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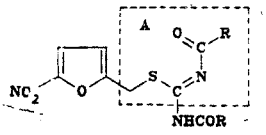
4-ACETYL-1-(R-BENZYLIDENE)-3-(5-NITRO-2-FURFURYL)THIOSEMICARBAZIDES — CARRIERS OF SYNTHONES FOR OBTAINING THIAZOLE AND TRIAZOLE RINGS

G. D. Krapivin, E. B. Usova, and V. G. Kul'nevich

UDC 547.497.1'722: 543.422'51

The corresponding thiosemicarbazonium salts, which form 4-acetyl- and 2,4-diacetyl-1-benzylidene-3-(5-nitro-2-furfuryl)thiosemicarbazides with acetic anhydride, were obtained by the reaction of 5-nitrofurfuryl bromide with 1-benzylidenethiosemicarbazides. Under the influence of bases the monoacetylated derivatives undergo cyclization to the corresponding 2-benzylidenehydrazino-5-(5-nitro-2-furyl)thiazoles. Intramolecular cyclization of the monoacetylated products to 3-methyl-5-[(5-nitro-2-furfuryl)thio]-1,2,4-triazole, which is accompanied by the elimination of the corresponding benzaldehyde, occurs in the presence of hydrochloric acid.

It has been previously established [1] that S-(5-nitro-2-furfuryl)thiuronium bromide reacts with carboxylic acid anhydrides to give substituted 5-(5-nitro-2-furyl)thiazoles. An analysis of the reaction intermediates showed that the key intermediates are 1,3-diacyl-2-(5-nitro-2-furfuryl)thioureas that contain structural fragment (synthone) A, the intramolecular cyclization of which leads to the formation of a thiazole ring.



The products of the reaction of thiosemicarbazonium salts with carboxylic acid anhydrides should also have the same structural fragments. We therefore investigated the possibility of the use of S-(5-nitro-2-furfuryl) derivatives of thiosemicarbazide for the synthesis of 2-hydrazino-5-(5-nitro-2-furyl)thiazoles.

Refluxing the nitrofurfuryl bromide with an equimolar amount of the benzylidenethiosemicarbazide in alcohol leads to thiosemicarbazonium salts Ia-e. A characteristic band of NH stretching vibrations at 3300 cm^{-1} and its intense overtone at 1650 cm^{-1} are present in the IR spectra of salts I (Table 1).

Whereas S-(5-nitro-2-furfuryl)thiuronium bromide reacts with carboxylic acid anhydrides in one step to give 5-(5-nitro-2-furyl)thiazole derivatives [1, 2], thiosemicarbazonium salts I give complex mixtures of products under the same conditions. Colorless substances, the results of elemental analysis and the spectral characteristics of which correspond to monoacetylation products II or III, are obtained when the reaction is carried out in the presence

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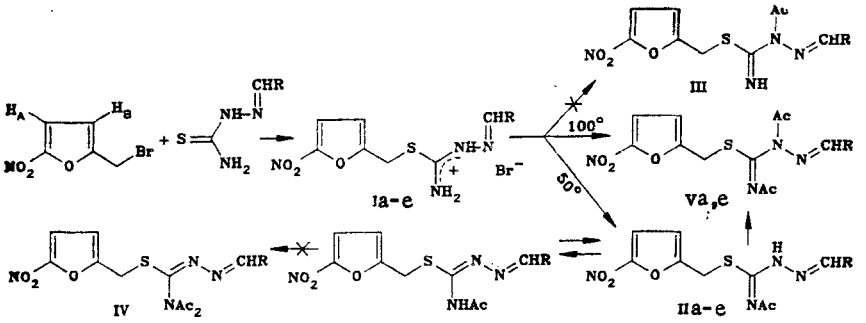
TABLE 1. Characteristics of the Synthesized Compounds

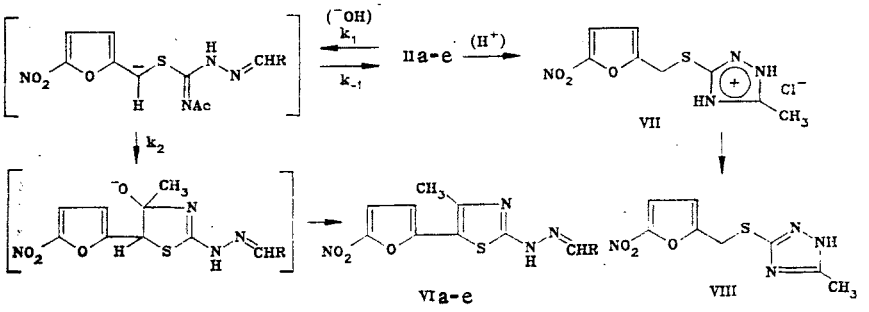
Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calculated, %			M^+	Yield, %
				C	H	S(N)		C	H	S(N)		
Ia	165	207 (4,37), 230 (4,21), 317 (4,49)	1650, 3300	40,9	3,0	(14,3)	$C_{13}H_{13}BrN_4O_3S$	40,5	3,4	(14,5)	—	80
Ib	162	208 (4,33), 226 (4,27), 320 (4,53)	1650, 3300	37,7	2,4	(13,7)	$C_{13}H_{12}BrClN_4O_3S$	37,2	2,9	(13,4)	—	70
Ic	178	207 (4,36), 240 (4,17), 350 (4,36)	1650, 3300	35,8	2,3	(16,6)	$C_{13}H_{12}BrN_5O_5S$	36,3	2,8	(16,3)	—	53
Id	176	210 (4,39), 320 (4,45)	1650, 3300	36,8	3,0	(16,6)	$C_{13}H_{12}BrN_5O_5S$	36,3	2,8	(16,3)	—	50
Ie	160	204 (4,37), 324 (4,53)	1650, 3300	40,9	3,1	(13,9)	$C_{14}H_{15}BrN_4O_4S$	40,5	3,6	(13,5)	—	88
IIa	112—113	225 (4,24), 313 (4,54)	1713, 3330	52,0	4,0	9,3	$C_{15}H_{14}N_4O_4S$	51,7	4,0	9,6	346	80
IIb	147—148	229 (4,22), 320 (4,52)	1710, 3330	47,8	3,1	8,9	$C_{15}H_{13}ClN_4O_4S$	47,3	3,4	8,4	380	67
IIc	195—196	213 (4,19), 234 (4,05), 340 (4,39)	1715, 3330	46,6	3,8	7,6	$C_{15}H_{13}N_5O_6S$	46,0	3,3	8,2	391	60
IIe	185—187	217 (4,28), 277 (4,15), 316 (4,47)	1720, 3330	46,4	3,7	7,6	$C_{15}H_{13}N_5O_6S$	46,0	3,3	8,2	391	64
IIe	161—162	229 (4,30), 323 (4,65)	1710, 3330	51,5	4,7	8,1	$C_{16}H_{16}N_4O_5S$	51,1	4,3	8,5	376	69
Va	164—165	221 (4,29), 294 (4,22), 314 (4,16)	1665, 1690	52,2	3,9	8,5	$C_{17}H_{16}N_4O_5S$	52,5	4,1	8,2	382	70
Ve	132—133	231 (4,35), 294 (4,14), 314 (4,05)	1673, 1703	51,2	3,9	7,9	$C_{18}H_{18}N_4O_6S$	51,7	4,3	7,6	418	63
VIa	243—245	243 (4,17), 265 (4,17), 347 (4,13), 450 (4,32)		54,4	3,2	9,4	$C_{15}H_{12}N_4O_3S$	54,8	3,7	9,8	328	85
VIb	225—226	243 (4,19), 268 (4,40), 350 (4,29), 450 (4,47)		49,3	2,8	9,1	$C_{15}H_{11}ClN_4O_3S$	49,6	3,0	8,8	362	55
VIc	250	243 (4,13), 279 (4,18), 294 (4,18), 456 (4,41)		48,7	2,6	8,2	$C_{15}H_{11}N_5O_5S$	48,3	2,9	8,6	373	79
VId	240	225 (4,30), 255 (4,31), 356 (4,07), 448 (4,30)		48,8	2,7	8,2	$C_{15}H_{11}N_5O_5S$	48,3	2,9	8,6	373	87
VIe	180—182	225 (4,16), 274 (4,25), 347 (4,24), 460 (4,25)		53,2	3,7	8,5	$C_{16}H_{14}N_4O_4S$	53,6	3,9	8,9	358	50
VII	129—132	210 (4,04), 232 (3,72), 320 (4,04)		34,3	3,8	11,1	$C_8H_9ClN_4O_3S$	34,7	3,3	11,5	—	63
VIII	144—145	210 (4,05), 232 (3,73), 322 (4,06)		39,6	3,8	13,2	$C_8H_8N_4O_3S$	40,0	3,4	13,0	240	97

of an equimolar amount of sodium acetate at 50°C. Diacetylation products, to which structures IV or V may correspond, were isolated when the reaction mixtures were heated to 100°C.



a R=C_6H_5; b R=C_6H_4Cl-4; c R=$C_6H_4NO_2$-4; d R=$C_6H_4NO_2$-3; e R=$C_6H_4OCH_3$-4

It is not possible to establish the precise location of the acetyl group in the monoacylation products by means of IR and PMR spectroscopy. However, the ability of the monoacetylated derivatives in the presence of bases to undergo conversion to 2-hydrazinothiazoles VI and to form triazole hydrochloride VII in the presence of HCl constitutes unequivocal evidence in favor of structure II.



The acetylation of II leads to diacetylation products that are identical to those isolated from the reaction mixtures heated to 100°C. The IR spectra of the diacetyl derivatives contain two bands of stretching vibrations of carbonyl groups at 1665-1673 and 1690-1703 cm^{-1}, and the PMR spectra contain two singlets of protons of two nonequivalent acetyl groups (Tables 1 and 2). Consequently, structure V can be assigned to the diacetylation products, and it may be assumed that the tautomeric isothiosemicarbazide form is the preponderant form for II.

It was demonstrated above that II are readily converted to the corresponding thiazoles VI. The formation of a thiazole ring occurs owing to the high CH acidity of the methylene link and proceeds through a number of successive steps. The kinetics of the cyclization of IIa to thiazole VIa in 95% ethanol are described by a first-order equation with $K = 7.3 \cdot 10^{-4}$ sec^{-1} (60.3°C, starting concentration $3.2 \cdot 10^{-5}$ M). The coincidence of the time and concentration orders of the reaction constitutes evidence that the intermediates do not accumulate during the process and do not affect the rates of the individual steps. In view of the fact that the second step in the cyclization is monomolecular, kinetic studies do not give an unequivocal answer regarding the rate-determining step in the formation of the thiazole ring.

Carrying out the cyclization in the ampul of a PMR spectrometer in a mixture of C_2D_5OD and NaOD showed that complete deuteration of the methylene link of IIa occurs after 3-5 min (50°C); the formation of cyclization products is not observed. Consequently, reaction rates k_1 and k_{-1} are much greater than k_2, i.e., the rate-determining step of the process is intramolecular attack on the carbon atom of the amide carbonyl group by the carbanion.

The activation parameters of the cyclization process ($\Delta G^{\neq}$ = 102 ± 13 kJ/mole, $A = 5 \cdot 10^9$ sec^{-1}, $\Delta S_a = -56$ $J \cdot mole^{-1} \cdot deg^{-1}$) show that the transition state is distinguished by high polarity and a high degree of orderliness and is situated on the reaction coordinate near the cyclization product.

Hydrazinothiazoles VIa-e are brightly colored compounds, the electronic absorption spectra of which contain four maxima (Table 1). Substituent R affects only the position of the

TABLE 2. PMR Spectra of the Synthesized Compounds

Compound*	Chemical shift, ppm (J, Hz)					
	$H_{(A)}$	$H_{(B)}$	J_{AB}	CH=N	CH_2	other signals
IIa	7,20	6,45	3,7	8,33	4,20	2,23 (3H, s, $COCH_3$); 7,1—7,7 (5H, m C_6H_5); 9,39 (1H, br.s., NH)
IIb	7,24	6,47	3,7	8,36	4,22	2,25 (3H, s, $COCH_3$); 7,10 (2H, d, 8,0) and 7,24 (2H, d 8,0); 9,40 (1H, br. s, NH)
IIc	7,25	6,46	3,7	8,48	4,21	2,25 (3H, s, $COCH_3$); 7,15 (2H, d 9,3) and 7,45 (2H, d, 9,3); 9,42 (1H, br.s NH)
IId	7,23	6,45	3,7	8,55	4,23	2,23 (3H, s, $COCH_3$); 7,0—7,5 (5H, m, C_6H_4—NO_2-3); 9,45 (1H, br. s, NH)
IIe	7,22	6,45	3,7	8,25	4,23	2,25 (1H, s, $COCH_3$); 3,82 (3H, s, OCH_3); 7,0—7,3 (4H, m, $C_6H_4OCH_3$); 9,38 (1H, br. s NH)
Va	7,18	6,53	4,0	6,88	4,25	1,86 (3H, s, $COCH_3$); 2,13 (3H, s, $COCH_3$); 7,0—7,4 (5H, m, C_6H_5)
Ve	7,18	6,49	4,0	6,95	4,23	1,88 (3H, s, $COCH_3$); 2,20 (3H, s, $COCH_3$); 3,85 (3H, s, CH_3O); 7,0—7,2 (4H, m, $C_6H_4OCH_3$)
VIa	7,35	6,45	4,0	8,00		2,24 (3H, s, CH_3); 7,0—7,4 (5H, m, C_6H_5)
VIb	7,37	6,42	4,0	8,06		2,20 (3H, s, CH_3); 7,12 (2H, d 8,2) and 7,25 (2H, d, 8,2)
VIc	7,35	6,44	4,0	8,15		2,25 (3H, s, CH_3); 7,18 (2H, d 9,7) and 7,62 (2H, d 9,7)
VId	7,36	6,42	4,0	8,17		2,25 (3H, s, CH_3); 7,0—7,4 (4H, m C_6H_4—NO_2-3)
VIe	7,35	6,44	4,0	7,96		2,20 (3H, s, CH_3); 3,88 (3H, s, OCH_3); 6,9—7,2 (4H, m $C_6H_4OCH_3$)
VII	7,21	6,40	4,0		4,45	2,30 (3H, s, CH_3)
VIII	7,25	6,44	4,0		4,48	2,32 (3H, s, CH_3)

*The solvents used were $CDCl_3$ for IIa-e and Va, e and CF_3COOH for VIa-e, VII, and VIII.

absorption band at 255-275 nm, which corresponds to a $\pi \rightarrow \pi^*$ transition localized on the arylazomethine fragment of the molecule. The remaining three absorption bands characterize the electron transitions in the 2-amino-5-(5-nitro-2-furyl)thiazole fragment. The position of the long-wave band depends only slightly on the nature of substituent R in the benzene ring and is due to excitation with charge transfer from the amino nitrogen atom to the nitro group through the system of conjugated bonds of the thiazole and furan rings. A similar transition in the 2-amino-5-(5-nitro-2-furyl)thiazole molecule is characterized by absorption with a maximum at 440 nm [2].

The PMR spectra of 2-hydrazinothiazoles VI (Table 2) contain signals of methyl, furan, phenyl, and azomethine protons; the signal of protons of a methylene link that is characteristic for II is absent.

The mass spectra of II, V, and VI contain molecular-ion peaks corresponding to the calculated molecular masses (Table 1). The ions with masses of (M − 42) and (M − 2·42) in the spectra of V constitute evidence for the presence of two acetyl groups. (An analysis of the mass spectra of the synthesized furylthiazoles and intermediates will be the subject of a separate publication.)

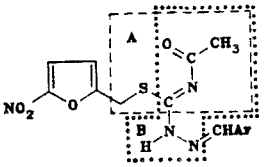
In acidic media all IIa-e give the same salt product VII; in addition to the formation of VII, the accumulation of equimolar amounts of the corresponding benzaldehydes is observed.

Hydrochloride VII – a colorless crystalline substance that decomposes on heating – readily splits out HCl with the formation of triazole VIII on treatment with water even in the absence of bases. Triazole VIII is more conveniently isolated from an aqueous alcohol medium by the addition of an equimolar amount of NaOH.

Solutions of hydrochloride VII and triazole VIII in trifluoroacetic acid have virtually identical PMR spectra (Table 1): two singlets of protons of methylene and methyl groups and two doublets of β protons of the furan ring.

The molecular ion of triazole VIII is quite stable (W_M = 11.6), its peak has the maximum intensity in the mass spectrum, and its fragmentation is typical for many 5-nitrofurfuryl sulfides [3]. The mass spectrum of hydrochloride VII is identical to the spectrum of triazole VIII.

In conclusion, let us note the following: 4-acetyl-3-(5-nitro-2-furfuryl)thiosemicarbazides II, in contrast to 1,3-diacyl-2-(5-nitro-2-furfuryl)isothiourea [1], contain two synthones A and B, which, depending on the conditions, ensure the formation of either a thiazole (synthone A) or triazole (synthone B) ring.



Synthone B is well known in the chemistry of amidrazones: acylamidrazones are cyclized (to triazoles) so readily that they cannot be isolated during the synthesis [4, 5].

The formation of a thiazole ring due to synthone A (a one-component synthesis of the [d(5)] type in the Schroth classification [6]) is a new variant of the formation of a thiazole ring.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer, which was also used for the kinetic studies. The IR spectra of suspensions in mineral oil were obtained with a UR-20 spectrometer. The PMR spectra were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were determined with a Varian CH-8 spectrometer with direct introduction of the samples into the ion source at 100-150°C and an ionizing voltage of 70 eV.

1-Benzylidene-3-(5-nitro-2-furfuryl)thiosemicarbazonium Bromide (Ia). A solution of 20.6 g (100 mmoles) of 5-nitrofurfuryl bromide in 20 ml of ethanol was added to a hot solution of 17.9 g (100 mmoles) of benzaldehyde thiosemicarbazone in 130 ml of ethanol. After 1 h, the solution was cooled, 500 ml of ether was added, and the resulting precipitate was recrystallized from ethanol. Salts Ib, e were similarly obtained.

1-(4-Nitrobenzylidene)-3-(5-nitro-2-furfuryl)thiosemicarbazonium Bromide (Ic). A solution of 5.87 g (26 mmoles) of 4-nitrobenzaldehyde thiosemicarbazone and 5.4 g (26 mmoles) of 5-nitrofurfuryl bromide in 100 ml of ethanol was refluxed for 3 h, after which the mixture was cooled and treated with 500-700 ml of ether, and the precipitate was recrystallized from ethanol. Salt Id was similarly obtained.

4-Acetyl-1-benzylidene-3-(5-nitro-2-furfuryl)thiosemicarbazide (IIa). A mixture of 15.4 g (40 mmoles) of salt Ia, 3.28 g (40 mmoles) of sodium acetate, 100 ml of acetic anhydride, and 100 ml of water was stirred without external heating for 30-40 min until it became completely homogeneous (the temperature of the reaction mass increased spontaneously to 40-60°C). The solution was cooled, and the precipitated crystals were removed by filtration and purified by low-temperature crystallization from ethanol. Compounds IIb-e were similarly obtained.

2,4-Diacetyl-1-benzylidene-3-(5-nitro-2-furfuryl)thiosemicarbazide (Va). A. A mixture of 7.7 g (20 mmoles) of salt Ia and 1.64 g (20 mmoles) of sodium acetate in 100 ml of acetic anhydride was stirred for 1 h at 100°C, after which it was cooled, and a solution of 10 g of NaOH in 100 ml of water was added in such a way that the temperature of the reaction mixture did not exceed 60°C. The solution was cooled, and the resulting precipitate was washed with water and purified by low-temperature crystallization from ethanol.

B. A solution of 1.73 g (5 mmoles) of IIa in 20 ml of acetic anhydride was refluxed for 1 h. The substance was isolated and purified as described above. The yield was 1.32 g (60%). No melting-point depression was observed for a mixture of this product with Va obtained by the method presented above. The spectra of the two compounds were identical.

Compound Ve was similarly obtained.

4-Methyl-2-[(4-methoxybenzylidene)hydrazino]-5-(5-nitro-2-furyl)thiazole (VIe). A solution of 1.0 g (27 mmoles) of IIe and 0.2 g (25 mmoles) of sodium acetate in 30 ml of ethanol was refluxed for 3 h, after which it was cooled to 0°C, and the precipitate was removed by filtration and recrystallized from acetic acid. Thiazoles VIa-d were similarly obtained.

3-Methyl-5-[(5-nitro-2-furfuryl)thio]-1,2,4-triazole Hydrochloride (VII). A 0.5 ml sample of concentrated HCl was added to a solution of 3.0 g (8.7 mmoles) of IIa in 40 ml of ethanol, and the mixture was refluxed for 5 min. It was then evaporated to a volume of 5 ml, and the concentrate was cooled and diluted with 15 ml of ether. The precipitate was washed with ether and air dried. Hydrochloride VII was similarly obtained from IIb-e.

3-Methyl-5-[(5-nitro-2-furfuryl)thio]-1,2,4-triazole (VIII). A 0.7 g (2.5 mmoles) sample of hydrochloride VII was added to a solution of 0.1 g (2.5 mmoles) of NaOH in 30 ml of a mixture of water and alcohol (1:1), and the mixture was stirred for 15 min. The precipitate was washed with water, dried, and recrystallized from ethyl acetate. Mass spectrum (m/z, relative intensity, %): 240 (100) M, 223 (73) (M − OH), 194 (46) (M − NO_2), 126 (32) (Fur − CH_2^+).

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SYNTHESIS OF SUBSTITUTED 1,3-THIAZINIUM PERCHLORATES

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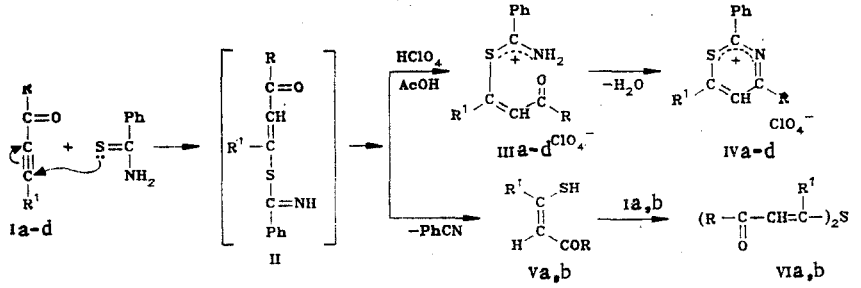
Substituted 1,3-thiazinium perchlorates were synthesized by the reaction of α-acetylenic ketones with thiobenzamide in acetic acid in the presence of perchloric acid.

It is known that the reaction of vinyl ketones with thioamides in acetic acid in the presence of perchloric acid leads to 3,6-dihydro-1,3-thiazinium perchlorates, which are dehydrogenated by trityl perchlorate to give substituted 1,3-thiazinium perchlorates [1]. Salts of this type were also obtained by the reaction of β-acylaminovinylthiocarbonyl compounds with perchloric acid in absolute ether at 20°C [2].

In the present research we studied the reaction of acylacetylenes Ia-d with thiobenzamide in the presence of perchloric acid.



I—VI a, b R=Ph; c, d R=α-C_4H_3S; a, c. R^1=H; b, d R^1=Ph

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