SYNTHESIS OF r-4-ETHOXYCARBONYLAMINO-t-3-HYDROXY-c-2-(δ-METHOXYCARBONYLBUTYL)-THIOPHAN

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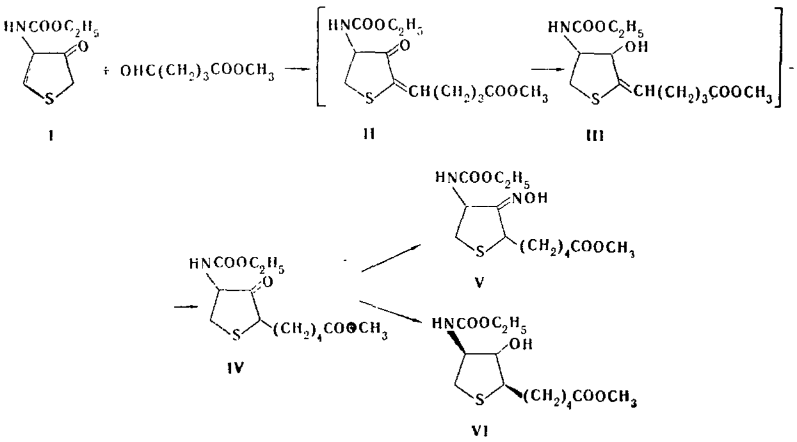
Condensation of 4-ethoxycarbonylamino-3-oxothiophan with methyl γ-formylbutyrate gives 4-ethoxycarbonylamino-3-oxo-2-(δ-methoxycarbonlybutyl)thiophan, its oxime, and r-4-ethoxycarbonylamino-t-3-hydroxy-c-2-(δ-methoxycarbonylbutyl)thiophan.

In a continuation of our research [1, 2] on the condensation of 4-aminosubstituted 3-oxothiophans with aldehydes and ketones, we have investigated the reaction of 4-ethoxycarbonylamino-3-oxothiophan [2] with methyl γ-formylbutyrate.

Condensation of 4-ethoxycarbonylamino-3-oxothiophan (I) with methyl γ-formylbutyrate in the presence of piperidine and pyridine acetate was unsuccessful, and starting I was recovered. We were able to effect the condensation in the presence of piperidine. This reaction was monitored by PMR spectroscopy.



If 4-ethoxycarbonylamino-3-oxo-2-(δ-methoxycarbonylbutylidene)thiophan (II) is formed in the reaction, the signal of a vinyl proton should appear in the PMR spectrum. In fact, a triplet at δ 6.57 ppm, which is characteristic for a proton attached to a double bond, is detected in the PMR spectrum of the mixture recorded 1 h after the start of the reaction. However, we were unable to isolate II in pure form, inasmuch as it is an oily substance that readily decomposes during high-vacuum distillation.

Compound II was subjected to reduction with NaBH$_4$ (without isolation from the reaction mixture). According to the PMR spectrum of the reaction product the signal of the proton attached to the exocyclic double bond is shifted to stronger field (δ 5.62 ppm), which attests to the formation of III [in the spectrum of 4-benzamido-3-hydroxy-2-(δ-methoxycarbonylbutylidene)thiophan the proton attached to the double bond appears at δ 5.92 ppm [3]].

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TABLE 1. Parameters of the PMR Spectra of Solutions of V and VI in Deuteropyridine

Compound	Concn., M	δ, ppm								J, Hz			
		2H	5H′	5H″	3H	4H	OCH_2	CH_3	$(CH_2)_4$	5H′, 5H″	5H′, 4H	5H″, 4H	4H, NH
V	0,4	4,57	3,35	2,81	—	5,15	4,16	1,12	1,40—2,55	−10,5	6,6	9,9	8,1
VI	0,5	3,10—3,50	3,23	2,84	3,90—4,60		4,10	1,19	1,40—2,45	−10,7	7,1	8,5	—

When the reaction product containing III is allowed to react with methanol saturated with hydrogen chloride it undergoes prototropic isomerization [4] – the signal of the proton attached to the double bond vanishes in the PMR spectrum – and primarily (~75-80%) one stereoisomer of 4-ethoxycarbonylamino-3-oxo-2-(δ-methoxycarbonylbutyl)thiophan (IV) is formed. Compound IV is an oily substance that readily forms crystalline oxime V in 42% yield.

4-Ethoxycarbonylamino-3-hydroxy-2-(δ-methoxycarbonylbutyl)thiophan (VI) was isolated in 78% yield on subsequent reduction of IV with $NaBH_4$ in methanol at 0°C.

The structures of V and VI and the configuration of VI were established by PMR spectroscopy. The spectrum of VI, like the spectrum of V, contains a group of signals, the chemical shifts of which are characteristic for protons attached to the α-carbon atoms of the thiophan ring, two complex signals at 1.40-2.55 ppm, which are affiliated with the protons of the methylene groups of the substituent attached to C_2 [3], and signals that characterize the portions of substituents attached to C_3 (in VI) and C_4 (see Table 1) [3]. The signals of the protons attached to C_2 and C_4 of V (δ_{2H} 4.57, δ_{4H} 5.15 ppm) are shifted to weak field as compared with the corresponding signals of VI (δ_{2H} 3.10-3.50, δ_{4H} 3.90-4.60 ppm), which is apparently explained by the deshielding effect of the hydroxylamino group. The signal of the proton attached to C_3 in the PMR spectrum of VI is found in one group of signals with the proton attached to C_4 and the protons of the methylene group of the ethoxycarbonyl substituent attached to the amino group (δ 3.90-4.60 ppm).

In an earlier study of the PMR spectra of isomers of 4-benzamido-3-hydroxy-2-methoxycarbonylthiophan [5] and 4-benzamido-3-hydroxy-2-(δ-methoxycarbonylbutyl)thiophan [3] it was shown that the r-4-t-3-t-2 configuration of the substituents is characterized by a relatively small value of the sum of the vicinal spin–spin coupling constants with respect to the C_4–C_5 bond (ΣJ_{4-5} = 8.9-12.4 Hz), while a substantially larger value of this sum (ΣJ_{4-5} = 16.4-18.5 Hz) is characteristic for the other three isomers (r-4-t-3-c-2, r-4-c-3-t-2, and r-4-c-3-c-2). Compound VI is characterized by a large value of the sum of $J_{4H,5H'}$ and $J_{4H,5H''}$ (15.6 Hz, Table 1) and, consequently, cannot be the r-4-t-3-t-2 isomer. The chemical shifts of the geminal protons attached to C_5 practically coincide ($\Delta\delta_{5H',5H''}$ 0-0.08 ppm) in the spectra of r-4-c-3-t-2-investigated compounds, just as in the spectra of a number of isomers of 3,4-substituted thiophans, that differ with respect to the substituent attached to the nitrogen in the 4-position [5]. For VI, $\Delta\delta_{5H',5H''}$ is 0.39 ppm (Table 1), which makes it possible to regard the r-4-c-3-t-2 configuration for it as improbable. The vicinal constant between the protons attached to C_3 and C_4 is small ($J_{3H,4H}$ 3.2 Hz) [3] in the spectrum of the complete cis-2,3,4-substituted thiophan. Inasmuch as the least distance between the two individually observed extreme compounds of the signal of the proton attached to C_4 for VI is 7.1 Hz, $J_{3H,4H}$ cannot be less than 7.1 Hz, i.e., the spectrum of the investigated compound is not in agreement with a cis configuration of all of the substituents. The large value of the sum of $J_{4H,5H'}$, $J_{4H,5H''}$ (15.6 Hz), and $J_{3H,4H}$ (≥7.1 Hz), as well as the observed difference in the chemical shifts of the geminal protons attached to C_5 ($\Delta\delta_{5H',5H''}$ 0.39 ppm) for VI, are in complete agreement with the r-4-t-3-c-2 configuration of the substituents ($\Sigma J_{4,5}$ 16.4, $J_{3H,4H}$ 8.1-9.0 Hz, $\Delta\delta_{5H',5H''}$ 0.37 ppm [3]). Thus, VI is r-4-ethoxycarbonylamino-t-3-hydroxy-c-2-(δ-methoxycarbonylbutyl)thiophan.

EXPERIMENTAL

The PMR spectra were recorded with a Hitachi P-20 A spectrometer. Tetramethylsilane was used as the internal standard. The accuracy in the determination of the chemical shifts was 0.01 ppm, while the accuracy in the determination of the spin–spin coupling constants was 0.1 Hz. The assignment of the signals to definite protons of the investigated compounds was confirmed by the ratio of the integral intensities of the signals and double-resonance experiments.

4-Ethoxycarbonylamino-3-oxo-2-(δ-methoxycarbonylbutyl)thiophan (IV). A 2.5-ml (22 mmole) sample of methyl γ-formylbutyrate and 0.4 ml of piperidine were added to a cooled (to 0 deg) solution of 4 g

(21 mmole) of 4-ethoxycarbonylamino-3-oxothiophan (I) in 26 ml of methanol, and the mixture was stirred at 0 deg for 2 h. A 0.52-g (14 mmole) sample of sodium borohydride was then added in the course of 30 min, and the mixture was stirred at 0 deg for 1 h. A 10-ml sample of methanol saturated with hydrogen chloride (up to 30%) was added, and the mixture was stirred for 30 min. Water (20 ml) was added, and the mixture was extracted with chloroform. The chloroform extracts were washed with saturated sodium carbonate solution and dried with sodium sulfate. The chloroform was removed in vacuo, and the syrupy residue was dried at 50-60° (0.5 mm) for 3 h to give 1.5 g (31.2%) of product. Found: C 51.8; H 6.6; N 4.8%. $C_{13}H_{21}NO_5S$. Calculated: C 51.5; H 7.0; N 4.6%.

4-Ethoxycarbonylamino-3-oximino-2-(δ-methoxycarbonylbutyl)thiophan (V). A 0.25-g (4 mmole) sample of hydroxylamine hydrochloride was added to a solution of 1 g (3 mmole) of IV in 5 ml of pyridine, and the mixture was stirred at 18-20° for 12 h. Chloroform (25 ml) and crushed ice were added, after which 2.5 N hydrochloric acid was added in portions with shaking until the aqueous layer had pH 1. The chloroform layer was washed with sodium bicarbonate solution and water and dried with sodium sulfate. The chloroform was removed in vacuo, 2 ml of alcohol was added to the residue, and the mixture was allowed to stand at 0 deg for 18-20 h. The resulting precipitate was separated to give 0.44 g (42%) of a product with mp 130-130.5 deg (from alcohol). Found: C 49.4; H 6.8; N 9.1%. $C_{13}H_{22}N_2O_5S$. Calculated: C 49.0; H 7.0; N 8.8%.

r-4-Ethoxycarbonylamino-t-3-hydroxy-c-2-(δ-methoxycarbonylbutyl)thiophan (VI). A 0.13-g (3 mmole) sample of sodium borohydride was added at 0 deg in the course of 30 min to a solution of 1 g (3 mmole) of IV in 8 ml of methanol, and the mixture was stirred at 0 deg for 2 h. Water (10 ml) was added, and the mixture was acidified to pH 1-2 with hydrochloric acid and extracted with chloroform. The solvent was removed, ether and alcohol in a ratio of 20 : 1 were added to the residue, and the mixture was held at 0 deg for 24 h. The resulting precipitate was separated to give 0.75 g (78%) of a product with mp 83-84 deg (from ether–methanol). Found: C 51.1; H 7.7; N 4.6%. $C_{13}H_{23}NO_5S$. Calculated: C 51.1; H 7.6; N 4.6%.

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