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Preparation of 5-Aminothiazole-4-carboxylic Acid Derivatives

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Cyclization of 2-acylamino-2-thiocarbamoylacetamides (Va,b) with acetic formic anhydride gave good yields of 5-formamidothiazole-4-carboxamides (VIa,b) which were converted to 5-aminothiazole-4-carboxamides (VIIa,b) by hydrolysis. For the purpose of the preparation of the free base (VIIa), however, cyclization of Va with polyphosphoric acid was proved to give better result, that is, heating of Va-c and ethyl 2-acylamino-2-thiocarbamoylacetates (Vd-f) in polyphosphoric acid gave VIIa—c and ethyl 5-aminothiazole-4-carboxylates (VIId-f) in excellent yields. 5-Aminothiazole-4-carbonitriles (VIIg,h) were prepared by treatment of Va,b with phosphorus oxychloride.

In connection with a study in our laboratory, 5-aminothiazole-4-carboxylic acid derivatives (VIIa—h) were needed. Several routes[2-4] have been reported on the syntheses of 5-aminothiazole-4-carboxylic acid derivatives. Cook, Heilbron and Smith[2e] have prepared 5-aminothiazole-4-carboxamide (VIIa) by reaction of 2-amino-2-cyanoacetamide with sodium dithioformate in 42% yield. Recently, Sekiya and Osaki[4] have reported that cyclization of 2-formamido-2-thiocarbamoylacetamide (Va) by refluxing in acetic anhydride gave 5-acetamidothiazole-4-carboxamide, whose hydrolysis gave VIIa, though in low yield. In order to improve the yield of VIIa, cyclizations of Va with polyphosphoric acid, acetic formic anhydride and phosphorus oxychloride were investigated. Heating Va in polyphosphoric acid gave VIIa in 92% yield and the procedure was proved to be an excellent and general method for the preparation of a variety of 5-aminothiazole-4-carboxylic acid derivatives shown in Table I. Cyclization of Va with acetic formic anhydride gave 89% yield of 5-formamidothiazole-4-carboxamide (VIa), but hydrolysis of VIa to VIIa was not satisfactory. Treatment of Va with phosphorus oxychloride gave 5-aminothiazole-4-carbonitrile (VIIg) in 25% yield.

Materials to be cyclized, 2-acylamino-2-thiocarbamoylacetamides (Va,[4] Vb[4] and Vc) and ethyl 2-acylamino-2-thiocarbamoylacetates (Vd, Ve[5] and Vf), were prepared by the routes shown in Chart 1. Reduction of 2-cyano-2-hydroxyiminoacetamide[6,7] (IIa) and ethyl 2-cyano-2-hydroxyiminoacetates[6,8] (IIb) with zinc powder or aluminum-amalgam followed by acylation yielded 2-acylamino-2-cyanoacetamides (IVa,[4] IVb[4,7] and IVc) and ethyl 2-acylamino-2-cyanoacetates (IVd, IVe[9a] and IVf[9b]). Reduction and subsequent

1) Location: 6-5, *Toneyama, Toyonaka, Osaka.*
2) *a*) A.H. Cook, Sir Ian Heilbron and A.L. Levy, *J. Chem. Soc.*, **1947**, 1594; *b*) *idem, ibid.*, **1947**, 1598; *c*) C.W. Capp, A.H. Cook, J.D. Downer and Sir Ian Heilbron, *ibid.*, **1948**, 1340; *d*) A.H. Cook, J.D. Downer and Sir Ian Heilbron, *ibid.*, **1948**, 2028; *e*) A.H. Cook, Sir Ian Heilbron and E. Smith, *ibid.*, **1949**, 1440; *f*) A.H. Cook, Sir Ian Heilbron and G.D. Hunter, *ibid.*, **1949**, 1443.
3) G. Show and D.N. Butler, *J. Chem. Soc.*, **1959**, 4040.
4) M. Sekiya and Y. Osaki, *Chem. Pharm. Bull.* (Tokyo), **13**, 1319 (1965).
5) A.G. Long and A. Tulley, *J. Chem. Soc.*, **1964**, 1190.
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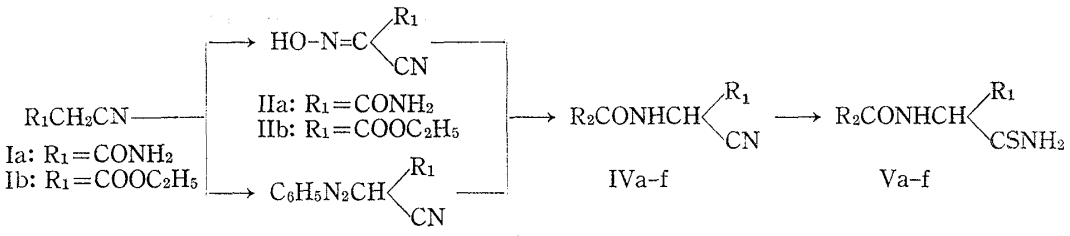
9) *a*) S. Tatsuoka, T. Kinoshita and R. Nakamori, *Yakugaku Zasshi*, **71**, 702 (1951); *b*) Wm. G.M. Jones, G.R. Ramage and Imperial Chemical Industries Ltd., Brit. Patent 596537 (1948) [*C.A.*, **42**, 7342e (1948)].

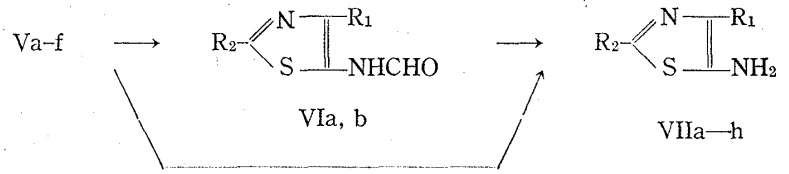
acylation of 2-cyano-2-phenylazoacetamide[10] (III) also gave IVa,b. Treatment of IVa—f with hydrogen sulfide in the presence of ammonia or triethylamine as a basic catalyst gave Va—f.



IVa, Va: $R_1=CONH_2$, $R_2=H$
IVb, Vb: $R_1=CONH_2$, $R_2=CH_3$
IVc, Vc: $R_1=CONH_2$, $R_2=C_6H_5$
IVd, Vd: $R_1=COOC_2H_5$, $R_2=H$
IVe, Ve: $R_1=COOC_2H_5$, $R_2=CH_3$
IVf, Vf: $R_1=COOC_2H_5$, $R_2=C_6H_5$

Chart 1

Cyclization of Va with acetic formic anhydride[11] at 80—90° for 4.5 hr gave 89% yield of 5-formamidothiazole-4-carboxamide (VIa) which was also prepared by formylation of 5-aminothiazole-4-carboxamide (VIIa) with acetic formic anhydride. Similar treatment of 2-acetamido-2-thiocarbamoylacetamide (Vb) produced 5-foramido-2-methylthiazole-4-carboxamide (VIb) in 61% yield. Hydrolysis of VIa,b with 5% hydrochloric acid gave 5-aminothiazole-4-carboxamides (VIIa,b) in 31% and 69% yields, respectively. However, cyclodehydration of Va—f with polyphosphoric acid described in the following paragraph was found to be superior for the preparation of VII a—f.



VI a, VII a: $R_1=CONH_2$, $R_2=H$
VI b, VII b: $R_1=CONH_2$, $R_2=CH_3$
VII c: $R_1=CONH_2$, $R_2=C_6H_5$
VII d: $R_1=COOC_2H_5$, $R_2=H$
VII e: $R_1=COOC_2H_5$, $R_2=CH_3$
VII f: $R_1=COOC_2H_5$, $R_2=C_6H_5$
VII g: $R_1=CN$, $R_2=H$
VII h: $R_1=CN$, $R_2=CH_3$

Chart 2

Heating Va in polyphosphoric acid at 100—110° for 8 hr gave 92% yield of VIIa which was identified with the authentic sample[2e,4] by comparison of the melting point, infrared (IR) and ultraviolet (UV) spectra. High yield and purity of the product (VIIa) would be partly owing to the stabilization of the product in polyphosphoric acid medium. Cyclization reactions of Va—f with the other condensing agents such as hydrogen chloride, phosphorus pentoxide, phosphorus trichloride, phosphorus pentachloride, polyphosphate ester and phosphorus oxychloride were attempted, but noticeable results were not obtained except reaction with phosphorus oxychloride, which will be mentioned below. Cyclization of Vb—f with polyphosphoric acid proceeded similarly and gave 5-aminothiazole-4-carboxamides (VIIb[4] and VIIc) and ethyl 5-aminothiazole-4-carboxylates (VIId,[2a,b] VIIe and VIIf) in 71—83% yields as shown in Table I.

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Table I. Reaction Conditions for the Preparation of 5-Aminothiazoles (VIIa—f) and Their Results

Starting material	Reaction conditions: Bath temp. (°C)	Reaction conditions: Time (hr)	Product	Yield (%)	mp(°C)[a] (Recryst. solvt.)	UV λ_{max}^{EtOH} mμ(log ε)
Va	100—110	8	VIIa	92	140—141[b,c] ($CHCl_3$)	279(3.96)
Vb	95—105	2.5	VIIb	80	182.5—183.5[d] ($CHCl_3$)	281(3.94)
Vc	70—80	1	VIIc	72	197—198.5 (C_2H_5OH)	338 291(sh.)
Vd	100—110	2.5	VIId	81	164—165[e,f] (C_2H_5OH)	280(3.69)
Ve	100—110	1.5	VIIe	83	158—159 (C_6H_6)	286(3.99)
Vf	65—70	2	VIIf	71	139—140 (CH_3OH-H_2O)	331(4.20) 291(sh.)

Product	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIIa	$C_4H_5ON_3S$	33.57	3.52	29.37	33.53	3.49	28.79
VIIb	$C_5H_7ON_3S$	38.22	4.49	26.74	38.52	4.38	26.37
VIIc	$C_{10}H_9ON_3S$	54.79	4.14	19.17	54.93	4.11	19.21
VIId	$C_6H_8O_2N_2S$	41.86	4.68	16.28	42.22	4.63	16.07
VIIe	$C_7H_{10}O_2N_2S$	45.15	5.41	15.04	45.70	5.34	14.92
VIIf	$C_{12}H_{12}O_2N_2S$	58.06	4.87	11.29	57.86	4.75	11.24

a) All melting points were uncorrected. *b*) lit.[3c] mp 140—141° *c*) lit.[4] mp 140—142°
d) lit.[4] mp 175—177° *e*) lit.[3a] mp 163.5° *f*) lit.[3b] mp 163°

Treatment of 2-acetamido-2-cyanothioacetamide (VIII) with polyphosphoric acid resulted in the cyclization with concomitant hydrolysis of the nitrile group to give 66% yield of VIIb. However, Vb and VIII when treated with phosphorus oxychloride provided 26% and 12% yields of 5-amino-2-methylthiazole-4-carbonitrile[3] (VIIh), respectively, which was converted by hydrolysis with polyphosphoric acid to VIIb in 93% yield. Similarly, Va was cyclized by phosphorus oxychloride to 5-aminothiazole-4-carbonitrile[3] (VIIg) in 25% yield. It was also found that phosphorus oxychloride effected cyclization of Ve to VIIe in 77% yield.

Experimental[12]

2-Cyano-2-formamidoacetamide (IVa)——To a stirred suspension of 25 g of zinc powder in 140 ml of of 99—100% formic acid was added in portions 9.6 g of 2-cyano-2-phenylazoacetamide[10] (III) at 30—35° over a period of 2 hr under a nitrogen atmosphere. After additional stirring for 30 min the solids were filtered from the reaction mixture and washed with formic acid. The filtrate and washing were combined and concentrated under reduced pressure. The concentration was repeated with several additions of water until the odor of the acid was no longer evident. The residue was taken up in about 50 ml of water and freed of zinc by means of hydrogen sulfide. The filtrate from the zinc sulfide was evaporated to dryness. The residue was dissolved in ethanol, concentrated and cooled to give 3.9 g (60%) of crystals. Recrystallization from methanol gave IVa, mp 153—154° [lit.[4] mp 154—155° (decomp.), mp 153—155°], which was identified with a sample prepared by the mthod of Sekiya.

12) All melting points were uncorrected.

2-Acetamido-2-cyanoacetamide (IVb)——To a stirred suspension of 15 g of zinc powder in 100 ml of glacial acetic acid was added in portions 9.3 g of III at 30—33° over a period of 2 hr. After additional stirring for 30 min the solids were filtered and washed with acetic acid. The filtrate and washing were combined, concentrated under reduced pressure to half volume and 10 ml of acetic anhydride was added. The precipitated material was removed by filtration and the filtrate was treated in a similar manner to that described for IVa to give 2.9 g (41%) of IVb, mp 171—174° (lit.[4] mp 173—174°), which was identified with a sample prepared by the method of Sekiya.

2-Benzamido-2-cyanoacetamide (IVc)——To a stirred solution of 10.2 g of 2-cyano-2-hydroxyiminoacetamide[6,7] (IIa) in 60 ml of ether containing 30 ml of water was added in pieces Al-Hg (prepared from 4.4 g of Al foil) at 30—35° over a period of 20 min. The stirring was continued for 4 hr. The precipitate was filtered and washed with 140 ml of water and 20 ml of ether. The filtrate and washing were combined, saturated with 15.2 g of sodium hydrogen carbonate and 10 ml of benzoyl chloride was added dropwise with vigorous stirring. After stirring for 2 hr the crystalline material was collected, washed with water and ether. Recrystallization from ethanol gave 4.9 g (26.8%) of IVc, mp 181.5—183°. *Anal.* Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.13; H, 4.33; N, 20.70.

Ethyl 2-Cyano-2-formamidoacetate (IVd)——To a stirred solution of 7.1 g of ethyl 2-cyano-2-hydroxyiminoacetate[6,8] (IIb) in 8 ml of ether were added in pieces Al-Hg (prepared from 4.4 g of Al foil) and 4 ml of water below 25° over a period of 10 min. After additional stirring for 2 hr the precipitate was removed by filtration and washed with 100 ml of ether. Acetic formic anhydride, prepared by warming 11.5 ml of anhydrous formic acid and 27.5 ml of acetic anhydride at 50—60° for 2 hr,[11] was added to the combined solution of filtrate and washing, kept at room temperature for 40 min and concentrated under reduced pressure. The concentration was repeated with several additions of ethanol to yield crystals, which were recrystallized from ethanol–ether to give 3.6 g (46.2%) of IVd as colorless needles, mp 61—61.5°. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.40; H, 5.04; N, 17.72.

2-Benzamido-2-thiocarbamoylacetamide (Vc)——To a solution of 1 g of IVc in 30 ml of ethanol and 10 ml of methanol was added 0.69 ml of triethylamine. Hydrogen sulfide was bubbled through the solution at room temperature for 4 hr. The precipitated crystals were collected by filtration. The filtrate was saturated again with hydrogen sulfide at 0° and kept overnight, during which time additional crystals were deposited. The combined crystals were recrystallized from ethanol to yield 0.85 g (73%) of Vc, mp 199—200.5°. *Anal.* Calcd. for $C_{10}H_{11}O_2N_3S$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.33; H, 4.52; N, 17.42.

Ethyl 2-Formamido-2-thiocarbamoylacetate (Vd)——A solution of 3.3 g of IVd in 22 ml of absolute ethanol and 3.6 ml of triethylamine was treated with hydrogen sulfide as described for Vc to yield crystals, which were recrystallized from water to give 3.2 g (80.7%) of Vd, mp 142—143°. *Anal.* Calcd. for $C_6H_{10}O_3N_2S$: C, 37.90; H, 5.30; N, 14.73. Found: C, 38.18; H, 5.20; N, 14.60.

Ethyl 2-Benzamido-2-thiocarbamoylacetate (Vf)——A solution of 1 g of ethyl 2-benzamido-2-cyanoacetate[9b] (IVf) in 20 ml of ethanol and 0.63 ml of triethylamine was treated with hydrogen sulfide as described for Vc to yield crystals, which were recrystallized from aqueous ethanol to give 0.97 g (85%) of Vf as colorless needles, mp 144—145°. *Anal.* Calcd. for $C_{12}H_{14}O_3N_2S$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.19; H, 5.22; N, 10.47.

2-Acetamido-2-cyanothioacetmaide (VIII)——*a*) A solution of 0.5 g of 2-amino-2-cyanothioacetamide[3] in 1.9 ml of acetic anhydride was heated at 75° for 1 min and the mixture was concentrated under reduced pressure. The residue was teken up in ethanol, treated with activated charcoal, concentrated and recrystallized from ethanol to yield 0.43 g (63%) of VIII, mp 186—189°. *Anal.* Calcd. for $C_5H_7ON_3S$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.74; H, 4.59; N, 26.29.

b) To a stirred solution of 0.5 g of 2-cyano-2-hydroxyiminothioacetamide[3] in 10 ml of 50% aqueous acetic acid was added 0.8 g of zinc powder in portions at 20—25°. After the addition was complete, the stirring was continued for 20 min. A mixture of ethanol and ether was added to the resulting suspension and 1 ml of acetic anhydride added. After standing for 2.5 hr at room temperature the solids were removed by filtration. The filtrate was evaporated under reduced pressure. The residue was taken up in water and freed of zinc by means of hydrogen sulfide. The filtrate from zinc sulfide was concentrated under reduced pressure and recrystallization of the residual crystals from ethanol gave 0.13 g (20%) of VIII which was identical with the specimen prepared in a).

5-Formamidothiazole-4-carboxamide (VIa)——a) A suspension of 200 mg of 2-formamido-2-thiocarbamoylacetamide[4] (Va) in acetic formic anhydride (prepared from 2 ml of anhydrous formic acid and 2 ml of acetic anhydride) was heated at 80—90° for 4.5 hr. The resulted yellow solution was cooled in an ice bath. The precipitated colorless needles were collected by filtration and washed with ether. The filtrate was concentrated to half volume under reduced pressure to give the second crop of colorless crystals. The crystals were combined and recrystallized from ethanol to afford 190 mg (89.6%) of VIa, mp 257—259°. *Anal.* Calcd. for $C_5H_5O_2N_3S$: C, 35.09; H, 2.95; N, 24.56. Found: C, 35.64; H, 3.02; N, 24.29. UV λ_{max}^{EtOH} mμ (log ε): 214.5 (4.31), 283 (4.21).

b) A suspension of 102 mg of 5-aminothiazole-4-carboxamide (VIIa) in acetic formic anhydride (prepared from 1 ml of anhydrous formic acid and 1 ml of acetic anhydride) was heated at 83° for 4 hr and cooled

in an ice bath to give 116 mg (95%) of VIa as colorless needles, which was identical with the specimen prepared in a).

5-Formamido-2-methylthiazole-4-carboxamide (VIb)——A suspension of 2.3 g of 2-acetamido-2-thiocarbamoylacetamide[4] (Vb) in acetic formic anhydride (prepared from 23 ml of anhydrous formic acid and 23 ml of acetic anhydride) was heated at 80—90° for 6 hr and cooled in an ice bath to yield colorless needles, which were recrystallized from ethanol to give 1.495 g (61.5%) of VIb, mp 262—262.5°. *Anal.* Calcd. for $C_6H_7O_2N_3S$: C, 38.92; H, 3.81; N, 22.70. Found: C, 39.45; H, 3.87; N, 22.64. UV λ_{max}^{EtOH} mμ (log ε): 215.5 (4.25), 288 (4.14).

General Procedure for Cyclization to 5-Aminothiazole-4-carboxamides (VIIa—c) and Ethyl 5-Aminothiazole-4-carboxylates (VIId—f) with Polyphosphoric Acid——In a typical run, a mixture of 1 g of Va—f and 10—16 g of polyphosphoric acid[13] was heated with occasional swirling at 70—140° for 1—8 hr, during which time a yellow to orange solution was reached. The reaction mixture was cooled, decomposed with 30—48 ml of water (3 ml of water per 1 g of polyphosphoric acid) and adjusted to pH 5—7 with 50% aqueous potassium hydroxide solution. The resulted crystals were collected by filtration. The filtrate was extracted with several portions of chloroform. The extracts were dried and evaporated under reduced pressure to give crystals. The crystals were combined and recrystallized from aqueous methanol, benzene, chloroform or ethanol to give VIIa—f.

5-Aminothiazole-4-carboxamide (VIIa)——a) The compound (VIIa), mp 140—141° (lit., mp 140—141°[1e], mp 140—142°[3]), was prepared from Va with polyphosphoric acid by the general procedure.

b) A suspension of 885 mg of VIa in 10 ml of 5% hydrochloric acid was gently refluxed for 30 min to give a yellow solution. After cooling, the reaction mixture was filtered. The filtrate was adjusted to pH 4 with 20% aqueous potassium hydroxide solution, concentrated to a small volume, made alkaline with K_2CO_3 and extracted with 60 ml of hot chloroform. The extract was concentrated to give crystals. Recrystallization from chloroform gave 227 mg (31.7%) of VIIa, which was identical with the specimen prepared in a).

5-Amino-2-methylthiazole-4-carboxamide (VIIb)——a) The compound (VIIb), mp 182.5—183.5° (lit.[3] mp 175—177°), was prepared from Vb with polyphosphoric acid by the general procedure.

b) Cyclization of 130 mg of VIII with 2 g of polyphosphoric acid at 98—102° for 5 hr according to the general procedure for VIIa—f yielded 86 mg (66%) of VIIb which was identical with the specimen prepared in a).

c) Hydrolysis of 50 mg of 5-amino-2-methylthiazole-4-carbonitrile (VIIh) with 800 mg of polyphosphoric acid at 100—120° for 5 hr according to the general procedure for VIIa—f yielded 52.5 mg (93%) of VIIb which was identical with the specimen prepared in a).

d) A suspension of 370 mg of VIb in 4 ml of 5% hydrochloric acid was gently refluxed for 1 hr and cooled. After removal of the precipitate by filtration, the filtrate was adjusted to pH 4 to yield crystals. Recrystallizafion from chloroform gave 219 mg (69.7%) of VIIb, which was identical with the specimen prepared in a).

Ethyl 5-Amino-2-methylthiazole-4-carboxylate (VIIe)——a) The compound (VIIe), mp 158—159°, was prepared from ethyl 2-acetamido-2-thiocarbamoylacetate[5] (Ve) with polyphosphoric acid by the general procedure.

b) Cyclization of 100 mg of Ve with 0.6 ml of phosphorus oxychloride at 80° for 20 min and at 95° for 35 min, follwed by decomposition with a small amount of ice–water and neutralization with 50% aqueous potassium hydroxide solution, yielded crystals. Recrystallization from benzene gave 71 mg (77.5%) of VIIe, which was identical with the specimen prepared in a).

5-Aminothiazole-4-carbonitrile (VIIg)——A suspension of 1 g of Va in 5 ml of phosphorus oxychloride was heated at 80° for 2.25 hr. The resulting dark-brown mixture was cooled in an ice bath and decomposed with 10 g of ice–water. After removal of the solid by filtration, the filtrate was neutralized with 50% aqueous potassium hydroxide solution. The precipitated crystals were collected and recrystallized from methanol to give 0.2 g (25.4%) of VIIg, mp 149—150° (lit.[3] 149—150°). *Anal.* Calcd. for $C_4H_3N_3S$: C, 38.40; H, 2.42; N, 33.60. Found: C, 39.00; H, 2.45; N, 33.30. UV λ_{max}^{EtOH} mμ (log ε): 266 (3.76), 278 (3.75).

5-Amino-2-methylthiazole-4-carbonitrile (VIIh)——a) A mixture of 1.54 g of Vb and 8.3 ml of phosphorus oxychloride was heated at 60° for 30 min and at 80—85° for 30 min. The resulting dark-brown solution was cooled, decomposed with 45 ml of water and neutralized with 50% aqueous potassium hydroxide solution. The precipitates were collected, taken up in 70 ml of acetone and purified through a short alumina column (to remove VIIb as a by-product). Evaporation of the solvent gave a crystalline mass which was recrystallized from ethanol to yield 0.316 g (25.9%) of VIIh, mp 235—236° [lit.[3] mp 272° (decomp.)]. *Anal.* Calcd. for $C_5H_5N_3S$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.35; H, 3.54; N, 29.97. UV λ_{max}^{EtOH} mμ (log ε): 259 (3.89), 284 (3.91).

b) A mixture of 100 mg of 2-acetamido-2-cyanothioacetamide (VIII) and 0.8 ml of phosphorus oxychloride was heated at 80° for 20 min and at 95° for 35 min. The resulted solution was treated as described in a) to give 10 mg (12%) of VIIh, which was identical with the specimen prepared in a).

13) R.C. Gilmore, Jr. and W.J. Horton, *J. Am. Chem. Soc.*, 73, 1411 (1951).