



Role of Thiazoles and Their Derivatives[#]

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Abstract: Have been investigated the reactions of acylation, bromation of 2-amino-4-phenylsubstituted thiazoles, and also reactions of aminothiazoles with phenylisocyanate, 1,2-epoxy-3-chloropropane, propylene oxide and propylene sulfide.

Keywords: 2-amino-4-phenylsubstituted thiazols; 4-phenylthiazolylsubstituted 1,2-aminoalcohols and 1,2-aminothiols; 2-amino-5-brom-4-phenylthiazole; 3-hydroxy-6-phenyl-2,3,4,5-tetrahydropyrimido[1,2-b]-thiazoline-4

Introduction

Last years interest to chemistry of heterocyclic compounds has considerably increased. It is connected with a lot of the special properties shown by similar compounds. The big interest is represented with the condensed derivatives of thiazole which can be used as potential biologically active compounds [3,6,9]. As is known, thiazoles possess antiviral, antiparasitic, febrifugal properties and are widely applied in medicine. Aminoalcohols, received on a basis of aminothiazoles are physiologically active compounds which possessing radioprotective, antihemolytic, hypotensive, curariform, ganglioblocking properties and find wide application in medical practice. Also they get the increasing value in technics as effective components of the polymeric materials raising radiating stability of polymers, overwhelming the oxidizing and corrosion processes possessing complexing properties.

Results and Discussion

Among products of transformation of thiiranes in reactions with various nucleophilic, electrophilic reagents, proceeding with disclosing of thiirane's cycle on the importance leading place borrow 1,2-aminothiols. For last decade interest to these researches has much more increased. Specified it is caused by that, first, among aminothiols only aminoethanthiol contains in structure of coferment A, playing an essential role in ability to live of organisms, secondly, aminothiols and their derivatives are physiologically active compounds and find wide application in a medical practice, and, thirdly, they get the increasing value in technics as effective components of the polymeric materials increasing radiating stability of polymers.

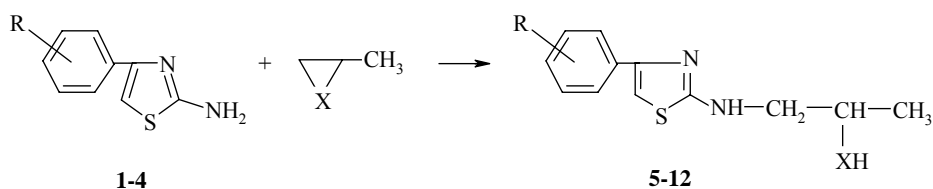
Nucleophilic disclosing of thiirane's cycle by various amines is considered in the monography [2]. However, till now, despite of the big number of researches in this direction, the general character of these reactions remains up to the end obscure.

Reactions of ethylensulfide with various amines have been investigated and obtained dates are resulted in works [4,8]. Reactions of alkoxy-, phenoxy- and others replaced thiiranes with various amines haven't almost been studied before our researches. There are references about synthesis of 1,2-aminothiols [5] on the basis of reaction of 1,2-epithio-3-methoxypropane with piperidine and morpholine and reactions of phenoxy-substituted thiirane with dibutylamine [7].

All the above-stated circumstances have induced us to more detailed research of reaction propylene oxide and propylene sulfide with various 2-amino-4-phenylsubstituted thiazoles (1-4) with formation 4-phenylthiazolylsubstituted 1,2-aminoalcohols and 1,2-aminothiols (5-12):

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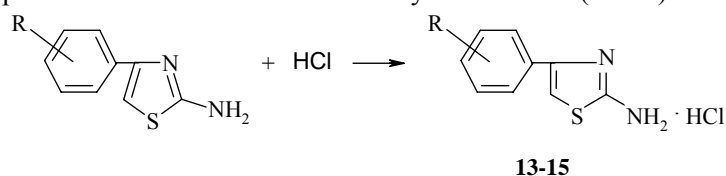
[#] This study has been presented at BIES'08 Symposium Giresun-Turkey



X = O, R = H (5), 2,5-(CH₃O)₂ (6), 2-OH (7), 4-Cl (8);

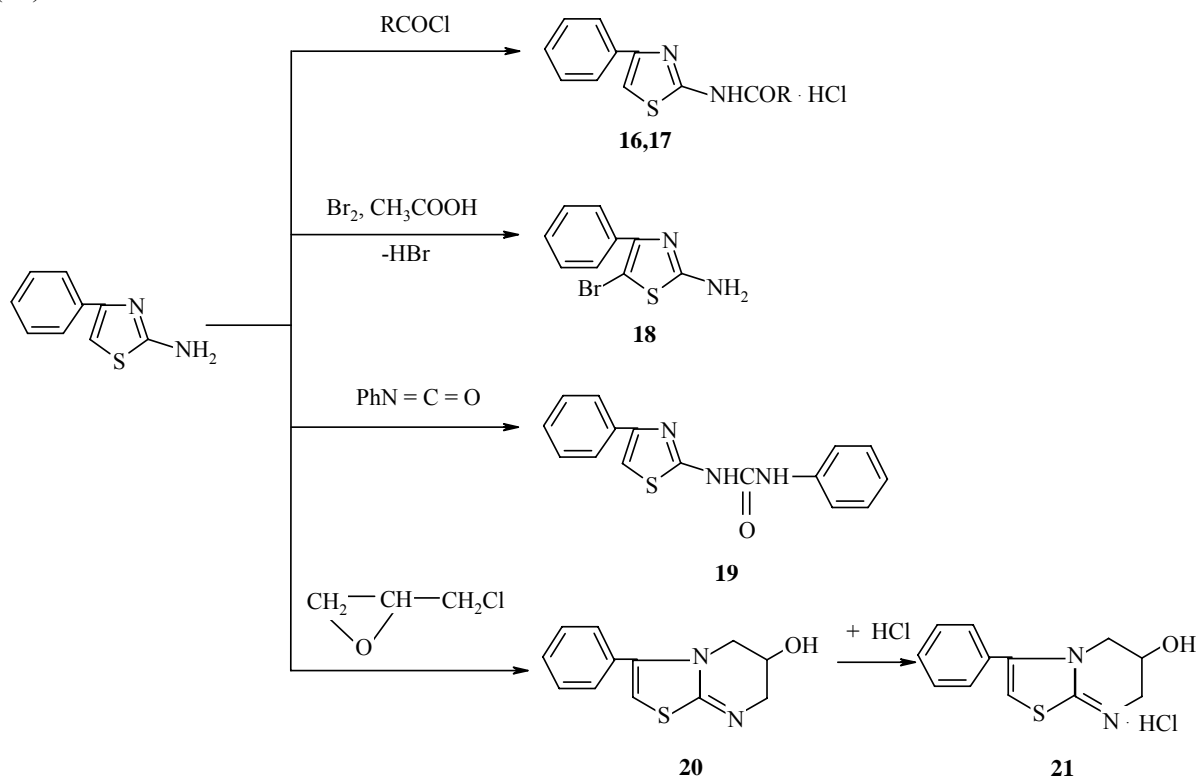
X = S, R = H (9), 2,5-(CH₃O)₂ (10), 2-OH (11), 4-Cl (12)

With the purpose of studying physiological activity 2-amino-4-phenylsubstituted thiazoles (1-4), the received compounds have been converted into hydrochlorides (13-15):



R = H (13), 2,5-(CH₃O)₂ (14), 4-Cl (15)

By acylation and bromation (at the presence of an acetic acid) of 2-amino-4-phenylthiazole (1) have been received amides as hydrochlorides (16,17) and 2-amino-5-brom-4-phenylthiazole (18) accordingly; by interaction of 2-amino-4-phenylthiazole (1) with phenylisocyanate it has been received derivative of ureas (19). By interaction of 2-amino-4-phenylthiazole (1) with 1,2-epoxy-3-chloropropane at the presence of an ice acetic acid has been received 3-hydroxy-6-phenyl-2,3,4,5-tetrahydropirimido[1,2-b]-thiazoline-4 (20); also we received the hydrochloride of this compound (21):



R = CH₃ (16), C₆H₅ (17)

Compositions and structures of obtained thiazoles and their derivatives have been confirmed by IR and NMR spectroscopy, but purity was controlled by thin layer chromatography.

In IR-spectra of synthesized 2-amino-4-phenylthiazole (I) there are strips of absorption at 1470, 1610, 1635-1680, 3375, 3290 cm⁻¹ concerning bonds C=C-, C=N-, NH₂.

In ^1H NMR-spectra of thiazole (I) signals of protons of phenyl radical are found out in the field of 6.8-7.27 p.p.m. in the form of multiplet. Six protons of two methoxy-groups in a molecule (2) give singlet in the field of 3.45 p.p.m. Two protons of amine fragment are found out in the form of doublet in the field of 3.8 p.p.m. ^{13}C NMR-spectra show, that chemical shifts of atoms of carbon are found out in the field of $\sigma=17.8, 19.8, 30, 31$.

Have been found out the wide strip of absorption in the field of $3470\text{-}3430\text{ cm}^{-1}$ in IR-spectra of all 4-arylthiazolylsubstituted 1,2-aminoalcohols (5-8) which concerns to valent fluctuations connected secondary hydroxyl group. However, a wide strip of absorption in the IR-spectrum at $3360\text{-}3380\text{ cm}^{-1}$, corresponding to primary hydroxyl groups, it was revealed not [1]. In IR-spectra of synthesized 1,2-aminoalcohols (6-8) the wide strip of absorption in the field of $3380\text{-}3345\text{ cm}^{-1}$ which characterizes valent fluctuations of the *NH* group participating in formation of intramolecular hydrogen connection with hydroxyl group also is found out. In all spectra also there is a strip of absorption in the field of $1125\text{-}1135\text{ cm}^{-1}$, concerning to valent fluctuations of connection *C-O* of the secondary hydroxyl. It is necessary to note, that a strip describing primary hydroxyl group, it is shown in the field of 1090 cm^{-1} [3]. In IR-spectra of all synthesized compounds (5-12) there are corresponding strips of absorption in the field of $1590\text{-}1600$ and $1490\text{-}1510\text{ cm}^{-1}$ which can be carried to valent fluctuations of *C=C* connection of an aromatic ring. The strip of absorption in the field of $3030\text{-}3040\text{ cm}^{-1}$ corresponds to valent fluctuations of *C-H* connection of an aromatic ring. In IR-spectrum of 4-arylthiazolylsubstituted 1,2-aminothiols (9-12), except the above-stated strip of absorption, there is also a strip of absorption in the field of $3370\text{-}3390\text{ cm}^{-1}$ which is characteristic for *NH* connections. Valent fluctuations of *S-H* connection are shown in the field of $2560\text{-}2570\text{ cm}^{-1}$.

In NMR ^1H spectra of synthesized 4-arylthiazolylsubstituted 1,2-aminoalcohols and 1,2-aminothiols (5-12) in the strongest field of 0.9-1.25 p.p.m. are found out signals of protons of CH_3 -group in the form of a triplet. Position of a signal of proton of *NH* group is established on the basis of change of position of multiplet, corresponding to signals of protons of CH_2CH group at addition D_2O . It has been established, that it is in the field of 3.46-3.65 p.p.m. In the weaker field of 6.35-6.45 and 6.65-6.90 p.p.m. are shown nonequivalent protons of an aromatic ring in the form of a triplet. In a molecule of 4-arylthiazolylsubstituted 1,2-aminoalcohols (6) and 1,2-aminothiols (10) six protons of two methoxygroups give singlet in the field of 3.45 p.p.m.

Experimental

Preparation of 2-(2'-hydroxypropyl)amino-4-phenylthiazole (5)

The mixture of 8.8 g (0.05 mol) of 2-amino-4-phenylthiazole (1), 2.9 g (0.05 mol) of propylene oxide and 20 ml of benzene was heated in the sealed ampoule at $60\text{-}70^\circ\text{C}$ during 8 h. After cooling an ampoule was opened, then was removed solvent and the received product recrystallized from ethyl alcohol. Yield 8.5 g (73%), m.p. $123\text{-}124^\circ\text{C}$. Found, %: C 61.32; H 6.19; N 11.78; S 13.83. $\text{C}_{12}\text{H}_{14}\text{N}_2\text{OS}$. Anal. calcd., %: C 61.51; H 6.02; N 9.52; S 10.89. Compounds (6-8) are received by a technique similar for compound (5).

Preparation of 2-(2'-hydroxypropyl)amino-4-(2'',5''-dimethoxyphenyl)thiazole (6)

Yield 8.8 g (67%), m.p. $151\text{-}152^\circ\text{C}$. Found, %: C 57.34; H 6.02; N 9.36; S 10.69. $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$. Anal. calcd., %: C 57.12; H 6.16; N 9.52; S 10.89.

Preparation of 2-(2'-hydroxypropyl)amino-4-(2''-hydroxyphenyl)thiazole (7)

Yield 9.0 g (80%), m.p. $148\text{-}149^\circ\text{C}$. Found, %: C 57.75; H 5.36; N 11.32; S 12.68. $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$. Anal. calcd., %: C 57.58; H 5.64; N 11.19; S 12.81.

Preparation of 2-(2'-hydroxypropyl)amino-4-(4''-chlorophenyl)thiazole (8)

Yield 8.8 g (65%), m.p. $154\text{-}155^\circ\text{C}$. Found, %: C 53.81; H 4.65; N 10.19; S 11.73. $\text{C}_{12}\text{H}_{13}\text{N}_2\text{OSCl}$. Anal. calcd., %: C 53.63; H 4.88; N 10.42; S 11.93.

Preparation of 2-(2'-mercaptopropyl)amino-4-phenylthiazole (9)

The mixture of 8.8 g (0.05 mol) of 2-amino-4-phenylthiazole (1), 3.7 g (0.05 mol) of propylene sulfide and 20 ml of benzene was heated in the sealed glass ampoule on a water bath at $60\text{-}70^\circ\text{C}$ during 8 h. After cooling an ampoule was opened, then was removed solvent and the received

product recrystallized from ethyl alcohol. Yield 11.2 g (72%), m.p. 143-144°C. Found, %: C 57.73; H 5.47; N 11.34; S 25.79. $C_{12}H_{14}N_2S_2$. Anal. calcd., %: C 57.56; H 5.64; N 11.19; S 25.61. Compounds (10-12) are received by a technique similar for compound (9).

Preparation of 2-(2'-mercaptopropyl)amino-4-(2'',5''-dimethoxyphenyl)thiazole (10)

Yield 11.2 g (72%), m.p. 166-167°C. Found, %: C 54.03; H 5.86; N 8.82; S 20.85. $C_{14}H_{18}N_2O_2S_2$. Anal. calcd., %: C 54.17; H 5.74; N 9.02; S 20.66.

Preparation of 2-(2'-mercaptopropyl)amino-4-(2''-hydroxyphenyl)thiazole (11)

Yield 12.0 g (69%), m.p. 171-172°C. Found, %: C 54.32; H 5.47; N 10.36; S 24.28. $C_{12}H_{14}N_2OS_2$. Anal. calcd., %: C 54.11; H 5.30; N 10.52; S 24.07.

Preparation of 2-(2'-mercaptopropyl)amino-4-(4''-chlorphenyl)thiazole (12)

Yield 10.6 g (75%), m.p. 176-177°C. Found, %: C 50.60; H 4.60; N 9.84; S 22.51. $C_{12}H_{13}N_2S_2Cl$. Anal. calcd., %: C 50.74; H 4.41; N 10.75; S 12.02.

Preparation of hydrochloride of 2-amino-4-phenylthiazole (13)

In cooled up to 0°C solution of 8.2 g (0.05 mol) of 2-amino-4-phenylthiazole (1) in izopropyl alcohol was passed dry chloride hydrogen. The received white deposit was filtered and some times was washed out a dry ether, then recrystallized from ethyl alcohol. Yield 8.5 g (85%), m.p. 175-177°C. Found, %: C 50.99; H 4.11; N 13.45; S 15.22. $C_9H_9N_2S_2Cl$. Anal. calcd., %: C 50.82; H 4.27; N 13.17; S 15.07. Compounds (14-15) are received by a technique similar for compound (13).

Preparation of hydrochloride of 2-amino-4-(2',5'-dimethoxyphenyl)thiazole (14)

Yield 11.6 g (89%), m.p. 197-198°C. Found, %: C 48.61; H 4.93; N 10.06; S 11.57. $C_{11}H_{13}N_2O_2S_2Cl$. Anal. calcd., %: C 48.44; H 4.80; N 10.27; S 11.76.

Preparation of hydrochloride of 2-amino-4-(4'-chlorphenyl)thiazole (15)

Yield 11.4 g (93%), m.p. 205-206°C. Found, %: C 43.56; H 3.42; N 11.49; S 12.57. $C_9H_8N_2S_2Cl_2$. Anal. calcd., %: C 43.74; H 3.26; N 11.33; S 12.97.

Preparation of hydrochloride of 2-acetylamino-4-phenylthiazole (16)

In cooled up to 0-5°C solution of 3.54 g (0.02 mol) of compound (1) in 10 ml of waterless toluene was added on drops a solution of 1.57 g (0.02 mol) acetylchloride. The dropped out colorless crystal deposit was filtered and recrystallized from acetone. Yield 4.58 g (90%), m.p. 168°C. Found, %: C 51.99; H 4.26; N 10.78; S 12.74. $C_{11}H_{11}N_2OS_2Cl$. Anal. calcd., %: C 51.86; H 4.35; N 11.00; S 12.59. Compounds (17) are received by a technique similar for compound (16).

Preparation of hydrochloride of 2-benzylamino-4-phenylthiazole (17)

Yield 5.51 g (87%), m.p. 195°C. Found, %: C 60.48; H 4.03; N 8.72; S 10.25. $C_{16}H_{13}N_2OS_2Cl$. Anal. calcd., %: C 60.66; H 4.14; N 8.84; S 10.12.

Preparation of 2-amino-4-phenyl-5-bromthiazole (18)

In solution of 3.54 g (0.02 mol) of compound (1) in 20 ml of an ice acetic acid at 20°C was added a solution of 3.2 g (0.02 mol) of bromine in 10 ml of an acetic acid and at the same temperature a reactionary mixture have been mixing during 30 minutes. Then was added 100 ml of water. A yellow deposit which dropped out through 2 h was filtered and recrystallized from ethyl alcohol. Yield 3.31 g (65%), m.p. 155-156°C. Found, %: C 42.58; H 2.44; N 10.68; S 12.73. $C_9H_7N_2SBr$. Anal. calcd., %: C 42.37; H 2.76; N 10.98; S 12.57.

Preparation of 2-(phenylaminocarbonylamino)-4-phenylthiazole (19)

In solution of 3.54 g (0.02 mol) of compound (1) in 20 ml of waterless toluene at stirring was added 2.4 g (0.02 mol) of phenylizocyanate. After further stirring for 24 h at 60°C the reactionary mixture was cooled up to a room temperature and the filtered colorless crystal deposit was recrystallized from acetone. Yield 5.4 g (91%), m.p. 209°C. Found, %: C 65.16; H 4.28; N 14.08; S 10.92. $C_{16}H_{13}N_3OS$. Anal. calcd., %: C 65.06; H 4.44; N 14.23; S 10.85.

Preparation of 3-hydroxy-6-phenyl-2,3,4,5-tetrahydropyrimido[1,2-b]thiazolyne-4 (20)

4.4 g (0.025 mol) of 2-amino-4-phenylthiazole (1) was dissolved in 30 ml of an ice acetic acid, was added 5.1 g (0.055 mol) of 1,2-epoxy-3-chloropropane and have been stirring for 10 h at 60-80°C. An acetic acid was evaporated, the oily rest was extracted by water, a water solution was neutralized by solution of ammonia. A deposit was filtered and recrystallized from acetone. Yield 3.31 g (57%), m.p. 170-171°C. Found, %: C 62.23; H 5.06; N 12.26; S 13.68. $C_{12}H_{12}N_2OS$. Anal. calcd., %: C 62.04; H 5.21; N 12.06; S 13.80.

Preparation of hydrochloride of 3-hydroxy-6-phenyl-2,3,4,5-tetrahydropyrimido[1,2-b]thiazolyne-4 (21)

In cooled up to 0°C solution of 4.6 g (0.02 mol) 3-hydroxy-6-phenyl-2,3,4,5-tetrahydropyrimido[1,2-b]thiazolyne-4 (20) in izopropyl alcohol was passed dry chloride hydrogen. The received white deposit was filtered and some times was washed by a dry ether and then was recrystallized from ethyl alcohol. Yield 4.8 g (90%), m.p. 118°C. Found, %: C 53.47; H 4.96; N 10.19; S 11.78. $C_{12}H_{13}N_2OSCl$. Anal. calcd., %: C 53.63; H 4.88; N 10.42; S 11.93.

Table 1. Yields, melting point and data of the element analysis of the derivatives of 2-amino-4-phenylthiazole (5-21)

Comp. No	Yield, %	M.p., °C	Founded, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
5	73	123-124	61.32	6.19	11.78	13.83	$C_{12}H_{14}N_2OS$	61.51	6.02	11.96	13.68
6	67	151-152	57.34	6.02	9.36	10.69	$C_{14}H_{18}N_2O_3S$	57.12	6.16	9.52	10.89
7	80	148-149	57.75	5.36	11.32	12.68	$C_{12}H_{14}N_2O_2S$	57.58	5.64	11.19	12.81
8	65	154-155	53.81	4.65	10.19	11.73	$C_{12}H_{13}N_2OSCl$	53.63	4.88	10.42	11.93
9	72	143-144	57.73	5.44	11.34	25.79	$C_{12}H_{14}N_2S_2$	57.56	5.64	11.19	25.61
10	72	166-167	54.03	5.86	8.82	20.85	$C_{14}H_{18}N_2O_2S_2$	54.17	5.74	9.02	20.66
11	69	171-172	54.32	5.47	10.36	24.28	$C_{12}H_{14}N_2OS_2$	54.11	5.30	10.52	24.07
12	75	176-177	50.74	4.41	9.69	22.67	$C_{12}H_{13}N_2S_2Cl$	50.60	4.60	9.84	22.51
13	85	176-177	50.99	4.11	13.45	15.22	$C_9H_9N_2SCl$	50.82	4.27	13.17	15.07
14	89	197-198	48.61	4.93	10.06	11.57	$C_{11}H_{13}N_2O_2SCl$	48.44	4.80	10.27	11.76
15	93	205-206	43.56	3.42	11.49	12.57	$C_9H_8N_2SCl_2$	43.74	3.26	11.33	12.97
16	90	168	51.99	4.26	10.78	12.74	$C_{11}H_{11}N_2OSCl$	51.86	4.35	11.00	12.59
17	87	195	60.48	4.03	8.72	10.95	$C_{16}H_{13}N_2OSCl$	60.66	4.14	8.84	10.12
18	65	155-156	42.58	2.44	10.68	12.73	$C_9H_7N_2SBr$	42.37	2.76	10.98	12.57
19	91	209	65.16	4.28	14.08	10.92	$C_{16}H_{13}N_3OS$	65.06	4.44	14.23	10.85
20	57	170-171	62.23	5.06	12.26	13.68	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	13.80
21	90	118	53.47	4.96	10.19	11.78	$C_{12}H_{13}N_2OSCl$	53.63	4.88	10.42	11.93

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