

Synthesis of Derivatives of Thiazolo[4,5-*d*]pyrimidine. Part II.¹

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An attempt to prepare thiazolo[4,5-*d*]pyrimidine-5,7-diol by the action of potassium hypobromite on thiazole-4,5-dicarboxamide revealed the instability of the thiazole portion of this condensed ring system when 2-substituents are lacking. The product obtained was bis-(4-amino-2,6-dihydroxypyrimidin-5-yl) disulphide, contrary to an earlier report. A number of thiazolo[4,5-*d*]pyrimidines have been prepared by cyclisation of the corresponding 4-aminopyrimidin-5-yl thiocyanates. Deamination of aminothiazolo[4,5-*d*]pyrimidines, with nitrous acid, has given a number of derivatives among which is the analogue of uric acid.

THE synthesis of 2-aminothiazolo[4,5-*d*]pyrimidine-5,7-diol (III; X = NH₂) from 2-aminothiazole-4,5-dicarboxamide (I; X = NH₂), and the preparation of the same compound from 2,5-diaminothiazolo[4,5-*d*]pyrimidine-7-ol (XVI; Y = NH₂, Z = OH), would provide additional

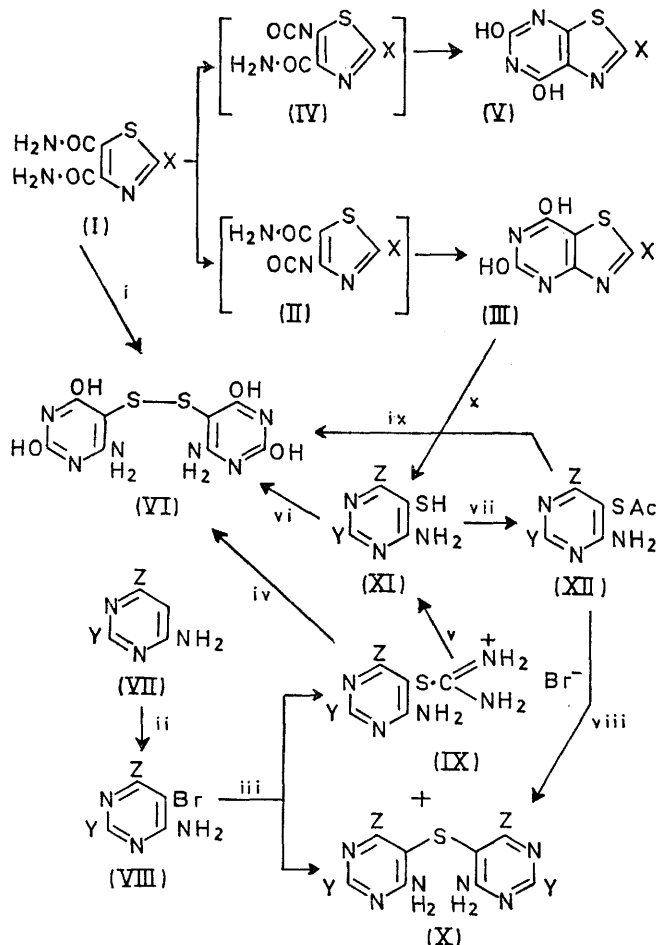
evidence for the structure of the compound which we have previously described as the latter thiazolopyrimidine.¹ Childress and McKee² have reported the preparation of thiazolo[4,5-*d*]pyrimidine-5,7-diol and its 2-methyl and 2-phenyl analogues (III; X = H, Me, or

¹ Part I, J. A. Baker and P. V. Chatfield, *J. Chem. Soc. (C)*, 1969, 603.

² S. J. Childress and R. L. McKee, *J. Amer. Chem. Soc.*, 1951, **73**, 3862.

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Ph, respectively) by the action of potassium hypobromite on the corresponding 2-substituted thiazole-4,5-dicarboxamides (I). These reactions presumably occur *via* intermediates of type (II) or (IV), and could give rise to derivatives of thiazolo[5,4-*d*]pyrimidine (V).



Reagents: i, KOB; ii, Br₂; iii, (NH₂)₂C=S; iv, NaHCO₃; v, NaOH; vi, Me₂S=O; vii, Ac₂O; viii, HCO·NH₂; ix, H₂SO₄; x, NaOH.

We found that treatment of 2-aminothiazole-4,5-dicarboxamide with potassium hypobromite gave ammonia, and we were unable to isolate any thiazolopyrimidine. Evolution of ammonia could have been due to hydrolysis of the carboxamide groups or to the decomposition of a di- or tri-aminothiazole formed by a complete Hofmann reaction. The instability of 2,4-diaminothiazoles has been reported.³ This failure to obtain the thiazolopyrimidine and the surprising difference between the u.v. data quoted by Childress and McKee for thiazolo[4,5-*d*]pyrimidine-5,7-diol (III; X = H) (λ_{max} , 270 and 337 nm.) and its 2-methyl analogue (III; X = Me) (λ_{max} , 317 nm.) prompted us to investigate their method.

The reaction of thiazole-4,5-dicarboxamide (I; X =

H) with potassium hypobromite afforded bis-(4-amino-2,6-dihydroxypyrimidin-5-yl) disulphide (VI). A brief period of heating was essential for closure of the pyrimidine ring, but when prolonged heating was employed, as described by Childress and McKee, decomposition occurred as shown by i.r. spectra. This agrees with our previous observations concerning the instability of bis-(2,4-diamino-6-hydroxypyrimidin-5-yl) disulphide in alkaline solution.¹

The disulphide (VI) was also prepared by a method essentially the same as that described in our previous paper.¹ Treatment of 6-amino-5-bromopyrimidine-2,4-diol (VIII; Y = Z = OH) with thiourea gave the isothiouonium bromide (IX; Y = Z = OH) together with a little bis-(4-amino-2,6-dihydroxypyrimidin-5-yl) sulphide (X; Y = Z = OH). Decomposition of the isothiouonium base in weakly alkaline solution yielded the disulphide (VI). It was found necessary to isolate the isothiouonium salt in order to obtain a pure specimen of the disulphide.

Brief treatment of the isothiouonium base with hot, air-free, aqueous sodium hydroxide gave slightly impure 6-amino-5-mercaptopyrimidine-2,4-diol (XI; Y = Z = OH), which slowly lost hydrogen sulphide and could not be purified. It was identified by the presence of a sharp, weak i.r. band at about 2550 cm.⁻¹ (SH), and by its conversion into the disulphide (VI) on treatment with dimethyl sulphoxide. The oxidation of thiols by this reagent has been reported.⁴

Oxidation of the thiol with potassium hypobromite solution afforded the crude disulphide as shown by i.r. spectra. The thiol, but not the disulphide, decolourised aqueous iodine. Reduction of the disulphide with zinc and cold sodium hydroxide solution was accompanied by decomposition (u.v. and i.r. spectra).

Acetylation of the thiol gave mono- and di-acetyl derivatives. The former appeared to be the S-acetyl derivative (XII; Y = Z = OH), since its i.r. spectrum did not have a band at about 2550 cm.⁻¹, and the sharp band at about 3440 cm.⁻¹ (NH), present in the spectrum of the thiol, appeared unaltered in that for the acetylated compound. The possibility that the product could be an O-acetyl disulphide was considered unlikely, because the disulphide (VI) was recovered unchanged after being refluxed in acetic anhydride for 9 hr.

Attempts to cyclise the monoacetyl derivative to the thiazolopyrimidine (III; X = Me) failed. Prolonged heating of the acetyl compound in acetic anhydride led to decomposition, and on brief heating (5 min.) in formamide at 180° the sulphide (X; Y = Z = OH) was formed. Treatment at 100° for 1 min. with concentrated sulphuric acid yielded crude disulphide (VI).

Thiocyanation of 6-aminopyrimidine-2,4-diol (VII; Y = Z = OH) in 96% acetic acid afforded the 5-thiocyanato-derivative (XIII; Y = Z = OH) and not the thiazolopyrimidine (III; X = NH₂) as claimed by Maggiolo and Hitchings.⁵ The thiocyanate was also

³ 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1957, vol. 5, p. 614.

⁴ W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67**, 247.

⁵ A. Maggiolo and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 4226.

obtained by treatment of 6-amino-5-bromopyrimidine-2,4-diol (VIII; $Y = Z = OH$) with potassium thiocyanate. Identification of the thiocyanato-compound rested on the presence of a sharp, medium-strong i.r. band at about 2130 cm^{-1} . The thiocyanate was isomerised to the thiazolopyrimidine (III; $X = NH_2$) when boiled for several hours in either water or dimethylformamide, the latter solvent being more convenient because of the low solubility of the thiocyanate in water.

Baker and Hill⁶ reported that treatment of diaminothiazolo[4,5-*d*]pyrimidines with nitrous acid at 0° gave dark, uncrystallisable solids. We have found this to apply to the aminothiazolo[4,5-*d*]pyrimidines (XVI; $Y = Z = OH$ and $Y = NH_2$, $Z = OH$). When, however, the thiazolopyrimidine (XVI; $Y = Z = OH$) was dissolved in aqueous sodium hydroxide, containing an excess of sodium nitrite, and gradually added at 80° to

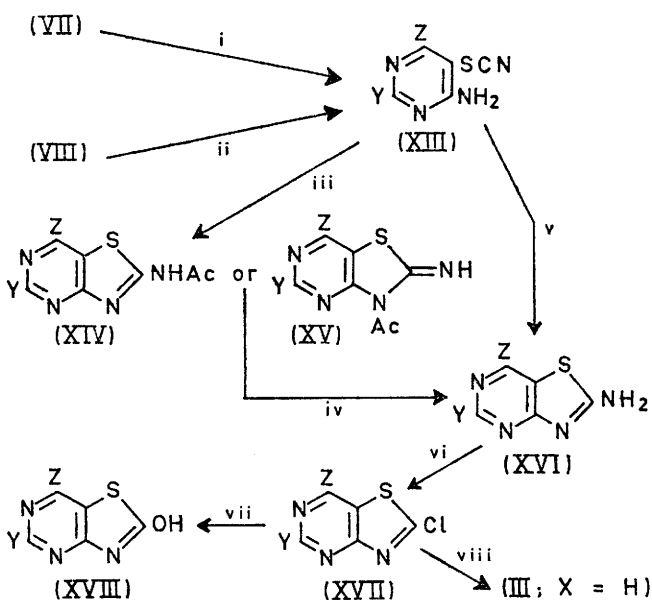
$Y = Z = OH$). This cleavage of the thiazole ring explains why the disulphide (VI), and not the thiazolopyrimidine (III; $X = H$), was obtained from the partial Hoffman reaction on thiazole-4,5-dicarboxamide. This instability of a thiazolo[4,5-*d*]pyrimidine unsubstituted in the 2-position contrasts with the stability of 2-aminothiazolo[4,5-*d*]pyrimidines, which have given sodium salts when crystallised from sodium hydroxide solution.

A number of other 2-aminothiazolo[4,5-*d*]pyrimidines (XVI) have been prepared by the cyclisation of the corresponding pyrimidin-5-yl thiocyanates (XIII), which were prepared either by direct thiocyanation or by treatment of 5-bromopyrimidines (VIII) with potassium thiocyanate. For some reason, as yet unexplained, the reactivity of the bromo-compounds varied widely. In some cases slightly acid ethanol appeared to be necessary as a solvent. (However, related work in these laboratories has shown that the addition of a little glacial acetic acid will not always catalyse the reaction between potassium thiocyanate and 4-chloro-6-methyl-2-methylthiopyrimidine.) The reaction of bromo-compounds with potassium thiocyanate was, therefore, satisfactory only for the preparation of 2,4,6-triamino- and 4-amino-6-hydroxy-pyrimidin-5-yl thiocyanates (XIII; $Y = Z = NH_2$ and $Y = H$, $Z = OH$ respectively). In all cases the i.r. spectra of the thiocyanates showed a sharp medium-strong band at $2130\text{--}2170\text{ cm}^{-1}$.

The m.p.s of some of the thiocyanates varied with the temperature at which the sample was placed in the apparatus, presumably owing to isomerisation on heating. A rough determination was, therefore, made by placing a number of samples in the apparatus at various temperatures and noting the lowest temperature at which melting was instantaneous. A sample was then placed in the apparatus at a temperature 2° below that for instantaneous melting, and an accurate value for the m.p. was thus found.

Although cyclisation of several pyrimidin-5-yl thiocyanates (XIII) to give the corresponding thiazolopyrimidines (XVI) occurred in boiling water, this procedure was satisfactory only for 4,6-diamino- and 4-amino-6-hydroxy-pyrimidin-5-yl thiocyanates; the former reacted rapidly. In other cases cyclisation was accompanied by hydrolysis to the corresponding disulphide, and possibly other substances, as indicated by the yellow colour of the products, analytical results, and i.r. spectra. Those thiocyanates which did not isomerise cleanly in boiling water, were cyclised in boiling acetic anhydride to yield acetamido-derivatives [(XIV) or (XV)], which were then hydrolysed to the thiazolopyrimidines (XVI). [For simplicity Z and Y have been retained in structures (XIV) and (XV) although they may represent NHAc whereas in structure (XIII) they may represent NH_2 . In these instances other tautomeric possibilities have not been drawn.]

The Tables show that the 5,7-disubstituted 2-aminothiazolo[4,5-*d*]pyrimidines (XVI) have a u.v. absorption maximum in the region $290\text{--}313\text{ nm}$. ($0.1N\text{-HCl}$;



Reagents: i, $Br_2\text{-KSCN}$; ii, $KSCN$; iii, Ac_2O ; iv, $NaOH$; v, H_2O or $Me_2N\text{-CHO}$; vi, HNO_2 ; vii, $NaOH$; viii, $Zn\text{-NaOH}$.

hydrochloric acid, 2-chlorothiazolo[4,5-*d*]pyrimidine-5,7-diol (XVII; $Y = Z = OH$) was precipitated. Similar treatment of the thiazolopyrimidine (XVI; $Y = NH_2$, $Z = OH$) gave the same compound, but, in this case the use of less sodium nitrite led to 5-amino-2-chlorothiazolo[4,5-*d*]pyrimidin-7-ol (XVII; $Y = NH_2$, $Z = OH$). Alkaline hydrolysis of the chloro-compounds gave the corresponding hydroxy-compounds (XVIII; $Y = Z = OH$ and $Y = NH_2$, $Z = OH$, respectively). I.r. spectra were used to establish that the latter compound was not identical with the isomeric thiazolopyrimidine (III; $X = NH_2$).

Reduction of 2-chlorothiazolo[4,5-*d*]pyrimidine-5,7-diol with zinc dust and sodium hydroxide solution at room temperature gave slightly impure thiazolo[4,5-*d*]pyrimidine-5,7-diol (III; $X = H$), which was converted by brief treatment with hot alkali into the thiol (XI;

⁶ J. A. Baker and S. A. Hill, *J. Chem. Soc.*, 1962, 3464.

ϵ 13,000—20,000). Similarly 2,6-disubstituted 4-aminopyrimidin-5-yl thiocyanates (XIII) and 2,2',6,6'-tetrasubstituted bis-(4-aminopyrimidin-5-yl) disulphides show maximum absorption in the regions 255—280 (0.1N-HCl; ϵ 4000—16,000) and 318—323 nm. (0.1N-HCl; ϵ 5000—

U.v. absorption data * for 5,7-disubstituted 2-aminothiazolo[4,5-*d*]pyrimidines (XVI)

		0.1N-HCl		0.1N-NaOH	
Y	Z	$\lambda_{\max.}(\text{nm.})$	ϵ	$\lambda_{\max.}(\text{nm.})$	ϵ
OH	OH	(220)	(22,300)	228	25,200
		306	13,100	291sh	5000
				312	9360
H	OH	235	39,250	284	7830
		271	14,100		
		291	15,600		
SMe	NH ₂	240	25,900	245	32,900
		313	19,900	304	9860
NH ₂	NH ₂	(222)	(26,800)	231	31,200
		233sh	18,400	308	9940
		312	17,200		
H	NH ₂	(220)sh	(14,200)	237	25,400
		236	22,300	291	9260
		302	18,200		
NH ₂	OH	(223)	(25,100)		
		256sh	6030		
		Data from ref. 1		305	12,900

* Figures in parentheses are less reliable than the others.

U.v. absorption data for 2,6-disubstituted 4-aminopyrimidin-5-yl thiocyanates (XIII)

Y	Z	0.1N-HCl	
		$\lambda_{\max.}(\text{nm.})$	ϵ
OH	OH	256	16,200
H	OH	258	4050
SMe	NH ₂	243	21,500
		279	12,400
NH ₂	NH ₂	266	14,500
H	NH ₂	259	6170
NH ₂	OH	259	15,100
Data from ref. 1.			

U.v. absorption data for 2,2',6,6'-tetrasubstituted bis-(4-aminopyrimidin-5-yl) disulphides

Y Z
 N S-S Z
 N H_2 N N Y
 H_2 H_2

0.1N-HCl

0.1N-NaOH

Y	Z	$\lambda_{\max.}(\text{nm.})$	ϵ	$\lambda_{\max.}(\text{nm.})$	ϵ
OH	OH	270	19,000	270	20,000
		323	5670	340	6000
NH ₂	OH	267	21,400	267	13,540
		318	6610	347	5040

Data from ref. 1

U.v. absorption data for compounds reputed to be 5,7-disubstituted 2-aminothiazolo[4,5-*d*]pyrimidines (XVI). The ϵ values in parentheses are calculated on the assumption that the compounds are disulphides

Y	Z	pH 1 *	
		$\lambda_{\max.}(\text{nm.})$	ϵ
OH	OH	262	15,200 (23,800)
		310	4500 (7040)
NH ₂	NH ₂	265	15,000 (25,700)
		330	10,000 (17,100)
H	NH ₂	268	9000
SMe	NH ₂	245	16,500
		278	10,500

* From ref. 5.

6000), respectively. A comparison of our data with those obtained by Maggiolo and Hitchings indicates that their samples were probably either disulphides or thiocyanates.

2,5,7-Triamino-, 2-amino-7-hydroxy-, and 2,5-diamino-7-hydroxy-thiazolo[4,5-*d*]pyrimidines possessed no activity against L1210 leukaemia in mice.

EXPERIMENTAL

I.r. spectra were run for potassium chloride discs with an Infracord spectrophotometer. U.v. data were obtained with a Uvispek spectrophotometer.

Thiazole-4,5-dicarboxamide.—An ice-cold solution of freshly prepared, crude thioformamide (9 g.) in ethanol (50 ml.) was added to a stirred, ice-cold solution of ethyl bromo-oxalacetate ⁷ (16 g.) in ethanol (50 ml.); the mixture was stirred for 30 min. and then refluxed for 5 min. The solution was cooled, aqueous ammonia (*d* 0.88; 60 ml.) was added, and the solution was filtered rapidly. Cream needles which separated overnight were collected from the chilled solution, washed with water and ethanol, and dried (100°) to yield the *diamide* (4.5 g.), m.p. 298—300° (decomp.) (from water) [lit.,² 298—300° (decomp.)] (Found: C, 34.7; H, 3.0; N, 24.7. Calc. for C₅H₅N₃O₂S: C, 35.1; H, 2.9; N, 24.6%).

Partial Hofmann Degradation of Thiazole-4,5-dicarboxamide.—A solution of bromine (2.4 ml.) in water (112 ml.) containing potassium hydroxide (20.4 g.) was prepared at 0°; this solution (30 ml.) was added to thiazole-4,5-dicarboxamide (2 g.). The mixture was stirred at 0° while the remaining hypobromite solution was added at a rate of 10 ml. every 15 min. until the diamide dissolved. After 2 hr. the solution was boiled for 15 sec., and then acidified with hot acetic acid (80 ml.). The yellow, crystalline precipitate was collected from the hot solution, washed with water, acetone, and ethanol, and dried (100°) to give *bis-(4-amino-2,6-dihydroxypyrimidin-5-yl) disulphide* (VI) (0.4 g.), identified by comparison (i.r. spectrum) with the product described later. A second crop (0.3 g.) of less pure material separated from the filtrate.

6-Amino-5-bromopyrimidine-2,4-diol (VIII; Y = Z = OH).—A mixture of 6-aminopyrimidine-2,4-diol (25 g.) and dimethylformamide (800 ml.) was heated to 100° to effect partial dissolution of the pyrimidine; the mixture was then cooled to 30° and bromine (10 ml.) was added with stirring during 15 min. The solution was stirred for a further 15 min., then filtered, and the *bromo-compound* was precipitated by the gradual addition of water (800 ml.). The cream crystals were collected from the chilled mixture, washed with water and ethanol, and dried (110°) to yield the product (37.8 g., 93%), m.p. >320° (from 45% dimethylformamide) (Found: C, 23.6; H, 2.0; Br, 37.5; N, 20.7. C₄H₄BrN₃O₂ requires C, 23.3; H, 2.0; Br, 38.8; N, 20.4%), $\lambda_{\max.}$ (0.1N-HCl) 274 nm. (ϵ 16,600), $\lambda_{\max.}$ (in 0.1N-NaOH) 275 nm. (ϵ 13,400).

An 86% yield of the same compound was obtained by bromination of the pyrimidine in aqueous sodium hydroxide (10%), followed by precipitation with acid.

Reaction of 6-Amino-5-bromopyrimidine-2,4-diol with Thiourea.—A mixture of the bromo-compound (10.3 g.), thiourea (4.0 g.), and water (600 ml.) was refluxed with stirring for 2 hr., and the almost white precipitate was

⁷ L. Bauer and C. S. Mahajanshetti, *J. Heterocyclic Chem.*, 1968, 5, (3) 331.

collected, washed with water, and dried *in vacuo* at 110° to yield slightly hydrated *bis*-(4-amino-2,6-dihydroxypyrimidin-5-yl) sulphide (X; Y = Z = OH) (0.7 g.), m.p. >320° (Found: C, 33.0; H, 2.9; N, 28.6; S, 11.3. $C_8H_8N_6O_4S_2 \cdot 0.4H_2O$ requires C, 33.0; H, 3.0; N, 28.6; S, 11.3%), λ_{max} (0.1N-NaOH) 246sh and 266 nm. (ϵ 15,500 and 20,300). The acidic filtrate was cooled and treated with sodium hydrogen carbonate (2.4 g.) dissolved in a little water. The white precipitate was collected, washed with water and acetone, and dried (110°) to yield crude 4-amino-2,6-dihydroxypyrimidine-5-isothiuronium hydroxide (IX; Y = Z = OH, OH⁻ instead of Br⁻) (9.5 g.). Crystallisation of 1 g. (twice) from dilute hydrochloric acid gave the *chloride* (0.5 g.) as white plates, m.p. >340° (Found: C, 25.2; H, 3.4; Cl, 14.6; N, 29.1; S, 13.4. $C_8H_8N_6O_2S_2HCl$ requires C, 25.3; H, 3.4; Cl, 14.9; N, 29.5; S, 13.5%), λ_{max} (0.1N-HCl) 231sh and 254 nm. (ϵ 9100 and 17,350).

6-Amino-5-mercaptopyrimidine-2,4-diol (XI; Y = Z = OH).—Aqueous 10% sodium hydroxide was boiled under reflux for 5 min. to expel air, the foregoing isothiuronium hydroxide (5 g.) was added, and the mixture was boiled for 1 min. It was then poured on ice, and acidified with concentrated hydrochloric acid. The off-white precipitate was collected, washed with water and acetone, and dried (110°) to give the *mercaptopyrimidine* (2.8 g.), m.p. >320° (Found: C, 30.3; H, 3.1; N, 26.1; S, 19.8. $C_8H_8N_6O_2S$ requires C, 30.2; H, 3.2; N, 26.4; S, 20.1%), ν_{max} ca. 2550 cm^{-1} (SH). It was too insoluble or unstable to permit the determination of u.v. spectra of solutions in water, 0.1N-hydrochloric acid, or 0.1N-sodium hydroxide.

Bis-(4-amino-2,6-dihydroxypyrimidin-5-yl) Disulphide (VI).—A boiling solution of the isothiuronium hydroxide (1.0 g.) in water (130 ml.) was clarified with charcoal, and sodium hydrogen carbonate (0.1 g.) was added. The mixture was refluxed for 1 hr., and the yellow *disulphide*, which precipitated, was collected (0.11 g.), washed with water, and dried (110°); m.p. >320° (Found: C, 30.7; H, 2.6; N, 26.7; S, 19.9. $C_8H_8N_6O_4S_2$ requires C, 30.4; H, 2.55; N, 26.6; S, 20.3%).

Oxidation of 6-Amino-5-mercaptopyrimidine-2,4-diol (XI; Y = Z = OH) to the *Disulphide* (VI).—A solution of the mercapto-compound (0.1 g.) in dimethyl sulphoxide (5 ml.) was clarified with kieselguhr, set aside overnight, and then heated at 100° for 0.5 hr. The yellow, crystalline rods were collected, washed with dimethyl sulphoxide and acetone, and dried (100°) to afford the *solvated disulphide* (30 mg.), ν_{max} 1015 cm^{-1} (S=O). The solvent was removed by dissolution of the solvated product in hot, aqueous 2.5% sodium hydroxide followed by reprecipitation with hot, dilute hydrochloric acid.

Acetylation of 6-Amino-5-mercaptopyrimidine-2,4-diol.—A mixture of the thiol (1.0 g.) and acetic anhydride (25 ml.) was refluxed with stirring for 6 hr. The white solid (0.8 g.) was collected from the hot solution, washed with acetone, and dried (110°). The compound (200 mg.) was purified by precipitation (twice) with water (2 ml.) from a solution in dimethyl sulphoxide (2 ml.) to yield 6-amino-5-acetylthiopyrimidine-2,4-diol (XII; Y = Z = OH), m.p. >300° (Found: C, 35.4; H, 3.5; N, 21.1; S, 16.3. $C_8H_8N_6O_3S$ requires C, 35.8; H, 3.5; N, 20.9; S, 15.9%). The filtrate from the reaction mixture slowly deposited further solid, which crystallised from acetic anhydride to afford a *diacetyl derivative* (Found: C, 39.5; H, 3.75; N, 17.0. $C_8H_8N_6O_4S$ requires C, 39.5; H, 3.7; N, 17.3%).

4-Amino-2,6-dihydroxypyrimidin-5-yl Thiocyanate (XIII;

Y = Z = OH).—To a hot solution of 6-aminopyrimidine-2,4-diol (12.0 g.) and potassium thiocyanate (39.0 g.) in dimethylformamide (650 ml.) pyridine (14 ml.) was added. The solution was then cooled to 3° and bromine (4.8 ml.) in dimethylformamide (25 ml.) was dropped in with stirring during 35 min. The temperature rose to 9°. The solution was stirred at 5° for a further 35 min., and water (1.1 l.) was added to precipitate the *thiocyanate*. After 1 hr. at 0°, the product (13.1 g., 75%) was collected, washed with water, acetone, ethanol, and ether, and dried (100°) to give white prisms, m.p. >300° [from 25% dimethylformamide (charcoal)] (Found: C, 32.6; H, 2.3; N, 30.3; S, 17.4. $C_8H_8N_4O_2S$ requires C, 32.6; H, 2.2; N, 30.4; S, 17.4%), ν_{max} ca. 2130 cm^{-1} (SCN).

The compound was also prepared by thiocyanation in 96% acetic acid (Maggiolo's method), and by the reaction of potassium thiocyanate with 6-amino-5-bromopyrimidine-2,4-diol in dimethylformamide at 80°. The i.r. spectra of all three products were identical.

Preparation of 2-Aminothiazolo[4,5-d]pyrimidine-5,7-diol (XVI; Y = Z = OH).—A solution of the foregoing thiocyanate (5 g.) in dimethylformamide (65 ml.) was refluxed with stirring for 2.5 hr. The precipitate was collected, washed with water, acetone, and ether, and dried (100°) to give a product (3.4 g.), m.p. >320°. Crystallisation from almost saturated sodium carbonate solution (charcoal) afforded white needles of a sodium derivative. A solution of this (2.8 g.) in boiling water (50 ml.) was gradually acidified with hot, 2% hydrochloric acid, then left overnight; the *thiazolopyrimidine* (2.2 g.) was collected, washed with water, acetone, and ether, and dried (100°) (Found: C, 32.6; H, 2.3; N, 30.2; S, 17.2%).

The isomerisation was also effected by refluxing an aqueous solution of the thiocyanate overnight.

Reaction of 2-Aminothiazolo[4,5-d]pyrimidine-5,7-diol with Nitrous Acid.—A solution of the thiazolopyrimidine (0.5 g.) and sodium nitrite (1.5 g.) in 10% aqueous sodium hydroxide was added gradually, at 80°, to a stirred solution of concentrated hydrochloric acid (16 ml.) in water (4 ml.), maintained at 70°, during 15 min. The mixture was stirred for a further 20 min. at 60°, then chilled in ice, and the precipitate was collected, washed, and dried (100°) to give the orange chloro-derivative (XVII; Y = Z = OH) (Found: C, 29.6; H, 1.1%), λ_{max} (0.1N-HCl) 240sh and 301 nm. (ϵ 5000 and 7230), λ_{max} 0.1N-NaOH) 327 nm. (ϵ 5110) (see following experiment).

Reaction of 2,5-Diaminothiazolo[4,5-d]pyrimidin-7-ol (XVI; Y = NH₂, Z = OH) with Excess of Nitrous Acid. — A solution of the sodium salt of the thiazolopyrimidine¹ was treated with nitrous acid as already described to yield (67%) 2-chlorothiazolo[4,5-d]pyrimidine-5,7-diol, identical with the material described in the preceding preparation (i.r. spectra), m.p. 322° (decomp.) (when placed in the bath at 320°) (Found: C, 29.3; H, 1.1; Cl, 17.7; N, 20.5; S, 15.6. $C_8H_8ClN_6O_2S$ requires C, 29.5; H, 1.0; Cl, 17.4; N, 20.6; S, 15.7%).

Thiazolo[4,5-d]pyrimidine-2,5,7-triol (XVIII; Y = Z = OH).—A solution of 2-chlorothiazolo[4,5-d]pyrimidine-5,7-diol (2.9 g.) in boiling water (10 ml.) and 10% aqueous sodium hydroxide (10 ml.) was made faintly acid with dilute hydrochloric acid, treated with charcoal, and rapidly filtered to remove a red impurity. Purification was completed by neutralisation with concentrated aqueous ammonia followed by boiling with charcoal. Aqueous sodium hydroxide (50%; 15 ml.) was added to the filtrate; the

solution was then refluxed for 20 min. and filtered hot. Acidification with concentrated hydrochloric acid, followed by chilling, precipitated the *trihydroxy-compound* (1.5 g.) which was collected, washed with water, and dried *in vacuo* at 110° for 4 hr. (Found: C, 32.5; H, 1.7; N, 22.4; S, 17.2. $C_5H_3N_3O_3S$ requires C, 32.4; H, 1.6; N, 22.7; S, 17.3%).

Reduction of 2-Chlorothiazolo[4,5-d]pyrimidine-5,7-diol.—A mixture of the chloro-compound (1.0 g.), zinc dust (2.0 g.), and 10% aqueous sodium hydroxide (25 ml.) was stirred at room temperature for 0.5 hr. After removal of excess of zinc, the filtrate was adjusted to pH 1 by slow addition of concentrated hydrochloric acid, and the mixture was chilled. The white precipitate (450 mg.) was collected, washed with water and ethanol, and dried (100°). The product, m.p. >320°, dissolved in hot water to give a feebly acid solution. It was too readily hydrolysed to permit recrystallisation. Analysis indicated that it was slightly impure thiazolo[4,5-d]pyrimidine-5,7-diol (III; X = H) (Found: C, 34.8; H, 1.8; N, 24.3. $C_5H_3N_3O_2S$ requires C, 35.5; H, 1.8; N, 24.8%).

Ring Cleavage of Thiazolo[4,5-d]pyrimidine-5,7-diol.—Boiling aqueous 10% sodium hydroxide (7 ml.) was added to the thiazolopyrimidine (250 mg.), and the solution was boiled for 1 min., cooled rapidly in ice, and acidified with concentrated hydrochloric acid. The white product was collected, washed with water and ethanol, and dried (100°) to give 6-amino-5-mercaptopyrimidine-2,4-diol (XI; Y = Z = OH) (200 mg., 86%), identical with the product obtained earlier (i.r. spectra).

5-Amino-2-chlorothiazolo[4,5-d]pyrimidin-7-ol (XVII; Y = NH₂, Z = OH).—A hot solution (80°) of 2,5-diaminothiazolo[4,5-d]pyrimidine-7-ol monohydrate¹ (1.0 g.) and sodium nitrite (1.0 g.), in aqueous 10% sodium hydroxide (10 ml.) was gradually added, with stirring, to concentrated hydrochloric acid (25 ml.) maintained at 80° during 15 min. The solution was stirred for a further 15 min. at 80°, boiling water (35 ml.) and charcoal were added, and the hot suspension was filtered and cooled overnight. The product (0.4 g.), crystallised (160 mg.) from water (550 ml.), gave needles of the *chloro-compound*, m.p. >320° (Found: C, 29.3; H, 1.5; Cl, 17.3; N, 27.8; S, 15.7. $C_5H_3ClN_4OS$ requires C, 29.6; H, 1.5; Cl, 17.5; N, 27.7; S, 15.8%), λ_{\max} (0.1N-HCl) (225) and 299 nm. (ϵ 22,000 and 5310), λ_{\max} (0.1N-NaOH) (224) and 318 nm. (ϵ 22,000 and 4700).

5-Aminothiazolo[4,5-d]pyrimidine-2,7-diol (XVIII; Y = NH₂, Z = OH).—The foregoing chloro-compound (0.5 g.), dissolved in aqueous 10% sodium hydroxide (10 ml.), was heated under reflux for 3 hr. A trace of ammonia was evolved (litmus). After treatment with charcoal, the solution was acidified with hot, dilute hydrochloric acid. The needles (320 mg.) of the *thiazolopyrimidine* were collected, washed with water, and dried (110°). A sample (150 mg.) was purified by adding water (40 ml.) to a solution in dimethylformamide (30 ml.) (Found: C, 32.9; H, 2.2; N, 30.2; S, 17.6. $C_5H_4N_4O_2S$ requires C, 32.6; H, 2.2; N, 30.4; S, 17.4%).

2,4,6-Triamino-5-bromopyrimidine (VIII; Y = Z = NH₂).—A warm solution of 2,4,6-triaminopyrimidine (10 g.) in 50% acetic acid (300 ml.) was clarified with charcoal, and the solution, cooled to 30°, was treated with bromine (4.2 ml.) in glacial acetic acid (6 ml.) with stirring during 45 min. After neutralisation of the mixture by the gradual addition of 50% aqueous sodium hydroxide (150 ml.),

followed by cooling, the *bromo-compound* (12.5 g., 77%) was collected, washed with water, and dried (100°); m.p. 206.5–208.5° (Found: C, 23.6; H, 3.1; Br, 39.2. $C_4H_5BrN_3$ requires C, 23.5; H, 3.0; Br, 39.2%), λ_{\max} (0.1N-HCl) 281 nm. (ϵ 14,650), λ_{\max} (0.1N-NaOH) 274 nm. (ϵ 9200).

2,4,6-Triaminopyrimidin-5-yl Thiocyanate (XIII; Y = Z = NH₂).—Potassium thiocyanate (1.0 g.) in ethanol (25 ml.) was added to a solution of the foregoing bromo-compound (2.0 g.) in ethanol (100 ml.) containing glacial acetic acid (0.13 ml.), and the mixture was refluxed for 0.5 hr. The *thiocyanate* (1.3 g., 72%) was collected from the hot solution, washed with water, ethanol, and acetone, and dried (100°) to give white needles, m.p. 219–219.5° (decomp.) (from pyridine) (Found: C, 32.9; H, 3.3; N, 46.4; S, 17.7. $C_5H_6N_6S$ requires C, 32.95; H, 3.3; N, 46.1; S, 17.6%), λ_{\max} (0.1N-HCl) 265 nm. (ϵ 14,480), ν_{\max} ca. 2160 cm.⁻¹ (SCN).

The same compound was obtained by thiocyanation in 95% acetic acid (Maggiolo's method).

Cyclisation of 2,4,6-Triaminopyrimidin-5-yl Thiocyanate with Acetic Anhydride.—A stirred mixture of the thiocyanate (1.0 g.) and acetic anhydride (20 ml.) was refluxed for 18 hr. The white solid was collected from the hot solution, washed with water, acetone, and ethanol, and dried (100°) to give 2(3),5,7-triacetamidothiazolo[4,5-d]pyrimidine (XIV or XV; Y = Z = NHAc) (1.5 g., 89%), m.p. >320° (Found: C, 42.7; H, 4.1; S, 10.4. $C_{11}H_{12}N_6O_8S$ requires C, 42.8; H, 3.9; S, 10.4%), λ_{\max} (0.1N-HCl) 235sh, 254, 275sh, and 331 nm. (ϵ 25,500, 31,680, 15,000, and 17,100), λ_{\max} (in 0.1N-NaOH) 256, 280sh, and 331 nm. (ϵ 26,730, 16,500, and 19,570).

2,5,7-Triaminothiazolo[4,5-d]pyrimidine (XVI; Y = Z = NH₂).—A solution of the foregoing triacetamido-compound (18 g.) in aqueous 10% sodium hydroxide (250 ml.) was clarified with charcoal, refluxed for 1 hr., and chilled. The white needles were collected, washed with water, acetone, and ethanol, and dried (100°) to give the *thiazolopyrimidine* (8 g., 75%), m.p. >300° (from water) (Found: C, 32.8; H, 3.4; N, 45.8; S, 17.4. $C_5H_6N_6S$ requires C, 32.95; H, 3.3; N, 46.1; S, 17.6%).

4,6-Diaminopyrimidin-5-yl Thiocyanate (XIII; Y = H, Z = NH₂).—A warm solution of 4,6-diaminopyrimidine (1.1 g.) (prepared by the Raney nickel desulphurisation of 4,6-diaminopyrimidine-2-thiol⁸) and potassium thiocyanate (3.0 g.) in methanol (40 ml.) was cooled to 2°, stirred, and treated with bromine (0.6 ml.) in methanol (2 ml.; saturated with potassium bromide) during a few min. The mixture was stirred for a further 15 min. at 5°; the white solid was then collected, added to ice-cold water (60 ml.), and made faintly alkaline with sodium hydrogen carbonate. The needles of the *thiocyanate* (0.7 g., 42%) were collected, washed with water, and dried (110°), m.p. 184–185° followed by resolidification (placed in the bath at 182°) (Found: C, 36.0; H, 3.0; N, 42.2; S, 19.3. $C_5H_5N_5S$ requires C, 35.9; H, 3.0; N, 41.9; S, 19.2%), ν_{\max} ca. 2160 cm.⁻¹ (SCN).

The thiocyanate was also prepared by the thiocyanation of 4,6-diaminopyrimidine sulphate in 80% acetic acid. It did not cyclise when the reaction mixture was heated (as claimed by Maggiolo⁵).

2,7-Diaminothiazolo[4,5-d]pyrimidine (XVI; Y = H, Z = NH₂).—A solution of the foregoing thiocyanate (0.5 g.) in water (65 ml.) was refluxed for 20 min., treated with charcoal, filtered hot, and cooled. The white needles (0.31 g.)

⁸ D. J. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

of the *thiazolopyrimidine* were collected, washed with water, acetone, and ether, and dried (60°); m.p. >330° (Found: C, 36.25; H, 3.1; N, 41.3; S, 19.3%).

4,6-Diamino-2-methylthiopyrimidin-5-yl Thiocyanate (XIII; Y = SMe, Z = NH₂).—A solution of 4,6-diamino-2-methylthiopyrimidine (15.6 g.) (obtained by treatment of 4,6-diaminopyrimidine-2-thiol with dimethyl sulphate in sodium hydroxide solution) in dimethylformamide was thiocyanated by the method given for 6-aminopyrimidine-2,4-diol. The crude product (10.2 g.) was dissolved in dimethylformamide (50 ml.), the solution was clarified with charcoal and kieselguhr, and hot water (60 ml.; 75°) was gradually added with stirring. The mixture was allowed to cool to 35°, and the pale cream, prismatic rods were collected, washed with water and dried (110°) to give the *thiocyanate* (8.6 g.), m.p. 211–214° (decomp.) (Found: C, 33.8; H, 3.3; N, 32.6; S, 29.9. C₆H₇N₅S₂ requires C, 33.8; H, 3.3; N, 32.8; S, 30.1%), ν_{\max} ca. 2170 cm.⁻¹ (SCN).

Cyclisation of 4,6-Diamino-2-methylthiopyrimidine-5-yl Thiocyanate.—A mixture of the thiocyanate (7.6 g.) and acetic anhydride (100 ml.) was refluxed with stirring for 1 hr., and allowed to cool. The white needles were collected, washed with acetic anhydride and acetone, and dried (110°) to give **2(3),7-diacetamido-5-methylthiothiazolo[4,5-d]pyrimidine** (XIV or XV; Y = SMe, Z = NHAc) (9.8 g., 93%), m.p. 328–330° (Found: C, 38.8; H, 3.8; N, 23.8. C₁₀H₁₁N₅O₂S₂ requires C, 40.4; H, 3.7; N, 23.6%). The presence of some unacetylated material was inferred.

2,7-Diamino-5-methylthiothiazolo[4,5-d]pyrimidine (XVI; Y = SMe, Z = NH₂).—A solution of the foregoing diacetamido-compound (8.8 g.) in aqueous 10% sodium hydroxide (50 ml.) was refluxed for 35 min., then chilled in ice. The crystals (6.0 g.) were collected; a portion (0.9 g.) crystallised from water (200 ml.) gave white needles (0.62 g.) of the *thiazolopyrimidine*, m.p. 269–271° (Found: C, 34.3; H, 3.3; N, 32.8; S, 30.0. C₆H₇N₅S₂ requires C, 33.8; H, 3.3; N, 32.8; S, 30.1%).

6-Amino-5-bromopyrimidin-4-ol (VIII; Y = H, Z = OH).—Ethyl cyanoacetate was treated with thiourea to give 6-amino-2-mercaptopyrimidin-4-ol, which was then desulphurised by the method of Brown.⁸ A solution of the

resulting 6-aminopyrimidin-4-ol (11.1 g.) in aqueous 10% sodium hydroxide (50 ml.) was treated with bromine (5 ml.) with stirring during 15 min. The mixture was diluted with water (50 ml.), stirred for a further 15 min., and neutralised with hydrochloric acid. The product was collected, washed with water, and acetone, and dried (100°) to give the *bromo-compound* (13.6 g., 72%) as white needles, m.p. 281–283° (decomp.) (placed in the bath at 278°) [from water (charcoal)] (Found: C, 25.3; H, 2.15; N, 22.2. C₄H₄BrN₃O requires C, 25.3; H, 2.1; N, 22.1%), λ_{\max} (0.1N-HCl) 264 nm. (ϵ 8250), λ_{\max} (0.1N-NaOH) 260 nm. (ϵ 5240).

4-Amino-6-hydroxypyrimidin-5-yl Thiocyanate (XIII; Y = H, Z = OH).—A solution of the foregoing bromo-compound (30 g.) and potassium thiocyanate (30 g.) in water (1 l.) was refluxed for 30 min., clarified with charcoal and kieselguhr, and cooled in ice. The product (20 g.) was collected, washed with water and acetone, and dried (100°). A sample (0.5 g.) crystallised twice from water, then precipitated with water (12 ml.) from a solution in warm dimethylformamide (10 ml.) gave the *thiocyanate* (0.13 g.), m.p. 260–262°, followed by resolidification (placed in the bath at 250°) (Found: C, 35.4; H, 2.45; N, 32.9; S, 18.9. C₅H₄N₄OS requires C, 35.7; H, 2.4; N, 33.3; S, 19.1%).

2-Aminothiazolo[4,5-d]pyrimidin-7-ol (XVI; Y = H, Z = OH).—A solution of the foregoing thiocyanate (18 g.) in boiling water (1 l.) was clarified with charcoal and refluxed for 5 hr. with stirring. The buff crystals (12.5 g.) were collected from the hot solution. A sample (10 g.) was crystallised from aqueous 10% sodium hydroxide to give the sodium derivative of the thiazolopyrimidine (10.7 g.), which was washed with 80% ethanol. A solution of this in warm water (500 ml.), when acidified with acetic acid and cooled, gave the *thiazolopyrimidine* (7.5 g.), which was washed with water and acetone and dried (110°); m.p. >300° (Found: C, 35.4; H, 2.5; N, 33.2; S, 19.2%).

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