), the solvent was removed in vacuo, and to the residue was added 13 g of P₂O₅. The mixture was heated, with the simultaneous vacuum distillation of the mixed nitriles (XIII) and (XIV) in a respective ratio of 2:1; yield 67%, bp 150° (24 mm); n²_D 1.5203; d²⁰₄ 1.2563. Found: C 36.75; H 4.51; Cl 34.88; S 16.88% MR 47.96. C₆H₉Cl₂NS. Calculated: C 36.36; H 4.54; Cl 35.86; S 16.16%; MR 47.33.

Nitrile of β -Chloro- α -(β -chloroethylthio)isobutyric Acid (XIV). To 3.3 g of methacrylonitrile in 30 ml of anhydrous CHCl₃ was added 6.45 g of ClCH₂CH₂SCl in 30 ml of CHCl₃ and the mixture was allowed to stand until colorless (5 days). The solvent was vacuum distilled, and the residue was distilled. We obtained (XIV) in 73% yield, bp 96-97° (4 mm); n_D^2 1.511; d_4^{20} 1.2856. Found: C 35.74; H 4.49; Cl 36.37%; MR 46.82. C₆H₉Cl₂NS. Calculated: C 36.36; H 4.54; Cl 35.86%; MR 47.33.

<u>Nitrile of β-Chloro-α-phenylthioisobutyric Acid.</u> The nitrile was obtained in the same manner as (XIV) in 90% yield, bp 106-107° (4 mm); n_D^{22} 1.5796; d_4^{20} 1.1982. Found: C 56.56; H 4.67; Cl 16.65%; MR 58.65. C₁₀H₁₀ClNS. Calculated: C 56.73; H 4.72; Cl 16.78%; MR 57.33.

<u>Nitrile of β -Chloro- α -methylthioisobutyric Acid.</u> To 1.88 g of $(CH_3S)_2$ in 8 ml of anhydrous CHCl₃ was added 2.72 g of SO₂Cl₂ and the mixture was cooled to room temperature. The reaction mixture was then added to 2.68 g of methacrylonitrile and the resultant mixture was allowed to stand overnight. The solvent was vacuum distilled and the residue was distilled. The yield of product was 78%, bp 54-55° (3 mm); n_D²² 1.4956; d₄²⁰ 1.1518. Found: C 39.45; H 5.37; Cl 22.43; N 9.13; S 20.60%; MR 37.85. C₅H₈ClNS. Calculated: C 40.13; H 5.35; Cl 23.74; N 9.36; S 21.40%; MR 37.85.

Acid Chlorides of β -Chloro- α -(β -chloroethylthio)- and α -Chloro- β -(β -chloroethylthio)isobutyric Acid. To 10.4 g of methacryloyl chloride in 30 ml of anhydrous CHCl₃ was added 13.1 g of ClCH₂CH₂SCl in 20 ml of CHCl₃ and the mixture was allowed to stand for two days. The solvent was vacuum distilled, and the residue was distilled. We obtained a mixture of the acid chlorides in a 1:1 ratio, yield 61%, bp 110-112° (4 mm); n²_D 1.5251; d²⁰₄ 1.3601. Found: C 30.28; H 4.09; Cl 43.44%; MR 52.94. C₉H₉Cl₃OS. Calculated: C 30.57; H 3.82; Cl 45.22%; MR 52.34.

<u>Benzylamide of α -Methylthio- β -chloroisobutyric Acid.</u> The benzylamide was obtained in a similar manner from CH₃SCl and the benzylamide of methacrylic acid in 44% yield, mp 48-50° (after repeated recrystallization from petroleum ether). Found: C 56.24; H 6.18; Cl 13.95; N 5.24; S 12.56%. C₁₂H₁₆ClNOS. Calculated: C 52.92; H 6.21; Cl 13.78; N 5.43; S 12.42%.

<u>Benzylamide of α -Phenylthio- β -chloroisobutyric Acid.</u> The benzylamide was obtained in a similar manner from $C_{6}H_{5}SCl$ and the benzylamide of methacrylic acid in 34% yield, mp 64-66° (from petroleum ether). Found: C 64.11; H 5.76; Cl 11.16; N 4.74; S 9.99%. $C_{17}H_{18}ClNOS$. Calculated: C 63.95; H 5.64; Cl 11.12; N 4.38; S 10.03%.

 $\frac{\text{Acid Chloride of } \alpha, \alpha'-\text{Dichloro-}\beta, \beta'-\text{dithiodiisobutyric Acid.}}{\text{of SOCl}_2 \text{ and the mixture was allowed to stand overnight, after which a catalytic amount of KCl was added and the mixture was heated at 75° for 2 h. We obtained (X) in 71.5% yield, bp 120-125° (0.02 mm).} Found: C 27.73; H 2.74; Cl 39.17; S 19.02%. C_8H_{10}Cl_4O_2S_2. Calculated: C 27.90; H 2.90; Cl 41.27; S 18.60%.}$

Dianilide of α, α' -Dichloro- β, β' -dithiodiisobutyric Acid (XII). To 0.01 mole of (X) in 50 ml of absolute ether at -20° was added in drops 0.04 mole of freshly distilled C₆H₅NH₂ in 50 ml of absolute ether, and the mixture was allowed to stand at room temperature for 2 h. The aniline hydrochloride was filtered, and the ether was vacuum distilled. The residue was dissolved in petroleum ether and recrystallized at -50°. We obtained (XII) in 57% yield, mp 108-110° (from benzene). Found: C 52.79; H 4.80; Cl 15.81; N 5.78; S 14.21%. C₂₀H₂₂Cl₂N₂O₂S₂. Calculated: C 52.51; H 4.81; Cl 15.53; N 6.12; S 14.00%.

<u>Methyl Ester of α , α '-Dichloro- β , β '-dithiodiisobutyric Acid (XI). With cooling, to 8.6 g (X) was added 8 ml of absolute methanol. The mixture was heated on the water bath for 1 h. We obtained (XI), bp 148° (0.04 mm). Found: C 36.29; H 4.88; Cl 19.77; S 18.50%. C₁₀H₁₆Cl₂O₄S₂. Calculated: C 35.82; H 4.77; Cl 21.19; S 19.10%.</u>

Ethyl Ester of β -Chloro- α -(β -chloroethylthio)isobutyryl-DL-valine. To 1.0 g of the ethyl ester of methacrylyl-DL-valine in 10 ml of anhydrous CHCl₃ was added 0.41 g of ClCH₂CH₂SCl in 10 ml of CHCl₃, and the mixture was allowed to stand overnight. The solvent was vacuum distilled, and the residual oil was dissolved in petroleum ether and placed in the refrigerator overnight. The solvent was decanted. We obtained the ester in 70% yield. Found: C 46.72; H 6.88; N 3.77%. C₁₃H₂₃Cl₂NO₃. Calculated: C 45.34; H 6.68; N 4.07%.

Ethyl Ester of β -Chloro- α -(β -chloroethylthio)isobutyryl-DL-phenylalanine. Obtained in a similar manner in 72% yield. Found: C 51.51; H 5.94; N 3.67%. C₁₇H₂₃Cl₂NO₃S. Calculated: C 52.04; H 5.87; N 3.57%.

CONCLUSIONS

1. Sulfenyl chlorides add to methacrylic acid and its derivatives preferentially with the formation of the β -chloro- α -alkthio derivatives of isobutyric acid.

2. In order to compare the properties the isomeric α -chloro- β -(β -chloroethylthio) derivatives of isobutyric acid were obtained by the cleavage of α -chloro- α -methyl- β -propiothiolactone.

3. Of the obtained β -chloro- α -alkthio derivatives of isobutyric acid, the esters and amides are unstable compounds and isomerize under ordinary conditions to the corresponding α -chloro- β -alkthio derivatives of isobutyric acid. The nitriles of the β -chloro- α -alkthioisobutyric acid are stable under ordinary conditions.

4. Isomerization of the β -chloro- α -phenylthic derivatives of isobutyric acid was not observed.

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