REACTION OF CIS- AND TRANS-4-ALKOXYCARBONYLAMINO-3-HYDROXYTHIOPHANS WITH THIONYL CHLORIDE

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The reaction of cis- and trans-4-alkoxycarbonylamino-3-hydroxythiophans with thionyl chloride gives chlorosulfites. trans-4-Alkoxycarbonylamino-3-chlorosulfitothiophans are converted to cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone by heating or by treatment with pyridine. cis-4-Carboalkoxyamino-3-hydroxythiophans form 3-carboalkoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxathiazolidones.

We have previously studied the reaction of 4-acylamino-3-hydroxythiophans with thionyl chloride [1]. It seemed of interest to study the reaction of thionyl chloride with 4-alkoxycarbonylamino-3-hydroxythiophans in order to ascertain the effect of a substituent attached to the amino group on the course of the reaction. We used two cis- and trans-isomeric pairs — 4-methoxycarbonylamino- (III) and 4-benzyloxycarbonylamino-3-hydroxythiophan (IV). The cis isomers, IIIa and IVa were synthesized by reaction of cis-4-amino-3-hydroxythiophan hydrohalide (I) [2] with the appropriate chlorocarbonate esters in aqueous media in the presence of sodium acetate. The trans isomers IIIb and IVb, were similarly obtained from trans-4-amino-3-hydroxythiophan hydrohalide (II) [2]. The structures of IIIa, b, and IVa, b were confirmed by their PMR spectra (Table 1). The signals in the PMR spectra were assigned to certain protons on the basis of a comparison with the spectra of similar compounds [3], and the assignments were confirmed by means of proton-proton double resonance (total double resonance $\gamma H_2/2\pi \gg J$). The isomers were assigned to the cis and trans series in conformity with the characteristic peculiarities of the spectra of isomers of substituted 4-amino-3-hydroxythiophans in pyridine [3].

After 4-alkoxycarbonylamino-3-hydroxythiophans (III and IV) are dissolved in thionyl chloride at —20°, the signal of the proton attached to C_3 in the PMR spectra of these compounds is shifted to weak field, and this attests to a change in the substituents attached to C_3 (Table 1). The PMR spectra of Va, b and VIa, b are close to the spectra of similar compounds [1].

Inasmuch as the difference in the chemical shifts of the geminal protons attached to C_5 ($\Delta\delta_{5H', 5H''}$) is smaller for the isomers of V and VIa and the range of the vicinal spin-spin coupling constants is broader than for the isomers of V and VIb (Table 1), the first two compounds were assigned to the cis series and the second two compounds were assigned to the trans series. Thus the configuration of the substituents is retained during the formation of the chlorosulfites, and this is in agreement with the previously obtained data for similar compounds [1].

The change in the cis- and trans-chlorosulfites Va, VIa, Vb, and VIb in a solution of thionyl chloride on heating or on addition of pyridine was also monitored by means of PMR spectroscopy.

trans-Chlorosulfites Vb and VIb do not change in solution in thionyl chloride up to 34°; when the temperature is raised further, a new compound — 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone (VII) [2,4] — begins to form. The addition of pyridine to a solution of

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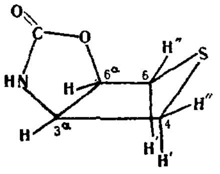
TABLE 1. Parameters of the PMR Spectra of Solutions of III, IV, and IX in Deuteropyridine (0.5 M) and of V and VI in Thionyl Chloride*

Compound	Isomer	Chemical shifts, δ, ppm								Spin-spin coupling constants, J, Hz							
		2H'	2H''	5H'	5H''	3H	4H	NH	$\Delta\delta_{5H',5H''}$	2H', 2H''	2H', 3H	2H'', 3H	5H', 5H''	4H, 5H'	4H, 5H''	3H, 4H	NH, 4H
III	cis (a)	3,18	3,03	3,12	3,12	4,64	4,36	7,68	0	−11,4	4,1	2,6		$\Sigma J_{4-5}=16,5$		4,1	
	trans (b)	3,20	3,01	3,42	2,84	4,64			0,58	−11,6	4,1	4,1	−11,2	5,4	4,1	4,1	
IV	cis (a)	3,32	2,99	3,07	3,07	4,50—4,80		7,91	0	−10,8	5,1	2,6		$\Sigma J_{4-5}=16,1$		3,8	6,8
	trans (b)	3,30	3,08	3,54	2,94	4,48—4,98		8,23	0,60	−11,0	4,5	3,4	−11,0	5,3	3,8		6,6
V	cis (a)	3,29	3,17	3,09	2,77	5,65	4,42		0,32	~9,6	3,4	2,6	−10,4	6,9	9,8	3,2	
	trans (b)	2,85—3,40		3,32	2,82	5,57	4,48		0,50		4,0	4,0	−11,8	5,0	5,0	4,0	
VI	cis (a)	2,95—3,45		3,07	2,74	5,63	4,42		0,33		$\Sigma J_{2-3}=6,6$		−10,8	7,1	9,2	3,3	
	trans (b)	3,26	3,05	3,27	2,76	5,58	4,49		0,51	−12,7	4,9	3,9	−11,8	4,6	3,9	4,3	
		6H'	6H''	4H'	4H''	6aH	3aH	NH		6H', 6H''	6H', 6aH	6H'', 6aH	$\Sigma J_{6,6a}$	3aH, 4H'	3aH, 4H''	ΣJ_{3a4}	3aH, 6aH
VII		2,88	3,07	2,86	2,86	5,24	4,54	8,80		−13,3	3,8	1,7	5,5			6,0	7,4

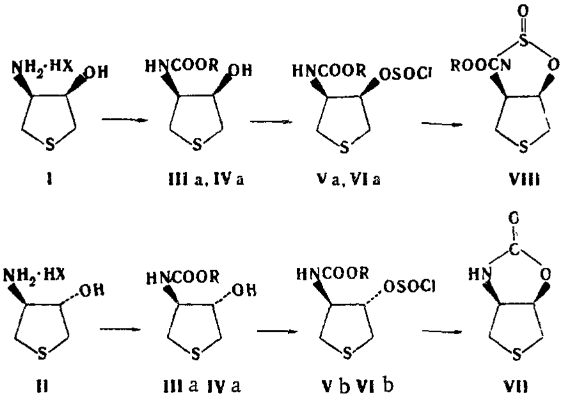
*The chemical shifts of the protons attached to C_3 and C_4 and of the proton attached to the nitrogen were found as the centers of the corresponding multiplets. The AB systems were isolated and calculated in order to determine the chemical shifts of the geminal protons attached to C_2 and C_5. The spin-spin coupling constants were determined as the distances between the appropriate lines in the PMR spectra.

chlorosulfites Vb and VIb in thionyl chloride at −20° also leads to the formation of oxazolidone VII, but the transformation of the chlorosulfites occurs at lower temperatures — at −10° for Vb and at 0° for VIb.

The parameters of the PMR spectrum of VII in deuteropyridine are presented in Table 1. The vicinal spin-spin coupling constants of this compound are characteristic for cis fusion of the thiophan and oxazolidone rings and suggest a preferred conformation similar to that found for the previously investigated 2-substituted 3a,4,6,6a-tetrahydrothieno[3,4-b]oxazolines [5-7].



The formation of VII in the reaction mixtures was determined from the characteristic (for this type of two-ring compound) signals of protons attached to C_3a and C_6a.



III, V, VIII R=CH_3; IV, VI R=$CH_2C_6H_5$

In thionyl chloride solutions, cis-chlorosulfites IIIa and IVa undergo changes at lower temperatures than trans-IIIb and IVb. The change in chlorosulfite IIIa commences at 0°, whereas the change in IVb commences at −10°; both compounds begin to change at −20° when pyridine is added.

Compound VIII, obtained from chlorosulfite IIIa, was isolated and had mp 86-87°. The characteristic absorption bands of OH and NH groups were absent in the IR spectrum of VIII, but there was a strong band at 1200 cm^{-1}, which corresponds to vibrations of the S=O group. The most characteristic feature in the mass spectrum of VIII is detachment of OSO groups (m/e 159) and subsequent loss of a $COOCH_3$ group (m/e 100). The ion with m/e 130 ($C_2H_5NO_4S$) demonstrates detachment from C_3 and C_4 simultaneously, and this provides a basis for assuming the presence of a second ring in VIII. The intensity of the molecular ion peak (m/e 223) of VIII is 30% of the maximum, and this is considerably greater than the intensity of the molecular ion peaks of monocyclic 3,4-substituted thiophans [1].

Thus, according to the data obtained, VIII is 3-methoxycarbonyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxathiazolidone and is a new two-ring system with three different heteroatoms. Studies to determine the three-dimensional structure of VIII are continuing.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the compounds were measured with a UR-10 spectrometer. The PMR spectra were recorded with a Hitachi R-20A spectrometer with tetramethylsilane as the internal standard. The accuracy in the determination of the chemical shifts was ± 0.01 ppm, whereas the accuracy in the determination of the spin-spin coupling constants was 0.1 Hz. The mass spectra were recorded with a JMS-01SG-2 mass spectrometer with direct introduction of the sample into the ion source at an ionizing voltage of 75 eV and an emission current of 100 μA. The temperature of the ion source was maintained at 100°, and the temperature of the inlet system was held at 80°.

cis-4-Methoxycarbonylamino-3-hydroxythiophan (IIIa). A 3.5-ml (27 mmole) sample of chlorocarbonate ester and 12 ml of a 20% solution of sodium acetate were added simultaneously at 0° to a solution of 3.5 g (23 mmole) of I in 7 ml of 2.5 N sodium hydroxide, and the mixture was stirred at 18-20° for 1 h. The resulting precipitate was separated and washed with water to give 2.7 g (68% of colorless plates with mp 104-105° (from methanol). Found: C 40.7; H 5.9; N 7.6%. $C_6H_{11}NO_3S$. Calculated: C 40.7; H 6.2; N 7.9%.

trans-4-Methoxycarbonylamino-3-hydroxythiophan (IIIb). A 2-ml (26 mmole) sample of chlorocarbonate ester and 7 ml of 20% sodium acetate solution were added simultaneously at 0° to a solution of 2 g (13 mmole) of II in 4 ml of 2.5 N sodium hydroxide, and the mixture was stirred at 18-20° for 1 h. It was then extracted with chloroform, and the chloroform extracts were washed with water and dried with sodium sulfate. The chloroform was evaporated to give 0.8 g (35%) of an oily substance. Found: C 40.5; H 6.3; N 7.4%. $C_6H_{11}NO_3S$. Calculated: C 40.7; H 6.2; N 7.9%.

cis-4-Benzoxycarbonylamino-3-hydroxythiophan (IVa). A 2.5 ml (17.5 mmole) sample of chlorocarbonate ester and 6 ml of a 20% solution of sodium acetate were added simultaneously at 0° to a solution of 2 g (13 mmole) of II in 4 ml of 2 N sodium hydroxide, and the mixture was stirred at 18-20° for 2 h, after which it was extracted with chloroform. The solvent was removed from the extract, alcohol was added to the residue, and the solution was maintained at 0° for 20 h. The resulting precipitate was separated to give 1.2 g (36%) of colorless plates with mp 120-121° (from alcohol). Found: C 57.2; H 6.0; N 5.4%. $C_{12}H_{15}NO_3S$. Calculated: C 56.9; H 5.9; N 5.5%.

trans-4-Benzyloxycarbonylamino-3-hydroxythiophan (IVb). A 5.8-ml (40 mmole) sample of chlorocarbonate ester and 8 ml of a 30% solution of sodium acetate were added simultaneously at 0° to a solution of 5 g (32 mmole) of II in 6.5 ml of 5 N sodium hydroxide, after which the mixture was stirred at 18-20° for 1 h. The resulting precipitate was separated and washed with water to give 2 g (24.8%) of colorless needles with mp 77-78° (from ether). Found: C 56.6; H 6.2; N 5.5%. $C_{12}H_{15}NO_3S$. Calculated: C 56.9; H 5.9; N 5.5%.

3a,4,6,6a-Tetrahydrothieno[3,4-d]oxazolidone (VII). A) A 1-g (5.6 mmole) sample of IVb was added at −10° to 3 ml of thionyl chloride, after which the mixture was stirred for 10 min, 1 ml (12.5 mmole) of pyridine was added, and the temperature was gradually raised to 30-35°. The mixture was then stirred for 1 h, after which it was concentrated and the residue was extracted with chloroform. The extracts were washed with water, the chloroform was removed, 2 ml of alcohol was added to the residue, and the mixture was allowed to stand at 0°. The resulting precipitate was separated to give 0.75 g (91.5%) of a product with mp 125-126°. No melting-point depression (mp 125-126°) was observed for a mixture of this product with a sample of oxazolidone obtained by the method in [2].

B) A 1-g (4.0 mmole) sample of IV was added at 0° to 3.5 ml of thionyl chloride, after which the mixture was stirred for 10 min and the temperature was gradually raised to 50°. The mixture was then stirred at this temperature for 1 h, the thionyl chloride was removed by vacuum distillation, and the residue was extracted with ether. The ether extracts were washed with water and dried, the ether was removed, and acetone was added to the residue. The acetone mixture was held at 0° for 16-18 h, and the resulting precipitate was separated to give 0.49 g (86%) of a product with mp 125-126°.

3-Methoxycarbonyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxathiazolidone (VIII). A 1-g (5.6 mmole) sample of IVa was added to 3 ml of $SOCl_2$ at −10°, and the mixture was stirred for 10 min. Pyridine (1 ml) was then added to the mixture, and the temperature was gradually raised to 35°. The mixture was then stirred for 1 h, after which it was concentrated, and the residue was extracted with carbon tetrachloride. The extracts were concentrated to a volume of 3 ml, and the concentrate was held at 0° for 20 h. The resulting precipitate was separated to give 0.7 g (56%) of colorless prisms with mp 86-87° (from carbon tetrachloride). Found: C 31.9; H 4.1; N 6.7; S 28.3%; m/e 223 (M^+, 30%), which correspond to an element composition of $C_6H_{10}NO_2S_2$. Calculated: C 32.1; H 4.5; N 6.3; S 28.6%; M 223.

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