SYNTHESIS OF ALL OF THE POSSIBLE STEREOISOMERS OF 4-BENZAMIDO-3-HYDROXY-2-(δ-CARBOMETHOXYBUTYL)THIOPHAN

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The stereospecific synthesis of the four possible isomers of 4-benzamido-3-hydroxy-2-(δ-carbomethoxybutyl)thiophan (III-VI) was accomplished from 4-benzamido-3-oxo-2-(δ-carbomethoxybutylidene)thiophan (I) using the stereospecificity of the reduction of the oxo group of I, the stereospecificity of the reduction of the exocyclic double bond of 4-benzamido-3-hydroxy-2-(δ-carbomethoxybutylidene)thiophan (II), and inversion of the hydroxyl group of III and IV. The configurations of the stereoisomers obtained were established by PMR spectroscopy.

We have previously [1,2] shown that the reduction of the oxo group by sodium borohydride proceeds stereospecifically for 4-monosubstituted and 2,4-disubstituted 3-oxothiophans. The hydroxyl group thus formed in the 3 position of the thiophan ring has the trans configuration with respect to the substituent attached to C_4. In the present research, we have accomplished the reduction of 4-benzamido-3-oxo-2-(δ-carbomethoxybutylidene)thiophan (I) [3] with sodium borohydride in methanol at 0°C. An amino alcohol – 4-benzamido-3-hydroxy-2-(δ-carbomethoxybutylidene)thiophan (II) – was isolated from the reaction mixture. A triplet with δ 5.935 ppm (J = 6.9 Hz), formed by the vinyl proton, is present in the PMR spectrum of a solution of II in pyridine. The spectrum of this compound also retains the characteristic features of the spectra of the previously [2] studied trans isomers of 4-amino-3-hydroxythiophan: $\Delta\delta_{5\text{-H}}$trans = $\delta_{5\text{-H}'} - \delta_{5\text{-H}''} = 0.41$ ppm; $J_{4\text{-H},5\text{-H}'} + J_{4\text{-H},5\text{H}''} = 12.0$ Hz (Table 1), which is evidence in favor of the trans configuration of the 4-benzamido group and the 3-hydroxy group in II. On the basis of previous investigations [1,2] and the PMR spectrum, the trans-4-benzamido-3-hydroxy-2-(δ-carbomethoxybutylidene)thiophan structure can be assigned to II.

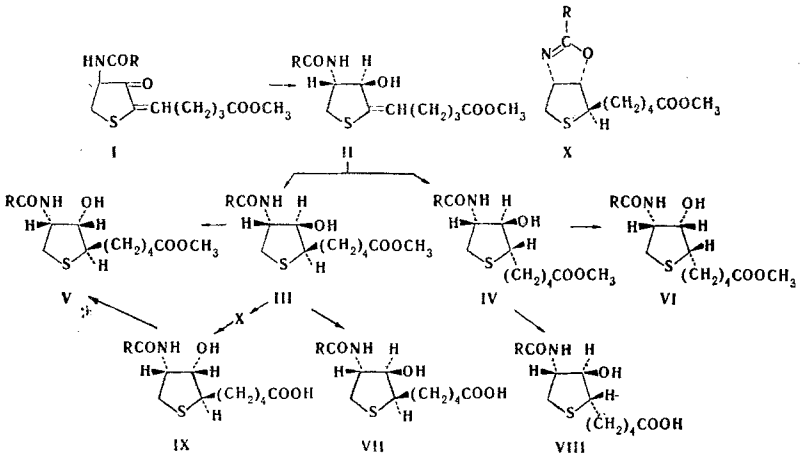

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TABLE 1. Parameters of the PMR Spectra of Pyridine Solutions of II-VI*

Comp.	δ, ppm					J, Hz					
	2-H	3-H	4-H	5-H′(″)	5-H″(′)	2-H, 3-H	3-H, 4-H	4-H, 5-H′	4-H, 5-H″	NH, 4-H	5-H′, 5-H″
II		4,70—5,20	4,70—5,20	3,63	3,22			5,0	7,0		10,9
III	3,40—3,90	4,83	5,17	3,69	3,00	4,0	4,0	5,7	3,2	6,8	11,0
IV	3,20—3,70	4,34	5,09	3,43	3,06	9,0	8,1	7,2	9,2	7,2	10,3
V	3,20—3,60	4,47	5,04	3,28	3,28	2,2	3,9	†		7,4	
VI	3,25—3,75	4,61	5,05	3,38	3,22	3,2	3,2	10,4	8,1	7,5	9,9

*The concentration of solutions of II-V was 0.5 M, compared with 0.4 M for VI.

† $J_{4-H,5-H'} + J_{4-H,5-H''} = 16.4$ Hz.

It is known that the steric accessibility of the bond undergoing reduction serves as one of the most important factors that affect the hydrogenation of a double bond [4]. Although cis addition of hydrogen proceeds from the less hindered side of the molecule, the stereospecificity of this reaction depends on the conditions used to carry out the hydrogenation [4,5]. We accomplished the hydrogenation of the exocyclic double bond of II over $Pd/BaSO_4$. We demonstrated that the stereospecificity of the reduction of II depends on the temperature and pressure: only one isomer – 4-benzamido-3-hydroxy-2-(δ-carbomethoxybutyl)-thiophan (III) (mp 110-111°) – is formed at 50 atm and 30-40°; at 100 atm and 90-100°, in addition to III, another possible isomer with respect to the 2 position (IV) (mp 140-141°) is formed in a ratio of 1 : 3. Since no melting-point depression was observed for mixtures of esters III and IV, they were hydrolyzed to the corresponding acids (VII and VIII) (mp 160-161 and 167-168°, respectively), for mixtures of which a melting-point depression was observed. Compounds III and IV were characterized by the PMR spectra as individual substances (Table 1) (no other signals than those presented in the table were present in the spectra).

As we have already established [2], the spectra of cis and trans isomers of 3,4-hydroxyaminothiophans in pyridine have characteristic features. The difference in the chemical shifts of the protons attached to C_5 is substantially larger for the trans isomers than for the cis isomers ($\Delta\delta_{5-H}$trans 0.36-0.47 ppm; $\Delta\delta_{5-H}$cis 0-0.08 ppm); at the same time, the trans isomers have a lower sum of the vicinal spin–spin coupling constants along the 4-5 bond than the cis isomers ($J_{4-H,5-H'}$trans + $J_{4-H,5-H''}$trans = 8.6-11.6 Hz; $J_{4-H,5-H'}$cis + $J_{4-H,5-H''}$cis = 14.0-17.4 Hz) [2]. It was also demonstrated that the features associated with the configuration of substituents in the 3 and 4 positions of the thiophan ring are retained in the spectra of 2,3,4-trisubstituted thiophans, if the substituent attached to C_2 has the trans configuration relative to the substituent attached to C_4 (for example, r-4-benzamido-t-3-hydroxy-t-2-carboxymethylthiophan has $\Delta\delta_{5-H}$ 0.63 ppm and $J_{4-H,5-H'} + J_{4-H,5-H''} = 12$ Hz, while r-4-benzamido-c-3-hydroxy-t-2-carbomethoxythiophan has $\Delta\delta_{5-H}$ 0 ppm and $J_{4-H,5-H'} + J_{4-H,5-H''} = 16.4$ Hz) [2]. The spectrum of III retains the features characteristic for trans-3,4-hydroxyaminothiophans – $\Delta\delta_{5-H}$trans 0.69 ppm and $J_{4-H,5-H'} + J_{4-H,5-H''} = 8.9$ Hz (Table 1). Consequently the r-4-benzamido-t-3-hydroxy-t-2-(δ-carbomethoxybutyl)thiophan structure should be assigned to this compound, and the r-4-benzamido-t-3-hydroxy-c-2-(δ-carbomethoxybutyl)thiophan structure should be ascribed to its isomer (IV).

In accordance with the previously proposed method [2,6], we accomplished the inversion of the hydroxyl group in the 3 position of III by heating it in acetic acid saturated with hydrogen bromide, while the hydroxyl group in IV was inverted by the action of thionyl chloride in chloroform in the presence of pyridine. The two possible isomeric esters (V and VI) (mp 101-102 and 131-132°, respectively) were isolated. The features characteristic for the spectra of cis-4-amino-3-hydroxythiophan – $\Delta\delta_{5-H}$cis 0 ppm and $J_{4-H,5-H'} + J_{4-H,5-H''} = 16.4$ Hz – are retained in the PMR spectrum of V (Table 1 and Fig. 1). Thus, in the present study we have once more confirmed the previously established principle [2] that a substituent in the 2 position in the trans configuration relative to the 4-benzamido group has practically no effect on the PMR spectra of 2,3,4-trisubstituted thiophans. Consequently, the structure of V corresponds to r-4-benzamido-c-3-hydroxy-t-2-(δ-carbomethoxybutyl)thiophan, while VI corresponds to r-4-benzamido-c-3-hydroxy-c-2-(δ-carbomethoxybutyl)thiophan.

We have also shown that the inversion of III and IV to V and VI proceeds through the intermediate formation of 2-phenyl-6-(δ-carbomethoxybutyl)tetrahydrothieno[3,4-d]oxazoline (X). This compound was obtained by the reaction of III with thionyl chloride in chloroform in the presence of pyridine or on heating

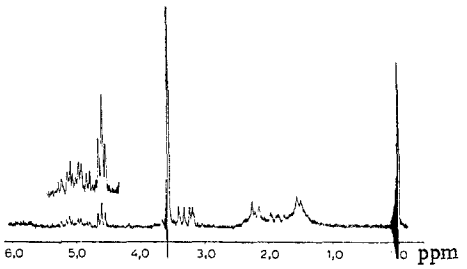

Fig. 1. PMR spectrum of a 0.4 M solution of r-benzamido-c-3-hydroxy-c-2-(δ-carbomethoxybutyl)thiophan (VI) in pyridine.

in acetic acid saturated with hydrogen bromide. The three-dimensional structures of X and its hydrochloride and hydrobromide (Xa and Xb) were established by means of PMR spectroscopy. As expected, the PMR spectra of pyridine solutions of X, Xa, and Xb were similar. The signals were assigned by means of proton-magnetic double resonance (PMDR) and by a comparison of these spectra with the spectra of similar compounds [2,6]. As was previously established in [2,6], inversion of substituted thiophans with a trans configuration of the substituents in the 3 and 4 positions proceeds through the formation of 2-phenyltetrahydrothieno[3,4-d]oxazoline and 2-phenyl-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline. The latter compound is characterized by cis fusion of the thiophan and oxazoline rings, and the oxazoline ring is planar or nearly planar. The vicinal spin–spin coupling constants of X, Xa, and Xb correspond completely to the same relative orientation of the rings. The vicinal spin–spin coupling constant along the 6–6a bond in X is 1.6 Hz. It is close to the analogous constant for 2-phenyl-trans-6-carbomethoxy-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline (0.6 Hz) [2]. Consequently, the methoxybutyl group in X, Xa, and Xb has the trans configuration with respect to the oxazoline ring.

Opening of the oxazoline ring in X under the influence of 10% ammonium hydroxide (with simultaneous hydrolysis of the ester group) gave r-4-benzamido-c-3-hydroxy-t-2-(δ-carboxybutyl)thiophan (IX). In accordance with the data in [2,6], this reaction is not accompanied by inversion at the 6 and 6a carbon atoms. Esterification of IX gives ester V.

EXPERIMENTAL

r-4-Benzamido-t-3-hydroxy-2-(δ-carbomethoxybutylidene)thiophan (II). A 1.13-g (0.03 mole) sample of sodium borohydride was added in the course of 1.5 h with stirring at 18-20° to a solution of 10.0 g (0.03 mole) of 4-benzamido-3-oxo-2-(δ-carbomethoxybutylidene)thiophan (I) [3] in 100 ml of methanol, and the mixture was stirred for 2 h. Water (50 ml) was added, and the mixture was acidified to pH 2 with 2 N hydrochloric acid. The precipitate was removed by filtration to give 7.8 g (77.8%) of colorless plates of II with mp 125-126° (from methanol). Found: C 60.8; H 6.4; N 4.1%. $C_{17}H_{21}NO_4S$. Calculated: C 60.9; H 6.3; N 4.2%.

r-4-Benzamido-t-3-hydroxy-t-2-(δ-carbomethoxybutyl)thiophan (III). An autoclave was charged with 12.0 g (0.06 mole) of II, 240 ml of methanol, and 47.0 g of 5% Pd/$BaSO_4$, and the mixture was hydrogenated at 30-40° and 50 atm for 10 h. The catalyst was separated, and the filtrate was concentrated to 10-15 ml and allowed to stand at 0-3° for 12 h. The precipitate was removed by filtration to give 9.84 g (82.2%) of colorless prisms of III with mp 110-111° (from methanol). Found: C 60.0; H 6.9; N 4.3%. $C_{17}H_{23}NO_4S$. Calculated: C 60.1; H 6.9; N 4.2%.

r-4-Benzamido-t-3-hydroxy-c-2-(δ-carbomethoxybutyl)thiophan (IV). An autoclave was charged with 2.0 g (0.01 mole) of II, 40 ml of methanol, 7.0 g of 5% Pd/$BaSO_4$, and the mixture was hydrogenated at 90-100° and 100 atm for 6 h. The catalyst was separated, the filtrate was concentrated to one fourth its original volume, and the residue was allowed to stand at 16-18° for 12 h. The precipitate was removed by filtration to give 1.36 g (67.7%) of colorless needles of IV with mp 140-141° (from methanol). Found: C 60.4; H 6.9; N 4.0%. $C_{17}H_{23}NO_4S$. Calculated: C 60.1; H 6.9; N 4.2%. Concentration of the filtrate yielded 0.5 g (24.9%) of III with mp 110-111°.

r-4-Benzamido-t-3-hydroxy-t-2-(δ-carboxybutyl)thiophan (VII). A 0.1-g (2 mmole) sample of sodium hydroxide was added to a solution of 0.4 g (1 mmole) of III in 4 ml of water and 6 ml of alcohol, and the mixture was refluxed for 2.75 h. It was then cooled and acidified to pH 2 with 2 N hydrochloric acid to give 0.38 g (98.9%) of V with mp 167-168° (from methanol). Found: C 59.0; H 6.1; N 3.7%. $C_{16}H_{21}NO_4S$. Calculated: C 59.4; H 6.5; N 4.3%.

r-4-Benzamido-t-3-hydroxy-c-2-(δ-carboxybutyl)thiophan (VIII). Under similar conditions, 0.4 g (1 mmole) of IV gave 0.34 g (88.5%) of VIII with mp 160-161° (from methanol). Found: C 59.2; H 6.5; N 4.1%. $C_{16}H_{21}NO_4S$. Calculated: C 59.4; H 6.5; N 4.3%. This product depressed the melting point of VII (mp 146-149°).

r-4-Benzamido-c-3-hydroxy-t-2-(δ-carbomethoxybutyl)thiophan (V). A. A solution of 1.0 g (3 mmole) of III in 10 ml of acetic acid saturated with hydrogen bromide was refluxed for 5 h and evaporated to dryness. Ammonium hydroxide (15 ml) was added to the residue, and the mixture was concentrated to half its original volume and extracted with chloroform. The chloroform was removed, and 2 ml of methanol was added to the residue. The mixture was held at 0°, and the resulting precipitate was separated to give 0.56 g (56%) of colorless prisms of V with mp 101-102° (from methanol). Found: C 60.3; H 6.6; N 4.5%. $C_{17}H_{23}NO_4S$. Calculated: C 60.1; H 6.9; N 4.2%.

B. A solution of 0.5 g (1.5 mmole) of IX in 5 ml of methanol and 0.3 ml of sulfuric acid was refluxed for 1.5 h. Water (4 ml) was added, and the mixture was extracted with chloroform. The chloroform extract was washed with sodium bicarbonate solution, and the chloroform was removed. Methanol (1 ml) was added to the residue, and the mixture was allowed to stand at 0° to give 0.39 g (75%) of a product with mp 101-102°. This product did not depress the melting point of the product obtained via method A.

r-4-Benzamido-c-3-hydroxy-c-2-(δ-carbomethoxybutyl)thiophan (VI). A solution of 1 ml (15 mmole) of thionyl chloride in 7 ml of chloroform was added at 0° to a solution of 1.0 g (3 mmole) of IV in 20 ml of chloroform and 0.24 ml (3 mmole) of pyridine, and the mixture was held at 20° for 2 h. The solvent was removed, 5 ml of water was added to the residue, and the mixture was extracted with chloroform. The chloroform extract was washed with water, and the chloroform was removed to give 0.59 g (61.3%) of colorless needles of VI with mp 131-132° (from methanol). Found: C 60.7; H 6.9; N 4.3%. $C_{17}H_{22}NO_4S$. Calculated: C 60.7; H 6.6; N 4.2%.

2-Phenyl-t-6-carbomethoxybutyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline (X). A. A solution of 1.5 ml (20 mmole) of thionyl chloride in 8 ml of chloroform was added at 0° to a solution of 1.5 g (4 mmole) of III in 45 ml of chloroform and 0.35 ml (4 mmole) of pyridine, and the mixture was held at 20° for 2 h. The solvent was removed, and the residue was neutralized with sodium bicarbonate solution. The alkaline mixture was extracted with chloroform, and the chloroform was removed. The residue was treated with 5 ml of alcohol, and the mixture was held at 0° for 2 h. The resulting precipitate was separated to give 1.12 g (81.3%) of X with mp 157-158° (from methanol). δ_{3^a-H} 5.12 ppm, $\delta_{4-H'}$ 3.30 ppm; $\delta_{4-H''}$ 3.06 ppm; δ_{6-H} 3.30-3.55 ppm; δ_{6a-H} 4.98 ppm; $J_{3^a-H,4-H'} = 5.2$ Hz; $J_{3a-H,4-H''} = 2.2$ Hz; $J_{3a-H,6^a-H} = 7.7$ Hz; $J_{4-H',4-H''} = 12.1$ Hz; $J_{6-H,6^a-H} = 1.6$ Hz. Found: C 63.3; H 6.3; N 4.3%. $C_{17}H_{21}NO_3S$. Calculated: C 63.7; H 6.6; N 4.4%.

B. A total of 8 ml of a saturated aqueous sodium bicarbonate solution was added to 1.0 g (3 mmole) of 2-phenyl-t-6-carbomethoxybutyl-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline hydrochloride (or hydrobromide) (Xa), and the mixture was stirred for 15 min and extracted with chloroform. The chloroform was removed, alcohol was added, and the mixture was held at 0° for 12-16 h. The resulting precipitate was separated to give 0.52 g (58.4%) of X with mp 157-158°. This product did not depress the melting point of the compound obtained via method A.

Hydrochloride of X (Xa). This compound [1.07 g (96.3%)] was obtained from 1.0 g (3 mmole) of II and 8 ml of alcohol saturated with hydrogen chloride and had mp 135-136° (from alcohol). Found: C 57.6; H 6.3; N 4.2; Cl 9.8%. $C_{17}H_{21}NO_3S \cdot HCl$. Calculated: C 57.4; H 6.2; N 4.2; Cl 10%.

Hydrobromide of X (Xb). A solution of 1.0 g (3 mmole) of III in 10 ml of acetic acid saturated with hydrogen bromide was refluxed for 5 h and evaporated to dryness. Methanol (3 ml) was added to the residue, and the mixture was held at 0° for 10 h. The precipitate was separated to give 0.8 g (69.5%) of Xb with mp 200-201° (from methanol). Found: C 50.4; H 5.5; N 8.5; Br 19.5%. $C_{17}H_{21}NO_3S \cdot HBr$. Calculated: C 51.0; H 5.5; N 8.5; Br 20.0%.

r-4-Benzamido-c-3-hydroxy-t-2-(δ-carboxybutyl)thiophan (IX). A solution of 1.0 g (3 mmole) of X in 11 ml of 10% ammonium hydroxide was refluxed for 5 h and held at 0° for 10-12 h. The precipitate was separated to give 0.87 g (83.2%) of IX with mp 153-154° (from alcohol). Found: C 59.5; H 6.7; N 4.0%. $C_{16}H_{21}NO_4S$. Calculated: C 59.4; H 6.5; N 4.3%.

The PMR and PMDR spectra were recorded with a Hitachi R-20A spectrometer. The chemical shifts were measured on the δ scale, and the internal standard was tetramethylsilane. The accuracies in measuring the chemical shifts and spin–spin coupling constants were ±0.005 ppm and ±0.1 Hz, respectively.

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