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CONDENSED SYSTEMS BASED ON 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLE

N. N. Kolos, V. D. Orlov,
E. K. Slobodina, E. Yu. Yur'eva,
S. P. Korshunov, and Zyong van Tué

1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazines, hydrazones, and β-thio adducts were obtained by reactions of 4-amino-3-mercapto-1,2,4-triazole with ω-bromoacetophenones, aldehydes, and α,β-unsaturated ketones. Conditions that promote the cyclocondensation of the β-thio adducts to the previously undescribed 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines were found. The chemical and spectral properties of the compounds obtained are discussed.

The aim of this research was to investigate the reactivity of 4-amino-3-mercapto-1,2,4-triazole (I) with respect to aromatic ketones and aldehydes. Only the reactions of 5-substituted I with phenacyl bromide [1] and β-bromo-γ-keto esters [2], which lead to the formation of triazolo[3,4-b]-1,3,4-thiadiazines, have been described in the literature.

The reaction of I with 4-R-ω-bromoacetophenones IIa-g proceeds without a catalyst by refluxing alcohol solutions for from 10-15 min (in the case of IIa-e) to 1-1.5 h (IIf, g). The resulting IIIa-g were identified by means of their spectral characteristics (Table 1) as 5-aryl-6H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (which is also in agreement with the results of elementary analysis for nitrogen and sulfur). Thus bands of stretching vibrations of azomethine (1582-1628 cm^{-1}) and methylene (2903-2923 cm^{-1}) groups are observed in their IR spectra. The long-wave absorption band in the UV spectra of triazolothiadiazines IIIa-f lies at 281-308 nm. It undergoes an appreciable bathochromic shift when electron-donor substituents R (IIIb, c) are introduced; this, in turn, reflects the π-deficient character of the triazole ring. (See scheme at the top of the next page.)

The development of a band at 352 nm and the pronounced high-frequency shift of the $\nu_{C=N}$ band in the spectra of IIIg (see Table 1) provide unambiguous evidence for the presence of a rather strong intramolecular hydrogen bond in its molecule. The PMR spectra of solutions of IIIa-f in $CDCl_3$ contain singlets of the protons of a methylene group and of a methylidyne proton of a triazole ring, as well as a multiplet of aromatic protons at 8.17-8.50 ppm.

The question of the manifestation of imine—enamine tautomerism often arises in the study of 1,4-thiazine derivatives [3]. From the set of spectral data obtained it follows unequivocally that IIIa-g exist exclusively in the 6H-tautomeric form; the intensity of the signal of the proton of the CH_2 group in the PMR spectra did not change even when solutions of IIIa, e were allowed to stand for 2-3 days.

A. M. Gor'kii Kharkov State University, Kharkov 310077.

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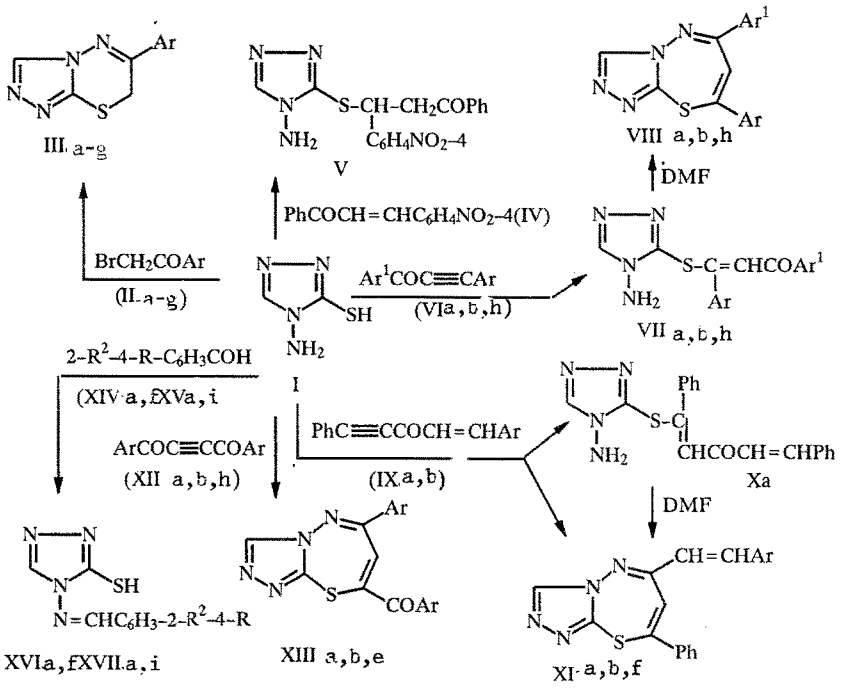


II—XVIIa R=H,b R=4-OCH_3, c R=4-OC_2H_5, d R=4-Br, e R=4-Cl, f R=4-NO_2, g R=2-OH-5-NO_2; VI—VIIIa,b R^1=H,h R=H, R^1=4-Cl; XIV, XVI a,f R^2=H; XV, XVII a R^2=OH, i R=Br, R^2=OH, Ar=C_6H_4R, Ar^1=$C_6H_4R^1$

The possibility of the oxidative dimerization of derivatives of benzo- and pyrazolothiazine when solutions of them in polar protic and aprotic solvents has been noted [4, 5]. Under similar conditions IIIa-g remain unchanged; the possible reason for this is the electron-acceptor effect of the triazole ring on the thiadiazine ring. The absence of dimerization for pyrimidothiazine derivatives also constitutes evidence in favor of this [6].

It is known [7] that chalcones react with o-aminothiophenol under conditions of catalysis by piperidine to give β-thio adducts, whereas in the presence of trace amounts of hydrochloric acid they undergo cyclization to substituted dihydrobenzothiazepines. This process has clearly expressed equilibrium character. Thus in [8] it was accomplished in one step in the case of catalysis by triethylamine; moreover, the addition of four to five drops of concentrated HCl to 10 ml of saturated alcohol solutions of dihydrobenzodiazepines leads to opening of the seven-membered ring. However, amino thiol I does not react with chalcone and substituted chalcones (4- and 4′-OCH_3, 4- and 4′-Br) in the case of either acidic or basic catalysis; in all cases the starting substances were recovered unchanged. Only 4-nitrochalcone (IV) forms β-thio adduct V with amino thiol I upon prolonged refluxing in methanol with added triethylamine, as evidenced by its spectral characteristics. The IR spectrum contains bands at 3253 and 3326 (NH_2), 1689 (C=O), and 1349 and 1553 cm^{-1} (NO_2). A quartet and an octet of protons of the CH—CH_2 fragment (an ABX system: δ = 4.32; 3.82 and 6.48 ppm; J = 9.5; 5.0 and 2.5 Hz), a broad singlet of protons of an amino group (5.8 ppm), a singlet of a methylidyne proton of a triazole ring (5.89 ppm), and a multiplet of aromatic protons at 7.51-8.50 ppm are observed in the PMR spectrum of V. The results of analysis for nitrogen and sulfur are in agreement with the calculated amounts of these elements.

These results undoubtedly reflect a decrease in the reactivity of amino thio I as compared with o-aminothiophenol. The addition of amino thiol I becomes thermodynamically justified only in the case of 4-nitrochalcone, the conjugation stabilization of the cinnamonial fragment of which is weakened as a consequence of the counterpolarization effects of the nitro group with respect to the carbonyl group.

In addition, β-thio adduct could not be cyclized by refluxing in alcohol, acetic acid, DMF, or hexametapol or by maintaining it at room temperature under conditions of acidic or basic catalysis. Consequently, even despite the hydrazine character of the amino group in the triazole ring cyclocondensation to form a dihydrothiazepine ring proved to be thermodynamically unfavorable in this case also.

In contrast to chalcones, acetylenic ketones VI, IX, and XII react readily with amino thiol I. The general principle [9] that the activity of a triple carbon—carbon bond intensified by its conjugation with a C=O group and the high

TABLE 1. Characteristics of IIIa-g

Compound	T_{mp}, °C	R_f	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	PMR spectrum, δ, ppm		Yield, %
			C=N	CH_2		6-CH_2	3-CH	
IIIa	186	0,88	1596	2905	281 (9,7)	4,05	8,63	58
IIIb	180	0,86	1596	2903	307 (17,0)	4,00	8,58	60
IIIc	183...184	0,80	1602	2917	308 (17,2)	3,99	8,59	54
IIId	203...204	0,84	1582	2923	285 (11,3)	4,03	8,60	68
IIIe	202	0,87	1582	2922	284 (11,9)	4,04	8,58	65
IIIf	281...282	0,79	1582	2923	295 (16,3)	4,46	9,19	62
IIIg**	217...218	0,83	1628	2923	280 (16,3); 352 (5,3)			58

*The spectrum of IIIf was obtained from a solution in d_6-DMSO.
**R = 2-OH.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	T_{mp}, °C (solvent)	R_f	UV spectrum, ν, cm^{-1}			IR spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Yield, % (method)
			C=O	C=N	NH_2		
V	197...198	0,20	1689	—	3226, 3253	255 (31,7)	67
VIIa	178...180 (methanol)	0,14	1642	—	3149, 3289	272 (8,0); 322 (11,0)	52
VIIb	190	0,16	1628	—	3149, 3280	274 (9,5); 330 (12,0)	62
VIIc	183...184	0,18	1638	—	3150, 3360	270 (7,2); 320 (10,8)	47
VIIIa	192 (DMF)	0,33	—	1600	—	263 (21,3)	37
VIIIb	164...166	0,36	—	1609	—	260 (19,4); 316 (18,97)	47
VIIIc	179	0,27	—	1600	—	265 (12,1)	40
Xa	164...165	0,21	1628	—	3183, 3303	270 (20,3); 345 (16,0)	35
XIa	186	0,48	—	1622	—	280 (21,3); 325 (31,0)	36 (A), 50 (B)
XIb	175...176	0,36	—	1622	—	300 (19,8); 364 (19,5)	44
XIf	193...194	0,38	—	1635	—	322 (15,0); 385 (16,0)	39
XIIIa	210...211	0,82	1628	1602	—	286 (sh); 357 (9,9)	29
XIIIb	240...242	0,84	1632	1596	—	290 (20,8); 356 (12,4)	33
XIIIc	231...232	0,83	1628	1622	—	288 (sh); 356 (10,3)	38
XVIa	177...178 (methanol)	0,47	—	1582	—	274, 330	76
XVIf	205...206	0,42	—	1582	—	269, 313, 360	57
XVIIa	232...233 (DMF)	0,35	—	1622	—	285, 335	71
XVIIi	257...258	0,31	—	1624	—	282, 337	64

*The following bands were also identified: ν_{NO_2}: 1350, 1519 (V); 1325, 1505 (XIf); 1348, 1553 cm^{-1} (XVIf); ν_{OH}: 3220 (XVIIa), 3280 cm^{-1} (XVIIi).

TABLE 3. Mass-Spectral Characteristics of VIIIh, XIIIa, b, and XVIIi

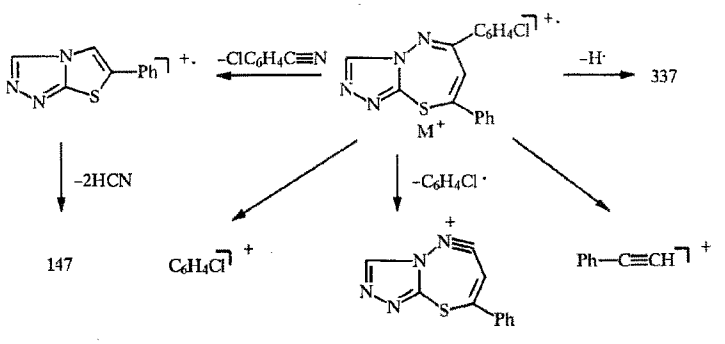
Compound	m/z (I_{rel} %)*
VIIIh	*338 (40)*▼, 337 (45)▼, 227 (10), 225 (17), 201 (100), 147 (53), 121 (48), 111 (12)▼, 102 (24), 91 (28), 75 (34), 51 (15)
XIIIa	*332 (34)*, 255 (19), 227 (24), 143 (10), 131 (17), 130 (59), 127 (24), 106 (25), 105 (100), 77 (86), 51 (33)
XIIIb	*326 (6)*, 257 (7), 135 (100), 107 (7), 92 (11), 77 (15)
XVIIi	*298 (8)*▼, 198 (28)▼, 197 (87)▼, 171 (28), 119 (12)▼, 102 (44), 101 (42), 91 (24), 79 (25), 78 (25), 62 (47)

*The molecular ions are given in italics; the ions containing ^{35}Cl and ^{79}Br are denoted by a solid triangle down (▼).

nucleophilicity of the mercapto group promote the occurrence of β-addition reactions is manifested here. This principle is confirmed by the reaction of 5-phenyl-4-amino-3-mercapto-1,2,4-triazole with α-acetylenic ketones, which leads to the formation of β adducts [10].

We obtained similar β adducts VIIa, b, h and Xa only under the condition of carrying out the reaction of amino thiol I with ketones VIa, b, h and IXa in refluxing ethanol. The spectral characteristics of VII and Xa (Table 2) and the β adducts described in [10] are similar. A doublet of ν_{NH_2} bands and a $\nu_{C=O}$ band are observed in the IR spectra of VII and Xa; retention of the chalcone π system is confirmed by the presence in the electronic spectra of long-wave absorption with λ_{max} 320-330 nm (λ_{max} of chalcone in ethanol is located at 312 nm [11]). The results of elementary analysis of β adducts VII and Xa are in agreement with the calculated values.

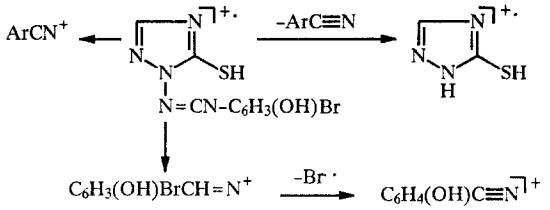
According to the data in [12], the β addition of thiols to acetylenic ketones in alcohols leads exclusively to the formation of Z isomers. In the case of adducts III and Xa this sort of structure predetermines drawing together of the carbonyl and amino groups, which, in turn, suggests the possibility of cyclocondensation with the participation of these groups. In fact, refluxing adducts VII and Xa or mixtures of amino thiol I with VIa, b, h and IXa in DMF for 2-5 h leads to the formation of derivatives of a new previously undescribed bicyclic system — 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepine (VIIIa, b, h and XIa). The characteristic bands of β adducts noted above vanish in the IR spectra of the compounds obtained, and an intense band at 1600 cm^{-1}, which was assigned to $\nu_{C=N}$, develops. Singlets of methylidyne protons of thiadiazepine (5.99 and 6.03 ppm) and triazole (8.30 and 8.32 ppm) rings, as well as the expected multiplets of the remaining protons, are observed in the PMR spectra of VIIIb and XIa (in d_6-DMSO). The UV spectra also change (see Table 2). Tying up of the polar NH_2 and C=O groups, which are inclined to specific interactions, markedly increases the R_f values of VIII and XIa as compared with the R_f values of adducts VII and Xa. The formation of a bicyclic system is confirmed unequivocally by the mass-spectral fragmentation of VIIIh (R = H, R^1 = Cl, Table 3):



Vinyl acetylenic (IXb, f) and diaryl acetylenic (XIIa, b, e) ketones behave differently on reaction with amino thiol I. 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazepine derivatives (XIb, f and XIIIa, b, e) are formed in 29-44% yields when these reaction systems are refluxed in ethanol. Thus there is direct evidence for pronounced intensification of the chemical activity of the

carbonyl groups that is observed when a second unsaturated group (C=C or C=O) is introduced into α-acetylenic ketones, which favors cyclocondensation. The spectral characteristics (IR, UV) of these compounds and VIII and XIa, obtained in DMF, are in agreement (see Table 2). The PMR spectrum of XIf contains singlet signals at 6.03 and 8.32 ppm due to resonance of the methylidyne protons of the two heterorings. Peaks of molecular ions and ions of $[M - 4\text{-}RC_6H_4CO]^+$, $[M - 4\text{-}RC_6H_4]^+$, $4\text{-}RC_6H_4CO^+$, and $4\text{-}RC_6H_4^+$ fragments (see Table 3), which confirm their structures, are observed in the mass spectra of XIIIa, b.

The hydrazine character of the 4-amino group of I is manifested in reactions with aromatic aldehydes XIV and Xv; the corresponding hydrazones XVI and XVII were obtained (see Table 2). Examples of the cyclocondensation of o-hydroxy azomethines, which leads to the formation of a seven-membered heteroring, were given in [13]. However, XV could not be cyclized under any conditions. The hydrazone structure of XVI and XVII is illustrated particularly graphically by the fragmentation of XVIIi:



EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-75 spectrometer. The UV spectra of solutions of the compounds in methanol [$(2\text{-}3)\cdot10^{-5}$ mole/liter] were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in d_6-DMSO and $CDCl_3$ were obtained with a Tesla BS-2487 spectrometer (80 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with a Varian MAT CH-6 spectrometer with direct introduction of the samples into the ion source. The individuality of the substances was monitored by TLC on Silufol UV-254 plates with elution by chloroform.

5-(4-Bromophenyl)-6H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (IIId). A mixture of 0.5 g (4 mmole) of amino thiol I and 1.11 g (4 mmole) of 4-bromo-ω-acetophenone in 40 ml of methanol was refluxed for 15-20 min, after which it was cooled, and the light-yellow crystals were removed by filtration, dried, and crystallized from methanol—DMF (4:1).

Compounds IIIa-c, e-g were similarly obtained.

1-(4-Amino-1,2,4-triazolo-3-mercapto)-1-nitrophenyl-3-phenyl-3-propanone (V). A mixture of 0.5 g (4 mmole) of amino thiol I and 1.01 g (4 mmole) of 4-nitrochalcone in 30 ml of ethanol containing 2 ml of triethylamine was refluxed for 24 h, after which the precipitate was removed by filtration and crystallized from ethanol to give 0.99 g of V.

1-(4-Amino-1,2,4-triazolo-3-mercapto)-1,3-diphenylpropen-3-one (VIIa). A 0.82-g (4 mmole) sample of diphenylpropynone was added to a solution of 0.5 g (4 mmole) of amino thiol I in 20 ml of ethanol, and the mixture was heated for 1.5 h. It was then diluted with water, and the resulting precipitate was removed by filtration to give 0.67 g of VIIa with mp 179-180°C (from methanol).

Compounds VIIb, h were similarly obtained.

5,7-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepine (VIIIa). A solution of 0.1 g (0.3 mmole) of VIIa in 5 ml of DMF was refluxed for 2 h, after which it was cooled and treated with water, and the resulting precipitate was removed by filtration to give 0.03 g of VIIIa.

Compounds VIIIb, h were similarly obtained.

1-(4-Amino-1,2,4-triazolo-3-mercapto)-1,5-diphenyl-1,3-pentadien-3-one (Xa). A 1.4-g (6 mmole) sample of 1,5-diphenyl-1-penten-4-yn-3-one was added to a solution of 0.75 g (6 mmole) of I in 25 ml of ethanol, and the mixture was heated for 1 h. The substance that precipitated from the hot solution was crystallized from ethanol to give 0.73 g of Xa.

5-Styryl-7-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiazepine (XIa). A. A solution of 0.1 g (0.28 mmole) of Xa in 5 ml of DMF was refluxed for 5 h, after which it was cooled and diluted with water, and the resulting precipitate was removed by filtration to give 0.03 g of XIa.

B. A 0.18-g (0.8 mmole) sample of 1,5-diphenyl-1-penten-4-yn-3-one was added to a solution of 0.1 g (0.8 mmole) of amino thiol I in 5 ml of DMF, and the mixture was heated for 1.5 h. It was then cooled and diluted with water, and the resulting precipitate was removed by filtration and crystallized from ethanol to give 0.18 g of XIa.

Compounds XIb, h and XIIa, b, e were similarly synthesized in ethanol; they precipitated from the hot solutions.

3-Mercapto-4-benzalamino-1,2,4-triazole (XVIa). A solution of 0.5 g (4 mmole) of amino thiol I and 0.42 g (4 mmole) of benzaldehyde in 15 ml of methanol was refluxed for 1 h, after which it was concentrated in vacuo to two thirds of its original volume and cooled. The resulting precipitate was removed by filtration to give 0.61 g of XVIa.

Compound XVIf was obtained by refluxing the reaction mixture for 5 min.

3-Mercapto-4-(2-hydroxybenzalamino)-1,2,4-triazole (XVIIa). A mixture of 0.5 g (4 mmole) of amino thiol I and 0.49 g (4 mmole) of salicylaldehyde was refluxed in 10 ml of DMF for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration to give 0.62 g of XVIIa.

Compound XVIIi was similarly synthesized.

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