SYNTHESIS, CONFIGURATION, AND CONFORMATION OF 3-ACYL DERIVATIVES OF 3a,4,6,6a-TETRAHYDROTHIENO[3,4-d][1,2,3]OXATHIAZOLINE 2-OXIDE

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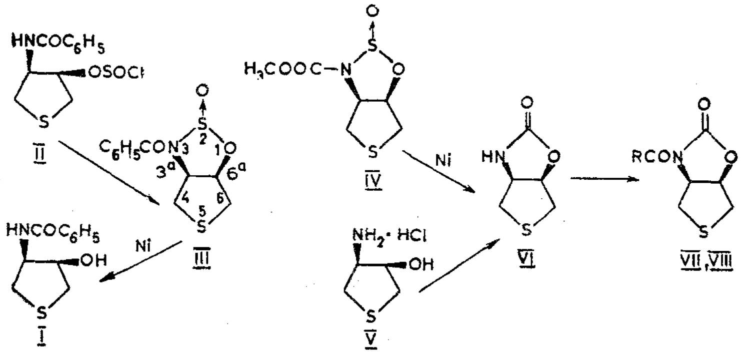
3-Benzoyl-3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxide is formed as a result of intramolecular cyclization of cis-4-benzamido-3-chlorosulfitothiophan. Only one sulfur atom – that of the sulfoxide group – is removed from the cyclization product and the analogous 3-methoxycarbonyl-3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxide by the action of Raney nickel; the products in this case are, respectively, cis-4-benzamido-3-hydroxythiophan and 3a,4,6,6a-tetrahydrothieno]3,4-d]oxazolidone. The three-dimensional structure of 3-acyl-3a,4,4,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxide was determined by ^{1}H and ^{13}C NMR spectroscopy. A difference between the conformational state of 3-substituted 3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxides and 3-substituted 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidones was established.

We have previously shown that cis-4-methoxycarbonylamino-3-chlorosulfitothiophan is capable of undergoing intramolecular cyclization in the presence of pyridine to give 3-methoxycarbonyl-3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxide (IV) [1]. Since IV is a new two-ring system, it seemed of interest to us to investigate the possibility of the formation of such compounds and to study their three-dimensional structure.



VII R = C_6H_5 ; VIII R = CH_3O

In the present research we synthesized 3-benzoyl-3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxide (III), the analog of IV, by subjecting cis-4-benzamido-3-chlorosulfitothiophan (II) to intramolecular cyclization in pyridine at 90-100°C. Cleavage of the molecule with detachment of the OSO group (m/e 205) is most characteristic in the mass spectrum of III. The IR spectrum of III is similar to the IR spectrum of IV [1]. The characteristic absorption bands of OH and NH groups are absent in the spectrum of III, but the spectrum contains a strong band at 1180 cm^{-1} corresponding to vibrations of the $S \rightarrow O$ group. The similarity between the structures of III and IV is also confirmed by data from the ^{1}H spectra (Table 1). The signal of

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TABLE 1. Parameters of the ^1H NMR Spectra of III, IV, VII, and VIII*

Compound	mp, °C	δ, ppm						J, Hz						
		3a-H	4-H′	4-H″	6-H′	6-H″	6a-H	3a-H, 6a-H	3a-H, 4-H′	3a-H, 4-H″	6-H′, 6a-H	6-H″, 6a-H	4-H′, 4-H″	6-H′, 6-H″
III	34	5,32	3,23	3,01	3,20	3,20	6,11	6,2	6,1	4,1	$EJ_{6,6a}=5,2$		−12,8	
VII	70	(5,19) 5,23	3,05	3,05	3,07	3,07	(5,23) 5,19	7,1	$EJ_{3a,4}=6,4$		$EJ_{6,6a}=5,6$			
IV†	32	4,88	3,16	2,95	3,21	3,12	6,08	5,82	6,52	4,19	4,65	1,96	−12,90	−13,40
VIII	31	4,91	3,00	3,14	2,95	3,04	5,23	7,2	$EJ_{3a,4}=6,4$		$EJ_{6,6a}=5,2$		−13,5	−13,4

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*The solvent used for III, IV, and VIII was C_5D_5N, and CD_3OD was used as the solvent for VII (0.4 M solutions).

†The parameters of the spectrum of IV were calculated with a Minsk-22 computer from an iteration program; the chemical shifts of the geminal protons in VIII and III and of the 3a-H and 6a-H protons in VII were calculated as an AB system. The chemical shifts of the remaining protons were determined as the centers of the multiplets, and the spin–spin coupling constants were determined as the distances between the appropriate lines in the spectra.

TABLE 2. Parameters of the ^{13}C NMR Spectra of IV and VIII

Compound	Solvent*	δ, ppm					J, Hz			
		C-3a	C-4, C-6	C-6a	O–CH$_3$	C=O	C-3a, H	C-6a, H	C-4, H	C-6, H
IV	$CDCl_3$	63,3	36,2, 36,8	91,4	53,9	152,6	152	162	141	141
VIII	$(CD_3)_2SO$	62,2	38,2, 38,9	79,4	53,6	151,3, 150,8	157	165	141	141

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*The spectra were obtained from 1 M solutions.

the 6a-H proton (δ^{III} 6.11 and δ^{IV} 6.08 ppm) is shifted appreciably to weak field as compared with the signal of the proton in the spectrum of 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone (δ 5.24 ppm) [1]; this is in agreement with the increase in the electronegativity of the substituent attached to 6a-C. The sum of the vicinal spin–spin coupling constants (SSCC) along the 3a-4 bond ($\varepsilon J^{III}_{3a,4} = 10.2$ Hz and $\varepsilon J^{IV}_{3a,4} = 10.7$ Hz) is greater than the sum along the 6-6a bond ($\varepsilon J^{III}_{6,6a} = 5.2$ Hz and $\varepsilon J^{IV}_{6,6a} = 6.6$ Hz), whereas they are close for 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone; consequently, there is a conformational difference between these compounds.

The change in the conformational state of III and IV as compared with the previously investigated 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone derivatives [1, 2] may be associated either with the appearance of a substituent attached to the nitrogen atom or with replacement of the carbonyl group by a sulfoxide grouping.

To clear up this problem, we synthesized the 3-benzoyl- and 3-methoxycarbonyl derivatives (VII and VIII) of 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone (VI) by acylation. Compound VI was obtained from cis-4-amino-3-hydroxythiophan by fusion with urea.

Comparison of the ^{13}C NMR spectra of IV and VIII (Table 2) confirms the correctness of the choice of structure IV and, consequently, III.

A singlet belonging to the substituent attached to nitrogen (δ 152.6 ppm) is observed in the spectrum of IV in the region of the signals of the carbonyl carbon atoms, in contrast to the spectrum of oxazolidone analog VIII, in which an additional signal – the signal of the carbonyl ring carbon (δ 151.3 and 150.8 ppm, Table 2) – is located in this region. In addition, as in the ^1H NMR spectra, the 6a-C signal in the spectrum of IV shifted appreciably to weak field as compared with the spectrum of VIII ($\Delta\delta_{6a\text{-}C}$ 12 ppm); this is also in agreement with the concept of an increase in the electronegativity of the substituent attached to 6a-C on passing from VIII to IV. The ionic character of the bond changes as the electronegativity of the substituent increases, and this leads to a change in the ^{13}C shielding constant [3].

The parameters of the ^1H NMR spectra of VII and VIII are presented in Table 1. The results of a study of the temperature dependences of the vicinal constants for IV and VIII are presented in Figs. 1 and 2, respectively.

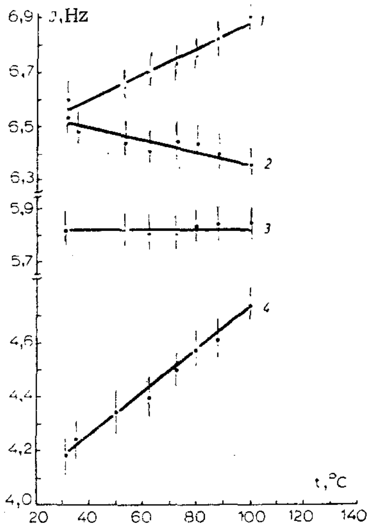


Fig. 1

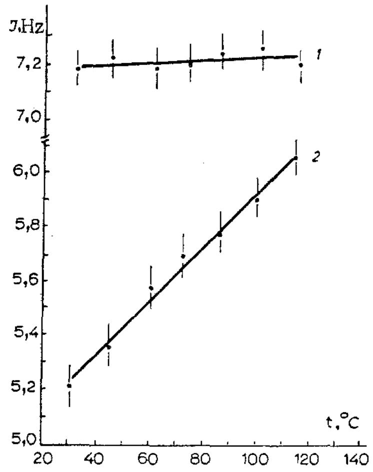


Fig. 2

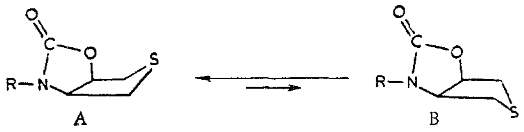
Fig. 1. Temperature dependences of the sum of $J_{6-H',6a-H}$ and $J_{6-H'',6a-H}$ ($\varepsilon J_{6,6a}$) (1), $J_{3a-H,4a-H'}$ (2), $J_{6a-H,3a-H}$ (3), and $J_{3a-H,4-H''}$ (4) for IV.

Fig. 2. Temperature dependences of $J_{3a-H,6a-H}$ (1) and sum of $J_{6-H',6a-H}$ and $J_{6-H'',6a-H}$ ($\varepsilon J_{6,6a}$) (2) for VIII.

It has previously been shown that the temperature dependences of trans-vicinal SSCC are substantially larger than the cis constants for five-membered rings [4]. In the case of IV, $J_{3a-H,4-H'}$ can therefore be ascribed to the cis constants ($\Delta J_{3a-H,4-H'} = 0.14$ Hz over the investigated temperature range; Fig. 1, curve 2) and $J_{3a-H,4-H''}$ can be assigned to the trans constant ($\Delta J_{3a-H,4-H''} = 0.50$ Hz; Fig. 1, curve 4). It can also be asserted that the change in the trans-vicinal constants (the temperature dependence of $\varepsilon J_{3a,4}$ for VIII could not be investigated in detail, but a comparison of the magnitudes of this sum at the two extreme points of the investigated temperature range – 6.43 Hz at 31° and 6.96 Hz at 114° – shows that $\varepsilon J_{3a,4}$ increases as the temperature rises) makes the chief contribution to the investigated change in the sums of the vicinal constants in the CH_2–CH fragment for IV and VIII ($\varepsilon J_{6,6a}$ for IV and VIII and $\varepsilon J_{3a,4}$ for VIII).

A comparison of the observed vicinal SSCC for III, IV, VII, and VIII (Table 1) with the values calculated for trans-fused rings [2] makes it possible to conclude that the experimental constants in these compounds do not correspond to trans fusion. In addition, in the case of trans fusion the thiophan ring should be practically rigid, and this is not in agreement with the existence of appreciable temperature dependences of the trans-vicinal constants in IV and VIII (Figs. 1 and 2).

The magnitudes of the SSCC and their temperature dependences are close for VII and VIII and for the previously investigated 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone derivatives [1, 5]. Cis fusion of the five-membered rings was proved for these derivatives by analysis of the magnitudes of the vicinal SSCC, and the form of the conformational equilibrium (A ⇄ B) and the preferred conformation (A) were found in [1, 5]. Consequently, one can assert that cis fusion of the thiophan and oxazolidone rings also occurs in VII and VIII, and an equilibrium between the A and B conformations with preferred conformation A is also characteristic for the molecules of these compounds. Thus the introduction of a substituent in the oxazolidone ring has practically no effect on the conformational state of tetrahydrothieno[3,4-d]oxazolidone.



Appreciable temperature dependences of the trans-vicinal SSCC are observed for IV (Fig. 1, curves 1 and 4). This makes it possible to assume that this compound is not conformationally pure. Evaluation of the conformational purity of III and IV by the criterion proposed by Abraham [6] also confirms this conclusion: The coefficients of angular dependence ($J^{\circ}_{6,6a} = 12.8$ and $J^{\circ}_{3a,4} = 20.3$; 21.2 Hz) calculated from the observed vicinal constants in the corresponding CH_2–CH fragment from the Karplus equation are clearly too high. The

TABLE 3. Calculated Ranges of the Vicinal Spin–Spin Coupling Constants (J, Hz) for Conformations Participating in Equilibria 1-3*

Conformational equilibrium	Phase angle†	$\Psi_{3a,4}$, deg	$J_{3a\text{-}H,4\text{-}H'}$	$\varphi_{3a\text{-}H,4\text{-}H''}$, deg	$J_{3a\text{-}H,4\text{-}H''}$	$\Psi_{3a,6a}$, deg	$J_{3a\text{-}H,6a\text{-}H}$	$\Psi_{6,6a}$, deg	$J_{6\text{-}H',6a\text{-}H}$	$\varphi_{6a\text{-}H,6\text{-}H''}$, deg	$J_{6a\text{-}H,6\text{-}H''}$
1	144	42	4,3—6,8	162	9,8—14,6	16	7,3—11,2	16	7,3—11,2	136	5,5—8,5
	504	42	4,3—6,8	78	0,3—0,5	16	7,3—11,2	16	7,3—11,2	104	0,6—1,0
2	180	30	6,0—9,0	150	8,1—12,3	0	8,0—12,0	30	6,0—9,0	150	8,1—12,3
	540	30	6,0—9,0	90	0	0	8,0—12,0	30	6,0—9,0	90	0
3	216	16	7,3—11,2	136	5,5—8,5	16	7,3—11,2	42	4,3—6,8	162	9,8—14,6
	576	16	7,3—11,2	104	0,6—1,0	16	7,3—11,2	42	4,3—6,8	78	0,3—0,5

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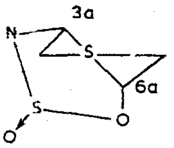
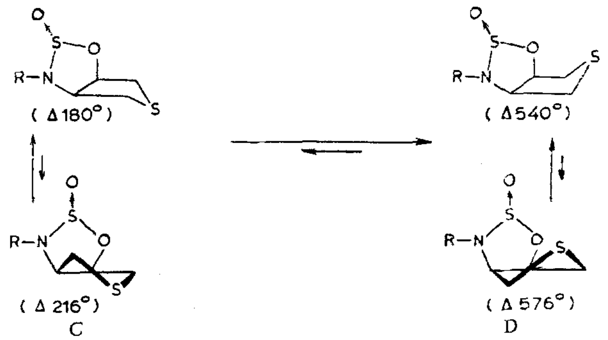
*The following symbols are used in the table: Δ is the phase angle of the folding amplitude [7], Ψ_{mn} is the torsion angle along the mn bond (it corresponds to a dihedral angle between the cis-vicinal substituents), and $\varphi_{H,H}$ is the dihedral angle between the trans-oriented hydrogen atoms. It was assumed that $\Psi_{max} = 50°$ (variation of Ψ_{max} does not change the conclusions regarding the form of the preferred conformations), $J^0 = 8\text{-}12$ Hz, and $J^{180} = 1.35\ J^0$ (J^0 and J^{180} are the coefficients in the equations of the angular dependence of the vicinal constants) in the calculations of the ranges of the vicinal constants.

†The conformation shown below was adopted as the origin (Δ = 0) in the chain of transformation of the thiophan ring:



conformational state of these compounds was therefore examined in the form of an equilibrium between the conformations. Equilibria between pairs of conformations, the phase angles of which (Δ) differ by 360° (the interconversion corresponds to ring inversion), are evidently most likely for the five-membered ring [4]. The similar trends of the changes with temperature in the trans-vicinal constants along the 3a-4 and 6-6a bonds (Fig. 1, curves 1 and 4) leave only three of the 10 possible pair equilibria for the thiophan ring likely (see Table 3). The ranges of the vicinal SSCC were calculated for the conformations participating in these equilibria as in [2, 6, 8]. From a comparison of the calculated constants (Table 3) with the experimental values (Table 1), the equilibrium between the conformations with Δ 144 and 504° can also be rejected ($J_{3a\text{-}H,6a\text{-}H} \approx J_{6\text{-}H',6a\text{-}H} > J_{3a\text{-}H,4\text{-}H'}$ for this equilibrium whereas $J_{3a\text{-}H,4\text{-}H'} > J_{6\text{-}H',6a\text{-}H} \approx J_{3a,6a}$ experimentally). The observed values of the vicinal constants can be explained (in the case of maximum torsion angle Ψ_{max} 50-60°, $J_{3a,4}{}^0 = 10\text{-}12$ Hz, and $J_{6,6a}{}^0 = 6\text{-}7$ Hz) by an equilibrium between asymmetrical conformations C and D, which are intermediate between conformations with Δ 180 and 216° (C) and 540 and 576° (D):*



In this case the contribution of the forms with Δ 180 and 540° (70-75%) is greater than that of the forms with Δ 216 and 576° (25-30%). The D conformation is preferred (60-70%). The choice of the preferred conformations is also confirmed by the direction of the change with temperature in the trans-vicinal constants (an increase as the temperature rises).

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*The three-dimensional structure of the oxathiazolidone ring is not considered.

Thus an asymmetric conformation arises when the sulfoxide group is introduced, probably because of the less planar structure of the 1,2,3-oxathiazoline 2-oxide ring as compared with the oxazolidone ring.

Anomalously low coefficients of the angular dependence of the vicinal constants along the 6-6a bond ($J_{6,6a}$ = 6-7 Hz) are characteristic for derivatives of 3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxides. The decrease in $J_{6,6a}{}^{0}$ is probably associated with the substantial increase in the electronegativity of the substituent attached to 6a-C in III and IV.

Since 3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-oxide contains two sulfur atoms, it was of interest to subject it to desulfuration with Raney nickel. In this case it was found that the sulfoxide group is initially removed with cleavage of the oxathiazoline 2-oxide ring, as a result of which cis-4-benzamido-3-hydroxythiophan (I) was obtained from III, and 3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone (VI) was obtained from IV. A monocyclic thiophan derivative – cis-4-methoxycarbonylamino-3-hydroxythiophan – which subsequently undergoes intramolecular cyclization to give two-ring compound VI when it is heated, is evidently also formed in the second case.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The mass spectra were recorded with a JMS-01SG-2 mass spectrometer with direct introduction of the samples 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 admission system was maintained at 80°. The NMR spectra were recorded with Hitachi R-20A and Varian XL-100 spectrometers with tetramethylsilane as the internal standard. The accuracy in the determination of the chemical shifts of the protons was ±0.01 ppm, and the accuracy in the determination of the ^{13}C atoms was ±0.1 ppm; the accuracy in the determination of the $J_{H,H}$ constants was ±0.1 Hz, as compared with ±1.0 Hz for the $J_{^{13}C,H}$ constants. The proton total double resonance (PMDR) and a comparison with the spectra of related compounds [1, 2, 6, 8] were used in the assignment of the signals to definite protons in the ^{1}H NMR spectra; comparison with the spectra obtained by irradiation of the protons was used in the assignment of the signals in the ^{13}C NMR spectra.

In the study of the temperature dependences of the SSCC the corresponding intervals in the spectra were averaged with respect to 12-18 measurements at each temperature. Since the chemical shifts of the geminal protons (6-H' and 6-H") are close for IV and VIII, their change with temperature can introduce a considerable inaccuracy in the determination of the temperature dependences of $J_{6a-H,6-H'}$ and $J_{6a-H,6-H''}$ associated with a change in the populations of the conformations. The temperature dependences of the sums of the vicinal constants along the 6-6a bond ($\varepsilon J_{6,6a}$) were therefore studied for both compounds. Like the $J_{3a-H,6a-H}$ constants, the temperature dependences of $J_{4-H',3a-H}$ and $J_{4-H',3a-H'}$ for IV were corrected in conformity with the calculation of the spectra from an iteration program at 32 and 100°.

3-Benzoyl-3a,4,6,6a-tetrahydrothieno[3,4-d][1,2,3]oxathiazoline 2-Oxide (III). A 0.8-g (3.6 mmole) sample of cis-4-benzamido-3-hydroxythiophan (I) [2] was added to 3 ml of $SOCl_2$ at −10°, and the mixture was stirred for 20 min, after which the temperature was gradually raised to 20-22°. The thionyl chloride was removed in vacuo to isolate cis-4-benzamido-3-chlorosulfitothiophan (II) [8]. Dry pyridine was added to it, and the mixture was heated to 90-100° for 10 min. The pyridine was removed in vacuo, chloroform was added to the residue, and the chloroform solution was washed with water. The chloroform was removed, alcohol was added to the residue, and the mixture was cooled at 0° for 12-16 h. The resulting precipitate was separated to give 0.3 g (31%) of colorless needles with mp 107-108° (from alcohol). Found: C 49.3; S 23.5%. $C_{11}H_{11}NO_3S_2$. Calculated: C 49.1; H 4.1; S 23.8%. The filtrate was concentrated and the residue was recrystallized from alcohol to give 0.4 g of I.

3a,4,6,6a-Tetrahydrothieno[3,4-d]oxazolidone (VI). A 1.5-g (9.5 mmole) sample of cis-4-amino-3-hydroxythiophan hydrochloride (V) and 1.3 g (23 mmole) of thiophene were mixed, and the mixture was heated in vacuo at 160-200° for 1 h, after which it was cooled and treated with chloroform. The chloroform extracts were washed with water, the chloroform was removed in vacuo, and alcohol was added to the residue. The resulting precipitate was removed by filtration to give 1 g (72%) of colorless prisms with mp 125-126° (from alcohol). No melting-point depression was observed for a mixture of this product with a sample of oxazolidone [1].

3-Benzoyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone (VII). A 0.5-g (3.5 mmole) sample of VI and 0.31 g (5.5 mmole) of ground KOH were added with stirring to 5 ml of acetone, the mixture was heated to the boiling point, and 0.72 g (5.2 mmole) of benzoyl chloride in 2 ml of acetone was added. The mixture was refluxed for 1 h, after which it was concentrated to dryness, and the residue was dissolved in chloroform. The chloroform solution was washed with water, the chloroform was removed, and alcohol was added to the residue. The alcohol mixture was cooled at 0-3° for 12-16 h, after which the precipitate was removed by filtration and washed with water to 0.9 g (86%) of colorless needles with mp 102-103°. Found: C 57.7; H 4.2; S 12.8%. $C_{12}H_{11}NO_3S$. Calculated: C 57.8; H 4.5; S 12.9%.

3-Methoxycarbonyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazolidone (VIII). A 0.6-g (4.2 mmole) sample of VI and 0.39 g (6.9 mmole) of KOH were added to 5 ml of acetone, the mixture was heated to the boiling point, and 2.7 ml of an acetone solution of 0.66 g (6.9 mmole) of methyl chlorocarbonate was added gradually. The mixture was refluxed with stirring for 1 h, after which it was cooled to 0° and allowed to stand at that temperature for 12-16 h. The precipitate was separated and washed with water to give 0.5 g (59%) of colorless needles with mp 139-140° (from methanol). Found: C 41.2; H 4.5; S 16.0%. $C_7H_9NO_4S$. Calculated: C 41.4; H 4.5; S 15.8%.

Desulfuration of Tetrahydrothienooxathiazoline 2-Oxide III. A 0.5-g (1.9 mmole) sample of III and 6 g of Raney nickel were added to 9 ml of alcohol, and the mixture was refluxed for 9 h. It was then cooled and filtered, and the filtrate was concentrated to a volume of 2-3 ml and allowed to stand at 0-3° for 12-16 h. The resulting precipitate was separated to give 0.36 g (86%) of colorless prisms of cis-4-benzamido-3-hydroxythiophan (I) with mp 154-155°. No melting-point depression was observed for a mixture of this product with the compound previously obtained in [2].

Desulfuration of Tetrahydrothienooxathiazoline 2-Oxide IV. A 0.8-g (3.5 mmole) sample of IV [1] and 12 g of Raney nickel were added to 18 ml of alcohol, and the mixture was refluxed for 9 h. It was then cooled to 30-40° and filtered, and the filtrate was concentrated to 2-3 ml. The resulting precipitate was removed by filtration to give 0.2 g (40%) of colorless prisms of VI with mp 125-126° (from alcohol). No melting-point depression was observed for a mixture of this product with VI obtained above.

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