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169. Minoru Sekiya and Yoshiro Osaki: Azole Series. I. Reaction of 2-(Acylamino)thioacetamides, leading to 5-Aminothiazoles and to Thiazolo[5,4-*d*]pyrimidines.

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A number of studies have been reported on the synthesis of 5-aminothiazoles. Among the compounds, 5-aminothiazole-4-carboxamides have been known as key intermediate for the synthesis of thiazolo[5,4-*d*]pyrimidines. It was recently found in this laboratory that formation of 5-acetamido-substituted thiazoles was readily effected on heating 2-(acylamino)thioacetamides with acetic anhydride. 5-Acetamidothiazole-4-carboxamides were prepared from 2-acylamino-2-thiocarbamoylacetamides, this fact having opened a new route for the synthesis of thiazolo[5,4-*d*]pyrimidines. The present paper deals with this new thiazole formation reaction together with the synthesis of some new starting 2-(acylamino)thioacetamide and some derived thiazolo[5,4-*d*]pyrimidines.

I. Syntheses of 2-(Acylamino)thioacetamides and 2-Acylamino-2-thiocarbamoylacetamides

2-(Acylamino)thioacetamides used as starting material for the thiazole formation reaction were following: Formamidothioacetamide (I), acetamidothioacetamide (II), 2-formamido-2-thiocarbamoylacetamide (III), and its N-methyl- (IV) and N,N-dimethylacetamide (V) analog, 2-acetamido-2-thiocarbamoylacetamide (VI), and its N-methyl- (VII) and N,N-dimethyl-acetamide (VIII) analog. The following deals with synthesis of these compounds.

Syntheses of I and II were performed according to the following routes.

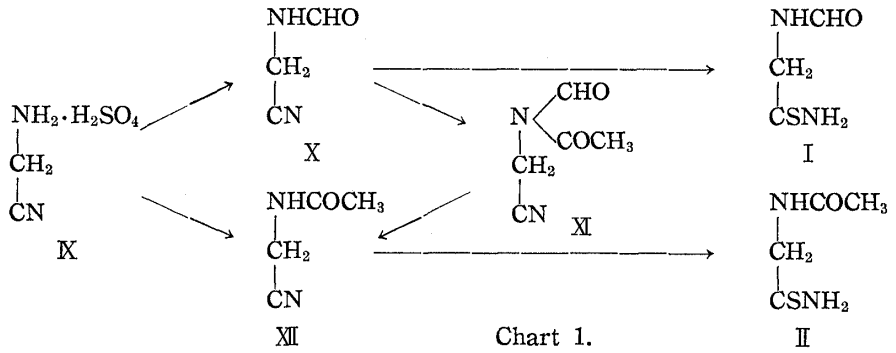

Chart 1.

Johnson, *et al.*[1] and Kotelko[2] reported preparation of N-cyanomethylacetamide (XII) from aminoacetonitrile by treatment with acetic anhydride or ketene and XII was converted to II[1] with hydrogen sulfide. N-Cyanomethylformamide (X) was prepared by the method in which a concentrated alcoholic solution of aminoacetonitrile liberated from its hydrogen sulfate (IX) by treatment with alcoholic ammonia was immediately allowed to reflux with ethyl formate. According to this method except that acetic anhydride was used instead of ethyl formate, XII was as well obtained. With hydrogen sulfide X was converted to I. Compounds, X and I, have not been reported previously.

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1) B. Johnson, E. Gatewood: J. Am. Chem. Soc., **51**, 1817 (1929).
2) A. Kotelko: Acta polon. Pharm., **19**, 109 (1962); C. A., **59**, 1482 (1963).

It was also found that by refluxing X with acetic anhydride N-cyanomethyl-N-formylacetamide (XI) was obtained, which seems to be an interesting compound to posses two different acyl groups attached to its nitrogen atom. By heating gently with water this compound was quantitatively hydrolyzed to XII suffering a split of its formyl group.

Compounds, III, IV, V, VI, VII, and VIII, which had not been reported previously were prepared from the corresponding 2-acylamino-2-cyanoacetamides by action of hydrogen sulfide.

Miller, *et al.*[3] has prepared 2-acetamido-2-cyanoacetamide (XIII) through the route in which hydroxyiminocyanoacetamide was converted to 2-amino-2-cyanoacetamide by selective hydrogenation over Raney nickel catalyst and then this compound was acetylated with acetic anhydride. This method was modified in the way in which hydrogenation was carried out in acetic anhydride over palladium-charcoal catalyst and, thus, the direct preparation of XIII was performed. In addition, reduction with zinc powder in aqueous acetic acid and with aluminum-amalgam in water, followed by acetylation with acetic anhydride without separation of the amine intermediate, was also applicable for the preparation of XIII. For the reduction with zinc powder to XIII, comparatively high concentration of the aqueous acetic acid reagent or high reaction temperature was not preferable, as a formation of acetamidomalondiamide occurred as result of the reduction accompanied with formation of XIII. As a reaction related to this side reaction, zinc reduction of the hydroxyimino compound in formic acid was previously[4] reported to result in a formation of formamidomalondiamide. Similarly by this zinc reduction method 2-formamido-2-cyanoacetamide (XIV) and N-methyl-2-cyano-2-formamidoacetamide (XV) were prepared from the corresponding hydroxyimino compounds using formic acid instead of acetic acid. Also by a method similar to the above aluminum-amalgam reduction of hydroxyimino grouping N-methyl-2-acetamido-2-cyanoacetamide (XVI) and N,N-dimethyl-2-acetamido-2-cyanoacetamide (XVII), and, using formic acid instead of acetic anhydride, XIV and XV and N,N-dimethyl-2-cyano-2-formamidoacetamide (XVIII) were also prepared. These analogs of 2-acylamino-2-cyanoacetamide, XV, XVIII, have not been described previously.

II. Syntheses of 5-Acetamidothiazoles and 5-Acetamidothiazole-4-carboxamides

Previously, there have been reported a number of papers on the reactions for the formation of 5-amino-substituted thiazoles. The reactions reported in these papers would be classified into two types, reactions, reported by Cook, of 2-aminoacetonitriles with carbon disulfide,[5] carbon oxysulfide,[6] dithiocarbonate,[7,8] and isothiocyanates,[9] and the other reaction, reported by Shaw,[10] of 2-aminothioacetamide with imidoether, as shown in Chart 2.

A new general method for formation of 5-acetamidothiazoles has been developed in this laboratory. Some 2-(acylamino)thioacetamides, whose preparation are described in the foregoing section, were converted to the corresponding 5-acetamidothiazoles by refluxing with a large excess of acetic anhydride for 30 minutes. Thus, 5-acetamidothiazole (XIX), 2-methyl-5-acetamidothiazole (XX), 5-acetamidothiazole-4-carboxamide (XXI), 2-methyl-5-acetamidothiazole-4-carboxamide (XXII), N-methyl-5-acetamidothia-

3) C. S. Miller, S. Gurin, D. W. Wilson : J. Am. Chem. Soc., **74**, 2892 (1952).
4) M. Conrad, A. Schulze : Ber., **42**, 738 (1909); C. A., **3**, 1175 (1909).
5) A. H. Cook, Sir Ian Heilbron, A. L. Levy : J. Chem. Soc., **1947**, 1598; *Ibid.*, **1948**, 201.
6) A. H. Cook, Sir Ian Heilbron, G. D. Hunter : *Ibid.*, **1949**, 1443.
7) A. H. Cook, Sir Ian Heilbron, A. L. Levy : *Ibid.*, **1947**, 1594.
8) A. H. Cook, Sir Ian Heilbron, E. Smith : *Ibid.*, **1949**, 1440.
9) A. H. Cook, J. D. Downer, Sir Ian Heilbron : J. Chem. Soc., **1948**, 1262; *Ibid.*, **1948**, 2028; C. W. Capp, A. H. Cook, J. D. Downer, Sir Ian Heilbron : *Ibid.*, **1948**, 1340.
10) G. Shaw, D. N. Butler : *Ibid.*, **1959**, 4040.

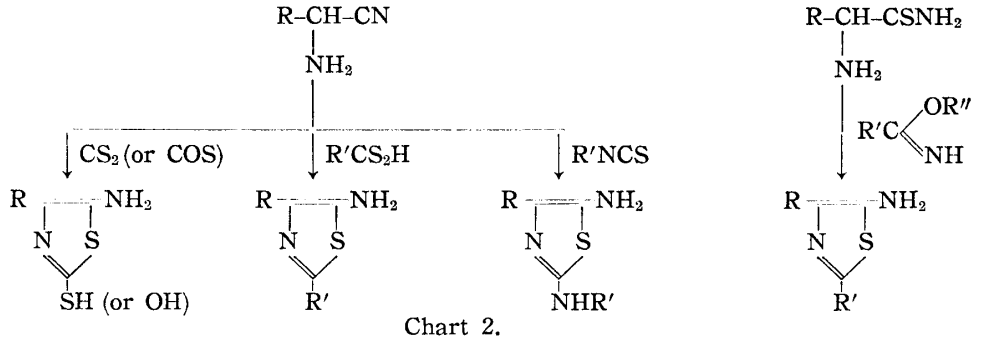
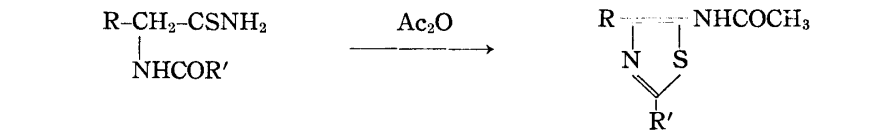


Chart 2.

zole-4-carboxamide (XXIII), N-methyl-2-methyl-5-acetamidothiazole-4-carboxamide (XXIV), N,N-dimethyl-5-acetamidothiazole-4-carboxamide (XXV) and N,N-dimethyl-2-methyl-5-acetamidothiazole-4-carboxyamide (XXVI) were obtained in a range of 23~53% yield respectively from I, II, III, VI, IV, VII, V, and VIII.



XIX : R=H, R′=H;
XXI : R=$CONH_2$, R′=H;
XXIII : R=$CONHCH_3$, R′=H;
XXV : R=$CON(CH_3)_2$, R′=H;
XX : R=H, R′=CH_3
XXII : R=$CONH_2$, R′=CH_3
XXIV : R=$CONHCH_3$, R′=CH_3
XXVI : R=$CON(CH_3)_2$, R′=CH_3

Chart 3.

Hellsing[11] first obtained XIX from chrysean (5-amino-2-thioamidothiazole). Erlenmeyer, *et al.*[12] and Prijs, *et al.*[13] prepared XIX and XX respectively from the corresponding thiazole-5-carboxylic acids through Curtius reaction route. The melting points of the compounds, XIX and XX, obtained were closely in agreement with those reported in the above literatures, and exhibited ultraviolet spectra characteristic of thiazole ring. Compound (XXI) was previously synthesized from iso-chrysean (5-amino-4-thiocarbamoylthiazole) by Adams,[14] the reported melting point agreeing with that obtained, while, its derivatives, XXII, XXIII, XXIV, XXV, and XXVI have not been reported previously. Their formulations were assigned by analogy with the thiazole formation reaction and on the basis of their ultraviolet spectra.

In order to prepare 5-aminothiazole-4-carboxamides applicable as materials for the syntheses of thiazolo[5,4-*d*]pyrimidines, hydrolyses of XXI and XXII were attempted. Under the condition of refluxing with six times as much 5% hydrochloric acid as the substrate for 45 minutes, 5-aminothiazole-4-carboxamide (XXVII) and 2-methyl-5-aminothiazole-4-carboxamide (XXVIII) were obtained in 22% and 15% yield respectively. The rather poor yields are presumably due to rupture of the thiazole ring. Melting point of XXVII was in good agreement with that previously reported by Cook, *et al.*[8] For XXVIII Weidel, *et al.*[15] reported its decomposing point of above 300° without melting and other physical data. These data were much different from those of the compound obtained, which showed melting point of 175~177°. This compound was assigned as the formulation XXVIII on the basis of analysis, ultraviolet spectrum, analogy with XXVII, and its reactions described in the succeeding section.

11) G. Hellsing : Ber., **36**, 3546 (1903).
12) v. H. Erlenmeyer, W. Mengisen, B. Prijs : Helv. Chim. Acta, **30**, 1865 (1947).
13) B. Prijs, H. V. Babo : *Ibid.*, **33**, 306 (1950).
14) A. Adams, R. Slack : J. Chem. Soc., **1956**, 1870.
15) H. Weidel, L. Niemilowicz : Monatsch., **16**, 740 (1895).

III. Syntheses of Thiazolo[5,4-*d*]pyrimidines

A variety of 5-aminoazolo-4-carboxamides have been used as intermediate for the syntheses of azolo[5,4-*d*]pyrimidines. The availability of 5-aminothiazole-4-carboxamides, XXVII and XXVIII described in section II, made it possible to synthesize thiazolo[5,4-*d*]pyrimidin-7-ol and -5,7-diol, through the routes using them as starting material. The report on the syntheses of thiazolo[5,4-*d*]pyrimidines unsubstituted or substituted with methyl at position 2 is rather rare, however, syntheses of thiazolo-[5,4-*d*]pyrimidin-7-ol and -5,7-diol, starting from XXVII, and of the analogs of 2-methylthiazolo[5,4-*d*]pyrimidines, starting from XXVIII, were performed through the routes shown in Chart 4.

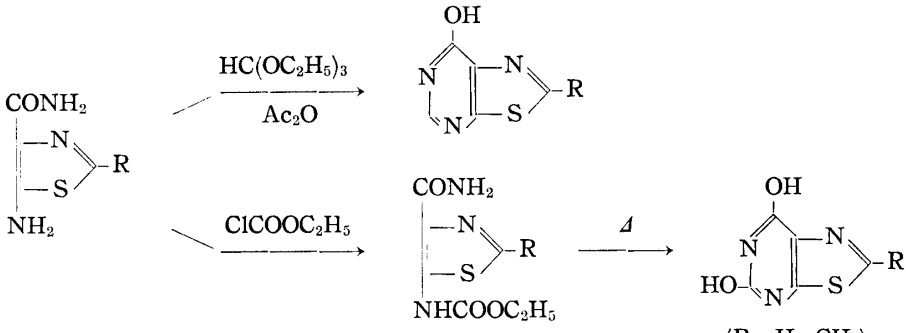


Chart 4.

With ethyl orthoformate and acetic anhydride the thiazoles, XXVII and XXVIII, were converted to thiazolo[5,4-*d*]pyrimidine-7-ol (XXIX) and 2-methylthiazolo[5,4-*d*]pyrimidin-7-ol (XXX) respectively, by a method similar to that reported for 2-alkylthio-substituted analogs by Cook, *et al.*[16]

On refluxing a suspension in a mixture of ethyl chloroformate and pyridine XXVII and XXVIII were converted to 5-ethoxycarbonylaminothiazolo-4-carboxamide (XXXI) and its 2-methyl analog (XXXII) respectively, which have not been described previously. The conversion of XXXI and XXXII respectively into thiazolo[5,4-*d*]pyrimidine-5,7-diol (XXXIII) and its methyl analog (XXXIV) occurred on heating at their decomposing temperature.

Compounds, XXIX,[17] XXX,[18] XXXIII[17], and XXXIV[19,20], have previously synthesized through the routes starting from pyrimidine moieties. The ultraviolet spectrum data given for XXIX[17], XXXIII[17] and XXXIV[19] are nearly in agreement with those for the compounds obtained. With dimethyl sulfate XXXIII and XXXIV were methylated to the corresponding 4,6-dimethyl analogs, 4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XXXV) and 2,4,6-trimethylthiazolo[5,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XXXVI) respectively. Compound (XXXV) has previously[20] reported and the melting point reported agreed closely with that obtained.

Experimental

N-Cyanomethylacetamide (X)——Into a suspension of 72 g. of finely powdered aminoacetonitrile hydrogen sulfate in 200 ml. of EtOH, dry NH_3 was introduced with occasional shaking. Immediately after removal of insoluble $(NH_4)_2SO_4$ by filtration the filtrate was evaporated to a small volume under reduced pressure. To the resulting solution 120 ml. of $HCOOC_2H_5$ was added and the solution was refluxed for 1 hr. After concentration the residue was distilled under reduced pressure to give a distillate, b.p_1 125~127°, weighing 33 g. (79%). *Anal.* Calcd. for $C_3H_4ON_2$: C, 42.84; H, 4.76; N, 32.14. Found : C, 42.68;

16) A. H. Cook, E. Smith : J. Chem. Soc., **1949**, 2329.
17) G. B. Elion, W. H. Lange, G. H. Hitchings : J. Am. Chem. Soc., **78**, 2858 (1956).
18) S. Inoue : This Bulletin, **6**, 352 (1958); M. Ishidate, H. Yuki : *Ibid.*, **8**, 137 (1960).
19) E. A. Falco, G. H. Hitchings : J. Am. Chem. Soc., **72**, 3203 (1950).
20) G. P. Hager, C. Kaiser : J. Am. Pharm. Assoc., **44**, 193 (1955).

H, 5.00; N, 32.50.

2-(Formamido)thioacetamide (I)——Through a solution of 4.2 g. of X dissolved in 12 ml. of 10% aq. NH_3, H_2S was passed until saturation. After standing overnight, crystals deposited were collected by filtration. The same material was obtained by usual treatment of the filtrate. Recrystallization from EtOH gave needles, m.p. 119~121°, weighing 3.9 g. (66%). *Anal.* Calcd. for $C_3H_6ON_2S$: C, 30.51; H, 5.12; N, 23.72. Found : C, 30.46; H, 5.16; N, 23.59.

N-Cyanomethyl-N-formylacetamide (XI)——A mixture of 4.2 g. of X and 20 ml. of Ac_2O was refluxed for 1 hr. The reaction solution was concentrated under reduced pressure. Crystals deposited on cooling was collected and recrystallized from EtOH to needles, m.p. 54~55°, weighing 3.7 g. (60%). *Anal.* Calcd. for $C_5H_6O_2N_3$: C, 47.60; H, 4.80; N, 22.22. Found : C, 47.95; H, 5.12; N, 21.78. IR*2 ν_{max}^{KBr} cm^{-1} : 1728 (C=O), 1667 (C=O), 2228 (CN).

N-Cyanomethylacetamide (XII)——To 18 ml. of H_2O 1 g. of XI was added and the mixture was refluxed for 1 hr. After concentration of the reaction solution 0.7 g. (91%) of almost pure crystals was obtained. Recrystallization from $CHCl_3$ gave prisms, m.p. 80~81° (lit., m.p. 77°,[1] 80°[2]). *Anal.* Calcd. for $C_4H_6ON_2$: C, 49.21; H, 6.17; N, 28.56. Found : C, 49.65; H, 6.08; N, 28.40.

2-Cyano-2-formamidoacetamide (XIV)——a) To a solution of 22.6 g. of 2-cyano-2-hydroxyiminoacetamide dissolved in 270 ml. of 30% HCO_2H 32 g. of Zn powder was added in small portion at 40~50° with vigorous stirring. After filtration of the reaction mixture the filtrate was concentrated under reduced pressure. The zinc formate which separated was removed by filtration. H_2S was passed into the filtrate and the precipitated zinc sulfide was removed. Concentration of the liquid gave 19.2 g. (75.5%) of the product, which was crystallized from H_2O to prisms, m.p. 154~155° (decomp.). *Anal.* Calcd. for $C_4H_5O_2N_3$: C, 37.80; H, 3.97; N, 33.06. Found : C, 37.71; H, 3.84; N, 32.84.

b) To a solution of 34 g. of 2-cyano-2-hydroxyiminoacetamide dissolved in 250 ml. of H_2O 16.5 g. of Al-Hg was slowly added in small portion with shaking. The temperature rose to about 60° due to exothermicity of the reaction. Following the addition, the reaction mixture was heated by external heating. The solid which deposited was filtered off and washed with H_2O. To the combined filtrate and washings 97 g. of 85% HCO_2H was added. Concentration of the mixture under reduced pressure gave a solid residue, from which crystals of 17 g. (45%) was collected. Recrystallization from H_2O gave prisms, m.p. 153~154°. No depression of melting point was observed on admixture with a sample obtained in a).

2-Acetamido-2-cyanoacetamide (XIII)——a) To a solution of 20 g. of 2-cyano-2-hydroxyiminoacetamide dissolved in 170 ml. of 40% AcOH 36 g. of zinc powder was added at 20~30° with stirring. After filtration, 40 g. of Ac_2O was added and allowed to stand overnight. Zinc acetate which deposited was removed by filtration. To remove zinc ion the filtrate was subjected to the usual H_2S introducing and filtering operation. Concentration of the resulting solution gave 16 g. (56.5%) of the product which was recrystallized from EtOH to prisms, m.p. 173~174° (lit.,[2] m.p. 173.5~174.5°). *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.45; H, 5.00; N, 29.78. Found : C, 41.91; H, 4.60; N, 30.37.

b) A suspension of 10 g. of finely powdered 2-cyano-2-hydroxyiminoacetamide in 60 ml. of Ac_2O was catalytically reduced with 1 g. of 10% Pd-C at 40~50° under ordinary pressure. Approximate 2 mole equiv. of H_2 was absorbed in about 4 hr. Suspensing product was collected by filtration together with the catalyst. To remove the catalyst this mixture was extracted with MeOH and the solvent was removed from the extract. Further small amount of the product was obtained when the foregoing filtrate was evaporated. Total yield, 9.2 g. (74%). No depression in the m.p. 172~173° was observed on admixture with a sample obtained in a).

c) To a solution of 34 g. of 2-cyano-2-hydroxyiminoacetamide dissolved in 250 ml. of H_2O 16.5 g. of Al-Hg was added in small portions. After stirring for about 4 hr. at 40~50°, $Al(OH)_3$ which precipitated was filtered, washed with hot H_2O. To the filtrate combined with the washings was added 54 ml. of Ac_2O with shaking. After standing 2 hr., the solution was concentrated and the residue was crystallized from EtOH to give crystals, m.p. 173~174°. Yield 21 g. (44%). No depression in the melting point was observed on admixture with a sample obtained in a).

N-Methyl-2-cyano-2-formamidoacetamide (XV)——a) This was prepared from 12.7 g. of N-methyl-2-cyano-2-hydroxyiminoacetamide, 130 ml. of 30% HCO_2H and 16 g. of Zn powder by a method similar to that described for XIV a). Yield, 8.5 g. (60%). Recrystallization from EtOH gave needles, m.p. 143~144°. *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.75; H, 5.00; N, 29.78. Found : C, 43.02; H, 5.40; N, 30.06.

b) To a solution of 38 g. of N-methyl-2-cyano-2-hydroxyiminoacetamide dissolved in 250 ml. of H_2O 16.5 g. of Al-Hg was added and processed according to XIV b). 49 ml. of 85% of HCO_2H was used for formylation. The product weighed 18 g. (43%). Recrystallization from EtOH gave needles, m.p. 143~144°, which showed no depression in the melting point on admixture with a sample obtained in a).

N-Methyl-2-acetamido-2-cyanoacetamide (XVI)——Prepared from 38 g. of N-methyl-2-cyano-2-hydroxyiminoacetamide, 16.5 g. of Al-Hg and 54 g. of Ac_2O by a method similar to that described for XIII c). The product weighed 22 g. (47%). Recrystallization from EtOH gave needles, m.p. 152~154°. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 47.34; H, 6.10; N, 26.71. Found : C, 46.94; H, 5.85; N, 27.08.

*2 Unpublished data in this laboratory.

N,N-Dimethyl-2-cyano-2-formamidoacetamide (XVIII)——Prepared from 43 g. of N,N-dimethyl-2-cyano-2-hydroxyiminoacetamide, 16.5 g. of Al-Hg and 49 g. of HCO_2H by a method similar to that described for XIV b). The product weighed 17.7 g. (38%). Recrystallization from EtOH gave needles, m.p. 94~96°. *Anal.* Calcd. for $C_6H_9O_2N_3$: 46.44; H, 5.85; N, 27.08. Found : C, 46.27; H, 5.90; N, 26.85.

N,N-Dimethyl-2-acetamido-2-cyanoacetamide (XVII)——Prepared from 43 g. of N,N-dimethyl-2-cyano-2-hydroxyiminoacetamide, 16.5 g. of Al-Hg and 54 ml. of Ac_2O by a method similar to that described for XIII c). The product weighed 15 g. (29%). Recrystallization from EtOH gave needles, m.p. 121~123°. *Anal.* Calcd. for $C_7H_{11}O_2N_3$: C, 49.69; H, 6.55; N, 24.84. Found : C, 49.85; H, 6.75; N, 24.62.

2-Formamido-2-thiocarbamoylacetamide (III)——XIV (12.7 g.) was dissolved in 70 ml. (appropriate volume to be dissolved) of 5% aq. NH_3. At room temperature H_2S was bubbled through the solution. In the course of this process the product was gradually precipitated. After overnight, the product was collected by filtration and weighed 12.3 g. (76%). Recrystallization from H_2O gave an analytical sample, needles, m.p. 185~186° (decomp.). *Anal.* Calcd. for $C_4H_7O_2N_3S$: C, 29.80; H, 4.38; N, 26.07. Found : C, 30.06; H, 4.41; N, 25.59.

2-Acetamido-2-thiocarbamoylacetamide (VI)——Similar treatment of 14 g. of XIII gave 13 g. (76%) of the product. Recrystallization from H_2O or EtOH gave needles, m.p. 184~186° (decomp.). *Anal.* Calcd. for $C_5H_9O_2N_3S$: C, 34.29; H, 5.18; N, 23.99. Found : C, 34.24; H, 5.35; N, 23.81.

N-Methyl-2-formamido-2-thiocarbamoylacetamide (IV)——Similar treatment of 14 g. of XVI gave 12 g. (68%) of the product. Recrystallization from H_2O gave an analytical sample, needles, m.p. 188~189°. *Anal.* Calcd. for $C_5H_9O_2N_3S$: C, 34.29; H, 5.18; N, 23.99. Found : C, 33.94; H, 5.49; N, 24.36.

N-Methyl-2-acetamido-2-thiocarbamoylacetamide (VII)——Similar treatment of 15.5 g. of XVI gave 16.5 g. (87%) of the product. Recrystallization from EtOH gave needles, m.p. 178~180° (decomp.). *Anal.* Calcd. for $C_6H_{11}O_2N_3S$: C, 38.09; H, 5.86; N, 22.21. Found : C, 37.94; H, 5.87; N, 22.20.

N,N-Dimethyl-2-formamido-2-thiocarbamoylacetamide (V)——Similar treatment of 15.5 g. of XVIII gave 15 g. (79%) of the product. Recrystallization from H_2O gave needles, m.p. 184~185° (decomp.). *Anal.* Calcd. for $C_6H_{11}O_2N_3S$: C, 38.09; H, 5.86; N, 22.21. Found : C, 37.68; H, 6.07; N, 21.69.

N,N-Dimethyl-2-acetamido-2-thiocarbamoylacetamide (VIII)——Similar treatment of 9 g. of XVII gave 6.6 g. (64%) of the product. Recrystallization from EtOH gave needles, m.p. 148~150°. *Anal.* Calcd. for $C_7H_{13}O_2N_3S$: C, 41.37; H, 6.45; N, 20.68. Found : C, 41.28; H, 6.54; N, 20.58.

General Procedure for Preparation of 5-Acetamidothiazoles——To 0.05 mole each of 2-(acylamino) thioacetamides or 2-acylamino-2-cyanothioacetamides 50 ml. of Ac_2O was added. The mixture was refluxed for 30 min. The reaction solution was concentrated under reduced pressure. Product was purified by recrystallization, when it crystallized in the residue, or by column chromatography. The following 5-acetamidothiazoles were prepared. UV spectra of these compounds in EtOH exhibited a characteristic peak representing thiazole ring.

5-Acetamidothiazole (XIX) was purified by chromatography on an alumina column using $CHCl_3$ as an eluent. Yield, 28%. Recrystallization from $CHCl_3$ gave an analytical sample, needles, m.p. 161~163° (lit.,[11] m.p. 159~160°). *Anal.* Calcd. for $C_5H_6ON_2S$: C, 42.42; H, 4.25; N, 19.71. Found : C, 41.97; H, 4.31; N, 19.78. UV λ_{max}^{EtOH} mμ (log ε) : 269 (4.04).

2-Methyl 5-acetamido thiazole (XX) was purified by chromatography on an alumina column using $CHCl_3$ as an eluent. Yield, 23%. Recrystallization from $CHCl_3$ gave needles, m.p. 146~148° (lit.,[12] m.p. 146~148°). *Anal.* Calcd. for $C_6H_8ON_2S$: C, 46.15; H, 5.16; N, 17.94. Found : C, 45.84; H, 5.05; N, 17.28. UV λ_{max}^{EtOH} mμ (log ε) : 264 (3.99).

5-Acetamidothiazole-4-carboxamide (XXI) was obtained in 53%. Recrystallization from MeOH gave needles, m.p, 209~210° (lit.,[13] m.p. 212~213°). *Anal.* Calcd. for $C_6H_7O_2N_3S$: C, 38.93; H, 3.81; N, 22.70. Found : C, 38.88; H, 3.97; N, 22.06. UV λ_{max}^{EtOH} mμ (log ε) : 282.5 (4.12), lit.,[13] λ_{max}^{MeOH} mμ (log ε) : 282 (4.15). Hydrolysis of this material was effected under the condition in which a solution of 9.2 g. of it in 55 ml. of 5% HCl was refluxed for 45 min. Prolonged hydrolysis or use of higher concenration of HCl resulted in lower yield. Then, the solution was neutralized with KOH, concentrated to a small volume under reduced pressure, and made strong alkaline with K_2CO_3, when a crude mixture was deposited. 5-Aminothiazole-4-carboxamide (XXVII) was extracted $CHCl_3$. After drying and evaporation of $CHCl_3$, the product was obtained as a solid residue in yield of 1.6 g. (22%). Recrystallization from $CHCl_3$ gave an analytical sample, plates, m.p. 140~142° (lit.,[8] m.p. 140~141°). *Anal.* Calcd. for $C_4H_5ON_3S$: C, 33.55; H, 3.52; N, 29.35. Found : C, 33.25; H, 3.59; N, 29.44. UV λ_{max}^{EtOH} mμ (log ε) : 279 (3.96).

2-Methyl-5-acetamidothiazole-4-carboxamide (XXII) was obtained in 44%. Recrystallization from MeOH gave needles, m.p. 227~228°. *Anal.* Calcd. for $C_8H_{10}O_2N_3S$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.60; H, 4.55; N, 20.88. UV λ_{max}^{EtOH} mμ (log ε) : 215 (4.23), 288 (4.12). Hydrolysis of this material to 2-methyl-5-aminothiazole-4-carboxamide (XXVIII) was worked up in the same manner as in the experiment with XXI. Yield, 14%. Recrystallization from $CHCl_3$ gave plates, m.p. 175~177°. *Anal.* Calcd. for $C_5H_7ON_3S$: C, 38.22; H, 4.49; N, 26.74. Found : C, 38.57; H, 4.52; N, 26.38. UV λ_{max}^{EtOH} mμ (log ε) : 281 (3.94).

N-Methyl-5-acetamidothiazole-4-carboxamide (XXIII) was obtained in 50%. Recrystallization from EtOH gave needles, m.p. 193~195°. *Anal.* Calcd. for $C_7H_9O_2N_3S$: C, 42.22; H, 3.62; N, 21.10. Found : C, 42.10; H, 3.90; N, 20.83. UV λ_{max}^{EtOH} mμ (log ε) : 280 (4.29).

N-Methyl-2-methyl-5-acetamidothiazole-4-carboxamide (XXIV) was obtained in 47%. Recrystallization from EtOH gave needles, m.p. 178~180°. *Anal.* Calcd. for $C_8H_{11}O_2N_3S$: C, 45.07; H, 5.20; N, 19.17. Found : C, 45.20; H, 5.30; N, 19.53. UV λ_{max}^{EtOH} mμ (log ε) : 215 (4.18), 287 (4.16).

N,N-Dimethyl-5-acetamidothiazole-4-carboxamide (XXV) was purified by chromatography on an alumina column using $CHCl_3$ as an eluent. Yield, 40%. Recrystallization from EtOH gave needles, m.p. 115~117°. *Anal.* Calcd. for $C_8H_{11}O_2N_3S$: C, 45.07; H, 5.20; N, 19.71. Found : C, 45.20; H, 5.27; N, 19.85. UV λ_{max}^{EtOH} mμ (log ε) : 274 (4.04).

N,N-Dimethyl-2-methyl-5-acetamidocarboxamide (XXVI) was purified by chromatography on an alumina column using $CHCl_3$ as an eluent. Yield, 25%. Recrystallization from EtOH 161~163° (decomp.). *Anal.* Calcd. for $C_9H_{13}O_2N_3S \cdot H_2O$: C, 44.08; H, 6.17; N, 17.14. Found : C, 44.31; H, 6.34; N, 17.04. UV λ_{max}^{EtOH} mμ (log ε) : 286 (4.19).

Thiazolo[5,4-*d*]pyrimidine-7-ol (XXIX)——A solution of 0.7 g. of XXVII dissolved in a mixture of 15 ml. of $CH(OC_2H_5)_3$ and 2.5 ml. of Ac_2O was refluxed for 1 hr. Evaporation of the solvents gave the product weighed 0.7 g. (93%). Recrystallization from EtOH gave prisms. *Anal.* Calcd. for $C_5H_3ON_3S$: C, 39.22; H, 1.98; N, 27.45. Found : C, 39.82; H, 2.10; N, 27.10. UV $\lambda_{max}^{0.1N\ HCl}$ mμ (log ε) : 251 (3.79), 257 (3.78), 276 (3.70). lit.,[16] λ_{max}^{pH1} mμ (log ε) : 252 (3.76), 257 (3.76), 276 (3.65).

2-Methylthiazolo[5,4-*d*]pyrimidine-7-ol (XXX)——This was prepared from 0.4 g. of XXVIII, 12 ml. of $CH(OC_2H_5)_3$ and 2 ml. of Ac_2O in the same manner as above. The product weighed 0.36 g. (85%). Recrystallization from EtOH gave prisms. *Anal.* Calcd. for $C_6H_5ON_3S$: C, 43.12; H, 3.02; N, 25.15. Found : C, 43.56; H, 2.67; N, 24.75. UV $\lambda_{max}^{0.1N\ HCl}$ mμ (lor ε) : 251 (3.88), 258 (3.89), 279 (3.77).

5-Ethoxycarbonylaminothiazole-4-carboxamide (XXXI)——A suspension of 1.4 g. of XXVII in a mixture of 30 ml. of ethyl chloroformate and 0.5 ml. of pyridine was refluxed for 1 hr. A suspensing solid material was collected by filtration and washed with 50% EtOH. This material, weighing 1.9 g. (89%) was recrystallized from a large volume of H_2O to an analytical pure sample, m.p. 245° (decomp.). *Anal.* Calcd. for $C_7H_9O_3N_3S$: C, 39.07; H, 4.22; N, 19.53. Found : C, 39.38; H, 4.36; N, 19.80.

2-Methyl-5-ethoxycarbonylaminothiazole-4-carboxamide (XXXII)——This was prepared from 1.6 g. of XXVIII, 30 ml. of ethyl chloroformate and 0.5 ml. of pyridine in the same manner as above. Yield, 19.7 g. (86%). Recrystallization from a large volume of H_2O gave an analytical sample, m.p. 195~197° (decomp.). *Anal.* Calcd. for $C_8H_{11}O_3N_3S$: C, 41.92; H, 4.84; N, 18.34. Found : C, 42.42; H, 5.43; N, 18.60.

Thiazolo[5,4-*d*]pyrimidine-5,7-diol (XXXIII)——In a glass tube, 2.2 g. of XXXI was placed and allowed to be decomposed at 245~250° by external heating on a H_2SO_4 bath. The decomposed material was crystallized from a large volume of H_2O to a pure material, fine needles. *Anal.* Calcd. for $C_5H_3O_2N_3S$: C, 35.50; H, 1.79; N, 24.48. Found : C, 35.25; H, 2.04; N, 24.45. UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 256.5 (4.49). lit.,[16] λ_{max}^{pH1} mμ (log ε) : 257 (3.97).

2-Methylthiazolo[5,4-*d*]pyrimidine-5,7-diol (XXXIV)——This was prepared from 0.23 g. of XXXII in the same manner as above. Yield, 0.15 g. (82%). Recrystallization from a large volume of H_2O gave an analytical sample, needles. *Anal.* Calcd. for $C_6H_5O_2N_3S$: C, 39.35; H, 2.75; N, 22.95. Found : C, 39.80; H, 3.20; N, 22.56. UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 212 (4.28), 257 (3.91). lit.,[18] λ_{max}^{pH1} mμ (log ε) : 255 (3.995).

4,6-Dimethylthiazolo]5,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XXXV)——To a suspension of 0.5 g. XXXIV in 10 ml. of H_2O, 0.75 g. of $(CH_3)_2SO_4$ was added and then aq. 5% NaOH was added with small portions, while the mixture was maintained to be weakly basic. On concentration of the reaction solution, the product crystallized and weighed 0.21 g. (37%). Recrystallization from H_2O gave an analytical sample, m.p. 285~286°, lit.,[19] m.p. 286~286.5°. *Anal.* Calcd. for $C_7H_7O_2N_3S$: C, 42.64; H, 3.58; N, 21.32. Found : C, 42.16; H, 3.56; N, 21.14. UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 283 (4.67).

2,4,6-Trimethylthiazolo[5,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XXXVI)——This was prepared from 0.37g of XXXIV by the same procedure as above, the product weighed 0.21 g. (51%). Recrystallization from EtOH gave an analytical sample, m.p. 196~197°, lit.,[20] m.p. 197~198°. *Anal.* Calcd. for $C_8H_9O_2N_3S$: C, 45.50 ; H, 4.30; N, 19.90. Found : C, 45.75; H, 4.51; N, 19.67. UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 282 (4.32).

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Summary

Formation of 5-acetamido-substituted thiazoles was found to be readily effective on heating 2-(acylamino)thioacetamides with acetic anhydride. In addition, preparation of some starting 2-(acylamino)thioacetamides is described and 5-acetamidothiazole-4-carboxamides obtained by the thiazole formation reaction were led to some thiazolo-[5,4-*d*]pyrimidines.

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