ESTABLISHMENT OF THE CONFIGURATION OF 4-BENZAMIDO-3-OXO-2-(α-HYDROXYAMINO-δ-CARBOMETHOXYBUTYL)-THIOPHANE

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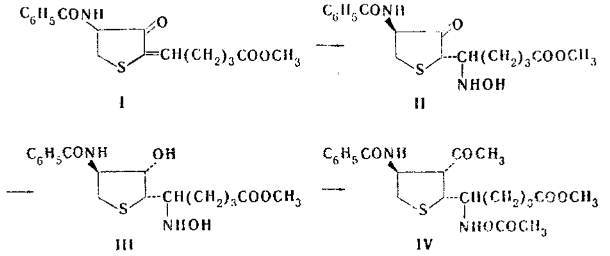
Proton magnetic resonance spectroscopy was used to establish that the addition of hydroxylamine to the exocyclic double bond of 4-benzamido-3-oxo-2-(δ-carbomethoxybutylidene)-thiophane occurs stereospecifically; the compound formed has the trans configuration with respect to the substituents in the 2 and 4 positions.

The nucleophilic addition of hydroxylamine to 4-benzamido-3-oxo-2-(δ-carbomethoxybutylidene)-thiophane [1] (I) has been previously studied, and it was shown that, depending on the reaction conditions, hydroxylamine may add to both the carbonyl group and the double bond to give, in the latter case, 4-benzamido-3-oxo-2-(δ-hydroxyamino-δ-carbomethoxybutyl)thiophane (II) [2]. In the present investigation, we established the configuration of II using PMR spectroscopy.

We first reduced the oxo group in II to a hydroxyl group with sodium borohydride to give 4-benzamido-3-hydroxy-2-(δ-hydroxyamino-δ-carbomethoxybutyl)thiophane (III), and the hydroxyl groups were then acetylated (III was converted to IV) in order to increase the solubility.



In accordance with the data in [3,4], the hydroxyl group of III is trans oriented with respect to the benzamido group.

We have previously formulated the differences in the spectra of solutions of the cis and trans isomers of 4-amino-3-hydroxythiophane derivatives in pyridine, and we showed that the substituent in the 2 position in the trans configuration with respect to the substituent in the 4 position has practically no effect on the conformational state of the 2,3,4-substituted thiophanes and, consequently, on the parameters of their PMR spectra [3,4]. The characteristic peculiarities of the spectra of the cis and trans isomers of 3,4-substituted thiophanes are therefore retained in the spectra of the isomeric (with respect to the 3 and 4 positions) 2,3,4-substituted thiophanes with a trans configuration of the substituents in the 4 and 2 positions, while these spectral peculiarities vanish for 2,3,4-substituted thiophanes with a cis configuration of the substituents in the 2 and 4 positions.

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TABLE 1. Parameters of the PMR Spectrum of a 0.5 M Solution of IV in Deuteropyridine

Chemical shift, δ, ppm					Spin—spin coupling constants, J, Hz					
2-H	3-H	4-H	5-H (5-H′)	5-H′ (5-H)	2-H, 3-H	3-H, 4-H	4-H, 5-H (5-H′)	4-H, 5-H′ (5-H)	5-H, 5-H′	4-H, NH
4,59	6,04	5,33	3,44	3,12	4,6	4,6	6,1	4,4	11,0	7,1

The spectrum of a solution of IV in deuteropyridine (see Table 1) has the characteristic peculiarities of the spectra of the trans isomers of 3,4-substituted thiophanes in this solvent: $\Delta\delta_{5-H,5-H'}$ = 0.32 ppm, while the J^{vic} values are close in magnitude. On the basis of this, we proposed the r-4-benzamido-t-3-acetoxy-t-2-(δ-O-acetoxyamino-δ-carbomethoxybutyl)thiophane configuration for IV.

Hydroxylamine consequently adds stereospecifically to the exocyclic double bond of the side chain of 4-benzamido-3-oxo-2-(δ-carbomethoxybutylidene)thiophane (I), and the compound formed (II) has the trans configuration of the substituents in the 2 and 4 positions.

EXPERIMENTAL

r-4-Benzamido-t-3-hydroxy-t-2-(δ-hydroxyamino-δ-carbomethoxybutyl)thiophane (III). A 0.75-g (20 mmole) sample of sodium borohydride was added in the course of 1 h at 18-20° to a solution of 5.0 g (14 mmole) of r-4-benzamido-3-oxo-t-2-(δ-hydroxyamino-δ-carbomethoxybutyl)thiophane (II) in 40 ml of ethanol, and the mixture was stirred for 2 h. Water (50 ml) was added, and the mixture was acidified with 2 N hydrochloric acid and extracted with chloroform. The chloroform was removed to give 4.1 g (81%) of III with mp 126-126.5° (from methanol). Found,%: C 55.6; H 6.2; N 7.4. $C_{17}H_{14}N_2O_4S$. Calculated,%: C 55.4; H 6.6; N 7.6.

r-4-Benzamido-t-3-acetoxy-t-2-(δ-O-acetoxyamino-δ-carbomethoxybutyl)thiophane (IV). A solution of 1 g (2.7 mmole) of III in 5 ml of acetyl chloride was stirred at 30° for 2 h, after which it was concentrated in vacuo, treated with 3 ml of water, and extracted with chloroform. The chloroform was removed to give 0.83 g (67%) of IV with mp 221-222° (from methanol). Found,%: C 56.1; H 5.9. $C_{21}H_{28}N_2O_7S$. Calculated,%: C 55.7; H 6.2.

The PMR 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 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.

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