STUDY OF THE INVERSION OF

4-BENZAMIDO-3-HYDROXYTHIOPHANE

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Inversion during the acid hydrolysis of trans-4-benzamido-3-hydroxythiophane is accomplished through the intermediate formation of cis-2-phenyltetrahydrothieno[3,4-d]oxazoline. The latter has cis ring fusion, and the oxazoline ring is planar. Opening of the oxazoline ring is not accompanied by inversion and leads to cis-3,4-substituted thiophanes. Migration of the acyl group from the nitrogen to the oxygen atom was detected in substituted thiophanes.

In [1] it was shown that the acid hydrolysis of trans-4-benzamido-3-hydroxythiophane (Ia) is accompanied by inversion with the formation of cis-4-amino-3-hydroxythiophane (Ib); it was assumed that the inversion proceeds through the intermediate formation of 2-hydroxy-2-phenyltetrahydrothieno[3,4-d]oxazoline. In this paper we present the results of an investigation of the isolation, identification, and establishment of the configuration of 2-phenyltetrahydrothieno[3,4-d]oxazoline (II), which is formed as the first product of the reaction.

2-Phenyltetrahydrothieno[3,4-d]oxazoline (II) is formed by the action on trans-4-benzamido-3-hydroxythiophane (Ia) of boiling hydrogen bromide-saturated acetic acid, sulfuric acid in acetonitrile, or thionyl chloride in the presence of pyridine; in the first case it is isolated as the hydrobromide. Compound II readily gives a hydrobromide or hydrochloride in the presence of the corresponding acids. Compound II (base or hydrobromide) is hydrolytically cleaved by refluxing in water to cis-4-benzamido-3-hydroxythiophane (Ib).
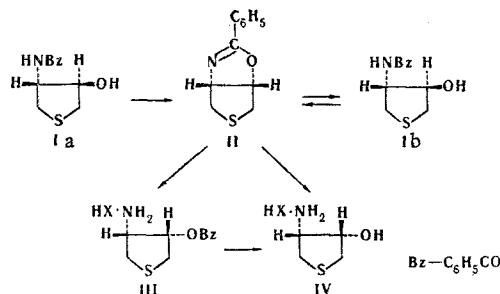
The same 2-phenyltetrahydrothieno[3,4-d]oxazoline (II) that is formed from trans compound Ia is obtained from cis compound Ib by refluxing with hydrogen bromide-saturated acetic acid. These results differ from those in [2], according to which the formation of the oxazoline ring occurs only from the cyclic trans amino alcohols.

In the conversion of Ia to II, one thus observes trans—cis inversion of the substituents, while the cis configuration is retained in the conversion of Ib to II, and inversion is not observed.

TABLE 1. Parameters of the PMR Spectra of II and Its Salts

| Compound	Solvent	Conc., "M"	6-H	6'-H	6a-H	3a-H	4-H	4'-H	$J_{6,6'}$	$J_{6,6a}$	$J_{6',6a}$	$J_{6,6a}+ +J_{6',6a}$	$J_{4,4'}$	$J_{4,3a}$	$J_{4',3a}$	$J_{4,3a}+ +J_{4',3a}$	$J_{3a,6a}$
Hydrobromide of II	CDCl$_3$	0,20	3,288 (4-H)	3,288 (4-H')	6,263	5,617	3,244	3,590		2,5	2,5	5,0	13,5	4,9	0,5	5,4	7,6
Hydrochloride of II	CDCl$_3$	0,30	3,333 (4-H)	3,333 (4-H')	6,238 (3a-H)	5,605 (6a-H)	3,319 (6-H)	3,615 (6-H')		2,5	2,5	5,0	13,5	5,0	0,5	5,5	7,6
II	CDCl$_3$	0,35	3,005 (4-H)	3,135 (4-H')	5,318 (3a-H)	4,997 (6a-H)	3,063 (6-H)	3,063 (6-H')	$J_{4,4'}$ 13,9	$J_{4,3a}$ 3,8	$J_{4',3a}$ 2,0	5,8		$J_{6,6a}$ 3,6	$J_{6',6a}$ 3,6	7,2	7,5
II	C$_5$D$_5$N	0,50	2,936	3,108	5,232	4,978	2,80—3,40		$J_{4,4'}$ 13,4	$J_{4,3a}$ 3,7	$J_{4',3a}$ 1,5	5,2		$J_{6,6a}$ 4,2	$J_{6',6a}$ 2,5	6,7	7,5

It should be noted that cleavage of the oxazoline ring of II was not accompanied by inversion and led to a cis-3,4-substituted thiophane. Compound II was hydrolyzed by boiling water to cis-Ib, as indicated by the melting point of the reaction product [1].

The structure of II was confirmed by the PMR spectra (Fig. 1). The complex groups of signals at 2.70–3.30 ppm (spectrum a) and at 3.00–3.80 ppm (spectrum b) are affiliated with the four protons attached to C_4 and C_6. The signals at 4.80–5.40 ppm (spectrum a) and the signals at 5.50–5.80 and 6.15–6.40 ppm (spectrum b) are formed by the protons attached to C_{3a} and C_{6a} [3–6]. The assignment of the signals to the C_4 and C_6 protons, respectively, was made by means of double proton magnetic resonance (DPMR) spectroscopy. A signal characteristic for an acid proton (NH, δ 12.8 ppm at −30°, δ 13.7 at −60°, Table 1) can be observed in the spectra of solutions of the hydrohalides of II in deuterochloroform at low temperatures. The appearance of a positive charge in the oxazoline ring simultaneously leads to a shift in the C_{3a} and C_{6a} protons to weaker field as compared with their position in the spectrum of the corresponding bases (Table 1). The assignment of these signals to the C_{3a} and C_{6a} protons, respectively, was made on the basis of the literature data for similar compounds [4,5]. The spectra of solutions of the hydrohalides of II in deuteropyridine practically coincide with the spectrum of the free base in this solvent.

Since 2-phenyltetrahydrothieno[3,4-d]oxazoline (II) was obtained from two epimeric amino alcohols (Ia and Ib), while both cis and trans coupling of the rings are known [7] for the two fused five-membered rings that include heteroatoms, the type of fusion in II cannot be selected a priori. The selection of the type of fusion was carried out using the angular dependence of the vicinal spin−spin coupling constants [8, 9]. All possible types of cis and trans fusion of the thiophane and oxazoline rings in II were considered.

The maximum torsion angle in both five-membered rings is about 60° for trans fusion. The ranges of the vicinal spin−spin coupling constants for the $6-6_a$, 6_a-3_a, and 3_a-4 bonds were calculated using the angular dependence (with allowance for the effects of substituents over wide ranges) [8–10]. Close values of the constants were obtained for both the C_2 and C_S conformations that the thiophane ring can assume: $J_{3a,6a} = 9.5-15.0$ Hz, $J_{6,6a} = 3.0-7.0$ Hz, $J_{6',6a} = 7.0-13.5$ Hz, $J_{4,3a} = 1.5-4.5$ Hz, $J_{4',3a} = 9.0-15.0$ Hz. It is apparent from a comparison of these data with the experimental results (Table 1) that the latter do not correspond to trans fusion of the rings.

There are considerably more variants of cis fusion of the rings than of trans fusion. The double bond in the oxazoline ring causes an envelope (C_S) (the maximum torsion angle is ψ_{3a6a}) [11] or planar conformation of this ring. Two types of cis ring fusion can be isolated for the envelope conformation of oxazoline:
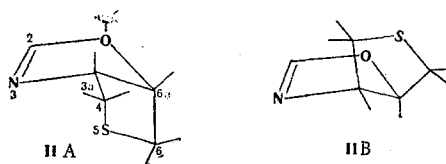
The most probable conformations of the thiophane ring for both the IIA type of fusion and the IIB type of fusion will be two envelope conformations (C_S) with maximum torsion angles 1) ψ_{3a6a} and ψ_{3a4}, 2) ψ_{3a6a} and ψ_{66a}, and three semichair conformations (C_2) with maximum torsion angles 1) ψ_{3a6a}, 2) ψ_{66a}, and 3) ψ_{3a4}. The values of the spin−spin coupling constants
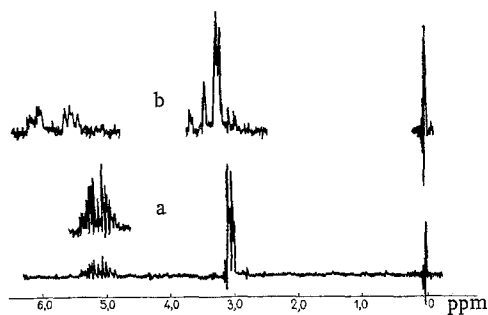
Fig. 1. PMR spectrum: a) 0.35 M solution of II in deuterochloroform; b) 0.30 M solution of the hydrochloride of II in deuterochloroform.

for the conformations within each type of IIA and IIB fusion differ only slightly. A greater sum of the constants for the $6-6a$ bond $(J_{6,6a} + J_{6',6a} = 10.5-19.0$ Hz) and a substantially smaller sum of the constants for the $3a-4$ bond $(J_{4,3a} + J_{4',3a} = 4.5-12.4$ Hz) are characteristic for the conformations of fusion IIA.* On the other hand, a greater sum of the constants for the $3a-4$ bond $(J_{4,3a} + J_{4',3a} = 10.5-19.0$ Hz) and a smaller sum of the constants for the $6-6a$ bond $(J_{6,6a} + J_{6',6a} = 4.5-12.0$ Hz) are characteristic for fusion of the IIB type. (Actually, in concrete cases the ranges of the sums of the constants for the $6-6a$ and $3a-4$ bonds do not overlap; the smaller sum of the constants for the $3a-4$ bond corresponds to the smaller sum of the constants for the $6-6a$ bond, since the substituents attached to C_{3a} and C_{6a} have comparable electronegativities.) These results were obtained for the maximum torsion angle of the oxazoline ring $(\psi_{66a} = 30°)$. Varying the angles of deflection of the ring in the interval $\pm 10°$ does not substantially affect the results. A comparison of the theoretically calculated sums of the constants with the experimental sums (Table 1) demonstrates that not one of the examined cis-fusion conformations of the IIA or IIB type explains the experimental spectra.

The conformations within each type of cis fusion (IIA and IIB) can interconvert as a result of vibration of the sulfur atom relative to the other atoms of the thiophane ring, the positions of which are determined by the conformations of the oxazoline ring. However, this sort of mixture of conformations should not lead to constants that differ substantially from the constants of each of the conformations, since the constants for the conformations within each type of fusion are close. Transition between the conformations of the two types of fusions is possible (bicyclic inversion). In this case, the constants will have values intermediate between the constants of the conformations of the type IIA and IIB fusions. Moreover, the sums of the spin−spin coupling constants should substantially exceed the experimental sums. In addition, the temperature dependence of the sums of the constants for the $6-6a$ and $3a-4$ bonds will have opposite sign. The experimental temperature dependence was studied for II in deuteropyridine from −15 to −125°. Both sums of constants for the $6-6a$ and $3a-4$ bonds increase as the temperature is raised, respectively, from 4.64 to 5.94 Hz $(J_{6,6a} + J_{6',6a})$ and from 6.32 to 7.61 Hz $(J_{4,3a} + J_{4',3a})$. Thus not one of the types of fusions (cis or trans) in which the oxazoline ring is folded, satisfies the experimental data.

Only cis fusion is possible for a planar oxazoline ring, and the thiophane ring can be only an envelope with a sulfur atom in the valve [7].
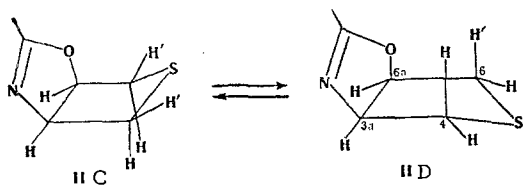
The constants for the $6-6a$ and $3a-4$ bonds for this type of conformation should be the same with an accuracy up to that of the substituent effect; this is experimentally observed (Table 1). The torsion angle for the $6-6a$ bond $(\psi_{6,6a})$ was varied from 20-40° in order to calculate the theoretical constants. The torsion angles for the $6-6a$ bond, the corresponding ranges of the vicinal spin−spin coupling constants for the $6-6a$ ($3a-4$) bond, and their sum for the two envelope conformations of thiophane (IIC and IID) are given in Table 2.

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*Here and subsequently, it is convenient to use the sum of the spin−spin coupling constants for the $6-6a$ and $3a-4$ bonds, since in the compounds under investigation the chemical shift between the geminal C_4 and C_6 protons is either absent or comparable in magnitude to the geminal spin−spin coupling constants, and the determination of the true values of the vicinal constants requires the calculation of the spectra by means of a computer.

TABLE 2. Calculated Vicinal Spin–Spin Coupling Constants for Conformers IIC and IID

Conforma-tion	$\psi_{6,6a}$	$J_{6,6a}$, Hz	$J_{6',6a}$, Hz	$J_{6,6a} + J_{6',6a}$, Hz
II C	20	6,5—10,5	0—0,5	6,5—11,0
	30	6,0—9,5	0	6,0—9,5
	40	4,5—7,0	0	4,5—7,0
II D	20	6,5—10,5	6,0—9,0	12,5—19,6
	30	6,0—9,5	7,0—11,0	13,0—20,5
	40	4,5—7,0	8,5—13,0	13,0—20,0

From a comparison of Tables 1 and 2, it is apparent that the experimental results satisfy the IIC $\rightleftharpoons$ IID conformational equilibrium in which the equilibrium is markedly shifted to favor conformation IIC $(J_{6,6a} + J_{6',6a} = 4.8-5.9$ Hz, $J_{4,3a} + J_{4',3a} = 5.4-6.8$ Hz, Table 1). It is apparent that an increase in temperature should result in an increase in the probability of finding a molecule in the IID conformation and in a corresponding increase in the sums of the constants; this is also observed experimentally (see above).

The cleavage of the oxazoline ring in II by refluxing it with 10% hydrochloric acid is accompanied by removal of the benzoyl group to form the hydrochloride of cis-4-amino-3-hydroxythiophane (IV) [1].

We detected the migration of an acyl substituent from the nitrogen atom of Ia through II to the oxygen atom in III. Thus the hydrochloride of 4-amino-3-benzoyloxythiophane (III) is formed in the solvolysis of II in 5% solution of hydrogen chloride in alcohol. To establish the structure of III, it was subjected to alkaline hydrolysis to the known cis hydrochloride of IV [1]. Although this sort of migration from N to O is often used to prove the configuration of compounds [12-14], in our case (the inversion of Ia to Ib), this cannot be used, since intermediate II is formed from both compounds.

EXPERIMENTAL

cis-2-Phenyltetrahydrothieno[3,4-d]oxazoline (II). 1) Sulfuric acid (3 ml) was added dropwise to a solution of 2.0 g (0.009 mole) of trans-4-benzamido-3-hydroxythiophane (Ia) in 3 ml of acetonitrile (the temperature rose to 100°), and the mixture was stirred for 1 h and poured into ice water. The mixture was extracted with chloroform. The extracts were washed with sodium bicarbonate solution and water. The solvent was removed, and alcohol was added to the residue to give 0.96 g (52%) of a product with mp 88-89° (from ether). Found: C 64.2; H 5.4; N 6.5; S 15.9%. $C_{11}H_{11}NOS$. Calculated: C 64.4; H 5.4; N 6.8; S 15.6%.

2) Thionyl chloride (5 ml) was added to a solution of 10 g (0.045 mole) of Ia in 50 ml of chloroform and 3.95 ml of pyridine at 0°, and the mixture was stirred at 18-20° for 1.5 h and concentrated to dryness in vacuo. A solution of sodium bicarbonate was added to the residue, and the mixture was extracted with ether. The ether extracts were washed with water, and the ether was removed to give 8.3 g (91%) of a product with mp 88-89° (from ether). This product did not depress the melting point of the compound obtained by method 1.

3) 2-Phenyltetrahydrothieno[3,4-d]oxazoline hydrobromide: A) A solution of 10 g (0.045 mole) of Ia or Ib in 100 ml of acetic acid saturated with hydrogen bromide was refluxed for 5 h and concentrated to dryness. Alcohol (50 ml) was added to the residue, and the mixture was held at 0° for 12-16 h. The precipitate was removed by filtration to give 9.64 g (75%, 68% from Ib) of a product with mp 175-176° (from alcohol). Found: C 45.5; H 4.2; Br 28.0%. $C_{11}H_{11}NOS \cdot HBr$. Calculated: C 46.2; H 4.2; Br 28.0%.

B) Hydrogen bromide-saturated alcohol (10 ml) was added to 5 g (0.024 mole) of II, and the mixture was held at 0° for 30 min and concentrated to dryness to give 5.8 g (83%) of product.

4) 2-Phenyltetrahydrothieno[3,4-d]oxazoline hydrochloride: Under conditions similar to those in method 3A, 5.0 g (0.024 mole) of II and 10 ml of hydrogen chloride-saturated alcohol gave 4.77 g (81%) of a hydrochloride with mp 160-161° (from acetone). Found: C 54.6; H 5.0; Cl 15.1%. $C_{11}H_{11}NOS \cdot HCl$. Calculated: C 54.6; H 5.0; Cl 14.7%.

5) Aqueous sodium bicarbonate (15 ml) was added to 2 g of the hydrochloride or hydrobromide of 2-phenyltetrahydrothieno[3,4-d]oxazoline, and the mixture was stirred for 15 min and extracted with chloroform. The extract was washed with water and dried with sodium sulfate. Alcohol (3 ml) was added to the

residue, and the mixture was held at 0° for 8-10 h. The resulting precipitate was removed by filtration to give 1.29 g (90%) of a product with mp 88-89°. The product did not depress the melting point of the compound obtained by method 1.

cis-4-Benzamido-3-hydroxythiophane (Ib). A solution of 2 g (0.01 mole) of II in 20 ml of water was refluxed for 5 h and held at 0° for 10-12 h. The precipitate was removed by filtration to give 1.7 g (78%) of a product with mp 154-155° (from alcohol) [1].

cis-4-Amino-3-benzoylhyoxythiophane Hydrochloride (III). A solution of 2 g (0.01 mole) of II in 100 ml of 5% hydrogen chloride in alcohol was stirred at 30-35° for 10 h and concentrated to dryness to give 1.56 g (62%) of a product with mp 165-166° (from alcohol). Found: C 50.7; H 5.6; Cl 14.0; S 12.4%. $C_{11}H_{13}NOS \cdot$ HCl. Calculated: C 50.9; H 5.4; Cl 13.7; S 12.3%.

Hydrochloride of cis-4-Amino-3-hydroxythiophane (IV). 1) A total of 4 ml of 2.5 N sodium hydroxide was added to a solution of 1 g (0.004 mole) of III in 10 ml of alcohol, and the mixture was refluxed for 30 min and acidified to pH 2 with 2 N hydrochloric acid. The mixture was extracted with benzene, the aqueous layer was evaporated to dryness, 3 ml of alcohol was added, and the solid was removed by filtration to give 0.52 g (89%) of a product with mp 167-168° (from alcohol) [1].

2) A solution of 1 g (0.005 mole) of II in 12 ml of 10% hydrochloric acid was refluxed for 5 h. The benzoic acid was extracted with benzene, and the aqueous layer was concentrated to dryness. The residue was crystallized from alcohol to give 1.06 g (83%) of a product with mp 167-168° (from alcohol).

The PMR and DPMR 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.

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