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CONDENSATION OF 4-BENZAMIDO-3-OXOTHIOPHAN WITH ACROLEIN. SYNTHESIS OF 1-BENZAMIDO-4-HYDROXY-6-THIABICYCLO[3.2.1]-OCTAN-8-ONE AND 6-BENZOYL-7-HYDROXY-2-THIA-6-AZASPIRO[4.4]-NONAN-4-ONE

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It is shown that acrolein adds to the 4 position (rather than to the 2 position) of 4-benzamido-3-oxothiophan under the influence of catalysts with basic character; the aldehyde group of the intermediate compound reacts with the amino group (if the reaction is carried out in chloroform) to give 6-benzoyl-7-hydroxy-2-thia-6-azaspiro[4.4]nonan-4-one or (if the reaction is carried out in a mixture of alcohol and chloroform) 1-benzamido-4-hydroxy-6-thiabicyclo-[3.2.1]octan-8-one as a result of intramolecular aldol condensation.

We have previously shown [1] that substituted 3-oxothiophans are capable of undergoing the Michael reaction with α,β-unsaturated ketones. In the present research we investigated the reaction of 4-benzamido-3-oxothiophan (I) with acrolein. Electrophilic attack on acylaminooxothiophan I by the β-carbon atom of the double bond of the unsaturated aldehyde may take place at the carbon atoms in both the 2 and 4 positions of the thiophan ring.

The reaction of acrolein with acylaminooxothiophan I was carried out in chloroform or in a mixture of chloroform and methanol in the presence of a basic catalyst (piperidine, diethylamine, sodium methoxide, or potassium hydroxide) at 0 to −50°C. It was established that the addition may proceed in different directions depending on the composition of the medium.

1-Benzamido-4-hydroxy-6-thiabicyclo[3.2.1]octan-8-one (III) was isolated in the condensation of I with acrolein in a mixture of chloroform and methanol. The characteristic bands of an amide [3400 (ν_{NH}) and 1600 cm^{-1} (ν_{CO})] and of an oxo group (1740 cm^{-1}), as well as the band of a free hydroxyl group (3580 cm^{-1}), are observed in the IR spectrum of III. The formation of oxime IV also constitutes evidence in favor of the presence

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TABLE 1. PMR Spectra of III–V

Compound	Temp. °C	δ, ppm					J, Hz			
		2-H, 3-H	4-H	5-H	7-H	8-H	J_{34}	J_{45}	J_{58}	J_{77}
III	90	1,10—2,90 m	4,25m	3,73d	3,39 d; 3,16d		6,1; 9,2	2,9		9,8
IV	85	1,70—3,20 m	4,21m	4,93 d	3,69 d; 3,11d		6,0; 8,8	2,6		10,5
V	70	1,70—2,60 m	5,24m	3,68 dd	3,43 d; 3,29d	5,90 d	5,2; 9,2	2,8	5,3	11,7

TABLE 2. ^{13}C NMR Spectra of V and VII

Compound	δ, ppm						
	$C_{(1)}$	$C_{(3)}$	$C_{(4)}$, $C_{(8)}$	$C_{(5)}$	$C_{(7)}$	COR	$COCH_3$
V	60,5 s		69,6d, 77,6d	46,1d		170,7 s 169,8 s 167,6 s	20,8 q 20,6 q
VII	71,41s 72,0 s	37,5 t 35,9 t	85,0 s		84,8 d 83,4 d	169,3 s 169,7 s	

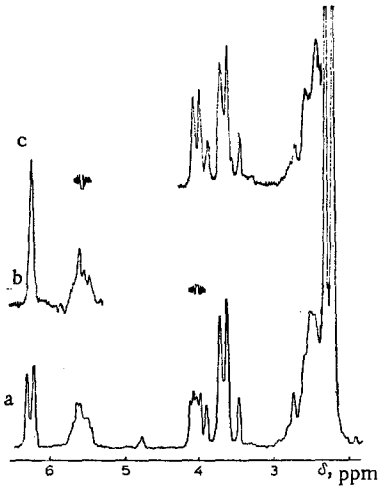
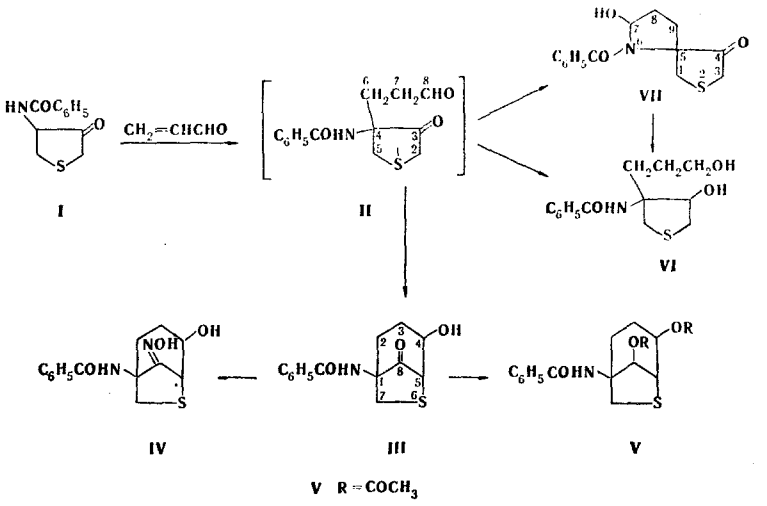


Fig. 1. PMR spectra of V in deuteropyridine: a) monoresonance; b) double resonance with irradiation of the 5-H nucleus; c) double resonance with irradiation of the 4-H nucleus.

of an oxo group. The reduction of III with sodium borohydride and subsequent acetylation give diacetate V, and this confirms the presence of a hydroxy group in III and IV.



In contrast to starting acylaminooxothiophan I, the PMR spectra of III-V do not contain the signal of a proton attached to the $C_{(1)}$ atom to which the benzamido group is also attached. The geminal protons of the 7-CH_2 group of III therefore form an AB system (J = 9.8 Hz) rather than the AB portion of an ABX system; the signal of the proton attached to the nitrogen atom of the benzamido group gives a singlet (a doublet in the case of I). The signal of the $C_{(1)}$ atom in the ^{13}C NMR spectrum of diacetate V without suppression of the spin-spin coupling at the frequency of the protons appears in the form of a singlet at δ 60.5 ppm. Consequently, there is a quaternary carbon atom in the 1 position of III-V.

Signals of only three protons attached to the α-carbon atoms of the thiophan ring (7-H, 7'-H, 5-H; Table 1) are observed in the PMR spectra of III-V, whereas there are four protons of this type in the spectra of acylaminooxothiophan I. A change in the chemical shift of the proton attached to the tertiary $C_{(5)}$ atom of oxime IV as compared with ketone III (a 1.2 ppm shift to weak field is characteristic for replacement of the latter with the given atom of the C=O group by a C=NOH group.

The signal of the 5-H proton in the PMR spectra of III and IV is a doublet (J_{45} = 2.9 and 2.6 Hz, respectively), whereas it is a doublet of doublets (J_{58} = 5.3 Hz, J_{45} = 2.8 Hz) in the spectrum of V. Consequently, the 4-CH methylidyne group is attached to the $C_{(5)}$ atom in these compounds (Table 1). The 4-CH group is spin-spin coupled with one of the two methylene groups, the complex signal of which is observed at 1.10-3.20 ppm. All of these assignments were confirmed by means of double resonance (Fig. 1). A new signal of a proton in the 8 position (5.90 ppm) appears in the spectrum of diacetate V.

A molecular ion with m/e 413 (relative intensity 5%) is observed in the mass spectrum of V at an ionizing-electron energy of 75 eV; its intensity increases to 60% at an electron energy of 16 eV. The amide substituent is detached from the molecular ion during fragmentation (at 75 eV), and $C_6H_5^+$ ion peaks with m/e 77 (51%), $C_6H_5CO^+$ ion peaks with m/e 105 (100%), and $H_2NC(OH)C_6H_5$ ion peaks with m/e 122 (25%) are formed; a fragment of the bicyclic portion with m/e 241 (14.5%) appears at an electron energy of 16 eV.

It follows from the data presented above that acrolein is attached by means of the β-carbon atom to the tertiary $C_{(4)}$ atom of acylaminooxothiophan I. Addition product II, which we were unable to isolate, is evidently an intermediate. However, if the condensation of oxothiophan I with acrolein is carried out at −10°C in chloroform-methanol and the reaction mixture is then reduced with sodium borohydride, 4-benzamide-4-(3'-oxopropyl)-3-oxothiophan (VI) is obtained in 50% yield. It is possible that this compound is formed as a result of reduction of intermediate II.

The IR spectrum of VI contains characteristic bands of amide stretching vibrations (ν_{NH} 3430 cm^{-1} and ν_{CO} 1660 cm^{-1}), of a free OH group (3620 cm^{-1}), of a bonded hydroxy group (3550 cm^{-1}), and a broad band of an intramolecular hydrogen bond at 3150 cm^{-1} (this band is retained when the solution is diluted to a great degree).

Neither the PMR spectrum of dihydroxy derivatives VI nor the PMR spectra of III-V (Table 1) contain a signal of a 4-H proton, and the signal of the proton attached to the nitrogen atom is a singlet (δ 8.64 ppm at 34°C). Signals of geminal protons of two α-methylene groups are observed in the spectrum; the 2 position of the thiophan ring consequently remains unsubstituted. One of these methylene groups (2-CH_2) is spin-spin coupled with the 3-H proton (δ 5.36 ppm), as confirmed by means of double resonance. A triplet of methylene protons of the CH_2OH group (δ 3.91 ppm) and a complex signal of two other side-chain methylene groups (1.68-3.05 ppm) are also observed in the spectrum. Thus there is a hydroxypropyl group attached to $C_{(4)}$ in VI.

The structure of VI is also confirmed by its mass spectrum. A low-intensity molecular ion with m/e 281 (3%) and $[M-1]^+$ ion peaks with m/e 280 (5.8%) and $[M-2]^+$ ion peaks with m/e 279 (30.5%) are observed during its fragmentation (16 eV). This sort of fragmentation is characteristic for primary alcohols [2]. No molecular ion is present at an electron energy of 75 eV, and the ion peaks with m/e 280 (1.2%) and 279 (9.3%) have low intensities. The $[M-31,-18]^+$ ion peak with m/e 232 (9.8%) corresponds to detachment of a hydroxymethyl (CH_2OH) radical and a water molecule from M^+, which indicates the presence in VI of two hydroxy groups. The magnitude of this peak decreases to 4.2% at 75 eV. The $[M-121]^+$ ion peak with m/e 160 (100%) at 16 eV corresponds to the elimination of a benzamido group from the molecular ion; its intensity decreases to 27.5% at 75 eV. The ion peaks with m/e 105 (21.7%) and 122 (75.2%) at 16 eV and with m/e 105 (100%) and 122 (35.1%) at 75 eV correspond to $C_6H_5CO^+$ and $[H_3NCOC_6H_5]^+$ fragments.

The reaction of acylaminooxothiophan I with acrolein in chloroform alone but in the presence of the same basic catalysts (piperidine, diethylamine, sodium methoxide, and potassium hydroxide) under the same temperature conditions (0 and −50°C) and for the same length of time proceeds in a different direction to give a spiro compound – 6-benzoyl-7-hydroxy-2-thia-6-azaspiro[4.4]nonan-4-one (VII). Absorption bands of an OH

group (3620 cm^{-1}) and an oxo group (1740 cm^{-1}) and an amide ν_{CO} band are observed in its IR spectrum, but there is no characteristic band of stretching vibrations of the NH group.

The signals of many protons and carbon atoms in the ^1H and ^{13}C NMR spectra of spiro compound VII are doubled (see the experimental section and Table 2), and this is evidently associated with the presence of two stereoisomers (VIIa and VIIb). The $C_{(5)}$ atom of the thiophan ring of VII is similar to the quaternary $C_{(1)}$ atom of III-V with respect to its chemical environment. The singlets (δ 71.4 and 72.0 ppm) in the ^{13}C NMR spectrum without suppression of the spin–spin coupling at the frequency of the protons belong to the $C_{(5)}$ atoms of diastereomers VIIa and VIIb. Singlets of four geminal protons attached to α-C are observed in the PMR spectrum, whereas in the ^{13}C NMR spectrum the $C_{(1)}$ and $C_{(3)}$ atoms give triplets (Table 2). In contrast to III-V, the PMR spectrum of spiro compound VII does not contain the signal of a proton attached to the nitrogen atom but does contain signals of a $CH_2CH_2CH(OH)$ fragment ($\delta_{CH_2CH_2}$ 1.80-2.70 ppm and $\delta_{7\text{-}H}$ 5.87 and 5.51 ppm).

The mass spectrum of spiro compound VII at an ionizing-electron energy of 75 eV does not contain a molecular-ion peak with m/e 277; at 16 eV the intensity of the molecular-ion peak is 6%. The absence of a molecular ion or the presence of a low-intensity molecular ion is characteristic for 3,4-disubstituted thiophans [3]. An $[M-18]^+$ ion with m/e 259 (17%), the intensity of which increases to 100% at 16 eV, is formed during the fragmentation (at 75 eV) as a consequence of detachment of water from the molecular ion. The formation of ions with m/e 77 (49%) and 105 (100%) at 75 eV corresponds to $C_6H_5^+$ and $C_6H_5CO^+$ fragments. The mass spectrum of spiro compound VII does not contain an ion peak with m/e 122, which could have been formed by detachment of a benzamido group from M^+; the presence of this ion is characteristic in the fragmentation of III-VI.

All of the material set forth above confirms a spiro structure for VII. Compound VI was obtained by reduction of VII with sodium borohydride in methanol. It is known that α-hydroxy-N-acylpyrrolidones are capable of tautomerism and may exist in the open form in protic media [4, 5]. The reduction of the aldehyde group that is formed when the pyrrolidone ring opens to a hydroxymethyl group converts spiro compound VII to VI.

Thus when there are two reaction centers in the α,β-unsaturated aldehyde and three in the 4-benzamido-3-oxothiophan (I) (the carbon atoms in the 2 and 4 positions and the acylamino group), the β-carbon atom of acrolein and the tertiary $C_{(4)}$ atom of oxothiophan I, which bears the acylamino group, display the greatest reactivity.

Considering the results of the present research it seems more likely that in the reaction of methyl vinyl ketone with 4-benzamido-3-oxothiophan the ketone adds to the 4 position rather than to the 2 position, as assumed in [1].

EXPERIMENTAL

The NMR spectra of solutions of the compounds in deuteropyridine were recorded with Hitachi R-20A and Varian XL-100 spectrometers with tetramethylsilane as the internal standard. The mass spectra were obtained with a JMS-01-JC-2 high-resoltuion spectrometer with direct introduction of the samples into the ion source; the temperature of the sample support was varied from 60 to 80°C, and the temperature of the ionization chamber ranged from 120 to 140°C. The IR spectra of solutions of the compounds in chloroform were recorded with UR-10 and Perkin–Elmer spectrometers.

1-Benzamido-4-hydroxy-6-thiabicyclo[3.2.1]octan-8-one (III). A solution of 3 ml (45 mmole) of acrolein in 10 ml of chloroform was added at −10°C to a suspension of 10 g (46 mmole) of 4-benzamido-3-oxothiophan (I) in 30 ml of methanol, 20 ml of chloroform, and 1 ml of triethylamine, and the mixture was stirred at 0°C for 1 h and at 30-40°C for 3 h. The precipitate was then removed by filtration to give 3 g (24%) of a product with mp 163-164°C (from alcohol). Found: C 60.3; H 5.4; N 5.0%. $C_{14}H_{15}NO_3S$. Calculated: C 60.7; H 5.4; N 5.0%.

1-Benzamido-4-hydroxy-8-oximino-6-thiabicyclo[3.2.1]octane (IV). A 0.25-g (3.4 mmole) sample of hydroxylamine hydrochloride was added to a solution of 0.5 g (1.7 mmole) of III in 3 ml of pyridine, and the mixture was maintained at 30°C for 24 h. The pyridine was then removed in vacuo, and the residue was dissolved in chloroform. The chloroform solution was washed with 2.5 N hydrochloric acid and water, dried with magnesium sulfate, and concentrated. Methanol was added to the residue, and the mixture was allowed to stand at 0-3°C for 12 h. The resulting precipitate was washed with ether to give 0.3 g (57%) of a product with mp 186-187°C (from methanol). Found: N 9.8%. $C_{14}H_{16}N_2O_3S$. Calculated: N 9.6%.

1-Benzamido-4,8-diacetoxy-6-thiabicyclo[3.2.1]octane (V). A 0.4-g (11 mmole) sample of sodium borohydride was added at 0°C to a suspension of 3 g (11 mmole) of III in 30 ml of methanol, and the mixture was

stirred at 18-20°C for 2 h. Acetyl chloride (10 ml) and 5 ml of acetic anhydride were added to the residue at 0°C, and the mixture was maintained at 30°C for 1 h. It was then concentrated in vacuo, and the residue was dissolved in chloroform. The chloroform solution was washed with water, and the chloroform was removed in vacuo. A mixture of ether and alcohol (1:1) was added to the residue, and the mixture was maintained at 0 to −3°C for 16-18 h. The resulting precipitate was separated to give 2.4 g (63%) of a product with mp 156-157°C (from alcohol). Found: C 59.5; H 5.8; N 3.6%. $C_{18}H_{21}NO_5S$. Calculated: C 59.5; H 5.8; N 3.9%.

6-Benzoyl-7-hydroxy-2-thia-6-azaspiro[4.4]nonan-4-one (VII). A solution of 1.5 ml (22 mmole) of acrolein in 5 ml of chloroform was added at −10°C to a suspension of 5 g (22 mmole) of I in 30 ml of chloroform and 0.5 ml of triethylamine, and the mixture was stirred at 0°C for 1 h and at 30-40°C for 3 h. It was then concentrated to half its original volume, and the concentrate was maintained at 0 to −3°C for 16-18 h. The resulting precipitate was separated to give 2.6 g (42%) of a product with mp 168-170°C (from acetone). PMR spectrum of isomer VIIa: δ 3.86 and 3.37 (d, J = 17.0 Hz, 1- or 3-CH_2), 4.21 and 3.03 (d, J = 10.9 Hz, 3- or 1-CH_2), and 5.60 ppm (m, J_{78} = 1.2 Hz, $J_{78'}$ = 3.5 Hz, 7-H). PMR spectrum of isomer VIIb: δ 3.62 and 2.87 (d, J = 14.9 Hz, 1- or 3-CH_2), 3.56 and 3.16 (d, J = 11.3 Hz, 3- or 1-CH_2), and 5.32-5.50 ppm (m, 7-H). Found: C 60.4; H 5.4; N 4.6%. $C_{14}H_{19}NO_3S$. Calculated: C 60.7; H 5.4; N 5.0%.

4-Benzamido-4-(3-hydroxypropyl)-3-hydroxythiophan (VI). A) A mixture of 10 ml of chloroform and 3 ml (45 mmole) of acrolein was added at −10°C to a suspension of 10 g (45 mmole) of I in 20 ml of methanol, 3 ml of chloroform, and 1 ml of triethylamine, and the mixture was stirred at 0°C for 2 h. Methanol (40 ml) was then added, and the resulting mixture was treated at 0°C with 3.5 g (93 mmole) of sodium borohydride and stirred at 18-20°C for 1 h. It was then acidified to pH 1-2 with 2.5 N hydrochloric acid and extracted with chloroform. The solvent was removed from the extract in vacuo, and a mixture of ethyl acetate, petroleum ether, and ether (1:1:1) was added to the residue. The mixture was maintained at 0°C for 16-18 h, and the resulting precipitate was separated to give 6.3 g (50%) of a product with mp 150-151°C (from ethyl acetate). PMR spectrum: δ 3.36 (m, $J_{22'} = J_{23}$ = 10.7 Hz, $J_{2'3}$ = 4.6 Hz, 2-H), 3.02 (m, $J_{2'3}$ = 3.9 Hz, 2'-H), 5.36 (m, 3-H), 3.60 and 3.32 (d, $J_{55'}$ = 10.3 Hz, 5-CH_2), 3.91 (t, J = 12 Hz, 8-CH_2O), and 7.81 ppm (60°C) (s, NH). Found: C 59.8; H 6.7; N 4.7%. $C_{14}H_{19}NO_3S$. Calculated: C 59.7; H 6.8; N 5.0%.

B) A 0.5-g (140 mmole) sample of sodium borohydride was added at 0°C to a suspension of 1.5 g (54 mmole) of VII in 15 ml of methanol, and the mixture was stirred at 18-20°C for 1 h. It was then acidified to pH 1-2 with 2.5 N hydrochloric acid and extracted with chloroform. The chloroform was removed, and a mixture of acetone and ether (1:1) was added to the residue. The mixture was maintained at 0°C for 16-18 h, and the precipitate was removed by filtration to give 1.2 g (80%) of VI with mp 150-151°C (from ethyl acetate). According to its PMR spectrum, the product was identical to a sample obtained by method a; no melting-point depression was observed for a mixture of the two samples.

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