# SYNTHESIS AND PROPERTIES OF 4-AMINO-5-(5-X-2-FURYL)THIAZOLE DERIVATIVES

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Received September 9th, 1983

Reaction of dipotassium cyanimidodithiocarbonate ($(KS)_2C{=}N{-}CN$) with 5-X-furfuryl halogenides (X = $NO_2$, CHO) and 4-nitrobenzyl bromide gives the disubstituted esters which, in alkali medium, gives the carbanions undergoing cyclization to 4-amino-5-(5-X-2-furyl)thiazoles and 4-amino-5-(4-nitrophenyl)-2-(4-nitrobenzylthio)thiazole, respectively. Reaction of 5-X-furfuryl halogenides or 4-nitrobenzyl bromide with potassium methyl cyanimidodithiocarbonate ($KSC(SCH_3){=}N{-}CN$) gives the esters which are cyclized to 4-amino-2-methylthio-5-substituted thiazoles. The starting esters with X = $COOCH_3$ give no carbanion and undergo no cyclization under the same conditions. The 4-amino group in the thiazole is easily acylated and diazotized, but it does not undergo alkylation. $^1$H NMR, UV, and IR spectra of the compounds prepared are discussed.

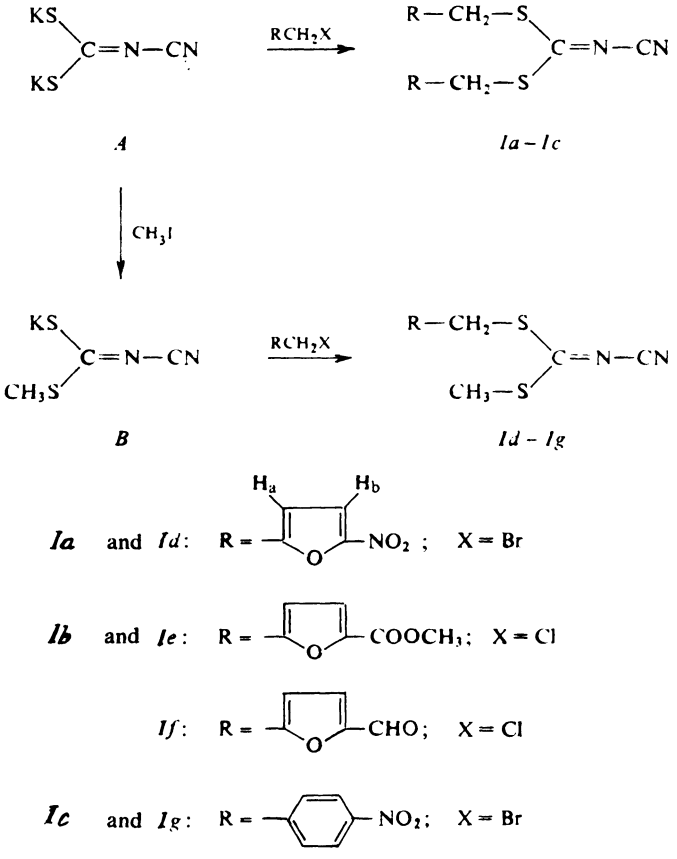
The compounds containing both 5-nitrofurane and, simultaneously, thiazole rings exhibit high biological activity against both gram-positive and gram-negative bacteria along with relatively low toxicity[1-3]. Such derivatives include especially 2-formylamino-4-(5-nitro-2-furyl)thiazole and 2-acetylamino-4-(5-nitro-2-furyl)thiazole (Furathiazole), the activity of the latter being not surpassed by any of further derivatives containing the 5-nitro-2-furyl residue at 4-position of thiazole ring[4,5].

This communication deals with synthesis, reactions, and properties of the compounds containing the 5-X-2-furyl residue at 5-position of thiazole ring. The synthesis of these compounds utilizes cyanimidodithiocarbonate esters containing the electron-withdrawing furfuryl or 4-nitrobenzyl residues (Scheme 1). Derivatives of this type represent sufficiently strong C—H acids which give the respective carbanions in basic media, and these carbanions undergo cyclizations[6].

The dipotassium salt *A* formed by reaction of cyanamide, carbon disulphide and potassium hydroxide in ethanol[7] reacts with equimolar amount of methyl iodide in aqueous–acetone solution to give the respective monopotassium salt *B* (ref.[8]). The salts *A* and *B* react with furfuryl halogenides and benzyl halogenides to give the corresponding furfuryl and benzyl esters of cyanimidodithiocarbonic acid *Ia–Ig*. These compounds are colourless to yellow substances soluble in most organic solvents

but slightly soluble in water. Their physico-chemical characteristics and elemental analyses are summarized in Tables I and II.

The electronic spectra of compounds *Ia–Ig* depend on the substituent R, the positions of absorption bands being unchanged on transition from the monofuryl (monophenyl) derivatives to difuryl (diphenyl) derivatives (the intensity only being changed). The IR spectra of compounds *Ia–Ig* contain the bands due to the functional groups present and to furane and benzene rings, and, besides that, also a characteristical absorption band at 2 100–2 200 $cm^{-1}$ due to valence vibrations of CN group. In the $^1H$ NMR spectra of compounds *Ia–Ic* the structural groupings $RCH_2S$— are magnetically equivalent due to the symmetry of these molecules. Substitution of one $RCH_2$— group by methyl group causes no distinct changes in chemical shifts of the protons of the other $RCH_2$— group, which indicates that mutual influence between these two groups through the —S—C(=S)—S— grouping is negligible.




SCHEME 1

TABLE I

Physical constants, elemental analyses, and UV and IR spectral data of the compounds synthetized

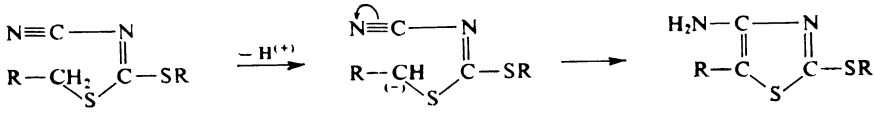
| Compound | Formula (m.w.) | M.p., °C (yield, %) | Calculated/Found | | UV $\lambda_{max}$[a], nm (log ε; $m^2$ $mol^{-1}$) |
|---|---|---|---|---|---|
| | | | % N | % S | |
| *Ia* | $C_{12}H_8N_4O_6S_2$ (368) | 115–116 (44) | 15·22 15·23 | 17·39 17·21 | 263 (3·23) 313 (3·44) |
| *Ib* | $C_{16}H_{14}N_2O_6S_2$ (394) | 135·5 (80) | 7·11 7·58 | 15·96 15·96 | 268 (3·61) |
| *Ic* | $C_{16}H_{12}N_4O_4S_2$ (380) | 130–131 (70) | 14·77 14·82 | 16·84 16·55 | 275 (3·39) |
| *Id* | $C_8H_7N_3O_3S_2$ (257) | 104 (86) | 16·34 16·43 | 24·20 24·32 | 261 (3·24) 316 (3·20) |
| *Ie* | $C_{10}H_{10}N_2O_3S_2$ (270) | 83·5 (82) | 10·37 10·55 | 23·70 23·38 | 268 (3·44) |
| *If* | $C_9H_8N_2O_2S_2$ (240) | 73·5 (66) | 11·67 11·69 | 26·67 26·83 | 282 (3·50) |
| *Ig* | $C_{10}H_9N_3O_2S_2$ (267) | 65–67 (96) | 15·73 16·26 | 23·97 23·74 | 270 (3·43) |
| *IIa* | $C_{12}H_8N_4O_6S_2$ (368) | 141 151–152 (55) | 15·22 15·38 | 17·33 17·02 | 315 (3·23) 474 (3·29) |
| *IIb* | $C_{16}H_{12}N_4O_4S_2$ (388) | 181–182 195 (65) | 14·74 14·45 | 16·84 16·49 | 273 (3·27) 418 (3·24) |
| *IIc* | $C_8H_7N_3O_3S_2$ (257) | 210–213 (69) | 16·34 16·31 | 24·30 24·50 | 243 (3·00) 272 (2·95) 302 (2·84) 336 (2·74) 472 (3·36) |
| *IId* | $C_9H_8N_2O_2S_2$ (240) | 46–46·5 (42) 123 (47) | 11·67 11·29 | 26·67 26·83 | 223 (3·07) 252 (3·00) 277 (2·78) 410 (3·38) |
| *IIe* | $C_{10}H_9N_3O_3S_2$ (267) | 177 (98) | 15·73 16·16 | 23·67 23·53 | 274 (2·98) 422 (3·23) |
| *IIIa* | $C_{14}H_{10}N_4O_7S_2$ (410) | 161–162 (91) | 13·66 14·08 | 15·61 15·04 | 314 (3·27) 394 (3·32) |
| *IIIb* | $C_{18}H_{14}N_4O_5S_2$ (430) | 187·5 (91) | 13·02 12·96 | 14·88 14·67 | 265 (2·97) 355 (2·85) |

TABLE I
(*Continued*)

| Compound | Formula (m.w.) | M.p., °C (yield, %) | Calculated/Found | | UV $\lambda_{max}$[a] (nm) (log ε; $m^2$ $mol^{-1}$) |
|---|---|---|---|---|---|
| | | | % N | % S | |
| *IIIc* | $C_{12}H_{11}N_3O_5S_2$ (341) | 148<br>208–210<br>(87) | 12·31<br>12·42 | 18·76<br>19·12 | 298 (2·90)<br>397 (3·21) |
| *IVa* | $C_8H_5N_5O_3S_2$ (283) | 140<br>(98) | 24·73<br>24·77 | 22·61<br>22·80 | 225 (3·00)<br>260 (3·06)<br>301 (2·90)<br>416 (3·23) |
| *IVb* | $C_{12}H_{11}N_3O_3S_2$ (309) | 196–197<br>(92) | 13·59<br>13·86 | 20·71<br>20·90 | 257 (3·01)<br>357 (3·13) |
| *IVc* | $C_{10}H_7N_5O_2S_2$ (293) | 120–121<br>(98) | 23·89<br>23·14 | 21·84<br>21·30 | 263 (3·17)<br>387( 3·23) |

[a] IR spectrum ($cm^{-1}$): ν(CN) *Ia* 2 190, *Ib* 2 170, *Ic* 2 180, *Id* 2 190, *Ie* and *If* 2 185, *Ig* 2 182 ν(CO) *Ib* 1 710, *Ie* 1 715, *If* 1 755, *IIIa* 1 670; $\nu(N_3)$ *IVa* 2 090, 2 150, *IVc* 2 095, 2 155.

The compounds *Ia*–*Ig* are stable in such solvents as dioxane, benzene, tetrachloromethane, acetic acid; however, in alcohols and especially in amines most of them undergo cyclizations to the corresponding 4-aminothiazole derivatives, the cyclization rate depending on character of the substituent. The more electron-withdrawing is the R substituent, the faster is the cyclization (Scheme 2). Thus the compounds



SCHEME 2

*Ia*, *Ic*, *Id*, *If*, and *Ig* are cyclized sufficiently fast in good yields to the derivatives *IIa*–*IIe* by action of triethylamine, pyridine, alkali hydroxides, *etc.* All our attempts at preparations of the thiazole derivatives from compounds *Ib* and *Ie* (which have $COOCH_3$ group at 5-position of the furane ring) at comparable conditions failed, due to the insufficient acidifying effect of the methoxycarbonyl group on the adjacent methylene hydrogen atoms. Such weak effect of $COOCH_3$ group on acidity of the adjacent $CH_2$ group was also observed with other C—H acids[9]. Instead of the cyclization they underwent nucleophilic substitution on action of bases at the —$SCH_3$

and —$SCH_2R$ groups to give the respective mercaptans. Similar reactions were also observed with dialkyl cyanimidodithiocarbonates[10]. The 4-aminothiazoles *IIa*–*IIe* mostly exist in several crystalline modifications, which is similar[1] to 2-amino-4-(5-nitro-2-furyl)thiazole. Thus *e.g.* 4-amino-2-(5-nitrofurfurylthio)-5-(5-nitro-2-furyl)thiazole (*IIa*) crystallizes from toluene in the form of red needles, m.p. 141°C, which recrystallize on melting into red prisms, m.p. 151–152°C. The crystals with m.p. 151–152°C are also obtained on cooling of a melted sample of the compound. 4-Amino-2-methylthio-5-(5-nitro-2-furyl)thiazole (*IIc*) gives red prisms (m.p. 210 to 211°C) from ethanol, but crystallization from toluene gives red needles which – at 170–180°C – change to other needles with m.p. 213°C. Also 4-amino-5-(5-formyl-2-furyl)-2-methylthiothiazole (*IId*) was obtained in two crystalline modifications, *viz.* yellow needles from toluene (m.p. 123°C) and yellow plates (m.p. 46–46·5°C)

TABLE II

$^1$H NMR spectral data of the compounds synthetized

| Compound | $H_a$ ($H'_a$) | $H_b$ ($H'_b$) | $J_{ab}$ ($J_{a'b'}$) | —$SCH_2$— | —$SCH_3$ | Other groups |
|---|---|---|---|---|---|---|
| *Ia* | 6·92 | 7·51 | 3·7 | 4·83 | — | — |
| *Ib* | 6·68 | 7·30 | 4·1 | 4·75 | — | 3·87 $COOCH_3$ |
| *Ic* | 7·68 | 8·18 | 8·7 | 4·68 | — | — |
| *Id* | 6·88 | 7·51 | 3·7 | 4·75 | 2·92 | — |
| *Ie* | 6·68 | 7·20 | 4·1 | 4·68 | 2·80 | 3·90 $COOCH_3$ |
| *If* | 6·67 | 7·44 | 3·7 | 4·64 | 2·67 | 9·49 CHO |
| *Ig* | 7·65 | 8·16 | 8·8 | 4·60 | 2·65 | — |
| *IIa* | 6·75 (6·90) | 7·65 (7·50) | 4·1 (3·5) | 4·75 | — | — |
| *IIb* | 7·76 (7·57) | 8·19 (8·17) | 8·4 (9·0) | 4·60 | — | — |
| *IIc* | 6·83 | 7·73 | 4·1 | — | 2·67 | — |
| *IId* | 6·71 | 7·52 | 4·0 | — | 2·63 | 9·35 CHO |
| *IIe* | 7·47 | 8·06 | 9·0 | — | 2·61 | — |
| *IIIa* | 6·87 (6·93) | 7·62 (7·47) | 4·1 (3·6) | 4·78 | — | 2·22 $NCOCH_3$ |
| *IIIb* | 7·80 (7·58) | 8·18 (8·19) | 7·8 (8·4) | 4·60 | — | 1·97 $NCOCH_3$ |
| *IIIc* | 6·81 | 7·50 | 4·04 | — | 2·85 | 2·60 $N(COCH_3)_2$ |
| *IVa* | 6·83 | 7·50 | 4·00 | — | 2·81 | — |
| *IVb* | 7·60 | 8·16 | 9·1 | — | 2·65 | 1·95 $NCOCH_3$ |
| *IVc* | 7·73 | 8·15 | 9·0 | — | 2·69 | — |

obtained from the ethanolic mother liquor after recrystallization from toluene. The $^1$H NMR, UV, and mass spectra of the said modifications of a given compound are identical, very small differences being only observed in the intensities of the absorption bands in the IR spectra measured by the KBr technique.

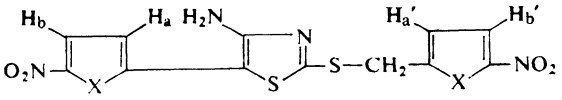
The electronic spectra of the aminothiazoles *IIa*–*IIe* (Table I) indicate strong conjugation between the 5-nitrofurane (or 4-nitrophenyl) residue and the thiazole ring. The electronic and $^1$H NMR spectra suggest that the nitrofurane and nitrophenyl rings have different effects on the thiazole ring. The nitrofurane residue behaves to the thiazole cycle as an electron-withdrawing substituent, whereas the nitrophenyl group shows an electron-donor effect. This can be seen very well when the $^1$H NMR spectra of compounds *IIa*, *IIb* are compared with those of the starting compounds *Ia* and *Ic*. The proton chemical shifts of the nitrofurane (or nitrophenyl) cycle directly bound with the thiazole cycle are shifted as compared with those of the same cycles bound through a methylene group, the $H_a$ proton signal of the nitrofurane nucleus being shifted upfield from that of $H'_a$, and $H_b$ downfield from $H'_b$ (Table II). These facts indicate the donor character of thiazole cycle with respect to 5-nitrofurane ring. In the nitrophenyl nucleus bound to the thiazole cycle, the both proton signals $H_a$ and $H_b$ are shifted downfield as compared with the proton signals $H'_a$ and $H'_b$, hence in this case thiazole cycle deshields the benzene nucleus.

The 4-aminothiazoles *IIa*–*IIe* do not react with alkyl halides, but react easily with acetanhydride, giving the respective monoacyl amines (after short boiling, below 30 min) or diacylamines (after longer boiling, above 1 h) *IIIa*–*IIIc* and *IVb* in high yields. 4-Amino-5-(5-formyl-2-furyl)-2-methylthiothiazole (*IId*) did not give the amide at these conditions, instead the reaction mixture resinified. Some of these amides exist in several crystalline modifications, which is similar to the 4-aminothiazole derivatives *IIa*–*IId*. Thus *e.g.* diamide *IIIc* crystallizes from dilute acetic acid in the form of yellow plates, m.p. 148°C, the melt being recrystallized to needles, m.p. 208–210°C.

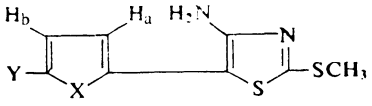
Amines *IIc* and *IIe* are easily diazotized with $NaNO_2$ in a mixture of acetic acid and concentrated sulphuric acid. The diazonium salts react quantitatively with $NaN_3$ to the corresponding azides *IVa* and *IVc* which are stable up to their melting points.

Comparison of electronic absorption spectra of the corresponding amines, amides, and azides *IIc*, *IIIc*, *IVa* shows that the K-band of these compounds is shifted hypsochromically from the amine (*IIc*, 472 nm) to azide (*IVa*, 416 nm), and diamide (*IIIc*, 397 nm). Hence, the azide group —$N_3$ represents a much weaker electron donor as compared with $NH_2$-group, but a stronger one with respect to the —$N(COCH_3)_2$ group. Analogous trends are also observed when comparing the K-bands of compounds *IIe*, *IVb*, *IVc*.

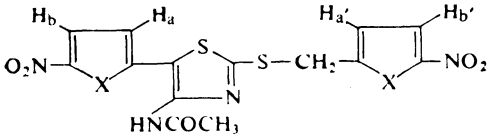
The mass spectra of the compounds synthetized show besides their molecular peaks also typical ionic peaks of decomposition of the furane ring, *i.e.* show the splitting off of Y$^\bullet$ radical and CO and formation of cyclopropenyl cation. All the



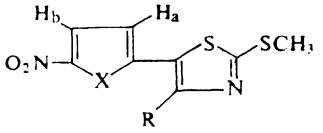
*IIa*, X = O
*IIb*, X = —CH=CH—



*IIc*, X = O; Y = $NO_2$
*IId*, X = O; Y = CHO
*IIe*, X = —CH=CH—; Y = $NO_2$

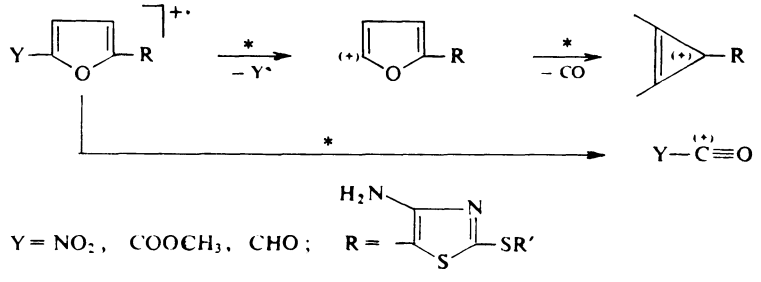


*IIIa*, X = O
*IIIb*, X = —CH=CH—



*IIIc*, X = O, R = $N(COCH_3)_2$
*IVa*, X = O, R = $N_3$
*IVb*, X = —CH=CH—; R = $NHCOCH_3$
*IVc*, X = —CH=CH—; R = $N_3$

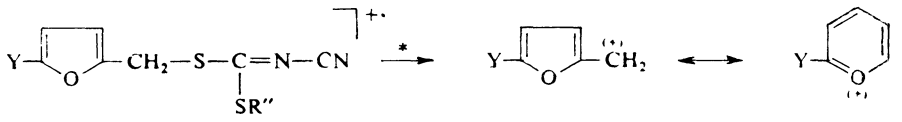
spectra exhibit the peaks due to the Y—C≡$O^{(+)}$ ion which characterize the Y substituents at 5-position of furane ring (Scheme 3). In addition, the acyclic esters *Ia*–*Ig* are



SCHEME 3

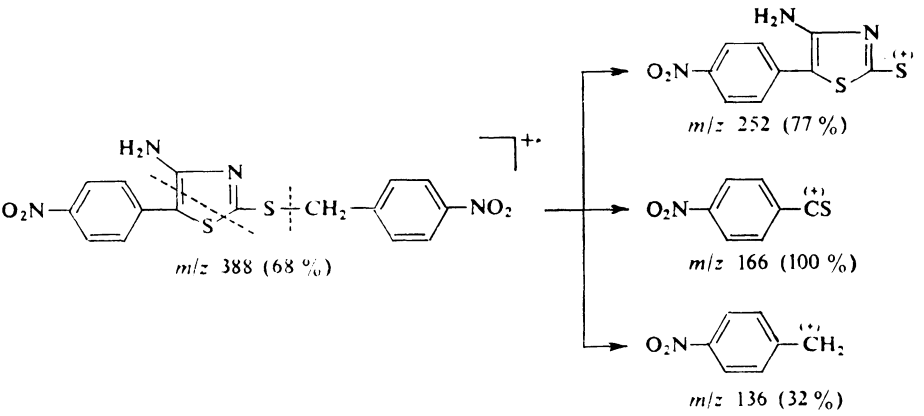
characterized by the decomposition to a 5-substituted furfuryl cation (Scheme 4). Structure of the cyclic products is also confirmed by analysis of their mass spectra.

The 4-aminothiazole derivatives *IIa–IIe* showed, in all cases, relatively intensive



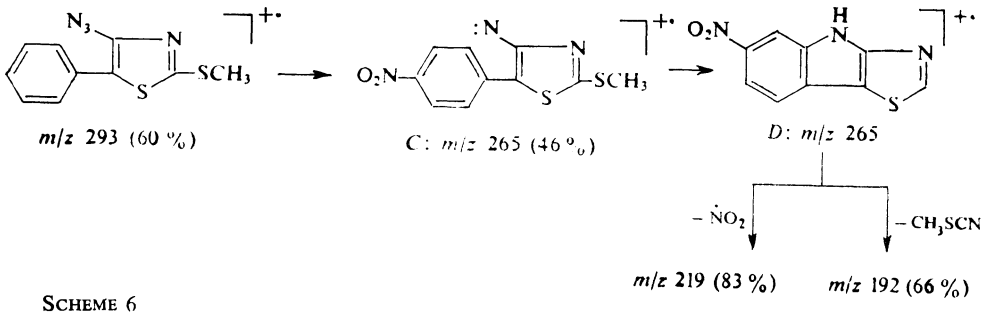
SCHEME 4

molecular peaks and the molecular fragments illustrated by the example of decomposition of the *IIb* molecule (Scheme 5). The most interesting decomposition is that of the azides *IVa* and *IVc* in which the molecular ion splits off a nitrogen molecule




SCHEME 5

to give the cation-radical *C* which is isomerized to a more stable ion-radical of benzopyrrolethiazole *D*, because none of subsequent fragmentations involves splitting of the exocyclic C—N bond present in structure *C* (Scheme 6). The azide *IVa* is fragmented in similar way.




SCHEME 6

## EXPERIMENTAL

The melting points were determined with a Kofler apparatus. The $H^1$ NMR spectra were measured with a Tesla BS 487 B 80 MHz apparatus in hexadeuteriodimethyl sulphoxide or hexadeuterioacetone with tetramethylsilane as internal standard. The IR spectra were measured with a UR-20 apparatus (Zeiss, Jena) in KBr discs (2 mg of the substance per 1 g KBr). The electronic absorption spectra were measured with a UV VIS apparatus in dioxane in 1 cm cells at the concentrations of the substances $5 \cdot 10^{-5}$ mol $l^{-1}$; the accuracy of readings was $\pm 1$ nm. The mass spectra were measured with an AEI MS-902 apparatus at 70 eV.

### Cyanimidodithiocarbonate Esters *Ia*—*Ic*

A suspension of 0·97 g (5 mmol) dipotassium cyanimidodithiocarbonate in 25 ml ethanol (*Ia*), ethyl acetate (*Ib*), or 80% acetone (*Ic*) was treated with a solution of 10 mmol respective halogenide in the same volume of the same solvent. The mixture was stirred at room temperature 4 h, the separated KCl was collected by suction, the filtrate was evaporated, and the residue was recrystallized from toluene (*Ia*), ethanol (*Ib*), or ethyl acetate (*Ic*).

### Cyanimidodithiocarbonate Esters *Id*—*Ig*

A solution of 1·7 g (10 mmol) potassium methyl cyanimidodithiocarbonate in 20 ml ethyl acetate (*Id*, *Ig*), 50 ml acetone (*Ie*), or 50 ml ethanol (*If*) was treated with 10 mmol respective halogenide in small amount of the same solvent. The mixture was stirred at room temperature 4 h (*Id*, *Ie*, *Ig*) or refluxed on water bath 5—10 min and then stirred at room temperature 4 h (*If*). The KBr precipitated was collected by suction, the filtrate was evaporated in vacuum, and the residue was recrystallized from toluene (*Id*), ethyl acetate–light petroleum (*Ie*), or ethyl acetate (*Ig*). For isolation of the product *If* the mixture was diluted with 300 ml water, the separated oil was extrated with 3 × 100 ml ethyl acetate, the extract was dried with $Na_2SO_4$, the solvent was evaporated in vacuum, and the residue was recrystallized from a 1 : 5 mixture diethyl ether–light petroleum at −78°C.

### 4-Amino-2,5-disubstituted Thiazoles *IIa*—*IIe*

For preparation of derivatives *IIa* and *IIb* the solution of 10 mmol respective halogenide in 20 ml methanol and acetone, resp., was treated with 5 mmol potassium cyanimidodithiocarbonate in the same volume of the same solvent and 2—3 drops triethylamine at room temperature. The solution turns red and, after 3 h, separates red crystals of *IIa*; the product was recrystallized from toluene. For isolation of derivative *IIb*, the mixture was diluted with 100 ml water, and the precipitated product was recrystallized from toluene.

The methylthio derivatives of 4-aminothiazole *IIc* and *IIe* were prepared in the following way: A solution of 2·71 g (16 mmol) methyl cyanimidodithiocarbonate in 25 ml methanol was treated with 15 mmol respective halogenide and 2—3 drops triethylamine. The exothermic reaction ceased after 2—5 min, the solution was cooled, the separated crystals were collected by suction, washed with water, and recrystallized from toluene. Derivative *IId* was prepared by cyclization of the corresponding ester *If* (1·7 g; 7·1 mmol) in 25 ml methanol with addition of 2—3 drops triethylamine. The mixture was left to stand overnight, then it was cooled at −20°C, the separated crystalline solid was collected by suction, washed with cold ethanol (−78°C), and recrystallized from toluene to give yellow needles, m.p. 123°C, yield 0·8 g (47)%. The filtrate was treated with 200 ml water, the separated crystalline solid was collected by suction and recrystallized from toluene to give yellow plates, m.p. 46—46·5°C, yield 0·7 g (42%).

Amides of 4-Aminothiazole Derivatives *IIIa—IIIc*, *IVb*

The respective amine (3 mmol) was boiled with 25 ml acetanhydride, the mixture was diluted with 20 ml water and slowly heated until an exothermic reaction, whereupon the mixture was poured in 100 ml cold water. The separated crystalline solid was collected by suction and recrystallized from toluene (*IIIa*), ethyl acetate (*IIIb*, *IVb*), or acetic acid (*IIIc*).

Azides *IVa* and *IVc*

A solution of 0·5 g (7·2 mmol) sodium nitrite in 15 ml acetic acid was cooled at 10—15°C and 5 ml concentrated sulphuric acid was added thereto. After 10—15 min, 4 mmol respective amine dissolved in 20 ml acetic acid was added with stirring. After 30 min, the mixture was treated with a solution of 0·5 g (7·7 mmol) sodium azide in 1 ml water, whereupon it was stirred until the nitrogen evolution ceased (about 1 h). The reaction mixture was poured in 100 ml ice water, the precipitate was collected by suction, washed with water until neutral, and recrystallized from ethyl acetate–toluene mixture (*IVa*) or toluene (*IVc*).

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Translated by J. Panchartek.