STUDY OF THE STRUCTURE AND INVERSION OF 4-BENZAMIDO-trans-3-HYDROXY-trans-2-CARBOMETHOXYTHIOPHAN

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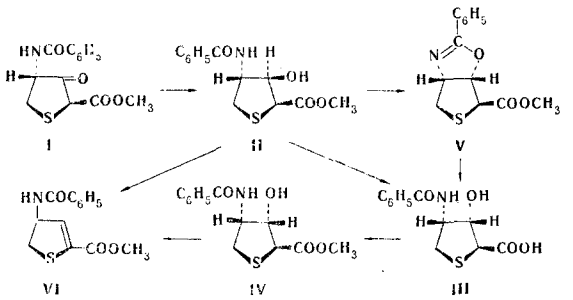
The structure of stereoisomeric 4-benzamido-3-hydroxy-2-carbomethoxythiophans was established by means of PMR and IR spectroscopy. The inversion of the trans,trans-isomer to the cis,trans-isomer was detected and studied. The inversion during the action of thionyl chloride in pyridine proceeds through the intermediate formation of tetrahydrothieno[3,4-d]oxazoline. The substituent in the 2 position does not undergo inversion. Tetrahydrothienooxazoline is not formed from 4-benzamido-2-carbomethoxy-4,5-dihydrothiophene.

We have previously demonstrated [1] that the acid hydrolysis of trans-4-benzamido-3-hydroxythiophan is accompanied by inversion with the formation of cis-4-amino-3-hydroxythiophan. It seemed of interest to investigate the possibility of inversion for 3,4-hydroxyaminothiophans that also contain a substituent in the 2 position. For this, we used 4-benzamido-3-hydroxy-2-carbomethoxythiophan (II), which was obtained from 4-benzamido-3-oxo-2-carbomethoxythiophan (I) by reduction with sodium borohydride in methanol. It might have been assumed that the amino alcohol (II) formed has a trans orientation of the amino and hydroxyl groups as in the stereospecific reduction of 4-amino-substituted 3-oxothiophan with sodium borohydride, which proceeds with the formation of the trans amino alcohol [1].



The action of thionyl chloride in the presence of pyridine in chloroform (water was added during workup) on 4-benzamido-3-hydroxy-2-carbomethoxythiophan (II) (mp 159-160°C) brings about inversion to give 4-benzamido-3-hydroxy-2-carboxythiophan (III), which, as a result of esterification with methanol, is converted to stereoisomeric (to ester II) IV (mp 154-154.5°). We established the three-dimensional structures of II and IV by PMR and IR spectroscopy.

The possibility of the formation of an intramolecular hydrogen bond between the hydroxyl and carbomethoxy groups was used to establish the spatial orientation of the substituent in the 2 position in II and IV with respect to the substituent in the 3 position. A preliminary investigation of the IR spectra of cis- and trans-4-benzamido-3-hydroxythiophans was made, and it was established that an intramolecular hydrogen bond is not formed between the substituents in the 3 and 4 positions.

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TABLE 1. Parameters of the PMR Spectra of Solutions of II, IV, VI, and VIIa-d in Deuteropyridine*

VII a-d

a R=$COCH_3$, R′=$COOC_2H_5$;
b R=$COCH_3$, R′=COC_6H_5;
c R=R′=COC_6H_5;
d R=H, R′=COC_6H_5

Compound	Type of isomer with respect to the 3 and 4 positions	Chemical shifts, δ, ppm						Spin–spin coupling constants, J, Hz		Spin–spin coupling constants, J, Hz						$\Delta\delta_{5\text{-H},5\text{-H}'}$, ppm	Concn., mole/liter
		2-H (2-H′)	2-H′ (2-H)	3-H	4-H	5-H (5-H′)	5-H′ (5-H)	$J_{2,2'}$	$J_{2,3}$ ($J_{2',3}$)	$J_{2',3}$ ($J_{2,3}$)	$J_{3,4}$	$J_{5,5'}$	$J_{5,4}$ ($J_{5',4}$)	$J_{5',4}$ ($J_{5,4}$)	$J_{NH,4\text{-H}}$		
VII a	cis	2,96	2,80	5,58	4,34—4,70	2,92	2,84	11,0	4,0	2,9	3,6	9,7	$J_{4,5}+J_{4,5'}=16,0$			0,07	
	trans	3,24	2,88	5,54	4,40—4,85	3,25	2,87	11,8	5,3	3,3	3,6	11,2	6,0	3,8		0,37	0,5
VIIb	cis	3,20	2,99	5,76	5,02	3,18	3,18	12,5	4,3	2,7	3,9		$J_{4,5}+J_{4,5'}=17,0$		8,2	0	
	trans	3,23	2,95	5,68	5,00	3,30	2,88	11,3	5,7	5,0	4,8	11,8	6,4	4,7	7,7	0,42	0,7
VIIc	cis	3,36	3,15	6,07	5,09	3,27	3,27	12,7	3,7	2,7	3,7		$J_{4,5}+J_{4,5'}=17,4$		7,0	0	
	trans	3,38	3,03	5,95	5,24	3,41	3,05	12,3	5,7	4,7	4,7	11,5	6,3	5,3	7,0	0,36	0,7
VIId	cis	3,13	2,99	4,60—5,15	4,60—5,15	3,20	3,20	10,1	3,3	1,7	3,3		$J_{4,5}+J_{4,5'}=15,4$			0	
	trans	3,21	3,04	4,75—5,30	4,75—5,30	3,49	3,00	10,0	4,2	1,1		9,6	4,7	4,0		0,49	0,7
IV	cis	4,36		5,20	5,49	3,38	3,38		1,8		4,0		$J_{4,5}+J_{4,5'}=16,4$		8,0	0	0,4
II	trans	4,60		5,30	5,55	3,81	3,18		5,6		6,5	10,4	6,6	5,8	6,7	0,63	0,5
VI				6,51	5,73	3,22	3,58				3,1	12,2	5,9	9,1			0,5

* The parameters of the spectra of II and VI were calculated from an iteration program with a Minsk-1 computer.

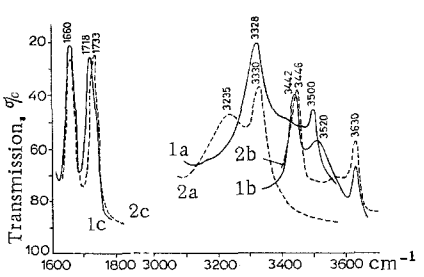


Fig. 1

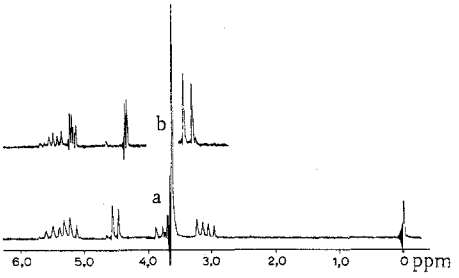


Fig. 2

Fig. 1. IR spectra of r-4-benzamido-c-3-hydroxy-t-2-carbomethoxythiophan in mineral oil (1a), in chloroform–carbon tetrachloride (c $2.5 \cdot 10^{-3}$ M, d 20 mm) (1b), and in chloroform (c $5 \cdot 10^{-2}$ M, d 1 mm) (1c) and of r-4-benzamido-t-3-hydroxy-t-2-carbomethoxythiophan in mineral oil (2a), in chloroform–carbon tetrachloride (c $2 \cdot 10^{-3}$ M, d 20 mm) (2b), and in chloroform (c $2 \cdot 10^{-3}$ M, d 5 mm) (2c).

Fig. 2. PMR spectra: a) 0.7 M solution of r-4-benzamido-t-3-hydroxy-t-2-carbomethoxythiophan (II) in deuteropyridine; b) 0.7 M solution of r-4-benzamido-c-3-hydroxy-t-2-carbomethoxythiophan (IV) in deuteropyridine.

TABLE 2. Parameters of the PMR Spectra of V and Its Hydrochloride (Va)*

Compound	Solvent	Concn., mole/liter	Spin–spin coupling constants, J, Hz					Chemical shifts, δ, ppm					
			$J_{6,6a}$	$J_{3a,6a}$	$J_{4,3a}$	$J_{4',3a}$	$J_{4,4'}$	6-H	6a-H	3a-H	4-H	4-H'	NH
V	C_5D_5N	0,4	0,6	7,3	5,7	0,9	12,3	4,34	5,58	5,28	3,48	3,20	
Va	C_5H_5N	0,5	0,5	7,2	6,2	0,7	12,3	4,26	5,54	5,26	3,40	3,11	15,01

$J_{4',6a} \approx J_{3a,6} \approx J_{4',6} \approx 0.5$ Hz.

*The spectral parameters of V were calculated from an iteration program [7] with a Minsk-1 computer.

TABLE 3. Calculated Vicinal Spin–Spin Coupling Constants for the 6–6a Bond for Conformers A-D

Parameters	Conformation											
	A			B			C			D		
$\Psi_{6,6a}$	20°	30°	40°	20°	30°	40°	20°	30°	40°	20°	30°	40°
$J_{6,6a}$, Hz	6,5–10,5	6,0–9,5	4,5–7,0	6,5–10,5	6,0–9,5	4,5–7,0	0–0,5	0	0	6,0–9,0	8,0–12,0	9,0–14,0

A comparison of the IR spectra of isomers II and IV in the solid state and in solutions in chloroform and in chloroform–carbon tetrachloride mixtures of various concentrations demonstrates the distinct difference between them (Fig. 1). The band of an associated hydroxyl group at 3520 cm^{-1} is retained in the IR spectrum of isomer II on pronounced dilution, along with the absorption of a free OH group at 3630 cm^{-1}, on the basis of which the cis configuration of the substituents in the 2 and 3 positions was assigned to this compound. Absorption of only a free OH group at 3630 cm^{-1} is observed in the spectra of IV, and this compound consequently has the trans configuration of the substituents. The formation of an intramolecular hydrogen bond is realized through the ester carbonyl group, since $\nu_{C=O}$ of the ester group in the spectrum of II is reduced by 15 cm^{-1} as compared with the corresponding absorption of IV. The frequencies of the vibrations of the amide carbonyl group are identical for II and IV; i.e., this grouping does not participate in the formation of hydrogen bonds in solutions. The small shift in ν_{OH} as a result of the formation of an intramolecular hydrogen bond $OH\cdots O=C\langle^{OR}$ is in agreement with the literature data and does not exceed 100 cm^{-1} for this sort of six-membered ring [2-4].

A preliminary examination of the PMR spectra of solutions of the cis and trans isomers of 3,4-substituted thiphans VIIa-d in pyridine (Table 1) was made to study the relative configuration of the 4-benzamido and 3-hydroxy groups in II and IV. It was found that a substantially larger (than for the cis isomer) chemical shift between the geminal 5-H protons and a lower sum of the vicinal spin–spin coupling constants for the 4–5 bond (Table 1) are typical for the trans isomers.

The 2-H proton in the spectra of II and IV in pyridine is characterized by a doublet with δ 4.60 and 4.36 ppm (Fig. 2 and Table 1). The complex group of signals at 5.10-5.80 ppm is affiliated with the 3- and 4-H protons. The protons of the methylene group in the 5 position form a group of signals at 3.00-4.10 ppm in the spectrum of II, while these protons are characterized by a doublet at 3.83 ppm in the spectrum of IV (Fig. 2, Table 1).

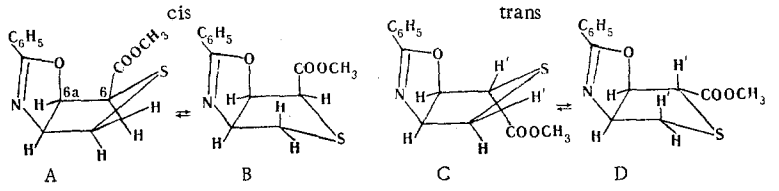
One's attention is drawn to the similarity in the spectral parameters of II and IV and those of the trans and cis isomers of 3,4-substituted thiophans, respectively (compare $\Delta\delta_{5\text{-H},5\text{-H}'}$ and $J_{4,5}+J_{4,5'}$, Table 1). It may be assumed that the substituent in the 2 position in this configuration does not have a substantial effect on the conformational state of these molecules and, consequently, on the parameters of the PMR spectra. This makes it possible to assign the trans configuration to the substituents in the 3 and 4 positions in II and the cis configuration to these substituents in IV. The assumption of the small effect of the substituent in the 2 position on the PMR spectra of II and IV will be rigorously proved below.

Thus, on the basis of the results obtained, it can be concluded that II has the r-4-benzamido-t-3-hydroxy-t-2-carbomethoxythiophan structure, while IV has the r-4-benzamido-c-3-hydroxy-t-2-carbomethoxythiophan structure.

If the reaction of II with thionyl chloride is carried out in the absence of water, 2-phenyl-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline hydrochloride (Va), which is converted to base V on treatment with sodium bicarbonate solution, is isolated. Compound V was also obtained from II by the action of sulfuric acid in acetonitrile. When an aqueous solution of V (or Va) is refluxed, the oxazoline ring opens with simultaneous hydrolysis of the ester group to give III, which is esterified to IV. Thus we have shown that the inversion of II is accompanied by the initial formation of two-ring compound V. This same two-ring compound (V) is also formed from IV under conditions similar to those in the inversion of II.

We established the three-dimensional structure of V (Va) by PMR spectroscopy. As should have been expected, the PMR spectra of solutions of V and Va in pyridine are similar to one another [6] (Table 2). The assignment of the signals in the spectra of these compounds was made by means of PMDR and by comparison of their spectra with the spectra of similar compounds [6].

It has been demonstrated [6] that cis fusion of the thiophan and oxazoline rings occurs for 2-phenyltetrahydrothieno[3,4-d]oxazoline and its hydrohalides, and the oxazoline ring is planar or nearly planar. The spectral parameters of V and Va correspond completely to the same relative orientation of the rings. For this structure of the two-ring compound, the thiophan ring can be found only in the envelope (C_S) conformation with the sulfur atom in the flap of the envelope. Then, depending on the configuration of the 6-carbomethoxy group with respect to the oxazoline ring, two types of conformational equilibria can exist:



The vicinal spin–spin coupling constants for the 6–6a bond for the four conformers (A, B, C, and D) of V (Va), which were calculated from the angular dependence [8-10] with allowance for the possible substituent effect, are presented in Table 3. The torsion angles for the 6–6a bond ($\Psi_{6,\,6a}$) were varied from 20 to 40°.

It follows from a comparison of the theoretical values of the constants (Table 3) with the experimental values ($J_{6,\,6a}$ = 0.6 Hz, Table 2) that the 6-carbomethoxy group has the trans configuration with respect to the oxazoline ring, and the preferred conformation is the C conformation.

Since it is known that opening of the oxazoline ring is not accompanied by inversion in the 6a position [6], the cis configuration of the substituents in the 4 and 3 positions is retained in IV, while these substituents consequently have the trans configuration in II. Thus through a rigorous proof we have arrived at the

same conclusion that we obtained by examining the similarity between the spectra of II and IV and the spectra of the cis and trans isomers of 3,4-substituted thiophans (see above). Consequently, the substituent in the 2 position in the trans configuration with respect to the 4-benzamido group does not substantially affect the spectral parameters of 2,3,4-substituted thiophans. This can apparently be used in the future as an analytical characteristic.

Although there are indications that inversion of the two asymmetrical atoms is possible in the formation of the oxazoline ring [11, 12], under the given conditions inversion occurs only in the 3 position, and the configuration of the substituent in the 2 position is retained in II, IV, and V.

Under pyrolysis conditions, 4-benzamido-2-carbomethoxy-4,5-dihydrothiophene (VI) was obtained from II and IV. The position of the double bond in VI was established by means of PMR spectroscopy. A signal at 6.51 ppm, which is characteristic for vinyl protons, appears in the PMR spectrum of VI. From a comparison of the spectra of II, IV, and VI (Table 1), it is easy to see that the signal at 4.40-4.60 ppm, which is characteristic for the 2-H proton in II and IV, is absent in the spectrum of VI, while the signals of the protons of the $5\text{-}CH_2\text{—}4\text{-}CH$ fragment are retained.

The fact that 2-phenyl-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline is not formed from VI again confirms the impossibility of the formation of the former through the unsaturated amide.

EXPERIMENTAL

r-4-Benzamido-t-3-hydroxy-t-2-carbomethoxythiophan (II). A 1.35-g (0.04 mole) sample of sodium borohydride was added in the course of 15 min with stirring to a cooled (0°) solution of 10 g (0.04 mole) of 4-benzamido-3-oxo-2-carbomethoxythiophan (I) [13] in 30 ml of methanol, and the mixture was stirred at 18-20° for 1 h. Water (20 ml) was added, and the mixture was acidified to pH 2 with hydrochloric acid and extracted with chloroform. The solvent was removed to give 6.0 g (60%) of a product with mp 159-160° (from alcohol). Found: C 55.8; H 5.7; N 4.6%. $C_{13}H_{15}NO_4S$. Calculated: C 55.6; H 5.4; N 5.0%.

r-4-Benzamido-c-3-hydroxy-t-2-carboxythiophan (III). A. A 0.8-ml (0.014 mole) sample of thionyl chloride was added to a cooled (0°) solution of 2 g (0.007 mole) of II in 10 ml of chloroform and 0.58 ml (0.007 mole) of pyridine, and the mixture was stirred at 18-20° for 1.5 h. Water (20 ml) was added, and the aqueous layer was separated, concentrated up to 5 ml, and held at 3° for 8-12 h. The precipitate was separated to give 0.97 g (51%) of a compound with mp 208-209° (from alcohol). Found: C 54.0; H 4.8; N 5.0%. $C_{12}H_{13}NO_4S$. Calculated: C 53.9; H 4.9; N 5.2%.

B. Water (20 ml) was added to 1.6 g (0.006 mole) of 2-phenyl-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline hydrochloride (Va), and the mixture was refluxed for 3 h and then held at 0° for 10-12 h. The precipitate was separated to give 1.25 g (77%) of a product with mp 208-209° (from alcohol). This product did not depress the melting point of the compound obtained by method A.

r-4-Benzamido-c-3-hydroxy-t-2-carbomethoxythiophan (IV). A solution of 0.56 g (0.002 mole) of III in 5 ml of methanol and 0.2 ml of sulfuric acid was refluxed for 4 h. The mixture was cooled, 5 ml of water was added, the the aqueous mixture was extracted with chloroform. The chloroform extract was washed with sodium bicarbonate, and the chloroform was removed to give 0.41 g (70%) of a product with mp 154-154.5° (from methanol). Found: C 55.4; H 5.3; N 5.0%. $C_{13}H_{15}NO_4S$. Calculated: C 55.5; H 5.4; N 5.0%. This product depressed the melting point of II.

cis-2-Phenyl-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline (V). A. Sulfuric acid (3 ml) was added dropwise to a solution of 2.0 g (0.007 mole) of II in 3 ml of acetonitrile (the temperature rose to 100°), and the mixture was stirred for 1 h and poured into ice water. The aqueous mixture was neutralized with sodium bicarbonate solution and extracted with chloroform. The solvent was removed to give 0.85 g (45%) of a product with mp 95-96° (from ether). Found: C 59.1; H 4.9%. $C_{13}H_{13}NO_3S$. Calculated: C 59.3; H 5.0%.

B. Aqueous sodium bicarbonate solution (15 ml) was added to 3.0 g (0.01 mole) of the hydrochloride of V (Va), and the mixture was stirred for 5-10 min and extracted with ether. The ether extract was washed with water, and the ether was removed. Alcohol (4 ml) was added to the residue, and the mixture was held at 0° for 8-10 h. The precipitate was separated to give 2.4 g (91%) of a product with mp 95-96° (from ether). This product did not depress the melting point of the compound obtained by method A.

cis-2-Phenyl-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline Hydrochloride (Va). A. A 0.8-ml (0.014 mole) sample of thionyl chloride was added to a cooled (0°) solution of 2.0 g (0.007 mole) of II in 10 ml of chloroform, and the mixture was stirred at 18-20° for 1 h and concentrated to dryness in vacuo to give 1.86 g (87%) of a product with mp 160-161° (from alcohol). Found: C 52.2; H 4.6; Cl 11.4; N 4.5%. $C_{13}H_{13}NO_3S \cdot HCl$. Calculated: C 52.1; H 4.7; Cl 11.8; N 4.7%.

B. A 5-g sample of V was added to 15 ml of alcohol saturated with hydrogen chloride at 0°, and the mixture was stirred for 30 min and concentrated to dryness to give 5.2 g (91%) of product.

4-Benzamido-2-carbomethoxy-4,5-dihydrothiophene (VI). A solution of 2 g of II in 40 ml of dioxane was heated at 100° for 1 h and at 150° for 1 h. The solvent was removed, 2 ml of alcohol was added to the residue, and the mixture was held at 0° for 8-10 h to give 1.4 g (79%) of a product with mp 128-129°. Found: C 59.4; H 5.1; N 5.1%. $C_{13}H_{13}NO_3S$. Calculated: C 59.4; H 5.0; N 5.3%.

Compound VI was similarly obtained from IV in 72% yield.

The PMR and PMDR spectra were recorded with a Hitachi R-20A spectrometer. The chemical shifts were measured on the δ scale. Tetramethylsilane was used as the internal standard. The accuracy in the measurement of the chemical shifts was ± 0.005 ppm, while the accuracy in the measurement of the spin–spin coupling constants was ± 0.1 Hz.

The IR spectra of the solids (in mineral oil) and of solutions in chloroform and chloroform–carbon tetrachloride mixtures (10^{-1}–10^{-3} M) were recorded with a UR-10 spectrophotometer.

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