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REACTIONS OF 4-ARYL-1,2,4-TRIAZOLIDINE-3,5-DITHIONE WITH SOME ELECTROPHILIC REAGENTS

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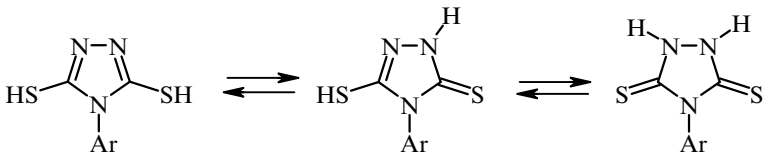
Reaction of 4-aryl-1,2,4-triazolidine-3,5-dithiones in an alkaline medium with chloroacetic acid and its derivatives, as well as with α-bromo ketones, results in their conversion to 4-aryl-1,2,4-triazole-3,5-bis(sulfides). The aminomethylation in a neutral medium leads to the formation of 1-(aminomethyl)-4-aryl-1,2,4-triazolidine-3,5-dithiones.

Keywords: 4-aryl-1,2,4-triazole-3,5-bis(sulfides), 1-(aminomethyl)-4-aryl-1,2,4-triazolidine-3,5-dithiones.

4-Aryl-1,2,4-triazolidine-3,5-dithiones have been known for a long time [1-3], but their chemical properties are virtually unstudied. 1,2,4-Triazole derivatives possessing varied biological activity have been actively investigated [4, 5]. Therefore, the study of the chemical properties of 4-aryl-1,2,4-triazolidine-3,5-dithione and the synthesis of its derivatives is a timely undertaking.

By analogy with 1,3,4-thiadiazolidine-2,5-dithione [6], 4-aryl-1,2,4-triazolidine-3,5-dithione (**1**) can occur in three isomeric forms (A, B, and C) due to thiol–thione tautomerism:



A **B** **C**

It can therefore be proposed that reactions of dithione **1** will proceed at one or at two reaction centers, which are presented both NH and SH groups.

Compounds containing the active hydrogen atom enter into the aminomethylation reaction (the Mannich reaction), and the mercapto compounds react with alkyl halides. For the heteroanalog of dithione **1** – 1,3,4-thiadiazolidine-2,5-dithione – the alkylation goes ambiguously [6], and the Mannich reaction proceeds as the N,N'-, S,S'-, or N,S-aminomethylation depending on the conditions and the type of the reagents [7].

In the study of the alkylation and aminomethylation of dithione **1**, alkylating reagents utilized were chloroacetic acid, its derivatives (ethyl chloroacetate and 2-chloroacetamide), and α-bromo ketones – 2-bromoacetophenone, 2-bromo-4'-chloroacetophenone, and 2-bromo-3',5'-di(*tert*-butyl)-4'-hydroxyacetophenone. The Mannich reaction was performed with formaldehyde and secondary amines – morpholine, N-phenylpiperazine, N-benzylpiperazine, and 4-[2-(1,3-dioxo-(1H,3H-benz[*d,e*]isoquinolin-2-yl)ethyl]piperazine. The following conversions were carried out:

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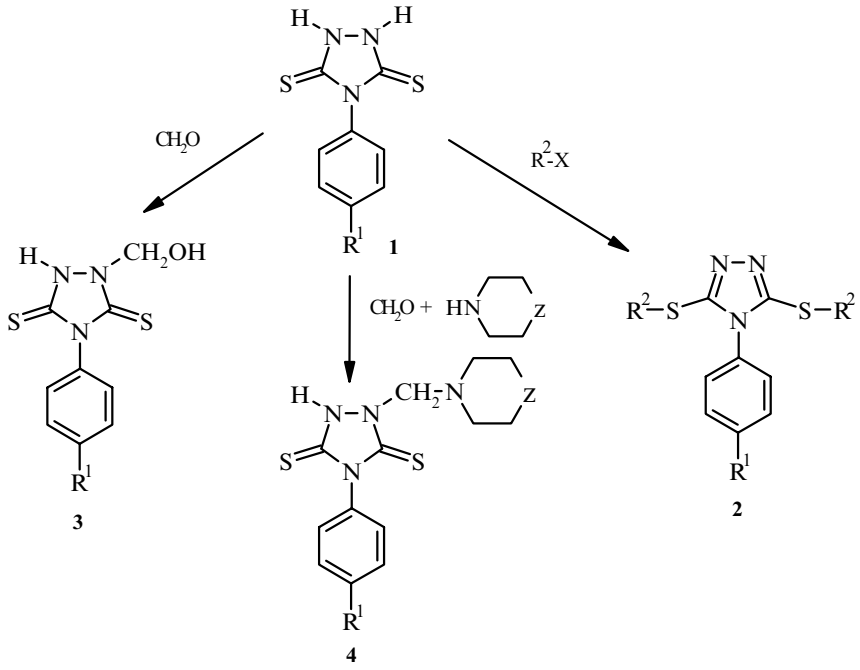
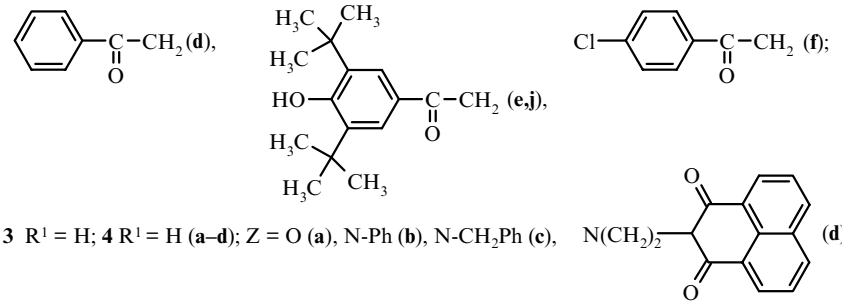


1 R^1 = H, C_2H_5O, CH_3; **2** R^1 = H (**a-f**), C_2H_5O (**g-i**), CH_3 (**j**);
R^2 = CH_2COOH (**a,g**), $CH_2COOC_2H_5$ (**b,h**), CH_2CONH_2 (**c,i**), X = Cl



3 R^1 = H; **4** R^1 = H (**a–d**); Z = O (**a**), N-Ph (**b**), N-CH_2Ph (**c**), (**d**)

The data of the elemental analysis, melting temperatures, ^{1}H NMR spectra, and yields of the synthesized compounds **2**-**4** are presented in the Tables 1, 2. In the ^{1}H NMR spectra of the 1,3,4-thiadiazolidine-2,5-dithione derivatives, the –CH_2N< group appears at lower field than the –CH_2S– (4.9-5.1 ppm and 4.2-4.3 ppm correspondingly) [7]. When dithione **1** reacts in an alkaline medium with chloroacetic acid and its derivatives, as well as with α-bromo ketones, the reaction proceeds *via* the dimercapto form A of dithione with the formation of 4-aryl-1,2,4-triazole-3,5-bis(sulfides) **2** with yields of 37-82%. For its heteroanalog, 1,2,4-thiadiazolidine-3,5-dithione, the reaction with alkyl halides leads to S,S'- or N,S-derivatives [6] depending on the reaction conditions, and the alkylation of the structurally close compound 4-amino-1,2,4-triazolidine-3,5-dithione by α-halogeno ketones proceeds as the S,S'-alkylation [8].

According to the ^{1}H NMR spectral data and elemental analysis, the Mannich reaction for dithione **1** with formaldehyde and secondary amines proceeds clearly as the N-aminomethylation at only one NH group with the formation of 1-(aminomethyl)-4-phenyl-1,2,4-triazolidine-3,5-dithiones (**4**) with the yield of 38-69%. We assume that the given reaction proceeds *via* the tautomeric form B of dithione **1**, the aminomethylation of which proceeds by analogy with the aminomethylation of 4-phenyl-1,2,4-triazoline-3-thione [9]. The Mannich reaction for 1,3,4-thiadiazolidine-2,5-dithione with secondary amines in a neutral medium gives the products of the N,S-aminomethylation [7]. Such a difference is probably explained by the fact that the N,N'-aminomethylation by formaldehyde and secondary amines at the positions 1 and 2 of dithione **1** and the positions 3 and 4 of 1,3,4-thiadiazolidine-2,5-dithione does not occur due to steric hindrance. The diverse reactivity of these

TABLE 1. Characteristics of the Synthesized Compounds **2**, **3**, and **4**

Compound	Empirical formula	Found, % / Calculated, %				mp,°C	Yield, %
		C	H	N	S		
2a	$C_{12}H_{11}N_3O_4S_2$	44.56 / 44.30	3.42 / 3.39	13.21 / 12.91	—	193	82
2b	$C_{16}H_{19}N_3O_4S_2$	50.45 / 50.38	5.17 / 4.99	10.96 / 11.02	—	79	43
2c	$C_{12}H_{13}N_5O_2S_2$	44.92 / 44.57	3.75 / 4.02	—	19.77 / 19.83	204	37
2d	$C_{24}H_{19}N_3O_2S_2$	64.48 / 64.70	4.22 / 4.30	9.35 / 9.43	14.72 / 14.39	221	49
2e	$C_{40}H_{51}N_3O_4S_2$	68.58 / 68.48	7.49 / 7.32	5.92 / 5.99	—	219	51
2f*	$C_{24}H_{17}Cl_2N_3O_2S_2$	—	—	—	12.78 / 12.47	204	39
2g	$C_{14}H_{15}N_3O_5S_2$	—	—	11.32 / 11.38	16.88 / 17.36	220	82
2h	$C_{18}H_{23}N_3O_5S_2$	50.63 / 50.81	5.54 / 5.43	10.12 / 9.88	14.94 / 15.08	76	58
2i	$C_{14}H_{17}N_5O_3S_2$	45.90 / 45.76	4.59 / 4.66	—	17.43 / 17.45	225	78
2j	$C_{41}H_{53}N_3O_4S_2$	68.89 / 68.78	7.56 / 7.46	—	8.84 / 8.91	208	64
3	$C_9H_9N_3OS_2$	45.18 / 45.36	4.03 / 3.79	17.82 / 17.56	—	161	30
4a	$C_{13}H_{16}N_4OS_2$	50.75 / 50.62	5.25 / 5.23	18.51 / 18.17	20.89 / 20.79	187	65
4b	$C_{19}H_{20}N_5S_2$	59.81 / 59.65	5.27 / 5.27	—	17.16 / 16.76	147	41
4c	$C_{20}H_{23}N_5S_2$	60.18 / 60.45	5.81 / 5.79	17.89 / 17.63	15.84 / 16.12	122	38
4d	$C_{27}H_{26}N_6O_2S_2$	60.70 / 61.11	4.81 / 4.91	15.94 / 15.84	12.32 / 12.08	197	69

* Found, %: Cl 13.45. Calculated, %: Cl 13.81.

TABLE 2. ^{1}H NMR Spectral Data of the Compounds **2a-j**, **3**, **4a-d**

Compound	^{1}H NMR spectrum (δ, ppm, DMSO-d_6)
2a	3.95 (4H, s, SCH_2CO); 7.60-7.70 (5H, m, Ph)
2b	1.17 (6H, t, $\underline{CH_3}CH_2O$); 4.01 (4H, s, SCH_2CO); 4.08 (4H, q, $CH_3\underline{CH_2}O$); 7.47-7.63 (5H, m, Ph)
2c	3.92 (4H, s, SCH_2CO); 7.34 (4H, br. s, $CONH_2$); 7.61-7.72 (5H, m, Ph)
2d	4.84 (4H, s, SCH_2CO); 7.46-7.96 (15H, m, Ar)
2e	1.44 (36H, s, $C(CH_3)_3$); 4.82 (4H, s, SCH_2CO); 6.89 (2H, br. s, OH); 7.30-7.50 (5H, m, Ph); 7.90 (4H, s, Ar)
2f	4.83 (4H, s, SCH_2CO); 7.50-8.01 (13H, m, Ar)
2g	1.36 (3H, t, $\underline{CH_3}CH_2O$); 3.96 (4H, s, SCH_2CO); 4.13 (2H, q, $CH_3\underline{CH_2}O$); 7.14 (2H, d, Ar); 7.36 (2H, d, Ar)
2h	1.17 (6H, t, $\underline{CH_3}CH_2O$); 1.34 (3H, t, $\underline{CH_3}CH_2OAr$); 4.01 (4H, s, SCH_2CO); 4.1 (6H, q, $CH_3\underline{CH_2}O$)
2i	1.38 (3H, t, $\underline{CH_3}CH_2O$); 3.86 (4H, s, SCH_2CO); 4.14 (2H, q, $CH_3\underline{CH_2}O$); 7.15 (2H, d, Ar); 7.26 (4H, br. s, $CONH_2$); 7.39 (2H, d, Ar)
2j	1.42 (36H, s, $C(CH_3)_3$); 2.53 (3H, s, CH_3); 4.79 (4H, s, SCH_2CO); 6.82 (2H, br. s, OH); 7.31 (2H, d, Ar); 7.44 (2H, d, Ar); 7.77 (4H, s, Ar)
3	5.52 (2H, d, CH_2OH); 7.10 (2H, m, Ar); 7.34 (1H, t, $CH_2\underline{OH}$); 7.52 (3H, m, Ar)
4a	2.70 (4H, br. s, NCH_2CH_2O); 3.57 (4H, br. s, NCH_2CH_2O); 5.12 (2H, s, NCH_2N); 7.09-7.30 (5H, m, Ph)
4b	2.87 (4H, br. s, NCH_2CH_2N); 3.10 (4H, br. s, NCH_2CH_2N); 5.20 (2H, s, NCH_2N); 6.77-7.60 (10H, m, Ar)
4c	2.60 (4H, br. s, NCH_2CH_2N); 2.81 (4H, br. s, NCH_2CH_2N); 5.11 (2H, s, NCH_2N); 7.23-7.58 (10H, m, Ar)
4d	2.74 (4H, br. s, NCH_2CH_2N); 4.17 (2H, br. s, $(O=C)_2\ NCH_2$); 5.08 (2H, s, NCH_2N); 7.18-8.4 (11H, m, Ar)

compounds in the alkylation and aminomethylation reactions is associated, in all probability, with the fact that the nitrogen atom of the heterocycle in dithione **1** is a weaker nucleophile than the sulfur atom of the heterocycle in 1,3,4-thiadiazolidine-2,5-dithione. Therefore, the reactivity of dithione **1** in relation to electrophilic reagents is lower than that of 1,3,4-thiadiazolidine-2,5-dithione.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on the Varian-300 instrument, and the internal standard was TMS.

Synthesis of 4-Aryl-3,5-di(carboxymethylthio)-1,2,4-triazoles (2a,g) (General Method). To a solution containing dithione **1** (10 mmol) and KOH (20 mmol) in water (10 ml) a solution of chloroacetic acid (20 mmol) and KOH (20 mmol) in water (10 ml) was added. The mixture was heated for 20 min at 95°C, and was maintained for 24 h at 5°C. To the resulting mixture the 10% solution of HCl was added to pH 5-6. The precipitated residue was filtered off, washed with 20 ml of water, recrystallized from ethanol, and dried.

Synthesis of 4-Aryl-3,5-di(carbethoxymethylthio)-1,2,4-triazoles (2b,h), 4-Aryl-3,5-di(carbamoylmethylthio)-1,2,4-triazoles (2c,i), and 4-Aryl-3,5-di(aroylmethylthio)-1,2,4-triazoles (2d,e,j,f) (General Method). To a solution containing dithione **1** (10 mmol) and KOH (20 mmol) in ethanol (10 ml) a solution of the alkylating agent (20 mmol) in ethanol (10 ml) was added. The mixture was heated for 30 min at 80°C, and was then held for 24 h at 5°C prior to the addition of water (40 ml). The precipitated residue was filtered off, washed with water (20 ml), recrystallized from ethanol, and dried.

1-Hydroxymethyl-4-phenyl-1,2,4-triazole-3,5-dithione (3). To dithione **1** (10 mmol) 37% formalin (5 ml) was added, and the mixture was heated until the solution was effected. The precipitated residue, obtained after the cooling of the mixture, was filtered off.

Synthesis of 1-Aminomethyl-4-phenyl-1,2,4-triazole-3,5-dithiones (4a-d) (General Method). Dithione **1** (10 mmol) was dissolved in methanol (15 ml). To the resulting solution were added 37% formalin (5 ml) and the secondary amine (24 mmol). The residue was precipitated, filtered off, and dried.

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