STUDY OF THE FORMATION OF 2-SUBSTITUTED 3a,4,6,6a-TETRAHYDROTHIENO[3,4-d]OXAZOLINES FROM cis- AND trans-4-AMINO-3-HYDROXYTHIOPHANS

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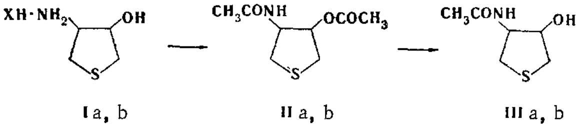
The formation of 2-substituted 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolines from N-acyl-substituted cis- and trans-4-amino-3-hydroxythiophans in deuteroacetic acid and by the action of thionyl chloride was studied. Only the derivatives of cis-4-amino-3-hydroxythiophans are cyclized in deuteroacetic acid. The formation of an oxazoline ring from 4-amino-3-hydroxythiophan by the action of thionyl chloride depends both on the relative position of the hydroxy and amino groups and on the character of the acyl substituent attached to the amino group.

The inversion of trans-4-benzamido-3-hydroxythiophan (Vb) to cis isomer Va proceeds through the formation of 2-phenyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline (VI, R = C_6H_5) [1].

It seemed of interest to study the cyclization capacity of isomeric thiophanamino alcohols as a function of their cis and trans configuration and the character of the acyl substituent attached to the amino group. This was accomplished in the case of three isomeric pairs: 4-acetamido- (IIIa, b), 4-ureido- (IVa, b) [1], and 4-benzamido-3-hydroxythiophans (Va, b) [1, 3].

The isomeric 4-acetamido-3-hydroxythiophans (IIIa, b) were synthesized from cis- and trans-4-amino-3-hydroxythiophan hydrohalides (Ia, b) [1].

The action of acetyl chloride on hydrohalides Ia and Ib gave cis- and trans-4-acetamido-3-acetoxythiophans (IIa, b).



I–III a cis isomers; b trans isomers

These compounds were hydrolyzed with 2 N sodium hydroxide solution to cis- and trans-4-acetamido-3-hydroxythiophans (IIIa, b). Compound IIIa can be obtained directly from hydrobromide Ia when the acylation time is reduced. The configuration of the substituent in IIa, b and IIIa, b was established, while the configuration for IVa, b was confirmed from the PMR spectra (Tables 1 and 2) [3, 4].

The difference in the magnitudes of the chemical shifts between the geminal protons attached to C_5 is substantially larger in the PMR spectra of IIb-IVb than in the spectra of IIa-IVa (Table 1).

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TABLE 1. Chemical Shifts of the Protons of IIa, b-IVa, b*

Compound	Isomer type	Chemical shifts, δ, ppm										
		2-H	2-H′	3-H	4-H	5-H	5-H′	$\Delta\delta_{5\text{-H}, 5\text{-H}'}$	NH	$COCH_3$		Solvent
II	cis (a)	3,21	3,00	5,66	4,92	3,19	3,04	0,15		1,93	2,02	
	trans (b)	3,27	2,93	5,60	4,89	3,32	2,88	0,44	8,65	1,95	2,02	C_5D_5N
III	cis (a)	3,17	3,02	4,51—4,99	4,51—4,99	3,13	3,13	0	8,42		2,04	
	trans (b)	3,20	3,99	4,63—5,11	4,63—5,11	3,45	2,85	0,62	8,50		2,04	C_5D_5N
IV	cis (a)	3,01	2,68	3,90	4,60	2,98	2,71	0,27				
	trans (b)	3,06	2,76	4,00—4,50		3,20	2,62	0,58				CD_3COOD

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*The parameters of the PMR spectra of IIa, b were calculated with a Minsk-22 computer from an iteration program.

TABLE 2. Spin-Spin Coupling Constants of IIa, b-IVa, b

Compound	Spin-spin coupling constants, J, Hz							
	2-H, 2H′	2-H, 3-H	2-H′, 3-H	3-H, 4-H	4-H, 5-H	4-H, 5-H′	5-H, 5-H′	4-H, NH
II a	12,1	4,6	2,4	3,9	7,0	9,9	10,3	7,9
IIb	12,0	5,2	3,2	3,9	5,9	3,8	11,2	7,3
III a	11,4	3,8	2,3	3,7	$\Sigma J_{4.5} = 16,2$			8.7
IIIb	10,8	4,2	3,9		5,1	4,0	10,8	
IVa	12,0	5,2	2,6		6,7	9,0	10,6	
IVb	11,6	4,2	3,6		5,1	3,8	11,3	

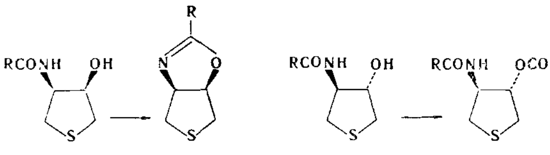
The vicinal spin-spin coupling constants for IIb-IVb are relatively close in magnitude (3.2-5.9 Hz, Table 2), while those for IIa-IVa are characterized by a broad range (from 2.3 to 9.9 Hz, Table 2).

The above-described characteristic peculiarities of the PMR spectra of the investigated compounds make it possible to assign isomers IIb-IVb to the trans series and isomers IIa-IVa to the cis series.

The intramolecular cyclization of IIIa, b-Va, b was studied in deuteroacetic acid and in the presence of thionyl chloride, i.e., under conditions where inversion is possible during the formation of the oxazoline rings [5, 6]. The course of the reaction was monitored by means of PMR spectroscopy.

The percentages of the oxazolines were determined from the ratio of the integral intensities of the signals of the protons attached to C_{3a} and C_{6a} of the oxazoline derivatives (Table 3) and the protons attached to C_3 and C_4 of the starting compounds (Table 1).

We have shown that only cis-amino alcohols IIIa-Va form 2-substituted 3a,4,6,6a-tetrahydrothieno-[3.4-d]oxazolines (VI-VIII) on heating in deuteroacetic acid, while trans-amino alcohols IIIb-Vb are acetylated at the hydroxyl group under the same conditions to give 3-acetoxythiophans IIb, IXb, and Xb.



III-Va VI-VIII III-Vb IIb, IXb, Xb

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

In the case of IIIa-Va, signals characteristic for protons attached to C_{3a} and C_{6a} of the 2-substituted 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolines were observed in the PMR spectra of the reaction mixtures. It should be noted that all of the substituted oxazolines formed in these reactions (VI-VIII) have cis fusion of the thiophan and oxazoline rings, as evidenced by the vicinal spin-spin coupling constants [2, 3].

The dependence of the amount of oxazoline derivative VII formed on the reaction time in the cyclization is shown in Fig. 1 (curve 1). The first observable conversion product for starting amino alcohols IIIa and Va is also a 2-substituted oxazoline. However, signals of the protons of the cis-4-acetamido- (IIa) and cis-4-benzamido-3-acetoxythiophan subsequently appear in the PMR spectra of the reaction mixture. In the case of IIIa, diacetyl derivative IIa remains practically the only product of conversion after refluxing for 16 h in deuteroacetic acid. Quantitative evaluations of the percentage of IIa as a function of the reaction

TABLE 3. Parameters of the PMR Spectra of VI-VIII

Compound	Solvent	Chemical shifts, δ, ppm						Spin–spin coupling constants, J, Hz			
		3a-H	4-H	4-H′	6-H	6-H′	6a-H	3a-H, 4-H	3a-H, 4-H′	3a-H, 6a-H	ΣJ 6a-6H
	$SOCl_2$	5,28	2,87—3,62		2,87—3,62		5,91	~1	5,7	7,5	4,4
VI	CD_3COOD	5,03					5,64	ΣJ_{3a-4}	6,3	7,5	5,4
VII	CD_3COOD	4,54					5,28	ΣJ_{3a-4}	8,4	6,9	5,6
	$CDCl_3$	5,58	3,53	3,22	3,29	3,29	6,21	0,5	5,0	7,5	5,0
VIII	CD_3COOD	5,16	2,73—3,40		2,78—3,40		5,52	ΣJ_{3a-4}	7,3	7,5	5,1

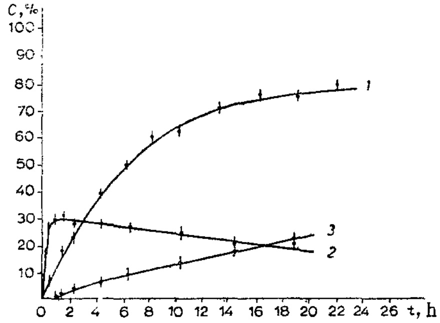


Fig. 1. Change in the concentration of the reaction products formed from amino alcohols IVa and Va (c 1 M) as a function of the refluxing time in deuteroacetic acid: 1) change in the concentration of the oxazoline derivative VII formed from IVa; 2) change in the concentration of oxazoline derivative VIII formed from Va; 3) change in the concentration of the product of acetylation at the hydroxyl group obtained from VIII (the mean square deviations are shown by the arrows near each point).

time are impossible because of overlapping of the observed signals in the PMR spectra of the reaction mixtures. The curves showing the change in the concentration of the reaction products as a function of time for Va are presented in Fig. 1 (curves 2 and 3).

Thus trans-amino alcohols IIIb-Vb do not undergo inversion to the cis configuration on heating in deuteroacetic acid, and oxazoline derivatives therefore cannot be formed. The substituent attached to the amino group affects the occurrence of intramolecular cyclization reactions. We have previously shown that VIII is formed from Va, b by the action of thionyl chloride [2]. The reaction for the trans isomer proceeds with inversion to the cis configuration.

Under the same conditions we were able to observe the formation of oxazoline derivative VI from IIIb in the PMR spectra. One hour after the start of the reaction, starting amino alcohol IIIb was practically completely converted to oxazoline VI. Just as in the case of Vb, inversion to the cis configuration occurs in this case during the formation of oxazoline VI. However, we were unable to isolate this compound from solution, inasmuch as it is apparently unstable and undergoes ring opening and hydrolysis during isolation. As a result, we obtained the known cis-4-amino-3-hydroxythiophan hydrochloride (Ia) [1].

Compounds IIIa and IVa, b proved to be incapable of undergoing intramolecular cyclization under these conditions.

Thus the formation of the oxazoline ring during the action of thionyl chloride depends on the configuration of the substituents of the starting amino alcohol and on the character of the substituent attached to the amino group. This sort of dependence can be explained if it is assumed that the intermediates in the formation of oxazolines from amino alcohols by the action of thionyl chlorode are the cis-1-amino-2-chloro derivatives [6], inasmuch as the relative position of the amino and hydroxyl group and the substituent attached to the amino group determine the type of substitution of the hydroxyl group by halogen [7, 8].

EXPERIMENTAL

The PMR spectra were recorded with a Hitachi R-20A spectrometer (60 MHz). Tetramethylsilane was used as the internal standard. The chemical shifts of the protons attached to C_3 and C_4 of the thiophan ring in the spectra of the 3,4-substituted thiophans and the chemical shifts of the protons attached to C_{3a} and C_{6a} in the spectra of the oxazoline derivatives were calculated 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 of the thiophan ring. Proton-magnetic double resonance was used in the analysis of the spectra.

cis-4-Acetamido-3-acetoxythiophan (IIa). A 6-ml sample of pyridine was added to 4 g (20 mmole) of Ia [1], and the mixture was stirred at 50-60° for 30 min. It was then cooled, and 10 ml of chloroform was added. A 4-ml (41 mmole) sample of acetyl chloride was added at 0°, and the mixture was stirred at 18-20° for 2 h. Water (20 ml) was added, and the mixture was extracted with chloroform. The solvent was removed in vacuo, 2 ml of alcohol was added to the residue, and the mixture was held at 0° for 18-20 h. The resulting precipitate was separated to give 2.4 g (59%) of colorless prisms with mp 131-132° (from alcohol). Found: C 47.2; H 6.4; N 6.8%. $C_{18}H_{13}NO_3S$. Calculated: C 47.2; H 6.4; N 6.9%.

trans-4-Acetamido-3-acetoxythiophan (IIb). Under conditions similar to those used to synthesize IIa 1.85 g (88%) of colorless needles of IIb with mp 94.5-95° was obtained from 3.2 g (19.6 mmole) of Ib [1] and 3.46 ml (20.2 mmole) of acetyl chloride. Found: C 47.2; H 6.4; N 6.4%. $C_{18}H_{13}NO_3S$. Calculated: C 47.2; H 6.4; N 6.8%.

cis-4-Acetamido-3-hydroxythiophan (IIIa). A) A 5-ml sample of 2 N sodium hydroxide solution was added to a solution of 1 g (4.9 mmole) of IIa in 16 ml of alcohol, and the mixture was refluxed for 25 min. It was then cooled and extracted with chloroform. The chloroform was removed to give 0.52 g (64%) of colorless plates of IIIa with mp 164-164.5° (from alcohol). Found: C 44.6; H 6.6; N 8.5%. $C_6H_{11}NO_2S$. Calculated: C 44.7; H 6.9; N 8.7%.

B) A 6-ml sample of pyridine was added to 28 g (14 mmole) of Ia, and the mixture was stirred at 50-60° for 30 min. It was then cooled, and 15 ml of chloroform was added. A 3-ml (31 mmole) sample of acetyl chloride was added at 0 deg, and the mixture was stirred at 18-20° for 30 min. Water (10 ml) was added, and the mixture was extracted with chloroform. The chloroform extracts were washed with 2 N hydrochloric acid and water, the chloroform was removed, and 1 ml of alcohol was added to the residue. The resulting precipitate was separated to give 0.7 g (31%) of a product with mp 164-164.5° (from alcohol). No melting-point depression was observed for a mixture of this product with the compound obtained by method A.

trans-4-Acetamido-3-hydroxythiophan (IIIb). A 6.5-ml sample of 0.5 N sodium hydroxide solution was added to a solution of 1.4 g (7 mmole) of IIb in 10 ml of alcohol, and the mixture was refluxed for 20 min. It was then cooled and extracted with chloroform. The chloroform was removed, 1 ml of alcohol was added to the residue, and the mixture was held at 0 deg for 12-16 h. The resulting precipitate was separated to give 0.84 g (76%) of colorless prisms with mp 107.5-108° (from alcohol). Found: C 44.6; H 6.7; N 8.3%. $C_6H_{11}NO_2S$. Calculated: C 44.7; H 6.9; N 8.7%.

cis-4-Amino-3-hydroxythiophan Hydrochloride (Ia). A 0.4-ml (7 mmole) sample of thionyl chloride was added at 0 deg to a solution of 1 g (6.2 mmole) of IIIb in 5 ml of chloroform, and the mixture was stirred at 18-20° for 1 h. It was then concentrated in vacuo to dryness, and 1.5 ml of alcohol was added to the residue. The mixture was held at 0 deg for 12-16 h, and the resulting precipitate was removed by filtration to give 0.76 g (79%) of a product with mp 206-207°. No melting-point depression was observed for a mixture of this product with a known sample of Ia [1].

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