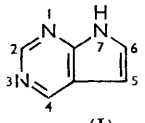
26. *Pyrrolo*[2,3-d]*pyrimidines.*

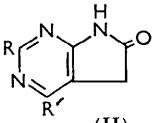
By J. DAVOLL.

Pyrrolo[2,3-*d*]pyrimidines have been obtained by spontaneous cyclisation of 4-aminopyrimidyl-acetaldehydes and -acetones, which in turn were prepared by hydrolysis of their acetals, and, in the case of the aldehydes, by oxidation of 4-amino-5-(2,3-dihydroxypropyl)pyrimidines. The compounds prepared include analogues of biologically important purines.

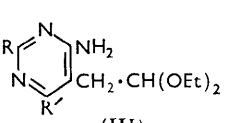
PYRROLO[2,3-*d*]PYRIMIDINE (I) may be regarded as an analogue of purine in which its $N_{(7)}$ has been replaced by a CH group, and the present series of compounds was prepared as possible antimetabolites to naturally occurring purine derivatives. When this work was prepared for publication, the only pyrrolo[2,3-*d*]pyrimidines reported were three derivatives of 5,6-dihydro-6-oxopyrrolo[2,3-*d*]pyrimidine (II; R = R′ = OH;[1] R = Me, R′ = OH;[2] and R = Me, R′ = H [3]), all obtained from derivatives of 4-amino-pyrimidylacetic acid, and the 4,6-dichloro-2-methyl derivative, prepared from the 4-hydr-



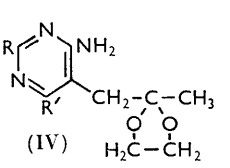
(I)



(II)

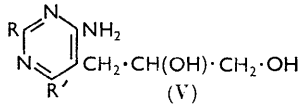


(III)

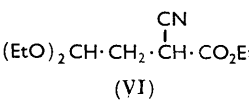


(IV)

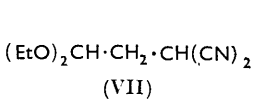
oxy-derivative (II; R = Me, R′ = OH).[2] Very recently, however, a patent [4] has described the preparation of compounds (VI) and (VII) by a different procedure from that given below, and their conversion into pyrrolo[2,3-*d*]pyrimidines by methods essentially similar to those described here. 2,4-Dihydroxypyrrolo[2,3-*d*]pyrimidine was also prepared from 6-aminouracil and chloroacetaldehyde. The properties of the compounds are in general agreement with our findings, although there is a considerable discrepancy in the ultraviolet spectra of 4-mercaptopyrrolo[2,3-*d*]pyrimidine [given in ref. 4 as λ 275 mμ (ε 9450) at pH 1].



(V)



(VI)



(VII)

The general method employed in the present work was to prepare by ring synthesis a 4-aminopyrimidine with a potential acetaldehyde (or acetone) group at the 5-position, either as an acetal (III) [or ketal (IV)] which yielded the aldehyde (or ketone) on acid hydrolysis, or as a 2,3-dihydroxypropyl group (V) which yielded the aldehyde on oxidation. In each case the aldehyde or ketone cyclised immediately to a pyrrolo[2,3-*d*]pyrimidine. The first method proved more versatile, although the second procedure was more convenient in a few cases.

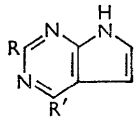
[1] Johnson and Kohmann, *Amer. Chem. J.*, 1913, **49**, 186.
[2] Foldi, Fodor, Demjén, Szekeres, and Halmos, *Ber.*, 1942, **75**, 755.
[3] Nesbitt and Sykes, *J.*, 1954, 3057.
[4] Wellcome Foundation, B.P. 812, 366 (April 22nd, 1959).

For the preparation of 4-amino-5-(2,2-diethoxyethyl)pyrimidines ethyl α-cyano-α-(2,2-diethoxyethyl)acetate (VI) and 2,2-diethoxyethylmalononitrile (VII) were required. Attempts to prepare the mononitrile (VI) from bromoacetal and ethyl sodiocyanoacetate were unsuccessful, but it was obtained in 46% yield from bromoacetal and excess of ethyl cyanoacetate in the presence of potassium carbonate.[5] Conversion into the amide followed by dehydration with phosphoric anhydride–triethylamine gave the malononitrile (VII). The sodio-derivative of the mononitrile (VI) was also prepared by ethoxycarbonylation of 4,4-diethoxybutyronitrile.

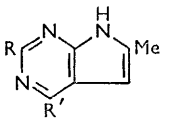
Condensation of the mononitrile (VI) with guanidine, urea, and thiourea gave the pyrimidines (III; R = NH_2, OH, and SH, R′ = OH); and the pyrimidines (III; R = NH_2, OMe, and SH, R′ = NH_2) were similarly prepared from the dinitrile (VII) with guanidine, *O*-methylisourea, and thiourea. [Like malononitrile [6] itself, the substituted malononitrile (VII) did not condense with urea to give a 2-hydroxypyrimidine.] The pyrimidines (III; R = H, R′ = OH and NH_2) were prepared by desulphurisation of the corresponding 2-mercapto-derivatives with Raney nickel.

Exactly similar syntheses were carried out from the ethylene ketal derived from ethyl acetonylcyanoacetate [7] and the malononitrile prepared from it *via* the amide. In this way the pyrimidines (IV; R = NH_2, OH, SH, and H, R′ = OH; and R = SH and H, R′ = NH_2) were prepared.

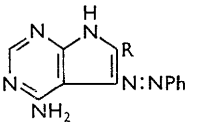
Schrage and Hitchings [8] prepared 5-2′-hydroxyethylpyrimidines from the condensation product of ethyl cyanoacetate and ethylene oxide in the presence of sodium ethoxide. Similarly, glycide was found to condense with ethyl cyanoacetate, and direct reaction of the product with guanidine or thiourea gave the pyrimidine (V; R = NH_2 or SH, R′ = OH). In the same way, malononitrile with glycide gave a product from which the cyclic compounds (V; R = NH_2 and SH, R′ = NH_2) were prepared. The two 2-mercapto-derivatives were desulphurised with Raney nickel.



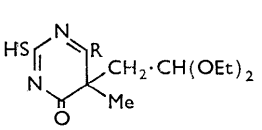
(VIII)



(IX)



(X)



(XI)

All the acetals and ketals were converted almost quantitatively into pyrrolo[2,3-*d*]-pyrimidines by treatment with dilute hydrochloric acid at room temperature. In this way the compounds (VIII; R = H, NH_2, OH, and SH, R′ = OH; and R = H, NH_2, OMe, and SH, R′ = NH_2) and (IX; R = H, NH_2, OH, and SH, R′ = OH; and R = H and SH, R′ = NH_2) were prepared. These include the pyrrolo[2,3-*d*]pyrimidine analogues of adenine, hypoxanthine, guanine, xanthine, and 2,6-diaminopurine. The isoguanine analogue (VIII; R = OH, R′ = NH_2) was prepared from the 4-amino-2-methoxy-compound and concentrated hydrochloric acid.

Oxidation of the 2,3-dihydroxypropyl compounds was less straightforward, since in some cases secondary reactions appeared to occur between the main product and the formaldehyde also produced, and quantitative studies indicated that further oxidation also occurred. When the dihydroxypropylpyrimidines (V; R = NH_2, R′ = OH and NH_2) were treated with excess of sodium metaperiodate, 2·4 mols. of oxidant were consumed in less than 2 hr., although compound (V; R = H, R′ = OH and NH_2) behaved normally, consuming approximately 1 mol. of metaperiodate, Even when the calculated amount of metaperiodate was added to a solution of the propanediol (V; R = NH_2, R′ = OH) the required pyrrolopyrimidine could only be obtained if formaldehyde was continuously

[5] G. M. Robinson, *J.*, 1924, **125**, 226; R. Robinson and Watt, *J.*, 1934, 1536.
[6] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3109; see, however, ref. 4.
[7] Klobb, *Ann. Chim.* (*France*), 1897, **10**, 205.
[8] Schrage and Hitchings, *J. Org. Chem.*, 1951, **16**, 1153.

removed by evaporation during the oxidation; an amorphous by-product also obtained appeared to be a reaction product of the bicyclic compound (VIII; R = NH_2, R′ = OH) and formaldehyde. Attempts to prepare 4-amino- and 2,4-diamino-pyrrolo[2,3-*d*]-pyrimidines by periodate oxidation failed, rather surprisingly in the first case, since the uptake of periodate was normal. However, 4-aminopyrrolo[2,3-*d*]pyrimidine was obtained in poor yield by use of lead tetra-acetate. Sodium bismuthate [9] was also tried, without success.

In general, the oxidation route was only satisfactory when the resulting pyrrolopyrimidine separated rapidly from the oxidation mixture; thus the four compounds (VIII; R = H, R′ = OH and R = SMe, R′ = OH and NH_2) were all obtained in good yield by periodate oxidation of appropriate dihydroxypropyl compounds.

Treatment of 4-hydroxypyrrolo[2,3-*d*]pyrimidine with phosphoryl chloride gave the 4-chloro-derivative, from which the 4-mercapto-compound was prepared by reaction with thiourea, and the 4-benzylamino-, 4-furfurylamino-, and 4-propylamino-compounds by reaction with appropriate amines. The parent compound, pyrrolo[2,3-*d*]pyrimidine, was prepared by reductive dehalogenation of the chloro-compound and by desulphurisation of the 4-mercapto-derivative. 4-Chloro- and 4-mercapto-6-methylpyrrolo[2,3-*d*]pyrimidine were also prepared.

Pyrrolo[2,3-*d*]pyrimidines might be expected to be nitrosated and azo-coupled at the 5-position (as analogues of indole) or at the 6-position (which is vinylogous to the pyrimidine

TABLE 1. *Ultraviolet spectra of pyrrolo*[2,3-d]*pyrimidines.*

Compound (VIII)		$\lambda_{max.}$ (mμ) ($10^{-3}\varepsilon$ in parentheses) In HCl	At pH 6·8	In NaOH
R = H	R′ = H	225 (27·3), 265 (3·1), 299 (1·5)	271 (4·0)	273 (3·9)
	Cl		223 (26·0), 275 (4·5) [a]	
	NH_2	225 (18·2), 274 (10·9)	271 (10·6)	272 (10·4)
	$NHPr^n$	227 (14·3), 273 (14·4)	273 (14·2)	274 (14·1)
	OH	215 (16·3), 263 (9·9)	215 (16·9), 263 (10·1)	266 (10·9)
	SH	267 (5·6), 323 (19·6)	267 (5·5), 322 (20·2)	228 (17·4), 310 (17·8)
R = NH_2	R′ = NH_2	225 (24·2), 262 (7·2), 292 (6·9)	220 (24·7), 258 (7·2), 287 (7·0)	259 (7·2), 285 (7·2)
	OH	221 (14·2), 259 (10·6), 263 (sh) (10·3)	216 (19·4), 256 (11·2), 277 (sh) (7·9)	257 (9·9), 270 (sh) (9·1)
R = OH	R′ = NH_2	224 (21·6), 293 (8·2)	222 (26·7), 245 (5·7), 296 (7·3)	252 (7·3), 288 (8·4)
	OH	238 (6·9), 274 (6·4)	213 (18·8), 243 (7·1), 275 (6·3)	249 (9·9), 284 (7·1)
R = OMe	R′ = NH_2	224 (22·4), 260 (5·7), 285 (7·5)	260 (sh) (7·2), 274 (8·1)	260 (sh) (7·2), 274 (8·3)
R = SH	R′ = NH_2	235 (13·2), 250 (sh) (10·1), 299 (18·0)	214 (16·9), 230 (sh) (14·6), 290 (16·2)	243 (22·6, 284 (14·1)
	OH	241 (11·0), 298 (19·7)	227 (13·4), 293 (17·8)	229 (13·5), 290 (17·4)
R = SMe	R′ = NH_2	224 (18·6), 283 (13·8)	233 (21·8), 281 (12·2)	237 (21·9), 283 (12·4)
	OH	217 (16·4), 283 (11·6)	219 (16·0), 280 (11·4)	274 (11·5)
(IX)				
R = H	R′ = OH	269 (10·3)	265 (10·8)	270 (11·6)
R = NH_2	R′ = OH	222 (10·9), 268 (9·5)	259 (9·9)	261 (9·4)
R = OH	R′ = OH	243 (8·8), 281 (6·5)	246 (8·2), 282 (6·6)	251 (11·1), 291 (7·2)
R = SH	R′ = OH	240 (11·2), 304 (19·8)	295 (17·2)	295 (17·2)
(X; R = H)			240 (sh) (8·7), 292 (10·5), 374 (14·1) [a]	
(X; R = Me)			248 (8·7), 294 (10·7), 384 (13·4) [a]	

[a] In ethanol.

5-position). With sodium nitrite in acetic acid the 2-amino-4-hydroxy- and the 2,4-dihydroxy-compounds gave immediate indigo-blue and deep violet precipitates, while with the 4-amino-2-hydroxy- and 4-amino-2-methylthio-derivatives brown precipitates

[9] Rigby, *J.*, 1950, 1907.

separated more slowly. 4-Amino- and 4-hydroxy-pyrrolo[2,3-*d*]pyrimidine did not give nitroso-compounds, but the former gave a crystalline phenylazo-derivative, apparently (X; R = H), since 4-amino-6-methylpyrrolo[2,3-*d*]pyrimidine gave an analogous compound (X; R = Me) with closely similar ultraviolet absorption.

An attempt was made to prepare a pyrrolopyrimidine with an angular methyl group. Methylation of the cyanoacetic ester (VI) and condensation with thiourea gave the acetal (XI; R = NH_2). Treatment of this with dilute acid, however gave the hydroxy-compound (XI; R = OH), without hydrolysis of the acetal group, while stronger acid destroyed the compound.

The ultraviolet absorption spectra of the pyrrolo[2,3-*d*]pyrimidines show a general resemblance to those of the corresponding purines. Details are given in Table 1.

All the pyrrolo[2,3-*d*]pyrimidines and most of the pyrimidine intermediates were tested against a range of pathogenic and non-pathogenic organisms. No significant inhibition was observed, other than inhibition of *Strep. pyogenes in vitro* by some of the mercapto-derivatives; these were ineffective against infection by the organism in mice.

Experimental

Except where otherwise stated, samples were dried for analysis in a high vacuum at 100°.

Ethyl 2,2-Diethoxyethylcyanoacetate.[4]—A mixture of bromoacetal [10] (160 g.), ethyl cyanoacetate (456 g.), anhydrous potassium carbonate (112 g.), and sodium iodide (8 g.) was stirred under reflux in an oil-bath at 145—150° until the vigorous reaction (evolution of carbon dioxide) had subsided, and then for a further 4 hr. at 140—145°. After cooling, the mixture was dissolved in water (800 c.c.) and ether (800 c.c.). The ether layer was washed with water, the aqueous portions were again extracted with ether, and the combined ether solutions were dried ($MgSO_4$) and evaporated. Evaporation of the ether and fractionation of the residue through a 6″ Fenske column gave the *ester* (86 g., 46%), b. p. 111—115°/1·3 mm., n_D^{20} 1·4300 (Found: C, 58·1; H, 8·5; N, 6·2. $C_{11}H_{19}O_4N$ requires C, 57·6; H, 8·4; N, 6·1%).

2,2-*Diethoxyethylmalononitrile.*—A solution of the above ester (40 g.) in methanolic ammonia (200 c.c.; saturated at 0°) was treated with methanol (80 c.c.) containing dissolved sodium (0·2 g.). After 18 hr. at 20° the red solution was evaporated, finally with benzene, and the residual crude amide was dissolved in benzene (60 c.c.) and triethylamine (49 c.c.) (both distilled from phosphoric anhydride) and treated with phosphoric anhydride (33 g.). The mixture, whose temperature rose to *ca.* 60°, was then stirred under reflux for 30 min. at room temperature and for 3 hr. at 100—120° (bath-temperature), then cooled and added to water (250 c.c.) containing ammonia (*d* 0·88; 40 c.c.). More benzene was added, the benzene layer was separated, and the aqueous layer extracted twice with benzene. The combined benzene solutions were dried ($MgSO_4$) and evaporated, and the residue was distilled, giving the *nitrile* (15·8 g., 50%), b. p. 100—103°/1 mm., n_D^{20} 1·4303, which slowly became yellow (Found: C, 59·6; H, 7·8; N, 15·2. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

Ethyl α-Cyano-α-(2-methyl-1,3-dioxolan-2-ylmethyl)acetate.—A mixture of ethyl acetonylcyanoacetate [7] (100 g.), ethylene glycol (40·4 g., 1·1 mol.), benzene (600 c.c.), and benzenesulphonic acid (1·2 c.c. of 32% solution) was boiled under a Dean and Stark head until evolution of water ceased (*ca.* 4 hr.). The mixture was treated with a little solid sodium hydrogen carbonate, cooled, filtered, and evaporated, and the residue was distilled, giving the *ketal* (110 g., 87%), b. p. 116°/0·6 mm., n_D^{20} 1·4461 (Found: C, 56·8; H, 7·2; N, 6·5. $C_{10}H_{15}O_4N$ requires C, 56·3; H, 7·1; N, 6·6%).

2-*Methyl*-1,3-*dioxolan*-2-*ylmethylmalononitrile.**—Prepared from the above ester by the procedure described for the 2,2-diethoxyethyl compound, the *nitrile* (33% yield) had b. p. 124—128°/2 mm., and formed needles (from ethanol), m. p. 36—37° (Found: C, 58·2; H, 6·4; N, 17·1. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·1; N, 16·9%).

Ethyl Cyanoacetate and Glycide.—Ethyl cyanoacetate (45·2 g.) was added to a solution of

* This nitrile and compounds derived from it were prepared by Dr. I. M. Lockhart of these Laboratories.

[10] Bedoukian, *J. Amer. Chem. Soc.*, 1944, **66**, 651.

sodium ethoxide prepared from sodium (9·2 g.) and absolute ethanol (200 c.c.) and previously cooled to 5—10°. The mixture was stirred for 5 min. at 10°, then treated with glycide (29·6 g.) and allowed to warm with stirring. The sodium salt dissolved, with evolution of heat, and the temperature was kept below 60° by cooling. At the end of the reaction the mixture was kept 30 min. at 55—60° and then treated with guanidine or thiourea (see below).

Malonitrile and Glycide.—To a solution of malononitrile (26·4 g.) and glycide (29·6 g.) in absolute ethanol (200 c.c.) at 3° was added a solution of sodium ethoxide prepared from sodium (9·2 g.) and absolute ethanol (200 c.c.) and previously cooled to 3°. The mixture was allowed to warm, but was kept below 50° by cooling. At the end of the reaction the mixture was allowed to cool for 30 min., then treated with guanidine or thiourea (see below).

Pyrimidines.—With the exception of the 2-methoxy- and 2-methylthio-derivatives, the 2-substituted pyrimidines listed in Table 2 were prepared by the following general procedure.

The ethanolic solutions of the sodio-derivatives of the dihydroxypropyl compounds derived from glycide were treated directly with guanidine (1 mol., prepared in filtered ethanolic solution from ethanolic solutions of equivalent quantities of the hydrochloride and sodium ethoxide) or thiourea (1 mol.). The other cyanoacetic esters were added to: (*a*) an ethanolic solution of guanidine (1 mol.) and sodium ethoxide (1 mol.); (*b*) an ethanolic solution of urea (1 mol.) and sodium ethoxide (2 mol.); or (*c*) an ethanolic solution of thiourea (1 mol.) and sodium ethoxide (1 mol.). The other malononitriles were added to (*a*) an ethanolic solution of guanidine (1 mol.) and sodium ethoxide (0·5 mol.), or (*b*) an ethanolic solution of thiourea (1 mol.) and sodium ethoxide (1 mol.).

The reaction mixtures were then boiled under reflux for 3—4 hr., with stirring if necessary to prevent bumping due to separated solid. With the exception of the 2,4,6-triamino-compounds, the products were isolated by evaporation, dissolution of the residue in water, washing with ether, and addition of an equivalent of acetic acid to the aqueous solution. The products separated either directly or on evaporation. In one case, (IV; R = SH, R′ = OH), the sodium salt was filtered directly from the cooled reaction mixture, dissolved in water, and acidified. The 2,4,6-triamino-compounds were isolated by evaporation of the reaction mixture and crystallisation from water (for the 2,3-dihydroxypropyl compound), or by evaporation of the reaction mixture to half-volume (for the 2,2-diethoxyethyl derivative).

Analytical samples of the acetals and ketals were dried at room temperature.

2,4-*Diamino*-5-(2,2-*diethoxyethyl*)-6-*hydroxypyrimidine from* γγ-*Diethoxybutyronitrile.*—A mixture of γγ-diethoxybutyronitrile [11] (15·7 g.) and ethyl carbonate (97 c.c.) was added to " foamed " sodium ethoxide (from 2·3 g. of sodium) and heated with stirring under a 6″ Fenske column with reflux ratio head until the temperature of the distillate remained above 100° (1 hr.). The mixture was evaporated to dryness under reduced pressure, and the residue heated under reflux for 3 hr. with guanidine (from 9·55 g. of hydrochloride) in absolute ethanol (100 c.c.). Isolated by the procedure described above, the *pyrimidine* (17 g. 70%) formed needles, m. p. 156—158° (decomp.) after recrystallisation, undepressed by the previously described material (Found: C, 46·3; H, 7·6; N, 22·1. $C_{10}H_{18}O_3N_4,H_2O$ requires C, 46·1; H, 7·8; N, 21·5%).

4,6-*Diamino*-5-(2,2-*diethoxyethyl*)-2-*methoxypyrimidine.*—To a cold solution of sodium ethoxide (prepared from 2·22 g. of sodium and 95 c.c. of absolute ethanol) was added a cooled solution of *O*-methylisourea hydrochloride (10·2 g.) in absolute ethanol (50 c.c.), followed at once by 2,2-diethoxyethylmalononitrile (16·9 g.). The mixture was boiled for 4 hr. under reflux, treated with water (120 c.c.), and evaporated to small bulk. The residue was shaken with water (200 c.c.), and the *pyrimidine* (16·3 g., 69%) was collected (see Table 2).

2-*Methylthiopyrimidines.*—The two compounds listed in Table 2 were prepared by adding dimethyl sulphate to solutions of the mercapto-compounds in N-sodium hydroxide, using equivalent quantities for compound (V; R = SMe, R′ = NH_2) and a 30% excess of each reagent for compound (V; R = SMe, R′ = OH). The mixtures were shaken vigorously, and the products were collected after standing.

2-*Unsubstituted Pyrimidines by Desulphurisation.*—Compounds of this type listed in Table 2 were prepared from the 2-mercapto-compounds as follows. The 2-mercapto-compound (10 g.), water (500 c.c.), ammonia (*d* 0·88; 30 c.c.), and Raney nickel [12] (from 30 g. of alloy) were boiled under reflux with stirring for 1 hr., then filtered hot, and the filtrate evaporated.

Pyrrolo[2,3-d]*pyrimidines from Acetals and Ketals.*—The pyrimidines listed in Table 2 (Nos.

[11] Manske, *Canad. J. Res.*, 1931, **5**, 592.
[12] Brown, *J. Soc. Chem. Ind.*, 1959, **69**, 353.

TABLE 2. *Pyrimidines.*

No.		Compound R	R′	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	Form	Yield (%)
1 [a]	III	NH_2	OH	157—158° [a]	46·2	7·7	22·6	$C_{10}H_{18}O_3N_4,H_2O$	46·1	7·8	21·5	Needles [d]	86
2 [a]	III	OH	OH	—	49·5	7·3	17·2	$C_{10}H_{17}O_4N_3$	49·4	7·0	17·3	Prisms [e]	83
3 [a]	III	SH	OH	—	46·6	6·7	15·7	$C_{10}H_{17}O_3N_3S$	46·3	6·6	16·2	Rods [e]	82
4 [a]	III	H	OH	185—186	52·7	7·3	18·2	$C_{10}H_{17}O_3N_3$	52·9	7·5	18·5	Laths [f]	75
5 [a]	III	NH_2	NH_2	88—100	50·7	9·2	25·1	$C_{10}H_{19}O_2N_5,C_2H_6O$	50·1	8·8	24·4	Plates [e]	67
6	III	OMe	NH_2	149—151	51·8	8·2	21·9	$C_{11}H_{20}O_3N_4$	51·6	7·9	21·9	Rods [g]	69
7 [a]	III	SH	NH_2	220—221	45·5	7·5	21·2	$C_{10}H_{18}O_2N_4S,\frac{1}{3}H_2O$	45·4	6·8	21·2	Needles [e]	82
8	III	H	NH_2	167—169	53·0	8·3	24·6	$C_{10}H_{18}O_2N_4$	53·1	8·0	24·8	Laths [f]	70
9	IV	NH_2	OH	243—244 [b]	44·8	6·6	23·1	$C_9H_{14}O_3N_4,H_2O$	44·3	6·6	22·9	Rhombs [f]	66
10	IV	OH	OH	—	43·6	6·5	16·6	$C_9H_{13}O_4N_3,H_2O$	44·1	6·2	17·1	Plates [d]	51
11	IV	SH	OH	—	44·3	5·7	17·4	$C_9H_{13}O_3N_3S$	44·4	5·4	17·3	Rods [d]	49
12	IV	H	OH	237—238	51·3	6·1	20·1	$C_9H_{13}O_3N_3$	51·2	6·2	19·9	Prisms [f]	86
13	IV	SH	NH_2	—	44·6	6·2	23·9	$C_9H_{14}O_2N_4S$	44·6	5·8	23·1	,, [c]	63
14	IV	H	NH_2	216	50·8	7·0	27·2	$C_9H_{14}O_2N_4$	51·4	6·7	26·7	,, [f]	51
15	V	NH_2	OH	248 [a]	41·8	6·0	27·5	$C_7H_{12}O_3N_4$	42·0	6·0	28·0	Needles [f]	58
16	V	SH	OH	246—247 [a]	38·3	5·3	19·2	$C_7H_{11}O_3N_3S$	38·7	5·1	19·3	Prisms [a]	45
17	V	SMe	OH	148—158	41·1	5·6	18·0	$C_8H_{13}O_3N_3S$	41·1	5·6	18·0	Needles [f]	58
18	V	H	OH	235—236	45·6	6·0	22·7	$C_7H_{11}O_3N_3$	45·4	6·0	22·7	,, [f]	65
19	V	NH_2	NH_2	214—215	42·3	6·7	35·6	$C_7H_{13}O_2N_5$	42·2	6·6	35·2	,, [d]	19
20	V	SH	NH_2	262—263 [a]	38·9	5·8	25·2	$C_7H_{12}O_2N_4S$	38·9	5·6	25·9	Leaflets [c]	40
21	V	SMe	NH_2	190—191	41·3	6·4	24·0	$C_8H_{14}O_2N_4S$	41·7	6·1	24·3	Needles [f]	71
22	V	H	NH_2	188—190	45·3	6·9	30·8	$C_7H_{12}O_2N_4$	45·6	6·6	30·4	Prisms [d]	63

[a] With decomp. [b] Slow heating. [c] By addition of acetic acid to solution in sodium hydroxide. [d] From H_2O–EtOH. [e] From EtOH. [f] From H_2O. [g] From EtOAc.

TABLE 3. *Pyrrolo*[2,3-d]*pyrimidines.*

	Compound R	R′	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	Form	Yield (%)
VIII [4a]	NH_2	OH	323—324° [c]	48·5	4·5	37·5 [d]	$C_6H_6ON_4$	48·0	4·5	37·5	Needles [j]	92
	,,	,,	315—317 [c]	42·4	4·8	33·6	$C_6H_6ON_4,H_2O$	42·9	4·8	33·3	,, [j]	46
VIII [4a]	OH	OH	—	47·3	3·4	28·2	$C_6H_5O_2N_3$	47·7	3·3	27·8	Powder [k]	93
VIII [4a]	SH	OH	—	43·1	3·0	25·4	$C_6H_5ON_3S$	43·1	3·0	25·1	Needles [k]	96
VIII [b]	SMe	OH	265—267 [c]	44·3	4·3	21·7	$C_7H_7ON_3S,\frac{1}{2}H_2O$	44·2	4·2	22·1	Powder [e]	83
VIII [4a]	H	OH	335—340 [c]	53·8	4·0	31·4	$C_6H_5ON_3$	53·3	3·7	31·1	Needles [j]	96
VIII [b]	,,	,,	338—340 [c]	53·1	4·0	30·7	$C_6H_5ON_3$	53·3	3·7	31·1	,, [j]	70
VIII [4a]	NH_2	NH_2	258—260 [f]	36·9	5·6	35·8	$C_6H_7N_5,2\frac{1}{2}H_2O$	37·1	6·2	36·1	,, [j]	40 [g]
VIII [a]	OMe	NH_2	275—277 [c]	51·1	5·3	33·9	$C_7H_8ON_4$	51·2	4·9	34·1	Rods [j]	100
VIII [4a]	SH	NH_2	—	41·3	4·2	31·6 [d]	$C_6H_6N_4S,\frac{1}{2}H_2O$	41·1	4·0	32·0	,, [k]	100
VIII [b]	SMe	NH_2	257—259 [c]	46·8	4·4	30·8	$C_7H_8N_4S$	46·7	4·5	31·1	Needles [h]	75
VIII [4a]	H	NH_2	252—254	54·0	4·5	41·4	$C_6H_6N_4$	53·7	4·5	41·8	,, [j]	97
IX [a]	NH_2	OH	321—323 [c]	50·9	5·3	34·4	$C_7H_8ON_4$	51·2	4·9	34·1	,, [j]	96
IX [a]	OH	OH	—	50·1	4·4	25·8	$C_7H_7O_2N_3$	50·9	4·3	25·5	Powder [i]	86
IX [a]	SH	OH	—	45·4	4·0	22·1	$C_7H_7ON_3S,\frac{1}{3}H_2O$	44·9	4·1	22·5	,, [i]	100
IX [a]	H	OH	333—335 [c]	56·5	4·7	28·6	$C_7H_7ON_3$	56·4	4·7	28·2	Needles [j]	90
IX [a]	H	NH_2	313—314 [c]	56·4	5·9	37·4	$C_7H_8N_4$	56·7	5·4	37·8	,, [j]	95

[a] Prepared from acetal or ketal. [b] Prepared from 2′,3′-dihydroxypropylpyrimidine. [c] With decomp. [d] Dried at 140°. [e] By addition of acetic acid to solution in hot dilute ammonia. [f] After drying at 100°. [g] 99% yield when isolated as sulphate (see Experimental) [h] By addition of ammonia to solution in hot 10% acetic acid. [i] By addition of hydrochloric acid to solution in hot aqueous-ethanolic sodium hydroxide. [j] From H_2O. [k] From H_2O–EtOH.

1—14) were converted into pyrrolo[2,3-*d*]pyrimidines as follows. Compounds 2—4 and 10—12 were shaken for 24 hr. with 0·2N-hydrochloric acid (1·5 equiv.), and the products were collected; compound 1 and 9 were dissolved in 0·2N-hydrochloric acid (1·5 equiv.), and the products were precipitated with ammonia after 3 hr.; and compounds 5—8, 13, and 14 were dissolved in N-hydrochloric acid (5 equiv.) and after 3 hr. the products were isolated by precipitation with ammonia (Nos. 7, 13), addition of the calculated amount of sodium hydroxide (Nos. 6, 8, 14), or addition of ammonia followed by evaporation to small bulk (No. 4).

The product of the last reaction was obtained in higher yield by evaporation of the neutralised hydrolysis solution to dryness and addition of 20N-sulphuric acid (8 equiv.) to an aqueous solution of the residue, giving 2,4-*diaminopyrrolo*[2,3-d]*pyrimidine sulphate hexahydrate* [4] (99%) as needles (from water) which lost five molecules of water at 100° *in vacuo* (weight loss, 19·7. $5H_2O$ requires 20·7%) [Found: C, 34·7; H, 4·6; N, 33·2; S, 7·7. $(C_6H_7N_5)_2,H_2SO_4,H_2O$ requires C, 34·8; H, 4·4; N, 33·8; S, 7·7%].

Pyrrolo[2,3-d]*pyrimidines from 2′,3′-Dihydroxypropylpyrimidines.*—The following procedure was used for compounds 17, 18 and 21 (Table 2). A solution of the pyrimidine in hot water was either cooled rapidly to 20° (No. 17) or added to an equal weight of crushed ice (Nos. 18 and 21) and treated at once with sodium metaperiodate (1 mol. of *ca.* 0·2M-solution). The products separated rapidly.

Compound 15 (2 g.) in hot water (300 c.c.) was evaporated at water-pump vacuum until the temperature fell to 25°. With continued evaporation from a bath at 35—40° a solution of sodium metaperiodate (2·14 g.) in water (50 c.c.) was added during 30 min.; the solution was then evaporated to 75 c.c., and 2-*amino*-4-*hydroxypyrrolo*[2,3-d]*pyrimidine* (0·78 g., 46%) was later collected (see Table 3). Its identity with the sample prepared from the acetal was confirmed by mised m. p., and by ultraviolet and infrared spectra. On a larger scale, the main product was an amorphous powder (Found: C, 45·9; H, 4·3; N, 30·4. $C_7H_8O_2N_4$ requires C, 46·7; H, 4·5; N, 31·1%).

A solution of compound 19 (18·4 g.) in water (400 c.c.) was cooled to room temperature and treated with lead tetra-acetate (44·3 g.) in hot glacial acetic acid (240 c.c.), added rapidly with stirring. After 30 min. the clear red solution was treated with N-sulphuric acid (200 c.c.), stirred for 15 min., and filtered. Evaporation and treatment with ethanol gave 4-*aminopyrrolo*-[2,3-d]*pyrimidine acetate* (7·6 g., 39%) as needles or prisms (from water), m. p. 249—251° (decomp.), with loss of acetic acid above 180° (Found: C, 49·8; H, 5·9; N, 28·8. $C_6H_6N_4,C_2H_4O_2$ requires C, 49·5; H, 5·2; N, 28·9%). Treatment with sodium hydroxide in aqueous solution gave 4-*aminopyrrolo*[2,3-d]*pyrimidine* (89%), identical with a sample prepared by the acetal route (mixed m. p.; infrared spectrum) (Found: C, 53·4; H, 4·8; N, 42·3%).

4-*Amino*-2-*hydroxypyrrolo*[2,3-d]*pyrimidine.*[4]—4-Amino-2-methoxypyrrolo[2,3-*d*]pyrimidine (5·15 g.) and concentrated hydrochloric acid (15 c.c.) were kept for 5 min. at 100°. Methyl chloride was evolved. Dilution with water, neutralisation with ammonia, and recrystallisation of the separated solid from 10% ethanol gave the 4-*amino-compound* (4·1 g., 87%) as laths, which did not melt (Found: C, 47·9; H, 4·3; N, 36·9. $C_6H_6ON_4$ requires C, 48·0; H, 4·0; N, 37·3%).

4-*Chloropyrrolo*[2,3-d]*pyrimidine.*[4]—4-Hydroxypyrrolo[2,3-*d*]pyrimidine (10 g.) and phosphoryl chloride (100 c.c.) were boiled together under reflux for 45 min. Phosphoryl chloride was removed *in vacuo* and the residue treated with crushed ice and extracted with ether (4 × 100 c.c.). Evaporation of the dried ($MgSO_4$) ether extract gave the *chloro-compound* (9 g., 79%) sufficiently pure for further use. After crystallisation from ethyl acetate (as laths) and sublimation at 110—120° (bath-temp.)/0·5 mm. it had m. p. 189—190° (decomp.) (Found: C, 47·3; H, 2·6; N, 27·1. $C_6H_4N_3Cl$ requires C, 46·9; H, 2·6; N, 27·4%).

4-*Mercaptopyrrolo*[2,3-d]*pyrimidine.*[4]—The crude chloro-compound (9 g.), thiourea (9 g.), and absolute ethanol (230 c.c.) were boiled together under reflux for 2 hr. Evaporation and crystallisation of the residue from water (750 c.c.) (charcoal) gave the *mercapto-compound* (6·2 g., 70%) as grey needles, m. p. 293—295° (decomp.) (Found: C, 47·3; H, 3·6; N, 27·3. $C_6H_5N_3S$ requires C, 47·7; H, 3·3; N, 27·8%).

4-*Mercapto*-6-*methylpyrrolo*[2,3-d]*pyrimidine.*—Similarly prepared from 4-hydroxy-6-methylpyrrolo[2,3-*d*]pyrimidine, without purification of the chloro-compound (which was extracted with chloroform), the *mercapto-compound* (24% overall yield) formed yellow rods (from 50% acetic acid) (Found: C, 51·2; H, 4·85; N, 25·6. $C_7H_7N_3S$ requires C, 50·9; H, 4·3; H, 25·5%).

Pyrrolo[2,3-d]*pyrimidine.*[4]—(a) *From the* 4-*mercapto-compound.* The procedure used was

that described above for desulphurisation of 2-mercaptopyrimidines. *Pyrrolo*[2,3-d]*pyrimidine* (69%) formed colourless prisms (from ethyl acetate), m. p. 131—133°, soluble in water (Found: C, 60·5; H, 4·7; N, 35·3. $C_6H_5N_3$ requires C, 60·5; H, 4·2; N, 35·3%).

(b) *From the 4-chloro-compound.* The chloro-compound (0·77 g.; recrystallised from ethyl acetate) was hydrogenated in ethanol with 10% palladised charcoal. One mol. of hydrogen was absorbed and after filtration N-sodium hydroxide (5 c.c.) was added to the filtrate. Evaporation and extraction of the residue with ethyl acetate gave pyrrolo[2,3-*d*]pyrimidine (0·44 g., 73%), m. p. 131—132° alone or mixed with the above sample (Found: N, 35·1%).

4-Propylaminopyrrolo[2,3-d]*pyrimidine.*—The crude 4-chloro-compound (4·6 g.), n-propylamine (8·2 g., 4 mol.), and butan-1-ol (46 c.c.) were boiled together under reflux for 4 hr. Evaporation and crystallisation from aqueous ethanol gave the *propylamino-compound* (3·75 g., 71%) as blades, m. p. 160—161° (Found: C, 61·7; H, 7·2; N, 31·8. $C_9H_{12}N_4$ requires C, 61·3; H, 6·9; N, 31·8%). Similarly, benzylamine (2·5 mol.) and furfurylamine (2·5 mol.) gave, respectively, *4-benzylamino-* (62%), needles, m. p. 203° (Found: C, 69·8; H, 5·8; N, 24·6. $C_{13}H_{12}N_4$ requires C, 69·6; H, 5·4; N, 25·0%), and *4-furfurylamino-pyrrolo*[2,3-d]*pyrimidine* (72%), needles, m. p. 150—152° (Found: C, 61·5; H, 4·8; N, 26·2. $C_{11}H_{10}ON_4$ requires C, 61·7; H, 4·7; N, 26·2%).

4-Amino-5-phenylazopyrrolo[2,3-d]*pyrimidine.*—A diazonium solution prepared from aniline (1·65 g.) in 2N-hydrochloric acid (50 c.c.) and sodium nitrite (1·2 g.) in water (50 c.c.) was added to a solution of 4-aminopyrrolo[2,3-*d*]pyrimidine (2·4 g.) in 0·5N-hydrochloric acid (120 c.c.). The mixture was added to a solution of sodium carbonate (20 g.) in water (400 c.c.), and the *phenylazo-compound* (3·8 g., 89%) collected after storage. Addition of ethanol to its solution in 75% acetic acid gave yellow prisms, m. p. 297—298° (decomp.) (Found: C, 60·0; H, 4·9; N, 35·9. $C_{12}H_{10}N_6$ requires C, 60·5; H, 4·2; N, 35·3%).

4-Amino-6-methyl-5-phenylazopyrrolo[2,3-d]*pyrimidine.*—Similarly prepared, the *phenylazo-compound* (79%) formed yellow needles, m. p. 312—314° (decomp.) (Found: C, 61·9; H, 5·4; N, 33·6. $C_{13}H_{12}N_6$ requires C, 61·9; H, 4·8; N, 33·3%).

Ethyl α-Cyano-α-(2,2-diethoxyethyl)propionate.—To a solution of sodium ethoxide (from 2·3 g. of sodium) in absolute ethanol (60 c.c.) was added, with stirring, ethyl α-cyano-α-(2,2-diethoxyethyl)acetate (23 g.), followed after 5 min. by methyl iodide (7·5 c.c.). The mixture was boiled under reflux for 3 hr., then evaporated, and the residue was shaken for 1½ hr. with 0·7N-sodium hydroxide (45 c.c.). Extraction with ether gave the *propionate* (16·2 g., 67%), b. p. 102—104°/1 mm., n_D^{20} 1·4297 (Found: C, 59·3; H, 9·0; N, 5·4. $C_{12}H_{21}O_4N$ requires C, 59·2; H, 8·7; N, 5·8%).

6-Amino-5-(2,2-diethoxyethyl)-4,5-dihydro-2-mercapto-5-methyl-4-oxopyrimidine.—To a solution of sodium ethoxide (from 0·92 g. of sodium) in absolute ethanol (20 c.c.) was added thiourea (1·52 g.), followed by the preceding ester (4·86 g.). The mixture was boiled for 5 hr. under reflux, cooled, and treated with glacial acetic acid (2·4 c.c.) and water (25 c.c.), giving the *oxopyrimidine* (4·61 g., 84%); it formed cream-coloured needles (from ethanol), m. p. 216° (decomp.) (Found: C, 48·3; H, 7·4; N, 15·2. $C_{11}H_{19}O_3N_3S$ requires C, 48·3; H, 7·0; N, 15·4%).

5-(2,2-Diethoxyethyl)-4,5-dihydro-6-hydroxy-2-mercapto-5-methyl-4-oxopyrimidine.—The preceding compound (8·64 g.) and 0·2N-hydrochloric acid were stirred together for 3 hr. Collected after cooling to 0°, the *product* (3·42 g., 40%) formed rods (from water), m. p. 94—96° (Found: C, 48·3; H, 6·6; N, 10·1. $C_{11}H_{18}O_4N_2S$ requires C, 48·2; H, 6·6; N, 10·2%).

The author thanks Dr. R. E. Bowman for many helpful discussions, Miss E. M. Tanner for determination of the spectra, and Mr. F. Oliver for the microanalyses.

CHEMICAL RESEARCH DEPARTMENT, PARKE, DAVIS & CO., LTD.,
HOUNSLOW, MIDDLESEX.

[*Received, June 18th*, 1959.]