STUDY OF THE REACTION OF cis- AND trans-4-ACYLAMINO-3-HYDROXYTHIOPHANS WITH THIONYL CHLORIDE

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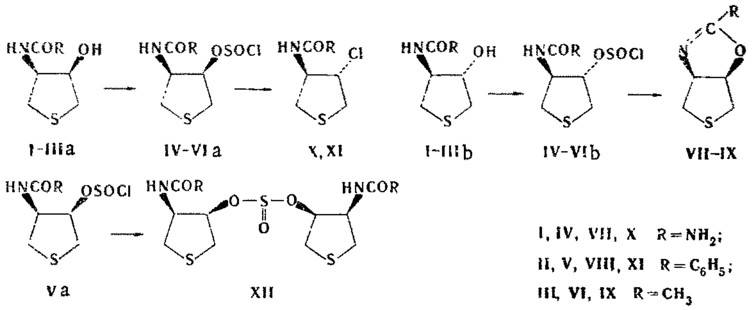
The reaction of cis- and trans-4-acylamino-3-hydroxythiophans with thionyl chloride was studied. It was found that chlorosulfites are initially formed with retention of the configuration of the starting compound. 2-Substituted 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline is formed from trans-4-acylamino-3-chlorosulfitothiophans by thermal reaction or in the presence of pyridine, whereas trans-4-acylamino-3-chlorothiophans are obtained from cis-4-acylamino-3-chlorosulfitothiophans; both reactions proceed with inversion of configuration.

It is well known that alkyl halides may be formed by the action of thionyl chloride on alcohols with retention or inversion of the configuration. We studied the reaction of thionyl chloride with three cis- and trans isomeric pairs of 4-acylamino-3-hydroxythiophans – 4-ureido- (Ia, b), 4-benzamido- (IIa, b), and 4-acetamido-3-hydroxythiophans (IIIa, b), which we previously obtained in [1, 2].

The reaction of hydroxythiophans I-III with thionyl chloride was carried out at –20° during which the PMR spectra of these compounds changed in a characteristic manner – the broad signal at 4-5 ppm, which is affiliated with two methylidyne protons (3-H and 4-H) with close chemical shifts [3], is separated into two signals. Moreover, the signal of one of the protons remains practically in the same place, whereas the signal of the other proton is shifted sharply to weak field; this attests to a change in the substitutent attached to this carbon center. At low temperatures (0° and –20°) the signal of the proton attached to the nitrogen atom is doublet as a result of spin–spin coupling with the proton attached to C_4 (Table 1); this makes it possible to ascertain that the signal of the proton attached to C_3 is shifted to weak field during the reaction of I-III with thionyl chloride and that this is associated with a change in the substituent attached to this carbon atom.



I-IIIa IV-VIa X, XI I-IIIb IV-VIb VII-IX

Va XII

I, IV, VII, X R = NH_2;
II, V, VIII, XI R = C_6H_5;
III, VI, IX R = CH_3

Compound IVa was isolated practically in quantitative yield in the form of an amorphous substance from the reaction mixture of Ia with thionyl chloride. The mass spectrum of this compound contained ion peaks with m/e 84, 102, 118, and 144, which, according to their elementary composition, can be assigned to the analogous ions of standard compound Ia with a free hydroxyl group (Table 2). At the same time,

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TABLE 1. Parameters of the PMR Spectra of IVa, b–VIa, b in Thionyl Chloride and of XI in Deuteropyridine*

Compound	Isomer	mp., °C	δ, ppm							J, Hz							
			2-H′	2-H″	5-H′	5-H″	3-H	4-H	NH at −30°	2-H′, 2-H″	2-H′, 3-H	2-H″, 3-H	5-H′, 5-H″	5-H′, 4-H	5-H″, 4-H	3-H, 4-H	NH,4-H at −30°
IV	cis (a)	34	3,55	3,26	3,16	2,91	5,70	4,54	8,30	12,8	4,3	3,8	10,5	6,2	9,0	3,3	6,9
	trans (b)	34	3,42	3,11	3,36	2,94	5,64	4,64	8,34	12,5	5,1	2,5	12,0	5,6	3,8	4,1	6,9
V	cis (a)	50	3,31	3,18	3,13	3,01	5,76	4,76	9,37	12,8	3,2	3,2	10,6	7,1	10,1	3,2	6,5
	trans (b)	−20	3,14		3,31	3,09	5,82	4,86	9,88	—	$\Sigma J = 12{,}8$		11,8	6,9	6,9	6,4	6,2
VI	cis (a)	60	—	—	—	—	5,82	4,67	10,26	13,3	3,4	3,4	—	$\Sigma J = 17{,}4$		3,4	7,7
	trans (b)	0	2,82		—	3,66	5,80	4,57	10,43	—	4,8	4,8	—	6,9	6,9	4,8	7,4
XI	trans	34	3,43	3,13	3,29	3,11	4,78—5,31		9,05	12,5	4,1	1,9	9,8	3,2	7,8	3.7	7,8

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*The chemical shifts of the protons attached to C_3 and C_4 were found as the centers of the corresponding multiplets. The corresponding AB systems were isolated and calculated in order to determine the chemical shifts of the geminal protons attached to C_2 and C_5. The spin-spin coupling constants were determined within the zero-order approximation.

TABLE 2. Relative Intensities (I, %) and Elementary Compositions (C) of the Characteristic Ions in the Mass Spectra of Ia, VIa, IIb, XI, and XII

m/e	Compound									
	I		IVa		IIb		XI		XII	
	I	C	I	C	I	C	I	C	I	C
36			475,0	HCl*						
64			290,0	OSO						
77					51,8	C_6H_5	71,3	C_6H_5	71,1	C_6H_5
84	46,1	C_4H_4S	60,2	C_4H_4S	21,5	C_4H_4S	29,1	C_4H_4S	24,1	C_4H_4S
100										
102	54,4	C_4H_6OS	36,0	C_4H_6OS	22,1	C_4H_6OS	—	C_4H_6OS	13,5	C_4H_6OS
105					100,0	C_7H_5O	100,0	C_7H_5O	100,0	C_7H_5O
114										
118	7,3	$C_3H_6N_2OS$	7,1	$C_3H_6N_2OS$						
120					—		7,0	C_4H_5SCl	—	
122					32,5	C_7H_8NO	68,7	C_7H_8NO	19,9	C_7H_8NO
126										
128										
139										
144	100,0	$C_5H_8N_2OS$	100,0	$C_5H_8N_2OS$						
146					6,1	C_9H_8NO	5,0	C_9H_8NO	4,1	C_9H_8NO
159										
205					20,5	$C_{11}H_{11}NOS$	49,1	$C_{11}H_{11}NOS$	20,4	$C_{11}H_{11}NOS$
222									1,0	
223					0,1	M^+	—		0,5	
224									1,0	
241							0,2	M^+		
269									0,9	
271									1,2	
490									0,02	
492									0,05	M^+

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*The elementary composition of the ions was determined from the high-resolution mass spectra from the isotopic composition.

the presence of ions with m/e 36 (HCl) and m/e 64 (OSO) constitutes evidence for substitution of the hydroxyl group in the 3 position by an OSOCl group. On the basis of the results of elementary analysis and low and high-resolution mass spectrometry, the 4-ureido-3-chlorosulfitothiophan structure was assinged to IVa. Unstable compounds Va and VIa have a structure similar to that of substituted 3-chlorosulfitothiophan.

The cis and trans configurations of IVa, b-VIa, b were established on the basis of the characteristic features of their PMR spectra, which retain the features of the spectra of starting Ia, b-IIIa, b [4]: the difference in the chemical shifts of the geminal protons attached to C_5 for IVa-VIa is less, whereas the range of vicinal spin–spin coupling constants is broader than for IVb-VIb; these differences are similar to the differences in the spectra of the cis (Ia-IIIa) and trans isomers (Ib-IIIb) (Table 1). The vicinal $J_{3H,4H}$ constants in the spectra of the cis and trans isomers of most of the investigated compounds are close to one another (Table 1) and therefore cannot be used for the analysis of the configurations. Consequently, the configuration of the substituents attached to C_3 and C_4 does not change during the formation of chlorosulfites IV-VI.

We studied the transformations of chlorosulfites IV-VI that occur in a solution of thionyl chloride when the mixture is heated or when pyridine is added.

According to the PMR spectra, cis-2-substituted 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolines (VII, VIII, and IX) are formed from trans-4-acylamino-3-chlorosulfitothiophans (IVb, VIb) at 0 to −10° or at 60° in the case of Vb in the absence of pyridine or when pyridine is added. The formation of 2-substituted 3a,4,6,6a-tetrahydrothieno[3,4-d]-oxazolines (VII, VIII, and IX) in the reaction mixtures was fixed in the PMR spectra from the characteristic (for these compounds) signals of protons attached to C_3a and C_6a [52]. The signals at δ 5.13-5.38 (H_3a) and 5.85-6.11 ppm (H_6a) in thionyl chloride are affiliated with these protons. The vicinal spin–spin coupling constants of these protons correspond to cis fusion of the oxazoline and thiophan rings and to the conformation previously found for such two-ring compounds [5] ($J_3a_{H,6}a_H$ 7.0-7.4 Hz; $\Sigma J_3a,_4$ 5.8-6.1 Hz; $\Sigma J_{6,6}a$ 5.2-5.4 Hz).

In the case of trans isomers IVb, Vb, and VIb, these transformations are accompanied by inversion to the cis configuration.

trans-4-Acylamino-3-chlorothiophans (X, XI) were obtained from cis isomers IVa and Va, and in this case the reaction also proceeds with **inversion of configuration.** The **transformation of cis-4-acetamido-3-chlorosulfitothiophan** VI was not studied because of its instability.

When cis isomer Va is heated to the boiling point in thionyl chloride, 4-benzamido-3-chlorothiophan (XI) is formed; XI was isolated in crystalline form in 77% yield. Its structure was proved by its IR and mass spectra.

The characteristic absorption band of a hydroxyl group is absent in the IR spectrum of XI, but a band of C–Cl stretching vibrations appears at 720 cm^{-1}. Low-intensity (~0.1% of the maximum peak) molecular ions are observed in the mass spectra of IIb and XI. On the basis of the mass spectra of standard compound IIb and the high-resolution mass spectra, the position and character of the substituents was established for XI (Table 2). Fragments with m/e 205 (detachment of a substituent from C_3) and also with m/e 77, 105, and 122 indicate the presence of an $NHCOC_6H_5$ group attached to C_4. The fragment with m/e 102 in IIb corresponds to the oxygen-containing group attached to C_3. The absence of an ion with m/e 102 and the appearance of an ion with m/e 120 $(C_4H_5SCl)^+$ in the mass spectrum of XI shows that the substituent attached to C_3 is a chlorine atom.

It is known [6, 7] that oxazolines are formed only from cis-1-amino-substituted 2-chloro derivatives. An oxazoline was not formed from XI when it was heated in pyridine, and a trans configuration can consequently be assigned to XI. Compound XI and trans-4-ureido-3-chlorothiophan (X) were obtained from VIa and Va, respectively, when pyridine was added to a solution of these compounds in thionyl chloride.

The parameters of the PMR spectrum of XI in deuteropyridine are presented in Table 1. It should be noted that the spectrum of this compound differs from the spectra of the trans isomers of 3,4-substituted thiophans [4], and it therefore does not seem possible to draw a conclusion regarding the trans configuration of the substitutents in XI on the basis of the characteristic features of the PMR spectrum.

It is noteworthy that cis-3,3-(sulfinyldioxy)bis-(4-benzamidothiophan) (XII) was obtained from the reaction of equimolecular amounts of cis-4-benzamido-3-chlorosulfitothiophan (Va) and cis-4-benzamido-3-hydroxythiophan (IIa) in dry chloroform. This reaction makes it possible to assume that chlorosulfite Va is a sufficiently reactive reagent for hydroxyl groups. The structure of XII was established on the basis of its elementary composition and its IR and mass spectra (Table 2). The fragment with m/e 490 is probably due to the loss of two hydrogen atoms from the molecular ion with m/e 492. The absorption band characteristic for the OH group is absent in its IR spectrum.

EXPERIMENTAL

The PMR spectra were recorded with a Hitachi R-20A spectrometer. Tetramethylsilane was used as the internal standard. The accuracy in the determination of the chemical shifts was 0.01 ppm, and the accuracy in the determination of the spin–spin coupling constants was 0.1 Hz. The IR spectra were recorded with a UR-10 spectrometer. The mass spectra were recorded with a Jms-01sg-2 mass spectrometer with direct introduction of the sample into the ion source at ionizing voltages of 75 eV and an emission current of 1 μA. The temperature of the ion source was maintained at 100°, and the temperature of the admission system was maintained at 80°, depending on the volatility of the investigated compounds.

cis-4-Ureido-3-chlorosulfitothiophan (VIa). A 1-g (6.2 mmole) sample of Ia was added to 4 ml of thionyl chloride at 0°, and the mixture was stirred for 30 min with gradual raising of the temperature to 20-22°. The thionyl chloride was then removed in vacuo, dry benzene was added to the residue, and the benzene was removed by distillation. The residue was maintained in vacuo for 1 h to give 1.45 g (96.7%) of a frothy product. Found: C 24.9; H 4.0; Cl 14.4; N 11.3%. $C_5H_9ClN_2O_3S_2$. Calculated: C 24.5; H 3.7; Cl 14.5; 11.4%.

trans-4-Benzamido-3-chlorothiophan (XI). A) A solution of 0.8 g (3.6 mmole) of IIa in 3 ml of thionyl chloride was refluxed for 1 h, after which the thionyl chloride was removed in vacuo, and the residue was dissolved in chloroform. The chloroform solution was washed with water and dried with sodium sulfate. The chloroform was removed, alcohol was added to the residue, and the alcohol mixture was maintained at 0° for 18 h. The resulting precipitate was removed by filtration to give 0.45 g (51%) of colorless needles with mp 158-159° (from alcohol). Found: C 54.8; H 5.0; Cl 14.7; N 5.7; S 12.9%. $C_{11}H_{12}ClNOS$. Calculated: C 54.7; H 5.0; Cl 14.7; N 5.8; S 13.3%.

B) A 1.6-g (7.2 mmole) sample of IIa was added to 6 ml of thionyl chloride at 0°, and the mixture was stirred for 30 min, after which it was cooled to −10°, and 1.6 ml (20 mmole) of pyridine was added. The mixture was then stirred at −10 to 0° for 30 min and at 18-20° for 2 h. It was then concentrated, and the residue was extracted with ether. The ether was removed, alcohol was added to the residue, and the mixture was held at 0° for 18 h. The resulting precipitate was separated to give 1.2 g (69.8%) of XI.

trans-4-Ureido-3-chlorothiophan (X). A 2-g (12.4 mmole) sample of Ia was added to 7.5 ml of thionyl chloride at 0°, and the mixture was stirred for 30 min. A 2.67 ml (33.2 mmole) sample of pyridine was added, and the mixture was stirred at 18-20° for 2.5 h. It was then concentrated, and 150 ml of chloroform was added to the residue. The chloroform solution was washed with 20 ml of water and dried with sodium sulfate. The chloroform was then removed, acetone was added to the residue, and the mixture was worked up to give 0.7 g (30%) of colorless prisms with mp 136-137° (from acetone). Found: 36.4; H 6.0; Cl 17.9%. $C_5H_9ClNOS \times (CH_3)_2CO$. Calculated: C 37.2; H 5.8; Cl 17.0%. Recrystallization from alcohol gave colorless prisms with mp 135-136°. Found: C 35.9; H 5.3; Cl 17.8%. $C_5H_9ClNOS \cdot C_2H_5OH$. Calculated: C 35.4; H 5.9; Cl 17.4%.

cis-3,3-(Sulfinyldioxy)bis-(4-benzamidothiophan) (XII). A 0.16-ml (2.3 mmole) sample of thionyl chloride was added at 0° to a solution of 0.5 g (2.3 mmole) of IIa in 5 ml of chloroform, and the mixture was stirred for 30 min (100% formation of chlorosulfite Va was determined by PMR spectroscopy), after which another 0.5 g (2.3 mmole) of IIa was added, and the mixture was stirred at 20° for 1 h. The resulting precipitate was separated to give 0.8 g (72.6%) of colorless needles with mp 207° (dec., from dimethyl sulfoxide). Found: C 53.6; H 4.8; N 5.5; S 19.3%. $C_{22}H_{24}N_2O_5S_3$. Calculated: C 53.6; H 4.9; N 5.7; 9.5%.

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