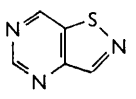
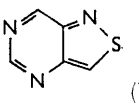
## 1337. *Isothiazoles. Part IX.*[1] *Isothiazolopyrimidines*

By A. Holland, R. Slack, T. F. Warren, and (in part) D. Buttimore

Syntheses of isothiazolo[4,5-*d*]pyrimidines and isothiazolo[4,3-*d*]pyrimidines are described. A general method is given for the oxidation of 3-methylisothiazole and its derivatives to the corresponding acids.

In continuation of our studies on the effect of introducing the isothiazole nucleus into compounds of biological interest [2] we have prepared derivatives of the ring systems isothiazolo[4,5-*d*]pyrimidine (I) and isothiazolo[4,3-*d*]pyrimidine (II), as analogues of purine in which the imidazole ring has been replaced by isothiazole. Goerdeler *et al.* have recently described the synthesis of derivatives of the isomeric isothiazolo[5,4-*d*]pyrimidine system (III).[3]


(I)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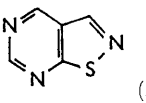
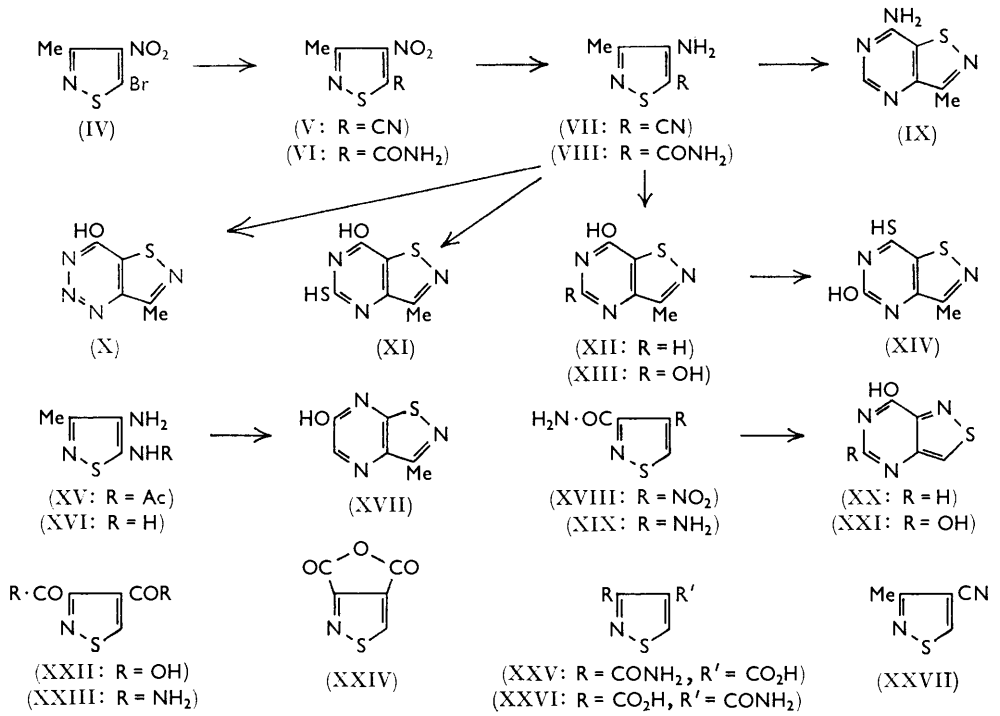

(III)

7-Amino-3-methylisothiazolo[4,5-*d*]pyrimidine (IX) was obtained in poor yield from the aminonitrile (VII) and formamide. In contrast, the corresponding 7-hydroxy- (XII) and 5,7-dihydroxy-derivatives (XIII) were readily prepared from the amino-amide (VIII) with formamide or urea, respectively. The intermediates (VII) and (VIII) were themselves



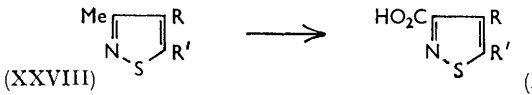

formed from 5-bromo-3-methyl-4-nitroisothiazole [4] (IV) *via* the nitrile (V) and amide (VI) as indicated in the reaction scheme.

[1] Part VIII, preceding Paper.
[2] B. A. Bennett, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1965, 3834.
[3] J. Goerdeler and H. Horn, *Chem. Ber.*, 1963, **96**, 1551; J. Goerdeler and K. Urich, *ibid.*, 1964, **97**, 3106.
[4] A. Adams and R. Slack, *J.*, 1959, 3061.

Diazotisation of the amide (VIII) gave 7-hydroxy-3-methylisothiazolo[4,5-*d*]-*v*-triazine (X), whilst treatment with potassium ethyl xanthate produced 7-hydroxy-5-mercaptoisothiazolo[4,5-*d*]pyrimidine (XI). The latter is isomeric with the product obtained by thiation of compound (XIII) with phosphorus pentasulphide in pyridine, which must consequently possess structure (XIV). Thiation of (XIII) is thus analogous to that of xanthine, which reacts selectively in the 6-position with phosphorus pentasulphide.[5]

6-Hydroxy-3-methylisothiazolo[4,5-*b*]pyrazine (XVII) was obtained from the condensation of n-butyl glyoxylate and 4,5-diamino-3-methylisothiazole hydrochloride in acid solution. The diamine (XVI) was conveniently prepared by hydrolysis of 5-acetamido-4-amino-3-methylisothiazole.[4]

The preparation of a series of isothiazolo[4,3-*d*]pyrimidines required 4-amino-3-carbamoylisothiazole (XIX) as an intermediate. Derivatives of isothiazole-3-carboxylic acid are not readily accessible and the parent acid has only been prepared by indirect methods.[1,6] It has now been found that 3-methylisothiazole and its derivatives (XXVIII) are readily oxidised to the 3-carboxylic acids (XXIX) by chromic acid in concentrated sulphuric acid (see Table). 4-Nitroisothiazole-3-carboxylic acid thus obtained was converted into the amide (XVIII) which was reduced catalytically to the required 4-amino-




(XXVIII) (XXIX)

3-carbamoylisothiazole (XIX). Condensation with formamide or urea gave 7-hydroxy- (XX) or 5,7-dihydroxy-isothiazolo[4,3-*d*]pyrimidine (XXI), respectively. Oxidation of 3-methylisothiazole-4-carboxylic acid gave the 3,4-dicarboxylic acid (XXII), which with thionyl chloride and ammonia afforded the diamide (XXIII). Treatment of the anhydride (XXIV) with ammonia gave a monoamide which differed from the isomeric amide (XXVI), obtained by oxidation of 4-cyano-3-methylisothiazole (XXVII), and which is therefore formulated as (XXV). The diamide (XXIII) did not undergo a Hofmann reaction of 1,2-diamides which would have been expected to yield 5,7-dihydroxyisothiazolo[4,3-*d*]-pyrimidine (XXI).

## Experimental

*5-Cyano-3-methyl-4-nitroisothiazole.*—Dimethylformamide (37·5 g.) was added to a stirred, refluxing suspension of 5-bromo-3-methyl-4-nitroisothiazole [4] (54·1 g.) and cuprous cyanide (43·8 g.) in light petroleum (b. p. 100—120°; 1200 ml.), and the reaction mixture was heated for a further 3·5 hr. The hot solution was decanted and the residue extracted with boiling light petroleum (b. p. 100—120°; 500 ml.). The combined extracts were concentrated to 250 ml. and cooled to 0°, and the solid (35·7 g.), m. p. 90—95°, which separated was recrystallised from light petroleum (b. p. 60—80°) to give *5-cyano-3-methyl-4-nitroisothiazole* in glistening white plates (32·8 g., 80%), m. p. 103—104°, raised by sublimation to 105—107°, $\lambda_{max.}$ 297 mμ (ε, 5300) (Found: C, 35·7; H, 1·8; N, 24·7; S, 18·9. $C_5H_3N_3O_2S$ requires C, 35·5; H, 1·8; N, 24·9; S, 19·0%).

*Isothiazole-3-carboxylic Acid.*—3-Methylisothiazole (15 g.) was added dropwise to concentrated sulphuric acid (270 ml.), the temperature being maintained below 30°. Powdered chromium trioxide (39 g.) was added portionwise during 6 hr. to the stirred solution at 28—30°, the stirring being continued for a further 12 hr. The reaction mixture was poured on to ice (500 g.) and extracted with ether (6 × 1 l.). The dried extract was evaporated to dryness, finally under reduced pressure. Crystallisation of the residue from benzene containing 2% v/v ethanol gave the pure acid (11·5 g., 59%), m. p. 137° (Found: N, 10·8; S, 24·9. Calc. for $C_4H_3NO_2S$: N, 10·9; S, 24·8%). The *derivatives* listed in the Table were prepared similarly.

*5-Carbamoyl-3-methyl-4-nitroisothiazole.*—5-Cyano-3-methyl-4-nitroisothiazole (74 g.) was

[5] A. G. Beaman, *J. Amer. Chem. Soc.*, 1954, **76**, 5633.
[6] D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1964, 3114.

Oxidation of 3-methylisothiazoles (XXVIII) to isothiazole-3-carboxylic acids (XXIX)

| No. | R | R′ | R″ | 3-Methyl-isothiazole (g.) | $CrO_3$ used (g.) | $H_2SO_4$ used (ml.) | Temp. | Reaction time (hr.) | Crude yield (%) | M. p. product * | Solvent for recryst. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $NO_2$ | H | $NO_2$ | 43·2 | 90 | 270 | 40—45° | 18 | 43 | 145° | Benzene |
| 2 | $NO_2$ | NHCOMe | $NO_2$ | 12·06 | 18 | 54 | 40—45 | 24 | 32 | 160 | $NH_4OH$–HCl |
| 3 | $CO_2H$ | H | $CO_2H$ † | 16·0 | 33 | 100 | 40—45 | 48 | 70 | 195 | Ethanol |
| 4 | H | $CO_2H$ | H | 1·43 | 3 | 9 | 40—50 | 24 | 29 | 205 | Water |
| 5 | CN | H | $CONH_2$ ‡ | 1·42 | 3 | 9 | 30 ± 2 | 28 | 29 | 212 | $NH_4OH$–HCl |

| | Analyses | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Found (%) | | | | | Required (%) | | | |
| No. | C | H | N | S | Formula | C | H | N | S |
| 1 | 27·9 | 1·5 | — | 18·4 | $C_4H_2N_2O_4S$ | 27·6 | 1·2 | — | 18·4 |
| 2 | — | — | 17·8 | 14·2 | $C_5H_5N_3O_5S$ | — | — | 18·2 | 13·9 |
| 3 | 34·5 | 1·7 | — | 17·9 | $C_5H_3NO_4S$ | 34·7 | 1·8 | — | 18·5 |
| 4 | 34·8 | 1·6 | 7·8 | — | $C_5H_3NO_4S$ | 34·7 | 1·8 | 8·1 | — |
| 5 | 35·3 | 2·1 | | 18·6 | $C_5H_4N_2O_3S$ | 34·9 | 2·3 | — | 18·6 |

* With decomp. † The *monosodium salt*, isolated by dissolving the dicarboxylic acid in hot water and saturating the solution with sodium chloride, had m. p. 298° (Found: C, 30·8; H, 1·4; Na, 12·1. $C_5H_2NNaO_4S$ requires C, 30·8; H, 1·0; Na, 11·8%). Acidification of its aqueous solution regenerated the acid and afforded a convenient means of purification. ‡ Bonded OH bands were insignificant in the i.r. spectrum.

heated with concentrated sulphuric acid (500 ml.) on a steam-bath until a clear solution was obtained. The cold solution was poured on to ice and the precipitated solid was collected, washed with water, and recrystallised from ethanol to give white needles (67 g., 84%), m. p. 166° (Found: C, 32·2; H, 2·5; N, 22·4. $C_5H_5N_3O_3S$ requires C, 32·1; H, 2·7; N, 22·5%).

3-*Methyl*-4-*nitroisothiazole*-5-*carboxylic Acid*.—5-Cyano-3-methyl-4-nitroisothiazole (22 g.) was added to a mixture of concentrated sulphuric acid (59 ml.) and water (14·2 ml.) and the solution was stirred at 85° for 6 hr. The cold solution was poured on to ice (200 g.) and the solid was dissolved in 2N-aqueous sodium hydroxide (100 ml.). Acidification of the filtrate gave the *acid* (13·5 g., 55%). Recrystallisation from toluene gave white needles, m. p. 120° (decomp.) (Found: N, 14·8; S, 17·6. $C_5H_4N_2O_4S$ requires N, 14·9; S, 17·0%).

4-*Amino*-5-*carbamoyl*-3-*methylisothiazole* (VIII).—5-Carbamoyl-3-methyl-4-nitroisothiazole (16·5 g.) was hydrogenated over Raney nickel in ethanol (350 ml.) at 30°/4·6 atm. for 1 hr. The filtrate was evaporated to dryness *in vacuo*, the residue was suspended in ethanol, then filtered off and washed with a small quantity of light petroleum (b. p. 40—60°). The *amine* (10 g., 72%) had m. p. 202—204° (Found: C, 38·4; H, 4·5; S, 20·8. $C_5H_7N_3OS$ requires C, 38·2; H, 4·5; S, 20·4%).

Similarly was prepared 4-*amino*-3-*carbamoylisothiazole* (85%), m. p. 145° (Found: N, 29·8; S, 22·3. $C_4H_5N_3OS$ requires N, 29·4; S, 22·4%). Addition of the amine (1·4 g.) to acetic anhydride (3 ml.) and acetic acid (3 ml.) below 35° produced the *acetyl derivative*, m. p. 198° (Found: C, 38·8; H, 3·9; S, 17·5. $C_6H_7N_3O_2S$ requires C, 38·9; H, 3·8; S, 17·3%).

4-*Amino*-5-*cyano*-3-*methylisothiazole* (VII).—5-Cyano-3-methyl-4-nitroisothiazole (16·5 g.), in water (350 ml.), was hydrogenated over platinum charcoal (20% w/w) at 50°/4·6 atm. for 11 hr. The catalyst was filtered off and washed with ethanol (3 × 200 ml.), and the filtrate and washings were evaporated to dryness. Recrystallisation of the residue from water gave 4-*amino*-5-*cyano*-3-*methylisothiazole* (6·5 g., 47%), m. p. 165—167° (Found: C, 43·4; H, 3·5; S, 23·4. $C_5H_5N_3S$ requires C, 43·1; H, 3·6; S, 23·0%).

4-*Amino*-3-*methylisothiazole*-5-*carboxylic Acid*.—Ferrous sulphate (206·4 g., $FeSO_4,7H_2O$) in water (2·2 l.) was added to barium hydroxide [1261·6 g., $Ba(OH)_2,8H_2O$] in water (6·6 l.) at 70°. 5-Cyano-3-methyl-4-nitroisothiazole (13·5 g.) was added to the well-stirred mixture which was maintained at 90° for 1¼ hr. The filtrate was extracted with ether (2·5 l.) and the aqueous solution was acidified to pH 1 at 0° and continuously extracted with ether. Evaporation of the extract and recrystallisation of the residue from water gave the *acid* (3 g., 25%) in colourless needles, m. p. 203° (decomp.) (Found: N, 17·4; S, 20·0. $C_5H_6N_2O_2S$ requires N, 17·7; S, 20·3%). The same acid, m. p. 192—193°, was obtained by catalytic reduction (Raney nickel) of 3-methyl-4-nitroisothiazole-5-carboxylic acid.

4-*Amino*-5-*bromo*-3-*methylisothiazole*.—5-Bromo-3-methyl-4-nitroisothiazole (23 g.) was reduced with ferrous hydroxide [from 258 g., $FeSO_4,7H_2O$ and 293 g., $Ba(OH)_2,8H_2O$] in water (3 l.) at 70°. Recrystallisation from light petroleum (b. p. 60—80°) gave 4-*amino*-5-*bromo*-3-*methylisothiazole* (15 g., 78%), m. p. 54—55° (Found: Br, 41·1; S, 16·4. $C_4H_5BrN_2S$ requires Br, 41·4; S, 16·6%); *acetyl derivative*, m. p. 131—132° (from toluene) (Found: Br, 33·9; S, 13·7. $C_6H_7BrN_2OS$ requires Br, 34·0; S, 13·6%).

4-p-*Acetamidobenzenesulphonamido*-5-*bromo*-3-*methylisothiazole*.—4-Amino-5-bromo-3-methylisothiazole (15 g.) was treated with *p*-acetamidobenzenesulphonyl chloride (20·2 g.) in dry pyridine (47 ml.). The *acetyl derivative* (21 g., 69%), m. p. 254—257°, was purified by dissolution in dilute ammonia and acidification with acetic acid (Found: C, 37·0; H, 3·3; N, 11·0. $C_{12}H_{12}BrN_3O_3S_2$ requires C, 36·8; H, 3·1; N, 10·8%).

4-p-*Aminobenzenesulphonamido*-5-*bromo*-3-*methylisothiazole*.—The foregoing derivative (18 g.) was heated under reflux with 2N-aqueous sodium hydroxide (180 ml.) for 2½ hr. Acidification with acetic acid afforded the *sulphonamide* (13 g., 81%), m. p. 224—225° (Found: C, 34·8; H, 3·1; N, 11·8. $C_{10}H_{10}BrN_3O_2S_2$ requires C, 34·5; H, 2·9; N, 12·1%).

4,5-*Diamino*-3-*methylisothiazole* (XVI).—5-Acetamido-4-amino-2-methylisothiazole (100 g.) was heated under reflux with 4N-aqueous hydrochloric acid (1230 ml.) during 1 hr. The dark coloured solution was evaporated to dryness *in vacuo*, the residue was taken up in water, and the filtered (charcoal, Hyflo) solution again evaporated. Trituration of the residue with dry acetone gave 4,5-diamino-3-methylisothiazole dihydrochloride (77 g., 67%), m. p. 335° (decomp.). Recrystallisation from ethanol (containing a small amount of water)–light petroleum (b. p. 40—60°) gave the *monohydrochloride* as white needles, m. p. 173—175° (after drying at 110°/0·01 mm.) (Found: N, 25·8; Cl, 20·9. $C_4H_7N_3S,HCl$ requires N, 25·4; Cl, 21·4%). The *base* * was regenerated from the hydrochloride by ethanolic sodium ethoxide and recrystallised from methylene chloride to give yellow needles, m. p. 123° (Found: C, 37·2; H, 5·4; S, 24·8. $C_4H_7N_3S$ requires C, 37·2; H, 5·4; S, 24·8%). The amine possessed a very persistent, objectionable odour.

3-*Aminoisothiazole*.—3-Carbamoylisothiazole [6] (13 g.) was added at 0° with stirring to a freshly prepared solution of sodium hypobromite [sodium hydroxide (17·4 g.), water (144 ml.), and bromine (6 ml.)]. The reaction mixture was gently heated until the exothermic reaction had subsided and subsequently at 100° for 30 min. The cold solution was extracted with ether, the extract was evaporated, and the residue crystallised from ether–light petroleum (b. p. 40—60°) to give white *needles* (6·3 g., 62%), m. p. 33—34° (Found: C, 35·7; H, 4·1; S, 31·6. $C_3H_4N_2S$ requires C, 36·0; H, 4·0; S, 32·0%). Acetic anhydride–acetic acid at 60° gave the *acetyl derivative*, m. p. 141° (Found: C, 42·4; H, 4·3; S, 22·7. $C_5H_6N_2OS$ requires C, 42·2; H, 4·2; S, 22·5%).

3-p-*Aminobenzensulphonamidoisothiazole*.—3-Aminoisothiazole (6·3 g.) was treated with *p*-acetamidobenzenesulphonyl chloride (16·8 g.) in dry pyridine (65 ml.). The *acetyl sulphonamide* (16·5 g., 90%), m. p. 248°, was purified by dissolution in dilute ammonia and acidification with dilute acetic acid (Found: C, 44·7; H, 3·8; S, 21·5. $C_{11}H_{11}N_3O_3S_2$ requires C, 44·4; H, 3·7; S, 21·6%).

The acetamido-derivative (16·5 g.) was hydrolysed by heating with 2N-aqueous sodium hydroxide (105 ml.) in the usual way. Recrystallisation from aqueous ethanol afforded the *sulphonamide* (11 g., 80%), m. p. 151° (Found: C, 42·8; H, 3·7; S, 25·0. $C_9H_9N_3O_2S_2$ requires C, 42·3; H, 3·6; S, 25·1%).

3-*Carbamoyl*-4-*nitroisothiazole* (XVIII).—4-Nitroisothiazole-3-carboxylic acid (20 g.) and thionyl chloride (114 ml.) were refluxed for 3 hr. The excess of thionyl chloride was removed *in vacuo* and the residue, in dry benzene (6 ml.), poured into ice and aqueous ammonia. Recrystallisation of the precipitated solid (12 g., 61%) from ethanol gave the *amide*, m. p. 166° (Found: C, 27·9; H, 2·0; S, 18·6. $C_4H_3N_3O_3S$ requires C, 27·7; H, 1·8; S, 18·5%).

*Isothiazole*-3,4-*dicarboxylic Acid Anhydride* (XXIV).—A solution of isothiazole-3,4-dicarboxylic acid (0·5 g.) and acetic anhydride (1 ml.) was heated at 100° for 1 hr., then evaporated to dryness *in vacuo*. The residue was extracted with hot dry toluene (2 × 50 ml.) and the cooled extract diluted with an equal volume of dry light petroleum (b. p. 40—60°). Recrystallisation of the residue from light petroleum (b. p. 60—80°) gave the *anhydride*, m. p. 92—93° (Found: C, 38·5; H, 0·7; S, 20·9. $C_5HNO_3S$ requires C, 38·7; H, 0·7; S, 20·7%). Treatment of the

* First prepared in these laboratories by Dr. M. S. Barber by chemical reduction.

anhydride with excess of ammonia (*d* 0·88), evaporation of the solution, and acidification of the residue gave **3-*carbamoylisothiazole*-4-*carboxylic acid*** (XXV), m. p. 220° (decomp.), $\nu_{max.}$ 1800—2500 cm.$^{-1}$ (bonded OH) (Found: C, 35·2; H, 2·5; S, 18·5. $C_5H_4N_2O_3S$ requires C, 34·9; H, 2·3; S, 18·6%).

*Isothiazole*-3,4-*dicarboxyamide* (XXIII).—Isothiazole-3,4-dicarboxylic acid (12 g.) and thionyl chloride (100 ml.) were refluxed for 4 hr. The excess of thionyl chloride was removed *in vacuo*, the residue dissolved in dry benzene (50 ml.), and poured into an excess of ammonia and ice. Crystallisation from aqueous ethanol gave the *diamide* (7 g.), m. p. 283° (Found: C, 35·3; H, 3·2; S, 18·7. $C_5H_5N_3O_2S$ requires C, 35·1; H, 3·0; S, 18·7%). The ammonical filtrate from above was evaporated and acidfied with dilute hydrochloric acid. The precipitated 3-carbamoylisothiazole-4-carboxylic acid (XXV) (2 g.) was washed with water and had m. p. 225° (decomp.), undepressed with a sample prepared as above (Found: C, 35·0; H, 2·3; S, 19·1%).

*Reaction of* 4,5-*Diamino*-3-*methylisothiazole with Diethoxyethyl Acetate*.—4,5-Diamino-3-methylisothiazole (0·5 g.) was heated at 120° for 1 hr. with diethoxyethyl acetate (10 ml.). The solvent was removed *in vacuo* and the residue dissolved in benzene and saturated with dry hydrogen chloride. Evaporation of the benzene solution and recrystallisation of the residue from propan-2-ol–ether gave a hydrogroscopic solid, probably 4(5)-acetoxymethyleneamino-5(4)-amino-3-methylisothiazole (Found: N, 17·6; S, 13·9. Calc. for $C_7H_9N_3O_2S$,HCl: N, 17·8; S, 13·6%).

6-*Hydroxy*-3-*methylisothiazolo*[4,5-b]*pyrazine* (XVII).—4,5-Diamino-3-methylisothiazole hydrochloride (6 g.) and n-butyl glyoxylate (6 g.) were treated with sulphuric acid (30 ml.; 78% w/w) with stirring at 0°. The temperature was allowed to rise to 20°, the solution was kept for 30 min. then cooled to 0° again and diluted with water (60 ml.). The product which separated was dissolved in dilute ammonia and precipitated with concentrated hydrochloric acid to give the *pyrazine* as a cream-coloured solid (3·6 g., 71%), m. p. 292—293° (decomp.) (Found: C, 43·5; H, 3·0; S, 18·9. $C_6H_5N_3OS$ requires C, 43·1; H, 3·1; S, 19·2%).

7-*Amino*-3-*methylisothiazolo*[4,5-d]*pyrimidine* (IX).—4-Amino-5-cyano-3-methylisothiazole (8 g.) and formamide (64 ml.) were heated at 160—170° during 5 hr. Recrystallisation from ethanol gave 7-*amino*-3-*methylisothiazolo*[4,5-d]*pyrimidine* as pale brown needles (5 g., 53%), m. p. 247—250° (Found: C, 43·3; H, 3·6; S, 18·9. $C_6H_6N_4S$ requires C, 43·4; H, 3·6; S, 19·3%).

7-*Hydroxy*-3-*methylisothiazolo*[4,5-d]*pyrimidine* (XII), was similarly prepared from 4-amino-5-carbamoyl-3-methylisothiazole (2·0 g.). Recrystallisation from ethanol gave cream-coloured micro-needles (1·5 g., 72%), m. p. 270—275° (Found: C, 43·1; H, 3·1; S, 18·7. $C_6H_5N_3OS$ requires C, 43·4; H, 3·0; S, 19·2%).

7-*Hydroxy*-3,5-*dimethylisothiazolo*[4,5-d]*pyrimidine* * was similarly prepared from 4-amino-5-carbamoyl-3-methylisothiazole (15·7 g.) and acetamide (100 g.) at 200—220° for 20 hr. Recrystallisation from ethanol gave colourless needles (11·8 g., 65%), m. p. 282—284° (Found: N, 23·5; S, 17·9. $C_7H_7N_3OS$ requires N, 23·2; S, 17·7%).

5,7-*Dihydroxy*-3-*methylisothiazolo*[4,5-d]*pyrimidine* (XIII).—This was similarly obtained from 4-amino-5-carbamoyl-3-methylisothiazole (30 g.) and urea (90 g.) at 170° for 5 hr. The cooled melt was extracted with warm 2N-ammonia, filtered (charcoal), and the extract acidified at 0° with concentrated hydrochloric acid to give cream *needles* (29 g., 83%), m. p. >360° (Found: C, 39·2; H, 3·4; S, 17·2. $C_6H_5N_3O_2S$ requires C, 39·3; H, 2·8; S, 17·5%).

7-*Hydroxy*-3-*methyl*-5-*mercaptoisothiazolo*[4,5-d]*pyrimidine* (XI).—A mixture of 4-amino-5-carbamoyl-3-methylisothiazole (1·6 g.) and potassium ethyl xanthate (1·8 g.), in ethanol (15 ml.) and water (75 ml.), was heated under reflux for 3 hr. The hot solution was filtered (charcoal), and the filtrate heated to 60—70° and diluted with water (10 ml.) and 50% acetic acid (4 ml.). The solid was filtered off and dissolved in dilute ammonia, and the solution was acidified with concentrated hydrochloric acid at 0° to give 7-*hydroxy*-3-*methyl*-5-*mercaptoisothiazolo*[4,5-d]*pyrimidine*, m. p. 310—311°, $\lambda_{max.}$ 233, 275, 344 mμ (ε 10,300; 17,700, 4700) (Found: N, 20·7; S, 31·8. $C_6H_5N_3OS_2$ requires N, 21·1; S, 32·2%).

7-*Hydroxy*-3-*methylisothiazolo*[4,5-d]-v-*triazine* (X).—Sodium nitrite (13·2 g.) was added to a mixture of concentrated hydrochloric acid (500 ml.) and water (500 ml.) with stirring at 0°, and 4-amino-5-carbamoyl-3-methylisothiazole (13·2 g.) was added portionwise during 30 min. When addition was complete a further portion of sodium nitrite (13·2 g.) was made and stirring

* Prepared by Mr. D. L. Pain.

was continued overnight. The solid was filtered off and dissolved in dilute ammonia, and the solution was acidified with concentrated hydrochloric acid at 0° to give the *triazine* as a cream-coloured solid (11 g., 78%), m. p. 163° (Found: C, 35·7; H, 2·3; S, 19·2. $C_5H_4N_4OS$ requires C, 35·7; H, 2·4; S, 19·1%).

*3-Methyl-7-mercaptoisothiazolo*[4,5-d]*pyrimidine.*—7-Hydroxy-3-methylisothiazolo[4,5-*d*]-pyrimidine (17 g.) and phosphorus pentasulphide (27·5 g.) were heated under reflux in dry pyridne (140 ml.) during 1 hr. The cold solution was poured into ice and water and set aside overnight. The precipitated solid was dissolved in hot dilute ammonia and reprecipitated with concentrated hydrochloric acid at 0° to give the *thiol* as a yellow powder (9 g., 51%), m. p. 250° (Found: C, 39·1; H, 3·1; S, 35·2. $C_6H_5N_3S_2$ requires C, 39·3; H, 2·8; S, 35·0%).

*5-Hydroxy-3-methyl-7-mercaptoisothiazolo*[4,5-d]*pyrimidine* (XIV.—5,7-Dihydroxy-3-methylisothiazolo[4,5-*d*]pyrimidine (1·8 g.) and phosphorus pentasulphide (5·5 g.) were heated under reflux in dry pyridine (28 ml.) during 2 hr. The *thiol* was isolated in the usual way; recrystallisation from dimethylformamide gave yellow micro-needles (0·5 g., 25%), m. p. >360°, $\lambda_{max.}$ 219, 251, 369 mμ (ε 17,600, 8800, 10,300) (Found: C, 36·3; H, 2·4; S, 32·4. $C_6H_5N_3OS_2$ requires C, 36·2; H, 2·5; S, 32·2%).

*3-Methyl-7-methylthioisothiazolo*[4,5-d]*pyrimidine.*—A fine suspension of 3-methyl-7-mercaptoisothiazolo[4,5-*d*]pyrimidine (4·5 g.) in 2N-aqueous sodium hydroxide (12·5 ml.) and water (25 ml.) was treated with methyl iodide (3·5 g.) with stirring for 1 hr., diluted with water (70 c.c.) and warmed on a steam-bath for 1 hr. The solid (4 g., 83%) which separated was recrystallised from ethanol to give *3-methyl-7-methylthioisothiazolo*[4,5-d]*pyrimidine* as white needles, m. p. 136—137° (Found: C, 42·9; H, 3·9; S, 32·7. $C_7H_7N_3S_2$ requires C, 42·6; H, 3·6; S, 32·5%).

*4-Amino-3-methylisothiazole-5-carboxyhydrazide.*—A mixture of 4-amino-5-carbamoyl-3-methylisothiazole (4 g.) and hydrazine hydrate (25 ml., 100%) was heated on a steam-bath for 2 hr. Recrystallisation of the product from ethanol gave the *hydrazide*, m. p. 208°, in nearly quantitative yield (Found: C, 34·8; H, 4·5; S, 19·0. $C_5H_8N_4OS$ requires C, 34·9; H, 4·6; S, 18·6%).

*4-Amino-3-N-isopropylidene-3-methylisothiazole.*—4-Amino-3-methylisothiazole-5-carboxyhydrazide (1 g.) was heated under reflux with dry acetone (75 ml.) for 6 hr. Recrystallisation from acetone gave the *isopropylidene derivative* as white needles (1 g.), m. p. 247° (Found: C, 46·0; H, 5·6; S, 14·7. $C_8H_{12}N_4OS$ requires C, 45·3; H, 5·5; S, 15·1%). When this material (0·5 g.) was heated with ethyl orthoformate (5 ml.) and dimethylformamide (10 ml.) no reaction occurred.

*7-Hydroxyisothiazolo*[4,3-d]*pyrimidine* (XX).—4-Amino-3-carbamoylisothiazole (20 g.), ethyl orthoformate (200 ml.), and dry dimethylformamide (400 ml.) were heated under reflux for 6 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue dissolved in dimethylformamide, and the solution filtered and diluted with water until precipitation of *3-hydroxyisothiazolo*[4,3-d]*pyrimidine* (14 g., 65%), m. p. 265°, was complete (Found: C, 39·7; H, 2·3; S, 20·7. $C_5H_3N_3OS$ requires C, 39·2; H, 2·0; S, 20·9%).

*5,7-Dihydroxyisothiazolo*[4,3-d]*pyrimidine* (XXI).—4-Amino-3-carbamoylisothiazole (13·5 g.) and urea (100·5 g.) were heated at 140° for 4 hr. *5,7-Dihydroxyisothiazolo*[4,3-d]*pyrimidine* (14·5 g., 91%), obtained by extraction of the cold melt with 2N-aqueous sodium hydroxide and precipitation with acid, had m. p. >360° (Found: C, 35·4; H, 1·8; S, 18·6. $C_5H_3N_3O_2S$ requires C, 35·5; H, 1·8; S, 19·0%).

The authors are indebted to Mr. S. Bance, B.Sc., F.R.I.C., for the analyses, Messrs. R. D. McDonald, B.Sc., and T. L. Threlfall, B.S.c., for the spectra, and Messrs. R. Philo and D. J. Sheffield for preparative assistance.

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[*Received, April 7th,* 1965.]