SYNTHESIS AND REACTIONS OF sym-TRIAZOLO-[1,5-*a*]-sym-TRIAZINONETHIONES*

R. P. Bokaldere and A. Ya. Liepin'

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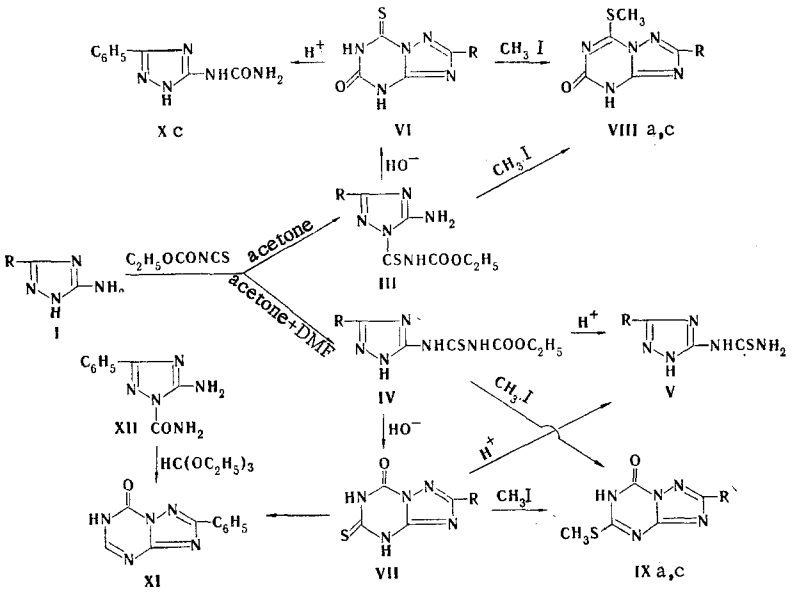
1-Carbethoxythiocarbamoyl-5-amino-1,2,4-triazoles and N-(1,2,4-triazol-5-yl)-N'-carbethoxythioureas are formed in the reaction of 5-amino-1,2,4-triazoles with carbethoxyisothiocyanate. The triazole derivatives obtained are cyclized to substituted sym-triazolo-[1,5-*a*]-sym-triazines in alkaline media.

Methods for the preparation of sym-triazolo-sym-triazines from a number of derivatives of aminotriazoles are well known [1-8]. Continuing investigations in this area [1-4], we have studied the reaction of 5-amino-1,2,4-triazoles (I) with carbethoxyisothiocyanate (II) and subsequent transformations of the compounds obtained to sym-triazolo[1,5-*a*]-sym-triazines.

The reaction of II with various aminoazoles was recently reported [8]. The reaction of Ia with II gave N-(1,2,4-triazol-5-yl)-N'-carbethoxythiourea (IVa), which is a yellow crystalline substance with mp 172°C. Refluxing IVa in pyridine gave 5-thiono-7-oxo-sym-triazolo[1,5-*a*]-sym-triazine (VIIa).

We have established that derivatives of two types can be obtained from I and II by changing the reaction conditions: derivatives at the exocyclic 1-N nitrogen atom – 1-carbethoxythiocarbamoyl-5-amino-1,2,4-triazoles (III) – and derivatives at the amino group – N-(1,2,4-triazol-5-yl)-N'-carbethoxythioureas (IV). Aminotriazoles III were obtained by reaction of I and II in acetone for 10 min; increasing the reaction



*See also [1, 2].

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time to 24 h gives only IV. Only thiourea derivatives IV are formed in a mixture of acetone and dimethylformamide (DMF) from I and II, regardless of the temperature and the reaction time. The effect of DMF in reactions of this type or of similar types has not been investigated. In analogy with the literature data on the catalyzing action of tertiary amines in the reactions of isocyanates and isothiocyanates [9], one can assume the initial formation of a complex of II with DMF that is more reactive with respect to the amino group.

Thioureas IV were also obtained as a result of isomerization of III to IV by heating in DMF, acetone, toluene, or water. The isomerization of III proceeds with splitting out of II and subsequent addition of it to the amino group to form thermodynamically more stable IV. A better solvent for the isomerization of III is DMF, in which IV were obtained even at room temperature.

The structure of IV was proved by acid hydrolysis of them to triazolylthioureas V [7, 10].

The IVa that we obtained differs from the compound reported in [8]. In all likelihood, Capuano and Schrepfer were dealing with a mixture of substances rather than pure IVa.

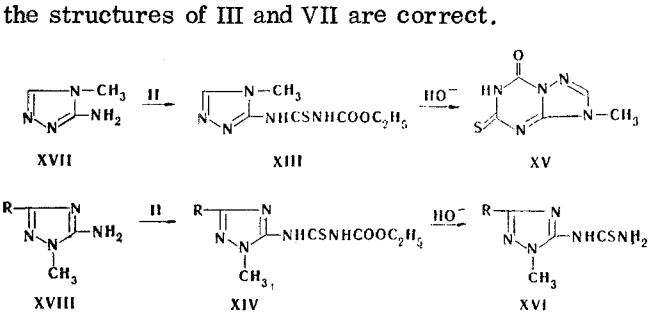
The IR spectra of III and IV contain frequencies of the stretching vibrations of the CO group in different regions: at 1770-1790 cm^{-1} for III, and at 1715-1740 cm^{-1} for IV. In this respect, III and IV recall N-acyl- and acylamino derivatives of aminotriazoles [11, 12], respectively.

In alkaline media, III and IV cyclize to form, respectively, 5-oxo-7-thiono- (VI) and 5-thiono-7-oxo-sym-triazolo[1,5-*a*]-sym-triazines (VII). The corresponding methylthio derivatives of triazolotriazinones VIII and IX were obtained by alkylation of VI and VII or III and IV with methyl iodide in alkaline media. Triazolotriazines VI and VII are resistant to acid and alkali media and are hydrolyzed only on prolonged refluxing. Acid hydrolysis of VIc and VIIc leads, respectively, to (3-phenyl-1,2,4-triazol-5-yl)urea (Xc) and (3-phenyl-1,2,4-triazol-5-yl)thiourea (Vc). The acid hydrolysis of VIc and the synthesis of 2-phenyl-7-oxo-sym-triazolo[1,5-*a*]-sym-triazine (XI) by desulfuration of VIIc confirm the presence of the sym-triazolo-[1,5-*a*]-sym-triazine system in VI and VII. Compound XI was also obtained by cyclization of 1-carbamoyl-3-phenyl-5-amino-1,2,4-triazole (XII) with ethyl orthoformate.

Closing of the triazine ring in IV may occur at the 1-N or 4-N nitrogen atoms, i.e., to form sym-triazolo[1,5-*a*]-sym-triazines or sym-triazolo[4,3-*a*]-sym-triazines. The alternative synthesis of XI shows that the cyclization of IV to triazolotriazines occurs at the same nitrogen atom at which electrophilic substitution (acylation and reactions with isothiocyanates, isocyanates, etc.) proceeds in the aminotriazole molecule. The investigation of the products of the reaction of aminotriazoles with electrophilic agents by physicochemical methods of analysis [13-15] and their alternative synthesis [16] are evidence in favor of reactions at the 1-N nitrogen atom.

For additional proof of the structure of VII, we made attempts to synthesize genuine samples of sym-triazolo[1,5-*a*]-sym-triazines and sym-triazolo[4,3-*a*]-sym-triazines from N-(4-methyl-1,2,4-triazol-5-yl)-N'-carbethoxythiourea (XIII) and, respectively, N-(1-methyl-1,2,4-triazol-5-yl)-N'-carbethoxythioureas (XIV). We found that XIII forms sym-triazolo[1,5-*a*]-sym-triazine XV in alkaline media, while XIVa and XIVb give only hydrolysis products XVIa and XVIb instead of sym-triazolo[4,3-*a*]-sym-triazine under similar conditions.

The UV spectra of VIIa and VIIb in alkaline media repeat the spectrum of XV; this indicates that these compounds have the same structure, i.e., the cyclization of IV proceeds with the participation of the 1-N nitrogen atom. Consequently, the reactions of aminotriazoles with electrophilic agents also occur at the 1-N nitrogen atom, and the structures of III and VII are correct.



XVII XIII XV

XVIII XIV XVI

XIV, XVI, XVIII a R=H; b R=C_6H_5

TABLE 1. 5-Oxo-7-thiono-sym-triazolo[1,5-*a*]-sym-triazines (VIa-c), 5-Thiono-7-oxo-sym-triazolo[1,5-*a*]-sym-triazines (VIIa-c), and Their Methylthio Derivatives (VIIIa,c and IXa,c)

Comp.	mp, °C	IR spectrum, ν_{CO}, cm^{-1}	UV spectrum, λ_{max}, nm (log ε) (in 0.01 N KOH)	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
VIa	>350[a]	1720 1740	237(3,30) 280(3,43)	$C_4H_3N_5OS \cdot H_2O$[b]	25,4	2,8	37,5	25,7	2,7	37,4	77
VIb	296[a,c]	1720	237(3,30) 280(3,43)	$C_5H_5N_5OS$	32,7	2,6	38,3	32,8	2,7	38,2	81
VIc	280—281[c,d]	1720		$C_{10}H_7N_5OS$	49,1	2,3	27,8	49,0	2,9	28,5	83
VIIa	>350[d]	1775	240(3,24) 282(3,28)	$C_4H_3N_5OS$	28,0	2,3	41,4	28,4	1,8	41,4	92
VIIb	>350[a]	1750	239(3,19) 282(3,27)	$C_5H_5N_5OS$	32,6	2,8	38,5	32,8	2,7	38,2	82
VIIc	274[c,d]	1738		$C_{10}H_7N_5OS$	48,7	3,1	28,6	49,0	2,9	28,5	78
XV	263[a,c]	1737	223(3,04) 240(3,07) 290(3,40)	$C_5H_5N_5OS$	32,6	2,9	37,8	32,8	2,7	38,2	77
VIIIa	241—242[e]			$C_5H_5N_5OS$	32,7	2,6	38,0	32,8	2,7	38,2	72 21
VIIIc	296[c,d]			$C_{11}H_9N_5OS$	51,0	3,6	27,7	50,9	3,5	27,0	80 32
IXa	291[a,c]			$C_5H_5N_5OS$	32,8	2,6	37,9	32,8	2,7	38,2	64 57
IXc	292[c,e]			$C_{11}H_9N_5OS$	50,4	3,4	26,3	50,9	3,5	27,0	81 48

[a]From water. [b]Found,%: H_2O 9.8. Calculated,%: H_2O 9.6. [c]With decomposition. [d]From aqueous DMF. [e]From ethanol.

TABLE 2. 1-Carbethoxythiocarbamoyl-5-amino-1,2,4-triazoles (IIIa-c) N-(1,2,4-Triazol-5-yl)-N'-carbethoxythioureas (IVa-c, XIII, XIVa,b), and (1,2,4-Triazol-5-yl)thioureas (XVIa,b)

Comp.	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IIIa	121[a]	1770	$C_6H_9N_5O_2S$	34,0	4,5	36,0	33,5	4,2	32,5	29
IIIb	122[a,b]	1790	$C_7H_{11}N_5O_2S$	36,2	4,9	30,6	36,7	4,8	30,5	24
IIIc	147[a,b]	1770	$C_{12}H_{13}N_5O_2S$	49,5	4,4	23,9	49,5	4,5	24,0	31
IVa	185[a,b]	1725	$C_6H_9N_5O_2S$	33,8	4,4	32,4	33,5	4,2	32,5	*A* 11 B 32
IVb	190[a,c]	1715	$C_7H_{11}N_5O_2S$	36,7	5,0	30,7	36,7	4,8	30,5	*A* 15 B 43
IVc	178[a,c]	1720	$C_{12}H_{13}N_5O_2S$	49,6	4,4	24,5	49,5	4,5	24,0	*A* 12 B 48
XIII	180[a,c]	1724	$C_7H_{11}N_5O_2S$	36,5	4,5	29,8	36,7	4,8	30,5	47
XIVa	156—159[d]	1740	$C_7H_{11}N_5O_2S$	36,3	5,4	30,3	36,7	4,8	30,5	31
XIVb	160[d]	1738	$C_{13}H_{15}N_5O_2S$	50,9	4,9	22,7	51,1	5,0	22,9	50
XVIa	167[b]	—	$C_4H_7N_5S$	30,3	4,4	44,2	30,6	4,5	44,5	50
XVIb	232[b]	—	$C_{10}H_{11}N_5S$	51,3	5,0	30,9	51,5	4,8	30,0	72

[a]With decomposition. [b]From ethanol. [c]From water. [d]From aqueous ethanol.

The stretching vibrations of the CO group in the IR spectra of VI, VII, and XV are found at 1720-1775 cm^{-1}. The 7-oxo derivatives have higher frequencies of the stretching vibrations of the CO group than the 5-oxo derivatives (see Table 1). The frequencies of VI, VII, and XV differ markedly from the frequencies of the corresponding starting compounds III and IV. The characteristic band of the mercapto group (2550-2600 cm^{-1}) is not observed. Thus VI, VII, and XV have oxo and thione structures in the solid state.

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EXPERIMENTAL

1-Carbethoxythiocarbamoyl-5-amino-1,2,4-triazoles (IIIa-c, Table 2). A hot solution of carbethoxyisothiocyanate (II) in anhydrous acetone, which was obtained via the method in [17] from 14.7 g (0.15 mole) of potassium thiocyanate and 14.2 ml (0.15 mole) of ethyl chlorocarbonate in 100 ml of anhydrous acetone,

was added to a suspension of 0.1 mole of aminotriazole Ia-c in 15 ml of anhydrous acetone. A yellow precipitate of IIIa-c formed after the aminotriazole had dissolved. After 10 min, the mixture was cooled, and the precipitate was removed by filtration. The melting points of IIIb,c changed only slightly on recrystallization; IIIa could not be recrystallized.

N-(1,2,4-Triazol-5-yl)-N'-carbethoxythioureas (IVa-c, XIII, XIVa,b, Table 2). A. The filtrate from the separation of IIIa-c (see above) was allowed to stand at room temperature for 24 h, after which the acetone was removed by distillation, and the oily residue was triturated with water to give IVa-c.

B. A solution of II, obtained as indicated above, was added to a solution of 0.1 mole of Ia-c or XVII, XVIII in the minimum amount of DMF, (5-15 mg). The reaction mixture was held at 50-60° for 30 min, after which the acetone was evaporated, the residue was treated with water, and the colorless product was removed by filtration.

C. Compounds IVa-c were obtained by heating IIIa-c in DMF for 5 min on a water bath or after standing in DMF for no less than 3 h at room temperature. The DMF solution was poured into water to isolate IVa-c in 65-80% yields.

D. Compounds IIIa-c were refluxed in water, acetone, or toluene for 2.5 h. The solutions were then cooled, and IVa-c were crystallized in yields of 20, 38, and 55%, respectively.

(1,2,4-Triazol-5-yl)thioureas (Vb,c). Compounds Vb,c, which were identical to those obtained in [4, 17], were obtained by refluxing IVb,c and VIIc, respectively, for 2 and 8 h with concentrated hydrochloric acid.

(3-Phenyl-1,2,4-triazol-5-yl)urea (Xc). A 0.24-g (1 mmole) sample of VIc was refluxed in 20 ml of concentrated hydrochloric acid for 6 h. Evaporation of the mixture gave 0.04 g (20%) of Xc with mp 236-238° (from aqueous DMF) (mp 236-240° [18]).

5-Oxo-7-thiono- and 5-Thiono-7-oxo-sym-triazolo[1,5-*a*]-sym-triazines (VIa-c and VIIa-c, Table 1). A 0.1-mole sample of IIIa-c or IVa-c was added to a solution of 0.2 mole of sodium hydroxide in 75-80% ethanol, and the mixture was heated for 20 min. The sodium salts of triazolotriazines VI and VII precipitated during heating or after the mixture was cooled; these salts were removed by filtration and dissolved in the minimum amount of water. The solution was acidified to pH ~ 3 with concentrated hydrochloric acid to precipitate VIa-c and VIIa-c.

5-Oxo-7-methylthio- and 5-Methylthio-7-oxo-sym-triazolo[1,5-*a*]-sym-triazines (VIIIa,c and IXa,c, Table 1). A 10-mmole sample of VIa,c or IIIa,c and VIIa,c or IVa,c was dissolved in 5 ml of 10% sodium hydroxide solution, and 15 mmole of methyl iodide was added. The mixture was held at room temperature for 30 min and at 0-5° for 1 h, during which the sodium salts of the methylthio derivatives precipitated. The salts were dissolved in the minimum amount of water, and the solution was acidified to pH ~ 3 with hydrochloric acid.

2-Phenyl-7-oxo-sym-triazolo[1,5-*a*]-sym-triazine (XI). A. A mixture of 0.3 g of VIIc, Raney nickel, and 30 ml of methanol was refluxed for 3 h. The catalyst was then removed by filtration, and the filtrate was evaporated. Water (5 ml) and a few drops of concentrated hydrochloric acid were added to the dry residue to give 0.14 g (45%) of XII with mp 300-303° (in a sealed capillary, from aqueous ethanol).

B. A 0.3-g (15 mmole) sample of XII was refluxed in 6 ml of ethyl orthoformate for 1.5 h. The XII dissolved, and XI began to crystallize after refluxing for 0.5 h. The mixture was worked up to give 0.2 g (64%) of a product with mp 300-303° (in a sealed capillary, from water). UV spectrum (in ethanol): λ_{max} 240 nm (log ε 4.27). Found,%: C 56.1; H 3.2; N 32.3. $C_{10}H_7N_5O_7$. Calculated,%: C 56.3; H 3.3; N 32.8.

2-Methyl-5-thiono-7-oxo-sym-triazolo[1,5-*a*]-sym-triazine (XV, Table 1). A mixture of 1.1 g (5 mmole) of XIII, 0.6 g of sodium bicarbonate, and 5 ml of water was heated on a water bath for 10 min, after which it was cooled and acidified with concentrated hydrochloric acid.

(1,2,4-Triazol-5-yl)thioureas (XVIa,b, Table 2). A. A mixture of 10 mmole of XIVa,b and 10 mmole of sodium carbonate in 5 ml of water was heated on a water bath for 15 min, after which it was cooled and acidified with acetic (XVIa) or hydrochloric (XVIb) acid.

B. A 0.01-mole sample of XIVa,b was heated in a solution of sodium ethoxide (0.01 g-atom of sodium in 30 ml of ethanol) for 30 min. The ethanol was evaporated, and the dry residue was dissolved in water. The aqueous solution was acidified with acetic or hydrochloric acid, respectively.

The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-14 spectrophotometer. The UV spectra were recorded with a Specord spectrophotometer.

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