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REACTION OF 2-(4-ARYLTHIAZOL-2-YL)-4-CHLORO-3-OXOBUTYRONITRILES WITH SECONDARY ALIPHATIC AMINES

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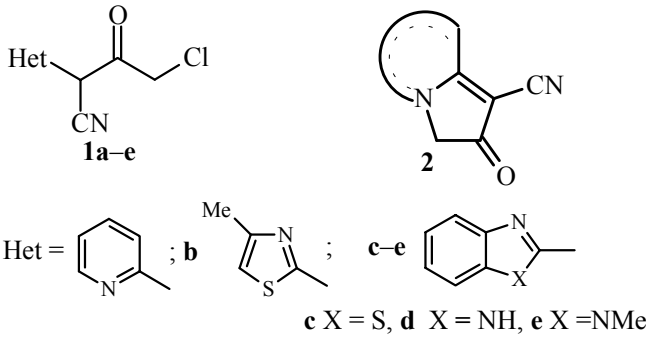
We have obtained 2-(4-arylthiazol-2-yl)-4-chloro-3-oxobutyronitriles by acylation of 4-aryl-2-cyanomethylthiazoles with α-chloroacetyl chloride. We have studied their reaction with secondary aliphatic amines, leading to formation of 4-dialkylamino-2-(4-arylthiazol-2-yl)-3-oxobutyronitriles, and also intramolecular alkylation with formation of 3-aryl-7-cyano-6(5H)-oxopyrrolo[2,1-b]thiazoles. We have determined some aspects of the tautomerism of the synthesized compounds.

Keywords: 4-aryl-2-cyanomethylthiazoles, α-chloroacetyl chloride, 2-(4-arylthiazol-2-yl)-4-chloro-3-oxobutyronitriles, 3-aryl-7-cyano-6(5H)-oxopyrrolo[2,1-*b*]thiazoles, 4-dialkylamino-2-(4-arylthiazol-2-yl)-3-oxobutyronitriles.

Earlier we developed a convenient method for synthesis of 2-(2-azahetaryl)-4-chloro-3-oxobutyronitriles **1a-e** from the corresponding 2-cyanomethylazaheterocycles [1-3] and showed that the chlorine atom in compounds **1a-e** is easily substituted by various nitrogen-containing nucleophiles, with the possibility of subsequent heterocyclization [2-6]. However, there have been practically no studies of substitution of the chlorine in the chloro derivatives **1** by secondary aliphatic amines [3]. When compounds **1** are reacted with highly basic dialkylamines, the reaction proceeds ambiguously: along with formation of the substitution products, there is intramolecular alkylation at the nitrogen atom of the heterocyclic substituent with cleavage of HCl and synthesis of 2(1H)-oxo-3-cyanopyrrolo[1,2-*a*]azaheterocycles **2**. The latter are the only products obtained when halonitriles **1** are heated in high-boiling solvents [7] or when they are treated with bases (Et_3N, K_2CO_3) [2].



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Thus nucleophilic substitution of the chlorine atom in compounds **1a-e** by a dialkylamino group is associated with certain difficulties due to the action of the amine as a base in intramolecular alkylation.

4-Amino-3-oxobutyronitriles are of interest from a pharmacological point of view [8, 9]. 2-Ethoxycarbonyl- [10-13], 2-iminoyl- [14], and 2-aryl-substituted [15, 16] 4-amino-3-oxobutyronitriles have been known for a long time, and so has their biological activity. It is specifically the presence of such biological activity that has stimulated synthesis of novel derivatives of such compounds [17-19], mainly as a result of variation in the amine moiety of the molecule. At the same time, 2-hetaryl-substituted 4-dialkylamino-3-oxobutyronitriles have been unknown so far. In this connection, it seems important to develop a method for obtaining 2-(2-azahetaryl)-4-dialkylamino-3-oxobutyronitriles by nucleophilic substitution of the halogen in compounds **1**. The need to exclude undesirable intramolecular alkylation imposes the following requirements on the properties of the heterocyclic substituent: the basicity of its nitrogen atom should be as low as possible and/or the nitrogen atom should be sterically hindered. Considering this, as the starting halonitriles we chose 2-(4-arylthiazol-2-yl)-3-oxo-4-chlorobutyronitriles **3-5**, since they satisfy the indicated requirements, and the 4-aryl-2-cyanomethylthiazoles **6-8** required to synthesize them are readily available [20-22].

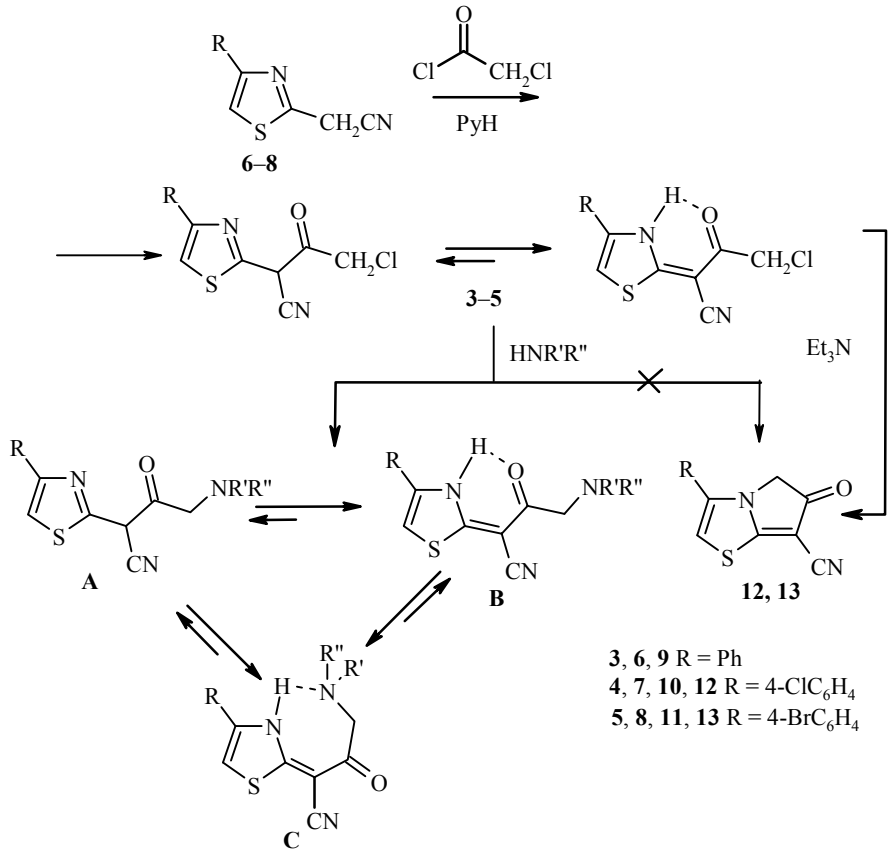
Halonitriles **3-5** were synthesized by C-acylation of cyanomethylthiazoles **6-8** by α-chloroacetyl chloride. The reaction was carried out in dioxane using pyridine as the base; the yields of compounds **3-5** were 60% to 90%. Their structure was confirmed by analytical and spectral data (Tables 1 and 2). According to the latter, halonitriles **3-5** exist in the NH tautomeric form with an intramolecular hydrogen bond. Thus in their IR spectra, we see an intense band for stretching vibrations of the conjugated nitrile group in the 2180-2195 cm^{-1} region. A medium intensity band for the stretching vibrations of the NH bond is observed in the 3130-3150 cm^{-1} region. In the ^1H NMR spectra of compounds **3-5**, recorded in DMSO-d_6, we observe a two-proton singlet for the methylene group in the 4.50-4.45 ppm region and a one-proton singlet at 7.61-7.58 ppm, corresponding to the proton in the 5 position of the thiazole ring. Since the chelate proton on the nitrogen atom is deshielded by the carbonyl group and the heterocyclic ring, its signal is observed downfield at 13.50-12.90 ppm, as a broadened one-proton singlet that disappears when D_2O is added. The protons of the substituent R resonate in the characteristic regions.

When we treated halonitriles **3-5** with a two-fold excess of secondary aliphatic amine in dioxane, we obtained 2-(4-arylthiazol-2-yl)-4-dialkylamino-3-oxobutyronitriles **9e-g,i,j,l-o,u, 10a-c,f,h-p,t-w, 11a-e,g,j-m,o-u,w** in 60% to 80% yields. In this case, we did not observe formation of the products of intramolecular alkylation of **12, 13** (Scheme 1).

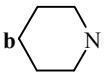
In contrast to the starting halonitriles **3-5**, for the aminonitriles **9-11**, along with the CH tautomer **A**, the existence of two more tautomeric forms with an intramolecular hydrogen bond is possible: **B** and **C**. As in the preceding case, in neither the IR spectra nor the ^1H NMR spectra do we observe signals from tautomeric form **A**, which allows us to eliminate its existence both in the liquid and solid phases. In the IR spectra of aminonitriles **9-11**, there is an intense band for the stretching vibrations of the conjugated nitrile group in the 2180-2200 cm^{-1} region and a medium intensity band for the stretching vibrations of the NH group in the 3140-3160 cm^{-1} region. Such data correspond to both form **B** and form **C**, so it is not possible to draw a conclusion based on these data concerning the ratio of tautomers **B** and **C** in the solid phase.

The ^1H NMR spectra allow us to assume that in DMSO-d_6, aminonitriles **9-11** exist in tautomeric form **C**. Thus the signal of the exchanging proton is observed in the ^1H NMR spectra of compounds **9-11** as a broadened one-proton singlet in the 9.80-9.08 ppm region, which is 3.5-4.0 ppm lower than in the starting chloronitriles **3-5**. On going from compounds **3-5** to tautomeric form **B** of aminonitriles **9-11**, the structural fragment of the six-membered chelate ring is retained, and substitution of the chlorine by an amino group cannot be the reason for such a significant diamagnetic shift. If we consider the tautomeric form **C**, then the nature of the diamagnetic shift becomes quite easily explainable. Thus formation of an intramolecular hydrogen bond with participation of the nitrogen atom of the dialkylamino group fixes the exocyclic orientation of the carbonyl group, as a result of which the chelate proton no longer is found within the zone of its deshielding effect.

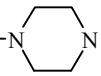
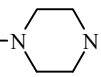
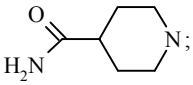
Scheme 1

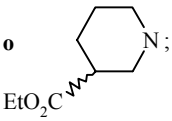
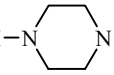


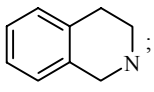
9 e–g, i,j, l–o, u; 10 a–c, f, h–p, t–w
11 a–e, g, j–m, o–u, w

R"R'N **a** *n*-Pr_2N; **b**  ; **c**  ; **d**  ; **e** $PhCH_2$  ;

f $PhCH_2$  ; **g** *n*-BuNMe; **h** $(Me_2CH–CH_2–CH_2)_2N$; **i** $(n\text{-}C_6H_{13})_2N$; **j** $(n\text{-}C_4H_9)_2N$;

k 2-$EtOC_6H_4$  ; **l** 2-$MeOC_6H_4$  ; **m**  ;

n 2-FC_6H_4  ; **o**  ; **p** Ph_2CH  ;

q  ; **r** Et  ; **s** Me  ; **t** Ph  ;

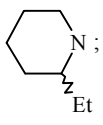
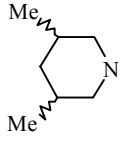
u *cyclo*-$C_6H_{11}NMe$; **v**  ; **w** 

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		N	S	Cl		
1	2	3	4	5	6	7
3	$C_{13}H_9ClN_2OS$	10.05 / 10.12	11.64 / 11.59	12.93 / 12.81	173	66
4	$C_{13}H_8Cl_2N_2OS$	8.93 / 9.00	10.28 / 10.30	22.84 / 22.79	211	73
5	$C_{13}H_8BrClN_2OS$	7.89 / 7.88	9.00 / 9.02		196	92
9e	$C_{25}H_{25}N_3OS$	10.05 / 10.11	7.78 / 7.72		286	74
9f	$C_{24}H_{24}N_4OS$	13.51 / 13.45	7.69 / 7.70		276	70
9g	$C_{18}H_{21}N_3OS$	12.84 / 12.83	9.82 / 9.79		218	62
9i	$C_{25}H_{35}N_3OS$	9.88 / 9.87	7.59 / 7.53		155	64
9j	$C_{21}H_{27}N_3OS$	11.30 / 11.37	8.63 / 8.68		221	75
9l	$C_{24}H_{24}N_4O_2S$	12.91 / 12.95	7.46 / 7.41		230	64
9m	$C_{19}H_{20}N_4O_2S$	15.18 / 15.21	8.74 / 8.70		270	71
9n	$C_{23}H_{21}FN_4OS$	13.33 / 13.32	7.66 / 7.62		238	79
9o	$C_{21}H_{23}N_3O_3S$	10.60 / 10.57	8.11 / 8.07		195	68
9u	$C_{20}H_{23}N_3OS$	11.82 / 11.89	9.10 / 9.07		236	71
10a	$C_{19}H_{22}ClN_3OS$	11.12 / 11.18	8.61 / 8.53	9.40 / 9.43	216	60
10b	$C_{18}H_{18}ClN_3OS$	11.74 / 11.68	8.87 / 8.91	9.87 / 9.85	291	74
10c	$C_{17}H_{16}ClN_3OS$	12.11 / 12.15	9.33 / 9.27	10.21 / 10.25	284	69
10f	$C_{24}H_{23}ClN_4OS$	12.48 / 12.42	7.08 / 7.11	7.91 / 7.86	231	59
10h	$C_{23}H_{30}ClN_3OS$	9.80 / 9.73	7.49 / 7.42	8.22 / 8.21	233	77
10i	$C_{25}H_{34}ClN_3OS$	9.12 / 9.13	6.92 / 6.97	7.74 / 7.71	209	70
10j	$C_{21}H_{26}ClN_3OS$	10.42 / 10.40	7.99 / 7.94	7.80 / 7.78	223	68
10k	$C_{25}H_{25}ClN_4O_2S$	11.69 / 11.65	6.62 / 6.67	7.33 / 7.37	204	62
10l	$C_{24}H_{23}ClN_4O_2S$	11.94 / 12.00	6.84 / 6.87	7.62 / 7.59	241	74
10m	$C_{19}H_{19}ClN_4O_2S$	14.01 / 13.91	8.01 / 7.96	8.82 / 8.80	269	71
10n	$C_{23}H_{20}ClFN_4OS$	12.29 / 12.31	7.11 / 7.05	7.74 / 7.79	250	78
10o	$C_{21}H_{22}ClN_3O_3S$	9.79 / 9.73	7.42 / 7.39	8.18 / 8.21	210	70
10p	$C_{30}H_{27}ClN_4OS$	10.61 / 10.63	6.01 / 6.08	6.76 / 6.73	219	64
10t	$C_{23}H_{21}ClN_4OS$	12.86 / 12.82	7.29 / 7.34	8.09 / 8.11	241	75
10u	$C_{20}H_{22}ClN_3OS$	10.86 / 10.83	8.24 / 8.27	9.19 / 9.14	>300	71
10v	$C_{20}H_{22}ClN_3OS$	10.75 / 10.83	8.26 / 8.27	9.09 / 9.14	173	73
10w	$C_{20}H_{22}ClN_3OS$	10.88 / 10.83	8.21 / 8.27	9.13 / 9.14	240	69

TABLE 1 (continued)

1	2	3	4	5	6	7
11a	$C_{19}H_{22}BrN_3OS$	9.98 10.00	7.62 7.63	18.97 19.01	213	75
11b	$C_{18}H_{18}BrN_3OS$	10.41 10.39	7.96 7.93	19.81 19.76	302	74
11c	$C_{17}H_{16}BrN_3OS$	10.74 10.77	8.21 8.22	20.45 20.47	271	78
11d	$C_{17}H_{16}BrN_3O_2S$	10.39 10.34	7.93 7.89	19.68 19.67	245	79
11e	$C_{25}H_{24}BrN_3OS$	8.48 8.50	6.51 6.48	16.14 16.16	281	71
11g	$C_{18}H_{20}BrN_3OS$	10.32 10.34	7.84 7.89	19.65 19.66	234	77
11j	$C_{21}H_{26}BrN_3OS$	9.35 9.37	7.12 7.15	17.85 17.82	213	77
11k	$C_{25}H_{25}BrN_4O_2S$	10.65 10.66	6.13 6.10	15.18 15.21	221	75
11l	$C_{24}H_{23}BrN_4O_2S$	11.01 10.95	6.21 6.27	15.59 15.62	252	74
11m	$C_{19}H_{19}BrN_4O_2S$	12.58 12.52	7.18 7.17	17.89 17.86	269	74
11o	$C_{21}H_{22}BrN_3O_3S$	8.79 8.82	6.74 6.73	16.74 16.77	212	76
11p	$C_{30}H_{27}BrN_4OS$	9.76 9.80	5.59 5.61	14.02 13.98	244	70
11q	$C_{22}H_{18}BrN_3OS$	9.32 9.29	7.11 7.09	17.59 17.66	275	71
11r	$C_{19}H_{21}BrN_4OS$	13.00 12.93	7.45 7.40	18.40 18.44	263	75
11s	$C_{18}H_{19}BrN_4OS$	13.29 13.36	7.68 7.65	19.09 19.05	278	64
11t	$C_{23}H_{21}BrN_4OS$	11.61 11.64	6.69 6.66	16.62 16.60	276	70
11u	$C_{20}H_{22}BrN_3OS$	9.70 9.72	7.41 7.42	18.40 18.48	>300	70
11w	$C_{20}H_{22}BrN_3OS$	9.79 9.72	7.40 7.42	18.49 18.48	238	76

Formation of a hydrogen bond as a result of the lone electron pair of the nitrogen atom of the dialkylamino group slightly reduces the electron density there, which should lead to some increase in its negative inductive effect and consequently to an additional paramagnetic shift of the signals of the α-protons of the substituents R' and R". In fact, the α hydrogen atoms of the substituents R' and R" in compounds **9-11** resonate 0.20-0.55 ppm downfield from the same atoms in the starting amines HNR'R", which supports the hypothesis that tautomeric form **C** predominates in solution. In this respect, the ^{1}H NMR spectra of 2-(4-arylthiazol-2-yl)-4-(4-benzylpiperazino)-3-oxobutyronitriles **9f, 10f** are most informative. In tautomeric form **B** of compounds **9f, 10f**, the piperazine ring is symmetric, the alkyl substituents are attached to both its nitrogen atoms and they have similar electronic properties; consequently, the magnetic environments for the protons in the 2 (6) and 3 (5) positions of the piperazine ring differ insignificantly, which allows us to expect similar chemical shifts for them. In contrast, in tautomer **C** of aminonitriles **9f, 10f**, the properties of the nitrogen atoms of the piperazine moiety are different, since one of them is involved in formation of a hydrogen bond. Consequently, the magnetic environments of those protons are different, and they should resonate at different δ values. In practice, in the ^{1}H NMR spectra of compounds **9f, 10f** the signals from protons of the piperazine ring are observed as two four-proton spin-coupled triplets at 3.33 ppm and 2.78 ppm. The 0.55 ppm difference is clear evidence in favor of tautomeric form **C**. An analogous nonequivalence of the protons of the piperazine ring also is apparent in the ^{1}H NMR spectra of 2-(4-arylthiazol-2-yl)-4-(4-alkylpiperazino)-3-oxobutyronitriles **11p,r,s**.

TABLE 2. ^{1}H NMR Spectra of Synthesized Compounds

Com-pound	δ, ppm, spin-spin coupling constants, *J* (Hz)
1	2
3	13.05 (1H, s, NH); 7.78 (2H, dd, *J* = 7.0, *J* = 2.0, 2'- and 6'-H_R); 7.58-7.47 (4H, m, 3'-, 4'-, 5'-H_R + S–CH=); 4.50 (2H, s, CH_2)
4	12.95 (1H, s, NH); 7.83 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.60+7.55 (3H, s+d, *J* = 8.5, S–CH= + 3'- and 5'-H_R); 4.47 (2H, s, CH_2)
5	13.42 (1H, s, NH); 7.71 (4H, distorted s, H_R); 7.61 (1H, s, S–CH=); 4.49 (2H, s, CH_2)
9e	9.48 (1H, br. s, NH); 7.92 (2H, dd, *J* = 8.0, *J* = 2.0, 2'- and 6'-H_R); 7.49-7.18 (9H, m, S–CH= + 3'-, 4'-, 5'-H_R + H_{Ph}); 4.14 (2H, s, C(O)CH_2N); 3.40 (2H, m, N(CH_2); 3.10 (2H, m, NCH_2); 2.31 (2H, d, *J* = 6.0, CH_2Ph); 1.74 (5H, m, –CH(CH_2)$_2$)
9f	9.18 (1H, br. s, NH); 7.93 (2H, dd, *J* = 7.5, *J* = 1.5, 2'- and 6'-H_R); 7.34 (9H, m, S–CH= +3'-, 4'-, 5'-H_R + H_{Ph}); 4.19 (2H, s, C(O)CH_2N); 3.67 (2H, s, NCH_2Ph); 3.33 (4H, t, *J* = 5.0, N(CH_2)$_2$); 2.78 (4H, t, *J* = 5.0, N(CH_2)$_2$)
9g	9.30 (1H, br. s, NH); 7.92 (2H, dd, *J* = 8.0, *J* = 2.0, 2'- and 6'-H_R); 7.37 (4H, m, S–CH= + 3'-, 4'-, 5'-H_R); 4.16 (2H, s, C(O)CH_2N); 3.09 (2H, t, *J* = 7.0, NCH_2); 2.80 (3H, s, NCH_3); 1.65 (2H, m, N$CH_2$$\underline{CH_2}$); 1.31 (2H, m, $\underline{CH_2}CH_3$); 0.90 (3H, t, *J* = 9.0, $CH_2$$\underline{CH_3}$)
9i	9.10 (1H, br. s, NH); 7.92 (2H, dd, *J* = 8.0, *J* = 1.5, 2'- and 6'-H_R); 7.47+7.37 (4H, s+m, S–CH= + 3'-, 4'-, 5'-H_R); 4.14 (2H, s, C(O)CH_2N); 3.09 (4H, distorted t, *J* = 5.0, N(CH_2)$_2$); 1.62 (4H, m, N($CH_2$$\underline{CH_2}$)$_2$); 1.25 (12H, br. distorted s, 2($\underline{CH_2}$)$_3$–CH_3); 0.86 (6H, t, *J* = 6.0, 2CH_3)
9j	9.13 (1H, br. s, NH); 7.91 (2H, dd, *J* = 8.0, *J* = 1.5, 2'- and 6'-H_R); 7.47+7.37 (4H, s+m, S–CH= + 3'-, 4'-, 5'-H_R); 4.16 (2H, s, C(O)CH_2N); 3.12 (4H, t, *J* = 7.5, NCH_2); 1.64 (4H, m, N($CH_2$$\underline{CH_2}$)$_2$); 1.29 (4H, m, 2$\underline{CH_2}CH_3$); 0.90 (6H, t, *J* = 7.0, 2CH_3)
9l	9.33 (1H, br. s, NH); 7.93 (2H, dd, *J* = 8.0, *J* = 1.5, 2'- and 6'-H_R); 7.44 (4H, m, S–CH= + 3'-, 4'-, 5'-H_R); 6.99 (4H, m, $H_{o\text{-phenylene}}$); 4.32 (2H, s, C(O)CH_2N); 3.80 (3H, s, OCH_3); 3.45 (4H, distorted t, N(CH_2)$_2$); 3.32 (4H, distorted t, N(CH_2)$_2$)
9m	9.35 (1H, br. s, NH···O); 7.92 (2H, dd, *J* = 8.0, *J* = 1.5, 2'- and 6'-H_R); 7.50-7.26 (5H, m, S–CH= + 3'-, 4'-, 5'-H_R + NH_{amide}); 6.91 (1H, br. s, NH_{amide}); 4.17 (2H, s, C(O)CH_2N); 3.48 (2H, m, NCH_2); 3.14 (2H, m, NCH_2); 2.32 (1H, m, >CH–CO); 1.92 (4H, m, $\underline{CH_2}$)$_2$CH–)
9n	9.15 (1H, br. s, NH); 7.93 (2H, dd, *J* = 7.5, *J* = 1.5, 2'- and 6'-H_R); 7.50–7.05 (8H, m, S–CH= + 3'-, 4'-, 5'-H_R + $H_{o\text{-phenylene}}$); 4.32 (2H, s, C(O)CH_2N); 3.42 (8H, two distorted t, 2N(CH_2)$_2$)
9o	9.41 (1H, br. s, NH); 7.93 (2H, dd, *J* = 8.0, *J* = 1.5, 2'- and 6'-H_R); 7.39 (4H, m, S–CH= + 3'-, 4'-, 5'-H_R); 4.25 + 4.14 (4H, s+q, *J* = 8.5, C(O)CH_2N + OCH_2); 3.64-3.02 (5H, m, –CH_2–N–CH_2–CH–CO); 1.92 (4H, m, >CH$\underline{CH_2}$$\underline{CH_2}$); 1.22 (3H, t, *J* = 8.5, CH_3)
9u	9.20 (1H, br. s, NH); 7.92 (2H, dd, J_1 = 7.5, J_2 = 1.5, 2'-, 6'-H_R); 7.45+7.33 (4H, s+m, S–CH= + 3'-,5'-,4'-H_R); 4.10 (2H, s, C(O)CH_2N); 3.15 (1H, m, N–CH<); 2.75 (3H, s, NCH_3); 2.00-1.28 (10H, m, (CH_2)$_5$)
10a	9.13 (1H, br. s, NH); 7.94 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.52+7.45 (3H, s+d, *J* = 8.5, S–CH= + 3'- and 5'-H_R); 4.15 (2H, s, C(O)CH_2N); 3.09 (4H, t, *J* = 9.5, N(CH_2)$_2$); 1.66 (4H, m, 2$\underline{CH_2}CH_3$); 0.90 (6H, t, *J* = 8.5, 2CH_3)
10b	9.27 (1H, br. s, NH); 7.94 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.45 (3H, s+d, *J* = 8.5, S–CH= + 3'- and 5'-H_R); 4.14 (2H, s, C(O)CH_2N); 3.10 (~4H, distorted t, N(CH_2)$_2$); 1.76 (6H, m, (CH_2)$_3$)
10c	9.73 (1H, br. s, NH); 7.94 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.50+7.44 (3H, s+d, *J* = 8.5, S–CH= + 3'- and 5'-H_R); 4.29 (2H, s, C(O)CH_2N); 3.33 (4H, t, *J* = 5.0, N(CH_2)$_2$); 1.95 (4H, t, *J* = 5.0, (CH_2)$_2$)
10f	9.20 (1H, br. s, NH); 7.94 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.50+7.45+7.35 (8H, s+d (*J* = 8.5)+s, S–CH= + 3'- and 5'-H_R + H_{Ph}); 4.20 (2H, s, C(O)CH_2N); 3.65 (2H, s, NCH_2Ph); 3.32 (4H, t, *J* = 5.0, N(CH_2)$_2$); 2.78 (4H, t, *J* = 5.0, N(CH_2)$_2$)
10h	9.10 (1H, br. s, NH); 7.95 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.53+7.45 (3H, s+d, *J* = 8.5, S–CH= + 3'- and 5'-H_R); 4.14 (2H, s, C(O)CH_2N); 3.13 (4H, distorted t, *J* = 5.0, N(CH_2)$_2$); 1.56 (6H, m, 2CH_2–CH<); 0.89 (12H, d, *J* = 6.0, 4CH_3)
10i	9.08 (1H, br. s, NH); 7.93 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.50+7.44 (3H, s+d, *J* = 8.5, S–CH= + 3'- and 5'-H_R); 4.15 (2H, s, C(O)CH_2N); 3.10 (4H, distorted t, *J* = 7.0, N(CH_2)$_2$); 1.61 (4H, m, N($CH_2$$\underline{CH_2}$)$_2$); 1.27 (12H, br. distorted s, 2($\underline{CH_2}$)$_3$–CH_3); 0.86 (6H, t, *J* = 6.0, 2CH_3)

TABLE 2 (continued)

1	2
10j	9.08 (1H, br. s, NH); 7.94 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.52+7.45 (3H, s+d, J = 8.5, S–CH= + 3'- and 5'-H_R); 4.15 (2H, s, C(O)CH_2N); 3.11 (4H, t, J = 7.5, N(CH_2)$_2$); 1.62 (4H, m, N(CH_2<u>CH_2</u>)$_2$); 1.31 (4H, m, (<u>CH_2</u>CH_3)$_2$); 0.90 (6H, t, J = 7.5, 2CH_3)
10k	9.10 (1H, br. s, NH); 7.95 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.52+7.46 (3H, s+d, J = 8.5, S–CH= + 3'- and 5'-H_R); 6.94 (4H, m, $H_{o\text{-phenylene}}$); 4.32 (2H, s, C(O)CH_2N); 4.03 (2H, q, J = 9.0, OCH_2); 3.44–3.10 (8H, m, N(CH_2CH_2)$_2$N); 1.36 (3H, t, J = 9.0, CH_3)
10l	9.60 (1H, br. s, NH); 7.95 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.52+7.44 (3H, s+d, J = 8.5, S–CH= + 3'- and 5'-H_R); 6.97 (4H, distorted q, $H_{o\text{-phenylene}}$); 4.32 (2H, s, C(O)CH_2N); 3.80 (3H, s, OCH_3); 3.40 (8H, m, N(CH_2CH_2)$_2$N)
10m	9.40 (1H, br. s, NH···O); 7.94 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.52+7.46+7.39 (4H, s+d (J = 8.5)+br. s, S–CH= + 3'- and 5'-H_R + NH_{amide}); 6.91 (1H, br. s, NH_{amide}); 4.18 (2H, s, C(O)CH_2N); 3.43 (2H, m, NCH_2); 3.10 (2H, m, NCH_2); 2.33 (1H, m, >CH–CO); 1.92 (4H, m, (<u>CH_2</u>)$_2$CH–)
10n	9.70 (1H, br. s, NH); 7.93 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.52+7.46 (3H, s+d, J = 8.5, S–CH= + 3'- and 5'-H_R); 7.12 (4H, m, $H_{o\text{-phenylene}}$); 4.33 (2H, s, C(O)CH_2N); 3.41 (8H, distorted s, N(CH_2CH_2)$_2$N)
10o	9.45 (1H, br. s, NH); 7.93 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.51+7.45 (3H, s+d, J = 8.5, S–CH= + 3'- and 5'-H_R); 4.23+4.12 (4H, s+q, J = 8.0, C(O)CH_2N + OCH_2); 3.67-3.11 (5H, m, –CH_2–N–CH_2–CH–CO); 1.90 (4H, m, >CH<u>CH_2CH_2</u>); 1.22 (3H, t, J = 8.0, CH_3)
10p	9.33 (1H, br. s, NH); 7.92 (2H, d, J = 8.0, 2'- and 6'-H_R); 7.35 (13H, m, 3'-, 5'-H_R + S–CH= + Ph_2); 4.51 (1H, s, Ph_2CH); 4.21 (2H, s, C(O)CH_2N); 3.33 (4H, t, J = 5.0, N(CH_2)$_2$); 2.65 (4H, t, J = 5.0, N(CH_2)$_2$)
10t	9.36 (1H, br. s, NH); 7.93 (2H, d, J = 8.0, 2'- and 6'-H_R); 7.50-7.20 (5H, m, S–CH= + 3'- and 5'-H_R + 3'- and 5'-H_{Ph}); 6.93 (3H, m, 2'-, 4'-, 6'-H_{Ph}); 4.29 (2H, s, C(O)CH_2N); 3.36 (8H, distorted s, N(CH_2CH_2)$_2$N)
10u	9.30 (1H, br. s, NH); 7.93 (2H, d, J = 8.0, 2'- and 6'-H_R); 7.47+7.43 (3H, s+d, J = 8.0, S–CH= + 3'- and 5'-H_R); 4.09 (3H, s, distorted C(O)CH_2N + N–CH<); 2.76 (3H, s, NCH_3); 1.91-1.00 (10H, m, (CH_2)$_5$)
10v	9.28 (1H, br. s, NH); 7.93 (2H, d, J = 9.0, 2'- and 6'-H_R); 7.51+7.45 (3H, s+d, J = 9.0, S–CH= + 3'- and 5'-H_R); 4.06 (3H, s, distorted C(O)CH_2N + N–CH<); 3.36 (2H, t, J = 5.0, NCH_2); 1.73 (8H, m, (CH_2)$_3$ + <u>CH_2</u>CH_3); 0.89 (3H, t, CH_3)
10w	9.15 (1H, br. s, NH); 7.92 (2H, d, J = 9.0, 2'- and 6'-H_R); 7.49+7.44 (3H, s+d, J = 9.0, S–CH= + 3'- and 5'-H_R); 4.14 (2H, s, C(O)CH_2N); 3.33 (4H, m, N(CH_2)$_2$); 2.01 (4H, m, CH_2(CH<)$_2$); 0.87 (6H, d, J = 7.5, 2CH_3)
11a	9.31 (1H, br. s, NH); 7.97 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.55 (2H, d, J = 8.5, 3'- and 5'-H_R); 7.43 (1H, s, S–CH=); 4.22 (2H, s, C(O)CH_2N); 3.43 (4H, t, J = 8.0, N(CH_2)$_2$); 1.86 (4H, m, <u>CH_2</u>CH_3); 1.02 (6H, t, J = 10.0, 2CH_3)
11b	9.40 (1H, br. s, NH); 7.89 (2H, d, J = 10.0, 2'- and 6'-H_R); 7.57+7.53 (3H, d (J = 10.0)+s, 3'- and 5'-H_R + S–CH=); 4.14 (2H, s, C(O)CH_2N); 3.06 (4H, distorted t, N(CH_2)$_2$); 1.75 (6H, m, (CH_2)$_3$)
11c	9.80 (1H, br. s, NH); 7.88 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.57+7.53 (3H, d (J = 8.5)+s, 3'- and 5'-H_R + S–CH=); 4.30 (2H, s, C(O)CH_2N); 3.33 (4H, distorted t, J = 6.0, N(CH_2)$_2$); 1.93 (4H, t, J = 6.0, (CH_2)$_2$)
11d	9.52 (1H, br. s, NH); 7.89 (2H, d, J = 9.0, 2'- and 6'-H_R); 7.56+7.50 (3H, d (J = 9.0)+s, 3'- and 5'-H_R + S–CH=); 4.24 (2H, s, C(O)CH_2N); 3.87 (4H, t, J = 5.0, O(CH_2)$_2$); 3.33 (4H, t, J = 5.0, N(CH_2)$_2$)
11e	9.10 (1H, br. s, NH); 7.88 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.58+7.49 (3H, d (J = 8.5)+s, 3'- and 5'-H_R + S–CH=); 7.24 (5H, m, H_{Ph}); 3.95 (2H, s, C(O)CH_2N); 3.33 (4H, m, N(CH_2)$_2$); 2.85 (2H, d, J = 10.0, CH_2Ph); 1.63 (5H, m, –CH(CH_2)$_2$)
11g	9,39 (1H, br. s, NH); 7.88 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.60+7.54 (3H, d (J = 8.5)+s, 3'- and 5'-H_R + S–CH=); 4.17 (2H, s, C(O)CH_2N); 3.09 (2H, t, J = 11.0, NCH_2); 2.80 (3H, s, NCH_3); 1.64 (2H, m, NCH_2<u>CH_2</u>); 1.31 (2H, m, <u>CH_2</u>CH_3); 0.90 (3H, t, J = 7.5, CH_2<u>CH_3</u>)
11j	9.18 (1H, br. s, NH); 7.95 (2H, d, J = 10.0, 2'- and 6'-H_R); 7.56 (2H, d, J = 10.0, 3'- and 5'-H_R); 7.42 (1H, s, S–CH=); 4.22 (2H, s, C(O)CH_2N); 3.47 (4H, t, J = 9.5, N(CH_2)$_2$); 1.86 (4H, m, N(CH_2<u>CH_2</u>)$_2$); 1.44 (4H, m, 2<u>CH_2</u>CH_3); 0.95 (6H, t, J = 8.0, 2CH_3)
11k	9.15 (1H, br. s, NH); 7.97 (2H, d, J = 8.5, 2'- and 6'-H_R); 7.56 (2H, d, J = 8.5, 3'- and 5'-H_R); 7.43 (1H, s, S–CH=); 7.00 (4H, m, $H_{o\text{-phenylene}}$); 4.36 (2H, s, C(O)CH_2N); 4.11 (2H, q, J = 7.0, OCH_2); 3.78+3.63 (8H, two t, J_1 = J_2 = 5.0, N(CH_2CH_2)$_2$N); 1.43 (3H, t, J = 7.0, CH_3)

TABLE 2 (continued)

1	2
11l	9.50 (1H, br. s, NH); 7.95 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.56 (2H, d, *J* = 8.5, 3'- and 5'-H_R); 7.41 (1H, s, S–CH=); 7.02 (4H, m, $H_{o\text{-phenylene}}$); 4.34 (2H, s, C(O)CH_2N); 3.89 (3H, s, OCH_3); 3.75 (4H, t, *J* = 6.0, N(CH_2)$_2$); 3.57 (4H, t, *J* = 6.0, N(CH_2)$_2$)
11m	9.60 (1H, br. s, NH); 7.88 (2H, d, *J* = 8.0, 2'- and 6'-H_R); 7.53 (4H, m, S–CH= + 3'-,5'-H_R + NH_{amide}); 6.91 (1H, br. s, NH_{amide}); 4.18 (2H, s, C(O)CH_2N); 3.44 (4H, m, N(CH_2)$_2$); 2.34 (1H, m, >CH–CO); 1.92 (4H, m, ($\underline{CH_2}$)$_2$CH–)
11o	9.25 (1H, br. s, NH); 7.96 (2H, d, *J* = 90, 2'- and 6'-H_R); 7.54 (2H, d, *J* = 9.0, 3'- and 5'-H_R); 7.43 (1H, s, S–CH=); 4.26 + 4.20 (4H, s+q, *J* = 9.0, C(O)CH_2N + OCH_2); 3.80-3.50 (5H, m, –CH_2–N–CH_2–CH–CO); 1.90 (4H, m, >CH$\underline{CH_2CH_2}$); 1.27 (3H, t, *J* = 9.0, CH_3)
11p	9.33 (1H, br. s, NH); 7.87 (2H, d, *J* = 9.0, 2'- and 6'-H_R); 7.62-7.20 (13H, m, 3'-, 5'-H_R + S–CH= + H_{Ph2}); 4.52 (1H, s, Ph_2CH); 4.20 (2H, s, C(O)CH_2N); 3.33 (4H, t, *J* = 5.0, N(CH_2)$_2$); 2.65 (4H, t, *J* = 5.0, N(CH_2)$_2$)
11q	9.27 (1H, br. s, NH); 7.96 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.54 (2H, d, *J* = 8.5, 3'- and 5'-H_R); 7.42+7.33 (5H, s+m, S–CH= + $H_{o\text{-phenylene}}$); 4.75 (2H, s, ArCH_2N); 4.38 (2H, s, C(O)CH_2N); 3.92 (2H, t, *J* = 6.0, N$\underline{CH_2}$$CH_2$); 3.41 (2H, t, *J* = 6.0, N$CH_2\underline{CH_2}$)
11r	9.45 (1H, br. s, NH); 7.88 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.56+7.48 (3H, d (*J* = 8.5)+s, 3'- and 5'-H_R + S–CH=); 3.95 (2H, s, C(O)CH_2N); 3.17 (4H, t, *J* = 5.0, N(CH_2)$_2$); 2.91 (4H, t, *J* = 5.0, N(CH_2)$_2$); 2.85 (2H, q, *J* = 6.0, N$\underline{CH_2}$$CH_3$); 1.07 (3H, t, *J* = 6.0, CH_3)
11s	9.29 (1H, br. s, NH); 7.88 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.58 (2H, d, *J* = 8.5, 3'- and 5'-H_R); 7.42 (1H, s, S–CH=); 3.98 (2H, s, C(O)CH_2N); 3.64 (3H, s, NCH_3); 3.33 (4H, t, *J* = 5.0, N(CH_2)$_2$); 2.91 (4H, t, *J* = 5.0, N(CH_2)$_2$)
11t	9.15 (1H, br. s, NH); 7.87 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.56+7.48 (3H, d (*J* = 8.5)+s, 3'- and 5'-H_R + S–CH=); 7.27 (2H, dd, *J* = 7.5, *J* = 8.5, 3'-, 5'-H_{Ph}); 6.94 (3H, m, *J* = 7.5, *J* = 8.5, 2'-, 4'-, 6'-H_{Ph}); 4.28 (2H, s, C(O)CH_2N); 3.47 (8H, distorted s, N(CH_2CH_2)$_2$N)
11u	9.20 (1H, br. s, NH); 7.86 (2H, d, *J* = 8.5, 2'- and 6'-H_R); 7.58 (2H, d, *J* = 8.5, 3'- and 5'-H_R); 7.48 (1H, s, S–CH=); 4.10 (3H, s, distorted C(O)CH_2N + N–CH<); 2.76 (3H, s, NCH_3); 2.00-1.32 (10H, m, (CH_2)$_5$)
11w	9.40 (1H, br. s, NH); 7.87 (2H, d, *J* = 9.0, 2'- and 6'-H_R); 7.57+7.50 (3H, d (*J* = 9.0)+s, 3'- and 5'-H_R + S–CH=); 4.14 (2H, s, C(O)CH_2N); 3.23 (4H, m, N(CH_2)$_2$); 1.94 (4H, m, CH_2(CH<)$_2$); 0.87 (6H, d, *J* = 7.5, 2CH_3)
12	7.81 (2H, d, *J* = 8.0, 2', 6'-H_R); 7.60+7.54 (3H, s+d, *J* = 8.0, 2-H + 3',5'-H_R); 4.48 (2H, s, CH_2)
13	7.79 (2H, d, *J* = 8.0, 2', 6'-H_R); 7.58+7.55 (3H, s+d, *J* = 8.0, 2-H + 3',5'-H_R); 4.41 (2H, s, CH_2)

The position of the signals from the residual protons in the ^{1}H NMR spectra of aminonitriles **9-11** is analogous to their position in the starting compounds **3-5**. The only exception is the two-proton singlet of the oxomethylene moiety, which for compounds **9-11** is observed upfield (4.38-3.95 ppm) due to the smaller negative inductive effect of the nitrogen atom compared with the chlorine atom. Elemental analysis data for aminonitriles **9-11** agree well with the calculated values (Table 2).

The existence of aminonitriles **9-11** in DMSO-d_6 solution in tautomeric form **C** is explained by realization in aprotic medium of the strongest possible hydrogen bond. The latter is more stable in tautomer **C** than in tautomer **B** for two reasons. First of all, the system of linked five-membered and seven-membered rings is less strained than the analogous system of five-membered and six-membered rings. Secondly, the lone electron pair of the nitrogen atom of the dialkylamino group, localized on an sp^3-hybridized orbital, is more suitable for creating a hydrogen bond than the lone electron pair of the oxygen atom, occupying an sp^2-hybridized orbital. The possibility is not excluded that in protic medium, the tautomeric equilibrium for compounds **9-11** will be different.

3-Aryl-6(5H)-oxo-7-cyanopyrrolo[2,1-*b*]thiazoles **12, 13**, which formation could be avoided when chloronitriles **3-5** reacted with secondary amines, were obtained from compounds **4, 5** by treatment with triethylamine. The structure of pyrrolothiazoles **12, 13** was confirmed by analytical and spectral data. Their IR spectra reveal an intense band for stretching vibrations of the conjugated nitrile group in the 2180-2190 cm^{-1} region but no absorption above 3050 cm^{-1}. In the ^1H NMR spectra of compounds **12, 13**, we observe a two-proton singlet for the methylene group in the 4.50-4.45 ppm region and a one-proton singlet at 7.60 ppm assigned to the proton in the 2 position. The protons of the substituent R resonate in the regions characteristic for them. According to the spectral data, the pyrrolothiazoles **12, 13** exist completely in the ketone form.

Thus applying the procedure in [1] to 4-aryl-2-cyanomethylthiazoles **6-8** allowed us to obtain 2-(4-arylthiazol-2-yl)-3-oxo-4-chlorobutyronitriles **3-5**. By nucleophilic substitution of the chlorine atom in compounds **3-5** by secondary aliphatic amines, we synthesized the series of 2-(4-arylthiazol-2-yl)-4-dialkylamino-3-oxobutyronitriles **9e-g,i,j,l-o,u, 10a-c,f,h-p,t-w, 11a-e,g,j-m,o-u,w**, which are potentially biologically active substances.

EXPERIMENTAL

The course of the reactions was monitored using TLC (Silufol UV-254, chloroform–methanol, 9:1). The IR spectra were recorded on a Pye Unicam SP 3-300 in KBr pellets. The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker WP-100 SY with operating frequency 100 MHz.

The analytical characteristics of the compounds obtained are indicated in Table 1. Their spectral characteristics are presented in Table 2.

4-Aryl-2-cyanomethylthiazoles **6-8** were obtained according to the procedure in [20-22].

2-(4-Arylthiazol-2-yl)-4-chloro-3-oxobutyronitriles 3-5. α-Chloroacetyl chloride (12 ml, 0.15 mol) was added, with stirring by hand, over a 3-5 min period to a solution of 4-aryl-2-cyanomethylthiazole **6-8** (0.15 mol) and pyridine (15 ml, 0.19 mol) in warm (40-50°C) absolute dioxane (100-130 ml). The mixture was heated on a water bath for 40-60 min. After cooling, the precipitate was filtered off and carefully washed with water. The halonitriles **3-5** obtained were suitable for further use. Analytical samples of compounds **3-5** were purified by recrystallization from dioxane (compounds **4, 5**) or *n*-butanol (compound **3**).

4-Dialkylamino-2(4-arylthiazol-2-yl)-3-oxobutyronitriles 9e-g,i,j,l-o, 10a-c,f,h-p,t-w, 11a-e,g,j-m,o-u,w. The corresponding secondary amine (6 mmol) was added to a suspension of the halonitrile **3-5** (3 mmol) in dioxane (5-10 ml) and then refluxed until the halonitrile dissolved. The solution obtained was refluxed for about 40 min longer, until compounds **3-5** disappeared from the reaction mixture (according to TLC). After this, the mixture was cooled, the precipitate was filtered off, carefully washed with water, dried, and recrystallized from dioxane (compounds **9e,i,j,m-o, 10b,c,h,i,l-p,u-w, 11a-e,g,j,l,m,q-u,w**) or *n*-butanol (compounds **9f,g,e,u, 10a,f,j,k,t, 11k,p**).

3-Aryl-7-cyano-6(5H)-oxopyrrolo[2,1-*b*]thiazoles 12, 13. Triethylamine (0.55 ml, 4 mmol) was added to a suspension of halonitrile **4, 5** (3 mmol) in dioxane (5 ml), and the mixture obtained was refluxed for 7-9 h until compounds **4-5** disappeared completely from the reaction mixture (according to TLC). After cooling, the precipitate was filtered off, washed with water, dried, and recrystallized from dimethylformamide.

3-(4-Chlorophenyl)-7-cyano-6(5H)-oxopyrrolo[2,1-*b*]thiazole 12. Yield 57%; mp 226°C. Found, %: Cl 12.93; N 10.17; S 11.64. $C_{13}H_7ClN_2OS$. Calculated, %: Cl 12.90; N 10.20; S 11.67.

3-(4-Bromophenyl)-7-cyano-6(5H)-oxopyrrolo[2,1-*b*]thiazole 13. Yield 46%; mp 211°C. Found, %: Br 25.08; N 8.81; S 9.99. $C_{13}H_7BrN_2OS$. Calculated, %: Br 25.03; N 8.78; S 10.05.

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