Isothiazoles. III. Synthesis of Isothiazolo[5,4-*d*]pyrimidines (1,2)

Richard C. Anderson and Y. Y. Hsiao

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322

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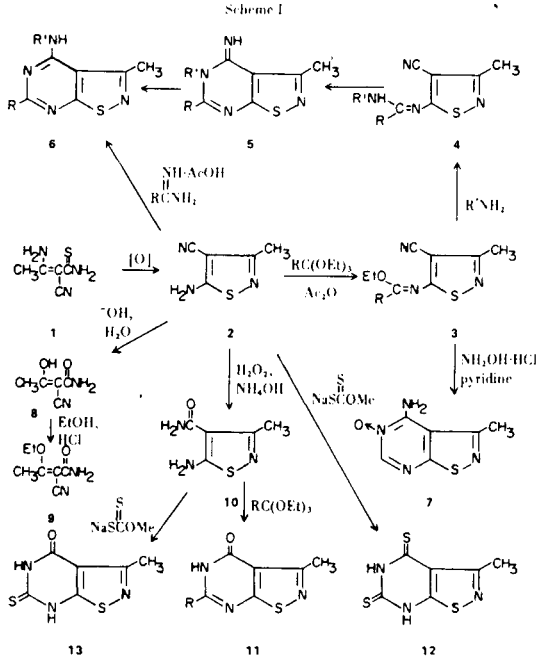
5-Amino-3-methylisothiazole-4-carbonitrile **2** was prepared by oxidation of 3-amino-2-cyanothiocrotonamide **1**. A series of 4-amino-3-methylisothiazolo[5,4-*d*]pyrimidines **6** was derived from **2** by reaction with orthoesters followed by cyclization with primary amines. Hydrolysis of **2** to the corresponding amide **10** followed by cyclization with orthoesters gave the corresponding 5*H*-isothiazolo[5,4-*d*]pyrimidin-4-ones **11**. Reactions of **2** and **10** with sodium methyl xanthate gave the corresponding pyrimidinethione derivatives **12** and **13**.

Since the pioneering work of Adams and Slack (3) on mononuclear isothiazoles, there has been relatively little reported concerning the synthesis of heterocyclic systems containing an isothiazole ring fused to other heterocyclic rings. A few examples of isothiazolopyrimidines have been characterized (4). This paper describes syntheses of some new isothiazolo[5,4-*d*]pyrimidines from mononuclear isothiazole precursors.

5-Amino-3-methylisothiazole-4-carbonitrile **2** was first synthesized by Goerdeler and Pohland (5). We have succeeded in preparing **2** in excellent yield using a different and more convenient approach *via* oxidative cyclization of

Scheme I



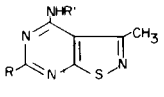
3-amino-2-cyanothiocrotonamide **1**. Peracetic acid, iodine in ethanol-pyridine, bromine in chloroform, ammonium persulfate in water, hydrogen peroxide in water, and hydrogen peroxide in methanol were all effective cyclization agents, the latter reagent being most efficient giving **2** in 95% yield.

Treatment of **2** with orthoesters and acetic anhydride gave the corresponding iminoethers **3a-c**. Ammonia in methanol converted **3a** to the corresponding amidine **4**, which required treatment with a strong base (lithium methoxide) to effect cyclization to give **6a**. When **3a** was allowed to react with primary amines in methanol, the intermediate amidines **4b-g** underwent spontaneous cyclization and rearrangement to form the corresponding isothiazolo[5,4-*d*]pyrimidines **6b-g** apparently *via* **5** (6). Treatment of **3b** and **3c** with ammonia in methanol gave **6h** and **6i**, respectively. The intermediate amidines could not be isolated. The yields, melting points, and analytical data for **6a-i** are given in Table I.

Intermediate species **5a**, **h**, **i** should rearrange rapidly to **6a**, **h**, **i** by prototropic tautomerism. The uv, ir, and nmr spectra of the products obtained when R′ ≠ H were very similar to those of **6a**, **h**, **i**, which confirmed that rearrangement had occurred under the reaction conditions. This behavior is consistent with previous observations (7) that iminopyrimidines similar to **5** usually undergo facile rearrangements to the corresponding aminopyrimidines.

Condensation of **2** with formamidine acetate and acetamidine acetate in 2-ethoxyethanol led to formation of **6a** and **6h** in one step, but the yields were low (8% and 7%, respectively). The iminoethers **3a-c** were unstable to ambient conditions, undergoing hydrolysis to form the corresponding amides. Treatment of **3a** with hydroxylamine hydrochloride in anhydrous pyridine gave 4-amino-

TABLE I



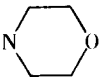
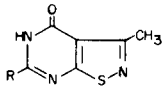
Cpd	R	R'	% Yield	M.p. °C	Formula	Calculated %C	Calculated %H	Calculated %N	Found %C	Found %H	Found %N
6a	H	H	77	272-274	$C_6H_6N_4S$	43.4	3.6	33.7	43.4	3.6	33.9
6b	H	CH_2CH_2N 	63	141-142	$C_{12}H_{17}N_5OS$	51.6	6.1	25.1	51.6	6.2	25.2
6c	H	$CH_2CH_2NEt_2$	86	99-100	$C_{12}H_{19}N_5S$	54.3	7.2	26.4	54.2	7.3	26.4
6d	H	$CH_2CH_2NMe_2$	74	100-102	$C_{10}H_{15}N_5S$	50.6	6.4	29.5	50.7	6.3	29.4
6e	H	$CH_2CH_2CH_2NMe_2$	74	163-165	$C_{11}H_{17}N_5S$	52.6	6.8	27.9	52.7	7.0	27.7
6f	H	$CH_2CHOHCH_2NEt_2$	20	72-74	$C_{13}H_{21}N_5OS$	52.9	7.2	23.7	52.6	7.2	23.8
6g	H	$CHCH_3CH_2CH_2NEt_2$	71	liquid	$C_{15}H_{25}N_5S$	58.6	8.2	22.8	58.3	8.3	22.8
6h	CH_3	H	44	227-229	$C_7H_8N_4S$	46.6	4.5	31.1	46.7	4.3	31.0
6i	CH_2CH_3	H	92	196-198	$C_8H_{10}N_4S$	49.5	5.2	28.7	49.3	5.1	28.7

TABLE II



Cpd	R	% Yield	M.p. °C	Calculated %C	Calculated %H	Calculated %N	Found %C	Found %H	Found %N
11a	H	84	241-243	43.1	3.0	25.1	43.3	3.3	25.2
11b	CH_3	47	245-246	46.4	3.9	23.2	46.0	3.8	23.4
11c	CH_2CH_3	40	221-222	49.2	4.7	21.5	49.3	4.5	21.7

3-methylisothiazolo[5,4-*d*]pyrimidine 5-oxide **7**. The infrared spectrum of **7** has a strong absorption band at 1290 cm^{-1} (7.75μ) characteristic of an N^+-O^- stretching mode, and the mass spectrum has a substantial peak at m/e 166 (M-16) which corroborates the presence of an *N*-oxide function.

3-Methylisothiazole-4-carbonitrile has been shown to undergo hydrolysis to the corresponding carboxylic acid through the action of 2*N* sodium hydroxide (3a). Attempted hydrolysis of **2** under the same conditions gave ring-scission, with 3-hydroxy-2-cyanocrotonamide **8** being isolated in 28% yield. Characterization of **8** was based on analytical and spectral data and was confirmed by conversion to the 3-ethoxy derivative **9** by the action of anhydrous ethanol containing a trace of hydrogen chloride. Compound **9** was identical with the product obtained by condensation of cyanoacetamide with triethyl orthoacetate.

When hydrolysis of **2** was effected by ammonium hydroxide and hydrogen peroxide (8), 5-amino-3-methylisothiazole-4-carboxamide **10** was produced in 78% yield. When **10** was caused to react with orthoesters and acetic anhydride, the corresponding 5*H*-isothiazolo[5,4-*d*]pyrimidin-4-ones **11a-c** were produced. The yields, melting points and analytical data for **11a-c** are shown in Table II.

Attempts to prepare 2-thione derivatives by reaction of **2** and **10** with thiourea, carbon disulfide, or phenyl isothiocyanate failed, but reaction of **2** with sodium methyl xanthate formed 3-methyl-5*H*,7*H*-isothiazolo[5,4-*d*]-pyrimidine-4,6-dithione **12**, and **10** gave 3-methyl-5*H*,7*H*-isothiazolo[5,4-*d*]pyrimidin-4-one-6-thione **13** with the same reagent.

Attempts to effect deamination of **6a** *via* diazotization and reduction with hypophosphorus acid failed. Under mild conditions **6a** was unaffected and under more drastic conditions extensive decomposition occurred, although a small amount of **10a** was isolated.

EXPERIMENTAL (9)

5-Amino-3-methylisothiazole-4-carbonitrile (**2**).

To a stirred solution of 3-amino-2-cyanothiocrotoamide **1** (10.0 g., 0.07 mole) (11) in 500 ml. of methanol was added dropwise 20 ml. (0.18 mole) of 30% hydrogen peroxide. The mixture was

stirred at 50-60° for four hours, then evaporated to about 50 ml. and chilled in an ice bath. The crude crystalline product was collected and recrystallized from ethyl acetate to yield 9.4 g. (95%) of **2**, m.p. 202-204° lit. (4a) m.p. 202-204°; ir (potassium bromide): 3448, 3333 (NH_2), 2212 (C≡N), 1558, 1408, 1299 cm^{-1}; uv 217, 264 nm; nmr (TFA): δ 3.20 (s, 3H); mass spectrum m/e (rel. int.): 139 (100), 112 (17), 98 (73), 74 (24), 72 (35), 60 (19), 44 (16), 42 (34).

5-Ethoxymethyleneimino-3-methylisothiazole-4-carbonitrile (**3a**).

A solution containing 80 ml. of acetic anhydride, 80 ml. (0.438 mole) of triethyl orthoformate and 20.3 g. (0.416 mole) of **2** was heated at reflux for two hours and then evaporated under reduced pressure. The red-brown, oily residue was chilled overnight. The resulting crystalline solid was collected by filtration and recrystallized from light petroleum ether to give 24.5 g. (86%) of **3a** as yellow needles, m.p. 77-78°; nmr (deuteriochloroform): δ 1.40 (t, 3H), 2.50 (s, 3H), 4.40 (q, 2H), 7.80 (s, OH); ir (potassium bromide): 2203 (C≡N), 1600 (C≡N), 1504, 1393 and 1342 cm^{-1}.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.20; H, 4.12; N, 21.50. Found: C, 48.95; H, 4.28; N, 21.25.

Similarly prepared were: **3b** (using triethyl orthoacetate) in 92% yield (yellow oil); nmr (deuteriochloroform): δ 1.40 (t, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 4.38 (q, 2H); and **3c** (using triethyl orthopropionate) in 88% yield (yellow oil); nmr (deuteriochloroform): δ 1.22 (t, 3H), 1.40 (t, 3H), 2.44 (q, 2H), 2.53 (s, 3H), 4.44 (q, 2H) which were unstable to ambient conditions and were used immediately, without purification.

5-Formamidino-3-methylisothiazole-4-carbonitrile (**4a**).

A solution containing 8.0 g. (0.041 mole) of **3a** in 100 ml. of absolute ethanol was saturated with ammonia and allowed to stand for two hours. The resulting solid was collected by filtration and the filtrate was treated with ammonia again. This procedure was repeated several times. The total solid collected was 5.5 g. (88%), m.p. 180-193°. Recrystallization from benzene gave **3a** as white needles; m.p. 174-176°; ir (potassium bromide): 3378, 3215 (NH_2); 2203 (C≡N), 1538, 1497, 1364, cm^{-1}; nmr (DMSO): δ 2.19 (s, 3H), 8.04 (s, 1H).

Anal. Calcd. for $C_6H_6N_4S$: C, 43.38; H, 3.64; N, 33.72; S, 19.26. Found: C, 43.36; H, 3.39; N, 33.89; S, 19.56.

4-Amino-3-methylisothiazolo[5,4-*d*]pyrimidine (**6a**).

A.

To a solution of 5.5 g. of **4a** (0.033 mole) in 100 ml. of methanol was added 21 ml. (0.047 mole) of lithium methoxide (10% in methanol). The reaction mixture was heated at reflux for two hours and then evaporated to dryness under reduced pressure. The white residue was sublimed at 165° to yield 4.5 g. of white powder (77%) m.p. 271-273°. Recrystallization from methanol gave **6a**, m.p. 271-273°; ir (potassium bromide): 3390, 3322 (NH_2), 1550, 1538, 1304 cm^{-1}; nmr (DMSO): δ 2.53 (s, 3H), 8.22 (s, 1H); uv 221, 265, 289 nm; mass spectrum, m/e (rel. int.): 166 (100), 149 (20), 139 (61), 125 (46), 98 (65), 97 (43), 83 (28), 82 (29), 73 (55), 71 (50), 70 (53), 66 (72).

B.

To a mixture of **2** (1.0 g., 0.007 mole) in 50 ml. of 2-ethoxyethanol was added 1.1 g. (0.01 mole) of formamidine acetate. The mixture was heated at reflux for four hours and then evaporated to dryness. The residue was triturated with 30 ml. of cold methanol to yield 0.1 g. (8.3%) of **6a**, m.p. 270-273°, whose ir spectrum was identical to that of the product obtained by method A.

4-(2′-Morpholinoethylamino)-3-methylisothiazolo[5,4-*d*]pyrimidine (**6b**).

To a stirred solution of 3.0 g. (0.015 mole) of **3a** in 15 ml. of absolute ethanol was added 2.1 g. (0.016 mole) of *N*-(2-aminoethyl)-morpholine in 15 ml. of absolute ethanol. The mixture was stirred at room temperature for four hours under dry nitrogen, then evaporated and the yellow residual liquid was chilled overnight. The resulting solid was collected and treated with 30 ml. of chloroform. A hydrolysis product (**2**) was removed by filtration. Evaporation of the filtrate gave a yellow solid which was recrystallized from methanol to yield 2.72 g. (63%) of **6b**, m.p. 141-142°; ir (potassium bromide): 3344 (NH), 2940-2840 (CH), 1580, 1430, 1350 cm^{-1}; nmr (deuteriochloroform): δ 3.60-3.85 (m, 6H), 2.50-2.72 (m, 6H), 2.81 (s, 3H), 8.52 (s, 1H); uv 297, 267, 244 nm; mass spectrum m/e (rel. int.): 279 (1), 193 (2), 179 (2), 150 (2), 139 (1), 113 (65), 100 (100), 83 (3), 82 (2), 70 (2), 56 (13).

4-(2′-Diethylaminoethylamino)-3-methylisothiazolo[5,4-*d*]pyrimidine (**6c**).

The procedure was similar to that used for preparation of **6b** except that *N,N*-diethylethylenediamine was used and the reaction mixture was heated at reflux for six hours. The initial residual liquid was diluted with 30 ml. of water and heated at reflux for 30 minutes. Evaporation of the water and recrystallization of the residue from aqueous methanol gave **6c** in 86% yield, m.p. 99-100°; ir (potassium bromide): 3401 (NH), 2976 to 2817 (C-H), 1592, 1437, 1370 cm^{-1}; nmr (deuteriochloroform): δ 1.08 (t, 6H), 2.63 (q, 4H), 2.78 (t, 2H), 3.65 (q, 2H), 2.83 (s, 3H), 8.48 (s, 1H); uv: 227 (ε = 15,500), 273 (ε = 5,860), 298 nm (ε = 6,880); mass spectrum, m/e (rel. int.): 261 (1), 250 (1), 192 (2), 179 (1), 150 (2), 139 (1), 109 (1), 99 (32), 86 (100), 72 (4), 71 (2), 70 (2), 58 (6).

Similarly prepared were the following compounds: Using *N,N*-dimethylethylenediamine, **6d** was prepared in 74% yield; m.p. 100-102°; ir (potassium bromide): 3443 (NH), 2890 to 2778 (C-H), 1580, 1437, 1359 cm^{-1}; nmr (deuteriochloroform): δ 2.34 (s, 6H), 2.79 (s, 3H), 6.62 (t, 2H), 3.67 (q, 2H), 8.48 (s, 1H); uv: 227 (ε = 16,400), 272 (ε = 5,770), 297 nm (ε = 7,000); mass spectrum, m/e (rel. int.): 237 (2), 193, (5), 191 (3), 179 (3), 167 (1), 83 (5), 83 (7), 72 (17), 71 (73), 70 (7), 58 (100).

Using *N,N*-dimethyl-1,3-diaminopropane, **6e** was prepared in 74% yield; m.p. 163-165°; ir (potassium bromide): 3448 (NH), 2924 to 2825 (C-H), 1587, 1443, 1307 cm^{-1}; nmr (deuteriochloroform): δ 2.30 (s, 6H), 2.76 (s, 3H), 3.78 (q, 2H), 183 (m, 2H), 2.59 (m, 2H), 8.48 (s, 1H); uv: 226 (ε = 15,700), 271 (ε = 5,910), 298 nm (ε = 6,550), mass spectrum, m/e (rel. int.): 251 (46), 207 (6), 193 (28), 180 (60), 167 (3), 166 (2), 150 (14), 124 (2), 109 (2), 97 (4), 85 (34), 84 (16), 72 (43), 70 (27), 58 (100), 44 (21), 42 (35).

Using *N,N*-diethyl-2-hydroxy-1,3-diaminopropane, **6f** was prepared in 20% yield; m.p. 72-74°; ir (potassium bromide): 3400 (NH), 2890-2817 (C-H), 1567, 1439, 1368 cm^{-1}; nmr (deuteriochloroform): δ 1.05 (t, 6H), 1.80-2.00 (m, 1H), 3.10-3.80 (m, 2H), 2.55 (m, 6H), 4.0 (s, 1H), 2.83 (s, 3H); uv: 281, 265, 296 nm; mass spectrum, m/e (rel. int.): 295 (1), 277 (12), 247 (3), 209 (10), 180 (3), 179 (3), 166 (2), 150 (3), 139 (1), 116 (5), 112 (5), 86 (100), 72 (4), 58 (9), 42 (8).

Using 4-amino-1-(*N,N*-diethylamino)pentane, **6g** was prepared in 71% yield; yellow liquid; ir (neat) 3400 (N-H), 2975-2810 (C-H), 1565, 1440, 1290 cm^{-1}; nmr (deuteriochloroform): δ 0.97 (t, 6H), 1.05 (d, 3t), 1.5 (m, 4H), 2.5 (m, 7H), 2.81 (s, 3H), 8.51 (s, 1H); uv: 224 (ε = 17,400), 266 (ε = 7,150), 299 nm (ε = 7,090).

4-Amino-3,6-dimethylisothiazolo[5,4-*d*]pyrimidine (**6h**).

A.

To 100 ml. of absolute ethanol saturated with ammonia was added, with stirring, 0.81 g. (0.004 mole) of **3b**. Ammonia was passed into the solution for two hours, after which it was evaporated to dryness. The residue was recrystallized from methanol to yield 0.29 g. (44%) of **6h**, m.p. 228-231°; ir (potassium bromide): 3448, 3333 (NH_2), 2967 (CH), 158, 1418, 1302 cm^{-1}; nmr (TFA): δ 2.34 (s, 3H), 2.49 (s, 3H); uv: 221 (ε = 21,200), 268 (ε = 5,070), 288 nm (ε = 6,250); mass spectrum, m/e (rel. int.): 180 (100), 165 (6), 164 (7), 163 (6), 139 (39), 134 (6), 98 (18), 97 (12), 73 (20), 71 (14), 70 (17), 66 (14), 46 (9), 42 (60).

4-Amino-6-ethyl-3-methylisothiazolo[5,4-*d*]pyrimidine (**6i**).

To 200 ml. of a stirred saturated solution of ammonia in absolute ethanol was added 6.63 g. (0.030 mole) of **3c**. Stirring was continued and ammonia was passed through the mixture for three hours. Evaporation of the reaction mixture followed by trituration with cold methanol gave 4.9 g. (92%) of **6i** as a white solid, m.p. 196-198°. Recrystallization from benzene gave white needles, m.p. 196-198°; ir: 3390, 3333 (NH_2), 2985 (CH), 1538, 1484, 1318 cm^{-1}; nmr (TFA): δ 1.01 (t, 3H), 2.50 (s, 3H), 2.60 (q, 2H); uv: 220 (ε = 22,600), 268 (ε = 5,160), 290 (ε = 6,620); mass spectrum, m/e (rel. int.): 194 (100), 193 (87), 176 (11), 166 (22), 153 (4), 139 (15), 98 (7), 97 (11), 82 (5), 73 (10), 72 (8), 71 (6), 70 (9), 54 (10), 42 (15).

4-Amino-3-methylisothiazolo[5,4-*d*]pyrimidine-5-Oxide (**7**).

To 100 ml. of a 1:1 solution of anhydrous pyridine and absolute ethanol were added 1.0 g. (0.005 mole) of **3a** and 0.36 g. (0.005 mole) of hydroxylamine hydrochloride. The mixture was heated at reflux for four hours then cooled in an ice bath. Compound **7** (0.35 g., 36%) was obtained as a yellow solid, m.p. 260° dec. After recrystallization from methanol, the m.p. was unchanged; ir (potassium bromide): 3400, 3165 (NH_2), 2899 (CH), 1290 cm^{-1} (N^+-O^-); nmr (DMSO): δ 2.43 (s, 3H), 8.33 (s, 1H); uv: 244 nm; mass spectrum, m/e (rel. int.): 182 (100), 166 (15), 165 (46), 155 (14), 150 (24), 144 (32), 96 (20), 83 (23), 71 (12), 70 (21).

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.55; H, 3.22; N, 30.75; S, 17.60. Found: C, 39.88; H, 3.51; N, 30.54; S, 17.40.

Hydrolysis of 5-Amino-3-methylisothiazole-4-carbonitrile (**2**).

A.

A suspension of 1.0 g. (0.007 mole) of **2** in 25 ml. of 2.0 *N* sodium hydroxide was heated at reflux for six hours. Upon cooling, 0.030 g. of a dimeric product (basic mass spectrum), m.p. 260° was obtained. The filtrate was acidified to *p*H 4 and cooled to give 0.26 g. (28%) of 2-cyano-3-hydroxycrotonamide **8** as pale yellow needles, m.p. 171-173° (from ethanol); ir (potassium bromide): 3400, 3200 (NH_2, OH), 2210 (CN), 1660 cm^{-1} (C=O); nmr (perdeuterioacetic acid): δ 1.85 (s); mass spectromotry m/e (rel. int.): 126 (64), 111 (26), 94 (5), 84 (13), 68 (50), 44 (39), 43 (100).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.42; H, 5.02; N, 21.94.

B.

To a stirred suspension of 8.0 g. (0.058 mole) of **2** in 250 ml. of concentrated ammonium hydroxide was added dropwise 100 ml. of 30% hydrogen peroxide. The temperature of the reaction mixture was maintained at 30-40° during the addition. Stirring was continued for four hours. The cooled reaction mixture was extracted with chloroform. The dried extract was evaporated to yield 7.8 g. (78%) of 5-amino-3-methylisothiazole-4-carboxamide, **10**, m.p. 162-165° (from methanol); ir (potassium bromide): 3520, 3390, 3280, 3230 (NH_2), 1670 (C=O), 1508, 1449, 1379 cm^{-1}; nmr (TFA): δ 2.38 (s, 3H); uv: 224 (ε = 22,700), 270 nm (ε = 9,910); mass spectrum m/e (rel. int.): 157 (86), 140 (100), 125 (17), 108 (12), 99 (14), 73 (26), 71 (20), 42 (33).

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.21; H, 4.49; N, 26.74. Found: C, 38.55; H, 4.69; N, 26.53.

3-Methyl-5*H*-isothiazolo[5,4-*d*]pyrimidin-4-one (**11a**).

A.

A mixture of 1.0 g. (0.006 mole) of **10** and 30 ml. (0.24 mole) of triethyl orthoformate was heated at reflux for three days and then evaporated. The yellow residual liquid was mixed with 60 ml. of benzene and evaporated to dryness. This treatment was repeated several times until a solid residue was obtained. Recrystallization from methanol:benzene (1:1) gave **11a** in 85% yield as pale yellow needles, m.p. 241-243°; ir (potassium bromide): 3450 (broad, OH, NH, 1690 (C=O), 1587, 1468, 1408 cm^{-1}; nmr (DMSO): δ 2.62 (s, 3H), 8.20 (s, 1H); uv: 219 (ε = 15,200), 282 nm (ε = 7,860); mass spectrum, m/e (rel. int.): 167 (100), 140 (5), 126 (54), 99 (7), 98 (4), 73 (16), 71 (15), 42 (9).

B.

To a solution of 0.5 g. (0.003 mole) of **6a** in 30 ml. of glacial acetic acid and 0.8 ml. of water was added 1.0 g. (0.014 mole) of sodium nitrite. The mixture was stirred at room temperature in the dark for two days, then evaporated. The residue was sublimed at 120° to give a 0.4 g. of solid, m.p. 180-220°, which after recrystallization from methanol and chromatography on neutral alumina gave 0.023 g. (5%) of **11a**, m.p. 243-245°, whose ir spectrum was identical with that of the product formed by method A.

3,6-Dimethyl-5*H*-isothiazolo[5,4-*d*]pyrimidin-4-one (**11b**).

A mixture of 1.0 g. (0.0064 mole) of **10**, 30 ml. of triethyl orthoacetate, and 5 ml. of acetic anhydride was heated at reflux for 48 hours, then evaporated to *ca.* 10 ml. The resulting solid was collected by filtration and recrystallized from methanol to give 0.54 g. (47%) of **11b** as white needles, m.p. 245-247°; ir (potassium bromide): 3400 (NH), 1700 (C=O), 1680, 1580, 1488, 1397 cm^{-1}; nmr (deuteriochloroform): δ 2.60 (s, 3H), 2.80 (s, 3H); uv: 221 (ε = 15,900), 284 nm (ε = 6,080); mass spectrum, m/e (rel. int.): 181 (100), 166 (5), 140 (70), 99 (7), 98 (6), 73 (15), 71 (8), 42 (69).

6-Ethyl-3-methyl-5*H*-isothiazolo[5,4-*d*]pyrimidin-4-one (**11c**).

A mixture of 0.4 g. (0.0025 mole) of **10**, 20 ml. (0.148 mole) of triethyl orthopropionate, and 50 ml. of acetic anhydride was heated at reflux for 24 hours and cooled to room temperature. The resulting solid was collected to yield 0.21 g. (40%) of **11c**, m.p. 221-222° (from acetone); ir (potassium bromide): 3450 (NH), 1670 (C=O), 1650, 1585, 1485, 1410 cm^{-1}; nmr (deuteriochloroform): δ 1.44 (t, 3H), 2.63 (s, 3H), 2.93 (q, 2H); uv: 200 (ε = 13,100), 282 nm (ε = 5,700); mass spectrum, m/e (rel. int.): 195 (100), 194 (48), 167 (7), 154 (23), 98 (6), 73 (9), 56 (26).

3-Methyl-5*H*,7*H*-isothiazolo[5,4-*d*]pyrimidine-4,6-dithione (**12**).

To a solution of sodium hydroxide (2.88 g., 0.072 ml.) in 50 ml. of methanol was added 2.0 g. (0.014 mole) of **2** followed by 5.5 g. of carbon disulfide. The mixture was heated at reflux for six hours, then evaporated to *ca.* 25 ml. and cooled. The resulting solid was collected, dissolved in 50 ml. of water and the *p*H adjusted

to 3 with dilute hydrochloric acid. The solid was collected, washed with cold water, triturated with 300 ml. of warm acetone, and the solid residue was collected to yield 0.77 g. (27%) of **12**, m.p. 268° dec.; ir (potassium bromide): 3390 (NH), 2890 (CH), 1515, 1449, 1282, 1129 cm^{-1} (C-S); mass spectrum, m/e (rel. int.): 215 (100), 183 (32), 157 (29), 156 (15), 141 (6), 116 (6), 115 (13), 102 (8), 100 (6), 88 (15), 83 (12), 82 (10), 81 (8), 74 (10), 73 (10), 70 (12), 60 (5), 59 (5), 45 (10), 42 (11).

Anal. Calcd. for $C_6H_5N_3S_3$: C, 33.47; H, 2.34; N, 19.52; S, 44.67. Found: C, 33.35; H, 2.24; N, 19.38; S, 44.62.

3-Methyl-5*H*,7*H*-isothiazolo[5,4-*d*]pyrimidin-4-one-6-thione (**13**).

To a mixture of 0.2 g. (0.0026 mole) of carbon disulfide, 0.10 g. (0.0018 mole) of potassium hydroxide, and 30 ml. of ethanol was added 0.3 g. (0.0019 mole) of **10**. The mixture was heated at reflux for three days, cooled to room temperature, diluted with sufficient water to dissolve the precipitated solid, and the *p*H adjusted to **3**. The resulting solid was collected and dired to yield 0.34 g. (74%) of **13**, m.p. 268° dec.; ir (potassium bromide): 3400, 3150 (NH), 1704, 1690 (C=O), 1558, 1470, 1393, 1200 cm^{-1} (C=S); mass spectrum, m/e (rel. int.): 199 (100), 166 (10), 141 (24), 140 (53), 99 (11), 73 (32), 71 (23), 59 (8).

Anal. Calcd. for $C_6H_5N_3OS_2$: C, 36.17; H, 2.53; N, 21.09; S, 32.18. Found: C, 36.54; H, 2.51; N, 21.31; S, 31.84.

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