THE NUCLEOPHILIC SUBSTITUTION OF CHLORINE IN DERIVATIVES OF β-CHLORO-α-METHYLTHIOISOVALERIC ACID

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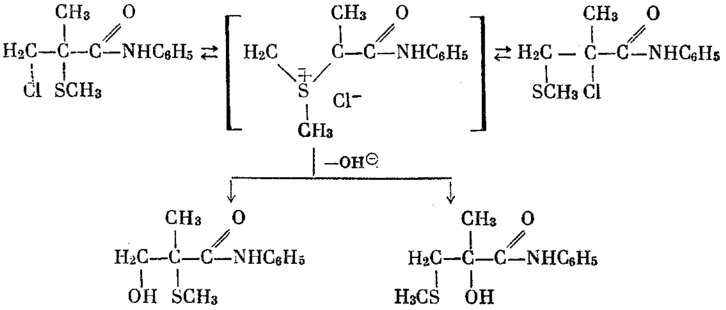
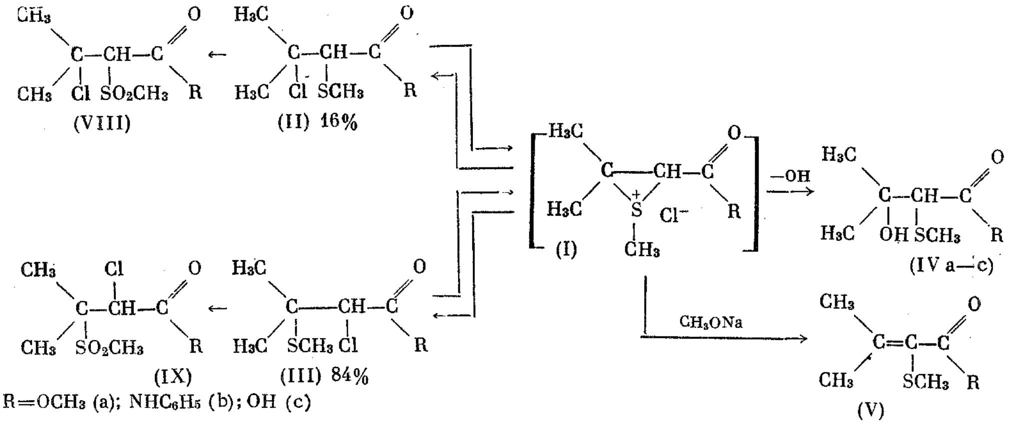
In spite of the large number of investigations on the addition of sulfenyl chlorides to olefins and on the determination of the mechanism of the isomerization of the vicinal β-chloroalkylthio derivatives so obtained [1], there are almost no investigations of the reactions of these compounds with nucleophilic reagents [2]. An investigation of the replacement of the halogen by an OH group in the isomeric anilides of α-chloro-β-methylthio- and β-chloro-α-methylthioisobutyric acids (IIIb and IIb) has shown that at 60° in aqueous dioxane both isomers give the same mixture of isomeric α-hydroxy-β-methylthio- and β-hydroxy-α-methylthioisobutyranilides in a ratio of 1:1 [3].



In the present work we have investigated the nucleophilic replacement of the chlorine atom in derivatives of β-chloro-α-methylthioisovaleric acid (II) and α-chloro-β-methylthioisovaleric acid (III) under various conditions. It has been found that the replacement of the chlorine atom in (IIa-c) by a hydroxy group in aqueous dioxane at 60° leads to a single isomer in each case (IVa-c).



R=OCH_3 (a); NHC_6H_5 (b); OH (c)

Under the action of aqueous dioxane at 20° on a mixture of 16% of (IIa) and 84% of (IIIa), a rapid isomerization of the unstable isomer (IIIa) into the stable isomer (IIa) and the formation of (IVa) (hydrolysis), was observed, the rate of isomerization being considerably greater than the rate of hydrolysis.

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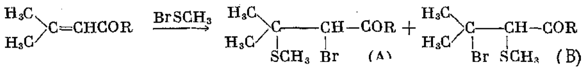
TABLE 1. Isomerization and Hydrolysis of the Adducts (IIa) and (IIIa)

Ratio of the adducts, %			T., °C	Time	Solvent
(IIIa)	(IIa)	(IVa)			
82	18	0	20	1 h	Acetone
83	17	0	20	1 h	Dioxane
21	70	9	20	1 h	Dioxane : water, 4 : 1
0	0	100	60	30 min	Acetone : water, 2 : 1
0	70	30	0	24 h	The same
0	41	59	0	7 days	"
0	20	80	0	14 days	"
0	60	40	0	24 h	" 0,42g $NaHCO_3$

TABLE 2. Adducts of the Reaction



Symbol	R	Time, h	T., °C	Yield of adducts, %	Ratio of the isomeric adducts, %	
					(A)	(B)
a	OH	2,5	−10	45	33	67
		18	20	100		100
b	OCH_3	3	−12	60	16	84
		18	20	100		100
c	NHC_6H_5	10 min	~20	50		50

Under these conditions, anhydrous acetone and anhydrous dioxane do not cause the isomerization of the unstable adduct (IIIa). The addition of $NaHCO_3$ somewhat accelerates hydrolysis. Figures for the isomerization and hydrolysis of the mixture of isomeric compounds (IIa) and (IIIa) are given in Table 1. Similarly, from (IIa and b) with methanol the methyl ester and anilide, respectively, of β-methoxy-α-methylthioisovaleric acid were obtained. At −15 to −5°, the action of CH_3ONa on (IIa) or a mixture of (IIa) and (IIIa) leads only to the splitting out of HCl with the formation of methyl β,β-dimethyl-α-methylthioacrylic acid (Va).

Since in neither case, even under very mild conditions, was it possible to record the second kinetically-controlled isomer (α-hydroxy-β-methylthio), it may be assumed that the substitution of the halogen in (IIa) takes place through an intermediate carbonium ion. However, a comparison of the rates of hydrolysis of β-bromoisovaleric acid and β-bromo-α-methylthioisovaleric acid has shown that that of the second compound is 175 times greater than that of the first. Thus, in this case nucleophilic substitution takes place through an intermediate episulfonium ion (I). The derivatives of β-bromo-α-methylthioisovaleric acid (VIa-c) were obtained by the addition of methanesulfenyl bromide to the corresponding derivatives of β,β-dimethylacrylic acid (Table 2). In this case, a more ready isomerization of the kinetically-controlled adduct into the thermodynamically more stable adduct than in the case of the α-chloro-β-methylthioisovaleric acid derivatives [4] was observed. It was impossible to obtain β-chloroisovaleric acid or its derivatives by the chlorination of isovaleric acid with sulfuryl chloride in the presence of benzoyl peroxide [5], since chlorination takes place preferentially not in the β- but in the γ-position, with the formation of γ-chloro-β-methylbutyric acid (as deduced from the PMR spectra).

The structures of all the compounds were confirmed by their PMR spectra (Table 3) and, in a number of cases, by chemical transformations. The oxidation of (IVa-c) with H_2O_2 gave the corresponding sulfones (VIIa-c) (Table 4).

Since no isomerization was observed in the sulfones, the replacement of the hydroxy groups in (VIIa-c) by chlorine atoms with PCl_5 or $SOCl_2$ could form the sulfones (VIII) or (IX), which were obtained specially by the oxidation of the mixture of sulfides (IIa) and (IIIa). However, the reactions with PCl_5 or $SOCl_2$ unexpectedly gave the sulfones of the methyl ester and anilide of 2-methylthio-3-methylbut-3-enoic acid (XIa, b), which unambiguously confirms the structures (VIIa and b):

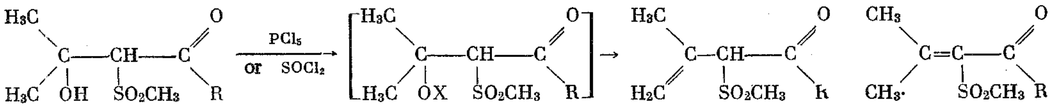
TABLE 3. PMR Spectra of the Substances Obtained ("Perkin-Elmer R-12" spectrometer, 60 MHz, 5% solution in CCl_4, internal standard HMDS)

$(CH_3)_2CR^1—CHR^2—COR^3$			Chemical shift, δ ppm		
R^1	R^2	R^3	$(CH_3)_2C$	SCH_3 or SO_2CH_3	CH
OH	SCH_3	OH	1,39	2,25	3 20
OH	SCH_3	NHC_6H_5	1,38	2,22	3,24
OH	SCH_3	OCH_3	1,29	2,18	3,05
OCH_3	SCH_3	OCH_3	1,25 1,30	2,16	3,33
OCH_3	SCH_3	NHC_6H_5	1,33 1,39	2,13	3,12
OH	SO_2CH_3	OH*	1,30 1,33	3,02	4,09
OH	SO_2CH_3	NHC_6H_5*	1,34 1,41	3,09	4,06
OH	SO_2CH_3	OCH_3	1,43	3,08	3,37
SCH_3	Br	OH	1,53 1,57	2,16	4,35
Br	SCH_3	OH	1,96	2,33	3,55
SCH_3	Br	OCH_3	1,48 1,52	2,09	4,33
Br	SCH_3	OCH_3	1,96	2,26	3,56
Br	H	OH	1,97	CH_2 3,05	—
Br	H	NHC_6H_5	1,92	CH_2 2,89	—
SO_2CH_3Cl		OCH_3	1,49 1,61	2,97	—
	Va		1,93 2,16	2,05	—
	(XI b)*		$CH_3—C$ 1,69	2,93	4,49 $CH_2{=}C$ 5,14 5,29
	(XIIb)*		1,81 1,96	2,94	

* 5% solution in CF_3 COOH.

TABLE 4. The Sulfones (VIIa-c) [$(CH_3)_2C(OH)-CH(SO_2CH_3)COR$ (VIIa-c)]

Compound	Yield, %	mp, °C (solvent)	Empirical formula	Found, %			Calculated, %		
				C	H	S	C	H	S
VIIa	81	65 (ether and CCl_4)	$C_7H_{14}O_5S$	39,47	6,63	15,49	39,98	6,71	15,25
VIIb	94	144,5—145 (ethyl acetate)	$C_{12}H_{17}O_4S$	53,03	6,15	12,18	53,11	6,31	11,81
VIIc	90	117—118 (ethyl acetate)	$C_6H_{12}O_5S$	36,73	5,97	16,77	36,72	6,16	16,34



(VII) (X) (XI) (XII)

R = OCH_3 (a); NHC_6H_5 (b); X = PCl_4, SOCl

This reaction probably takes place through the intermediate compound (X) and not through the stage of the formation of (VIII). The latter normally eliminates HCl with the formation of the corresponding sulfone of β,β-dimethyl-α-methylthioacrylic acid (XIIa, b). The sulfones (XIa, b) do not isomerize into the sulfones (XIIa, b) on prolonged heating. In the case of the sulfone of β-chloro-α-methylthioisovaleranilide (VIIIb), HCl splits off under mild conditions during the oxidation of (IIb). In contrast to the sulfones (VIIa, b), under the action of $SOCl_2$ the methyl ester (IVa) readily exchanges the hydroxy group with the formation of the ester (IIa).

Kinetic studies of the hydrolysis of derivatives of β-chloro-α-methylthio- and β-bromo-α-methylthioisovaleric acids will be published separately.

TABLE 5. Constants of the Compounds (IVa-e) [$(CH_3)_2C(OR')-CH(SCH_3)-COR$] (IVa-e)

Symbol	R′	R	Yield, %	bp, °C (p, mm Hg), n_D^{20}	Empirical formula	Found, %			Calculated, %		
						C	H	S	C	H	S
a	H	OCH_3	64	105 (3) 1,4765	$C_7H_{14}O_3S$	47,04	7,70	17,27	47,16	7,94	17,98
b	H	NHC_6H_5*	92		$C_{12}H_{17}NO_2S$	59,90	7,08	13,39	60,26	7,15	13,39
c	H	OH†	90	138 (4) 1,4980	$C_6H_{12}O_3S$	44,47	7,32	19,32	43,88	7,37	19,52
d	CH_3	OCH_3	89	75 (3) 1,4735	$C_8H_{16}O_3S$	49,95	8,36	16,71	49,97	8,38	16,67
e	CH_3	NHC_6H_5‡	91		$C_{13}H_{19}NO_2S$	61,80	7,53	12,61	61,62	7,55	12,65

*Oil.

†Cyclohexylammonium salt, yield 92%, mp 122.5-124°C (C_2H_5OH and ether). Found: C 54.69; H 9.49; S 12.21; N 5.95%. $C_{12}H_{25}NO_3S$. Calculated: C 54.72; H 9.56; S 12.17; N 5.31%.

‡mp 112.5-113°C (from aqueous CH_3OH).

TABLE 6. Melting Points and Analytical Characteristics of (VIa-c) [$(CH_3)_2CBr-CH(SCH_3)-COR$]

Symbol	R	mp, °C (solvent)	Empirical formula	Found, %				Calculated, %			
				C	H	Br	S	C	H	Br	S
a	NHC_6H_5	82–82,5 (CCl_4 and hexane)	$C_{12}H_{16}BrNOS$	47,13	5,14	26,02	14,68	47,68	5,33	26,44	10,60
b	OCH_3*		$C_7H_{13}BrO_2S$	34,90	5,54	33,41	13,51	34,86	5,43	33,13	13,29
c	OH	75–76 (hexane)	$C_6H_{11}BrO_2S$	31,73	4,86	35,87	14,59	31,72	4,88	35,18	14,11

*bp 80°C (3 mm); n_D^{20} 1.5051.

EXPERIMENTAL METHOD

β-Hydroxy-α-methylthioisovaleric Acid Derivatives (IVa-c). A solution of 0.005 mole of (IIa-c) or a mixture of (IIa) and (IIIa) in 9 ml of aqueous acetone (2 : 1) or 9 ml of aqueous dioxane (4 : 1) was heated at 56-60° for 0.5 h. The acetone was driven off, the residue was extracted with ether (in the case of aqueous dioxane, this was diluted with water and likewise extracted with ether), the extract was dried with $MgSO_4$, the solvent was driven off in vacuum, and the residue was distilled. The yield, properties, and analytical results are given in Table 5.

β-Methoxy-α-methylthioisovaleric Acid Derivatives (IVd-e). A solution of 0.005 mole of (IIa, b) in 6 ml of absolute CH_3OH was boiled for 1 h, the solvent was evaporated off in vacuum, and the residue was recrystallized or distilled (see Table 5).

Methyl β,β-Dimethyl-α-methylthioacrylate (Va). At −15°, 0.6 g of CH_3ONa in 24 ml of methanol was added to 1.1 g of (IIa) or to a mixture of 16% of (IIa) and 84% of (IIIa). The mixture was kept at −5° for 4 h, the precipitate was filtered off, the solvent was evaporated in vacuum, and the residue was distilled. The yield of (Va) was 83%; bp 62° (3 mm); n_D^{20} 1.4940. Found: C 52.40; H 7.56; S 20.00%. $C_7H_{12}O_2S$. Calculated: C 52.47; H 7.54; S 20.01%.

Addition of CH_3SBr to $(CH_3)_2C=CHCOR$. Methanesulfenyl bromide was added to the dimethylacrylic acid derivatives and the resulting adducts were isolated as described previously [4]. The reaction temperatures and yields of the adducts are given in Table 2, and their melting points and analytical characteristics in Table 6.

2-Methylsulfonyl-3-methylbut-3-enoate (XIa). a) A mixture of 0.42 g of (VIIa), 2.2 ml of absolute benzene, and 0.7 ml of $SOCl_2$ was boiled for 2.5 h. The solvent and the excess of $SOCl_2$ were driven off in vacuum, and the residue was distilled. b) A mixture of 0.21 g of (VIIa) and 0.19 g of PCl_5 was ground together for 10 min and left at ~20° for 1 h. The $POCl_3$ was driven off in vacuum at ~20°. The yield of (XIa) was 100%; bp 146° (4 mm); n_D^{20} 1.4810. Found: C 43.71; H 6.31; S 16.80%. $C_7H_{12}O_4S$. Calculated: C 43.73; H 6.29; S 16.67%.

Anilide of 2-Methylsulfonyl-3-methylbut-3-enoic Acid (XIb). A mixture of 0.23 g of the sulfone (VIIb) and 0.19 g of PCl_5 was ground together for 10 min and left at 20° for 1 h. The $POCl_3$ driven off in vacuum at 20°, and the residue was recrystallized. The yield of (XIb) was 87%, mp 132-133° (ethyl acetate and hexane). Found: C 56.78; H 5.91; S 12.99%. $C_{12}H_{15}NO_3S$. Calculated: C 56.89; H 5.96; S 12.65%.

Methyl β,β-Dimethyl-α-methylsulfonylacrylate (XIIa). A solution of 0.3 g of (IIa) in 6 ml of aqueous dioxane (1 : 1) was heated at 80-90° for 20 h and was then diluted with water and extracted with ether, and the extract was dried with $MgSO_4$ and evaporated, and the residue was distilled. The yield of XIIa was 80%, bp 115° (3 mm); n_D^{20} 1.4817. Found: C 43.50; H 6.07; S 16.60%. $C_7H_{12}O_4S$. Calculated: C 43.73; H 6.29; S 16.67%.

β,β-Dimethyl-α-methylsulfonylacrylanilide (XIIb). At 0°, 2 ml of 30% H_2O_2 was added dropwise to 0.9 g of (IIb) in 6 ml of glacial CH_3COOH and 1.2 ml of $(CH_3CO)_2O$. This gave (XIIb) with a yield of 20%, mp 164-166° (ethyl acetate and hexane, 1 : 1). Found: C 56.84; H 5.91; S 12.48%. $C_{12}H_{15}NO_3S$. Calculated: C 56.89; H 5.96; S 12.65%. The residue was a dark brown resin.

Methyl β-Chloro-α-methylthiovalerate (IIa). At 20°, 2 ml of $SOCl_2$ was added dropwise to 0.9 g of (IVa) in 3 ml of absolute benzene. There was a vigorous evolution of HCl. The solvent was evaporated in vacuum. Yield of (IIa) ~100%.

CONCLUSIONS

1. The nucleophilic replacement of the chlorine atoms in derivatives of β-chloro-α-methylthioisovaleric acid takes place through an intermediate episulfonium ion with the formation of derivatives of a single isomer of β-hydroxy-α-methylthioisovaleric acid derivative in each case.

2. With $SOCl_2$ or PCl_5, the methyl ester and anilide of β-hydroxy-α-methylsulfonylisovaleric acid eliminate water with the formation of the methyl ester and anilide of 2-methylsulfonyl-3-methylbut-3-enoic acid.

3. The methyl ester and anilide of β-chloro-α-methylsulfonylisovaleric acid eliminate HCl with the formation of the corresponding derivatives of β,β-dimethyl-α-methylsulfonylacrylic acid.

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