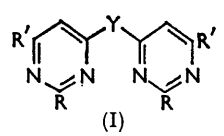
559. *Some* NN′*-Dipyrimidinylalkylenediamines and Related Compounds.*

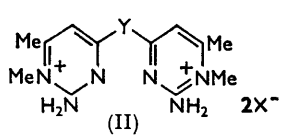
By E. W. Parnell.

A number of symmetrical *NN′*-dipyrimidinyl-alkylene- and -phenylene-diamines and some of their methyl quaternary derivatives are described.

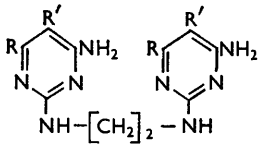
The trypanocidal activity of bisquaternary heterocyclic compounds and of diamidines is well known. A series of *NN′*-dipyrimidinylalkylenediamines (Ia, Id, and III) and their methyl quaternary salts (II), together with some similar pyrimidine derivatives (Ib, Ic,



(I)

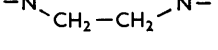


(II)



(III)

(a) Y = ·NH·[CH$_2$]$_n$·NH·

(b) Y = 

(c) Y = NH·C$_6$H$_4$·NH

(d) Y = NPh·[CH$_2$]$_2$·NPh

IIb, and IIc), have therefore been prepared and examined for trypanocidal, amœbicidal, and other biological activities.

The alkylenediamines (Ia; R = NH_2, substituted NH_2, H or Me; R′ = Me, Et, or NH_2) were mostly prepared by reaction of the appropriate 4-chloropyrimidine with a polymethylenediamine in boiling phenol,[1] but 2-ethoxyethanol was the preferred solvent for large-scale preparations. The dipyrimidinylpiperazine (Ib; R = NH_2, R′ = Me) was obtained in good yield from 2-amino-4-chloro-6-methylpyrimidine and piperazine in aqueous sodium hydroxide, conditions which gave only a poor yield of compounds of type (Ia). Analogous reactions between 2-amino-4-chloro-6-methylpyrimidine and the phenylenediamines or *NN′*-diphenylethylenediamine proceeded readily in dilute aqueous acid, affording the bases (Ic) and (Id) respectively.

Condensation [2] of 2,4-dimercapto-6-methylpyrimidine with a polymethylenediamine provided a further route to compounds of formula (Ia). Subsequent methylation of the 2-mercapto-group and replacement of methylthio with 2-hydroxyethylamino gave further members of this series.

The dipyrimidin-2-yl compound (III; R = Me, R′ = H) was prepared by reaction [3] of ethylenediamine with 4-hydroxy-6-methyl-2-methylthiopyrimidine, followed by chlorination and amination; and the nitropyrimidine (III; R = H, R′ = NO_2) was obtained from 4-amino-2-chloro-5-nitropyrimidine and the diamine.

The quaternary salts could be isolated only with difficulty after treatment of the corresponding bases with methyl iodide or methyl sulphate. The salts (IIa and b) were, however, readily prepared by reaction of the appropriate polymethylenediamine with 2-amino-4-chloro-6-methylpyrimidine methiodide in boiling water (maintained slightly alkaline by sodium hydroxide), whilst the benzene derivatives (IIc) were formed from the phenylenediamine and the pyrimidine quaternary salt in aqueous acid.

Refluxing the compound (Ia; *n* = 2, R = NH_2, R′ = Me) with acetic anhydride led to a tetra-acetyl derivative. In an attempt to prepare a 2,2′-diacetyl derivative (Ia; *n* = 2, R = NHAc, R′ = Me), 2-amino-4-hydroxy-6-methylpyrimidine was acetylated and then chlorinated, yielding 2-acetamido-4-chloro-6-methylpyrimidine. However, reaction of the latter with ethylenediamine resulted in hydrolysis of the acetyl groups and formation of the base (Ia; *n* = 2, R = NH_2, R′ = CH_3).

Biological Results.—Several bases (I) showed high amœbicidal activity in rats, the most active being (Ia; *n* = 2, R = NH_2, R′ = Me). Some of the quaternary salts (II) showed low activity against *T. congolense* in mice and others exhibited a weak ganglion-blocking and neuromuscular blocking action in cats, under chloralose anæsthesia.

Experimental

The *compounds* listed in Tables 1—3 were prepared by the following general methods.

Preparation of Free bases (*Tables* 1 *and* 2).—*Method* 1: The chloropyrimidine and the diamine were condensed in phenol by the method of Jacob and Liakhoff.[1]

Method 2: NN′-*di*-(2-*amino*-6-*methylpyrimidin*-4-*yl*)*ethylenediamine*. 2-Amino-4-chloro-6-methylpyrimidine [4] (500 g.), ethylenediamine (120 ml.), and dry 2-ethoxyethanol (2·0 l.) were refluxed and stirred for 4 hr., during which the hydrochloride of the product separated. After being cooled, this was filtered off, washed with ethanol, and dried to give a white solid (585 g.). This was dissolved in warm water (4·7 l.), the solution was filtered from insoluble material (*ca.* 30 g.), and the filtrate was basified at 45—50° with 50% w/w aqueous sodium hydroxide (180 ml.), giving the base (418 g., 87%), m. p. 191—193°.

Method 3: 1,4-*di*-(2-*amino*-6-*methylpyrimidin*-4-*yl*)*piperazine dihydrochloride*. 2-Amino-4-chloro-6-methylpyrimidine (29·6 g.), piperazine hexahydrate (20 g.), and water (50 ml.) were refluxed and 2N-sodium hydroxide (23·5 ml.) was added during 30 min. to maintain a solution alkaline to phenolphthalein. After being refluxed for a further 30 min. the hot mixture was filtered, and the solid residue washed with water. This product (18·0 g., 64%), m. p. 300—304°, could not be easily crystallised; it was dissolved in boiling 2N-hydrochloric acid (105 ml.),

[1] Cf. Jacob and Liakhoff, G.P. 899,656/1953.
[2] Russell, Elion, Falco, and Hitchings, *J. Amer. Chem. Soc.*, 1949, **71**, 2279.
[3] Cf. Curd and Rose, *J.*, 1946, 362.
[4] Gabriel and Colman, *Ber.*, 1899, **32**, 2921.

TABLE 1.

NN'-Di(pyrimidin-4-yl)ethylenediamines (Ia).

R	R'	*n*	Method	Yield (%)	Solvent [a]	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
NH_2	Me	2	1	67	H_2O	190—193°,	$C_{12}H_{18}N_8,H_2O$ [b, c]	49·85	6·5	38·3	49·4	6·9	38·3
			2	74		215—216 *							
			3	10									
NH_2	Me	3	1 [d]	24	NMe_2·CHO	192—193 †	$C_{13}H_{20}N_8$	54·0	6·8	38·9	54·1	6·95	38·9
NH_2	Me	4	1	54	MeOH–H_2O	255—256 †	$C_{14}H_{22}N_8$	55·3	7·35	37·4	55·6	7·3	37·1
NH_2	Me	5	1	52	NMe_2·CHO	268—270 †	$C_{15}H_{24}N_8$	56·8	7·55	35·24	56·95	7·6	35·45
NH_2	Me	6	1	50	Pyridine	226—229 †	$C_{16}H_{26}N_8$ [e]	58·4	7·4	34·1	58·2	7·8	33·9
NH_2	Me	7	1	31	NMe_2·CHO–H_2O	175	$C_{17}H_{28}N_8$	59·5	8·3	32·6	59·3	8·15	32·55
NH_2	Me	10	1	31	NMe_2·CHO–H_2O	180·5—182	$C_{20}H_{34}N_8$ [f]	62·1	8·8	29·1	62·2	8·8	29·0
			2	92·5	—	177—179							
NH_2	Me	11	1	63	EtOH–H_2O	105—115	$C_{21}H_{36}N_8,0·75H_2O$	61·2	9·65	27·1	60·9	9·1	27·1
NHMe	Me	2	1	51	EtOH	225—227	$C_{14}H_{22}N_8$	55·6	7·4	37·0	55·6	7·3	37·1
NMe_2	Me	2	1	40	EtOH	170—171	$C_{16}H_{26}N_8$	58·3	7·9	33·9	58·1	7·9	33·9
NH·$[CH_2]_2$·OH	Me	2		35	EtOH–H_2O	187—189	$C_{16}H_{26}N_8O_2,0·25H_2O$ [g]	52·6	7·35	30·8	52·4	7·25	30·6
p-NH·C_6H_4Cl	Me	2	1	45	Bu^{n}OH	210—212	$C_{24}H_{24}Cl_2N_8$ [h]	58·6	4·8	22·5	58·2	4·85	22·6
H	Me	2	1	44	H_2O	230—231	$C_{12}H_{16}N_6$	59·4	6·75	35·5	59·0	6·55	34·4
Me	Me	2	1	74	*i*	301—303 †	$C_{14}H_{20}N_6$	61·3	7·1	30·8	61·75	7·35	30·9
NH_2	Et	2	1	63 [j]	N-HCl	294—296 †	$C_{14}H_{22}N_8$,2HCl,$\frac{1}{2}H_2O$ [k]	43·6	6·5	28·9	43·75	6·5	29·2
Me	NH_2	2	1	49	*i*	340 †	$C_{12}H_{18}N_8$	52·0	6·4	40·7	52·55	6·6	40·85
NH_2	Me	2	1 [l]	42	NMe_2·CHO	257—259 †	$C_{14}H_{22}N_8$	55·4	7·4	36·9	55·6	7·3	37·1
NH_2	Me	2	4 [m]	36	OH·$[CH_2]_2$·OEt	273—274	$C_{24}H_{26}N_8$	67·3	5·8	26·35	67·55	6·1	26·3

[a] Solvent for recrystn. [b] Found: H_2O, 6·6. Required: H_2O, 6·2%. [c] Hydrochloride, m. p. 320° (decomp.) (Found: Cl, 18·95; N, 29·6; H_2O, 9·2. $C_{12}H_8N_8$,2HCl,2H_2O requires Cl, 18·5; N, 29·3; H_2O, 9·4%). [d] Prepared by Dr. D. A. A. Kidd. [e] Hydrochloride, m. p. 110—115°, resolidifying and remelting at 278—279° (decomp.) (Found: Cl, 15·5; N, 24·5; H_2O, 12·4. $C_{16}H_{26}N_8$,2HCl,3H_2O requires Cl, 15·5; N, 24·5; H_2O, 11·8%). [f] Lactate, m. p. 184·5—185·5° (Found: C, 54·5; H, 8·1; N, 19·65. $C_{20}H_{34}N_8$,2·1$C_3H_6O_3$ requires C, 54·9; H, 8·1; N, 19·5%).‡ [g] Found: H_2O, 1·3. Required: H_2O, 1·2%. [h] Found: Cl, 13·9. Required: Cl, 14·3%. [i] Purified by dissolution in N-HCl and pptn. by conc. aq. NH_3. [j] Isolated as the hydrochloride. [k] Found: Cl, 18·7; H_2O, 1·4. Required: Cl, 18·5; H_2O, 2·3%. [l] *NN'*-Di-(2-amino-6-methylpyrimidin-4-yl)ethylenediamine, prepared from NHMe·$[CH_2]_2$·NHMe. [m] Compound Id.

* Double m. p. † With decomp. ‡ This compound appears to crystallise with appreciably more than one mole of acid in the salt.

TABLE 2.

1,4-Dipyrimidinylpiperazine (Ib) and the phenylenediamines (Ic).

Y	Method	Yield (%)	Solvent [a]	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
See Ib	3	64 [d]	2N-HCl	<360°	$C_{14}H_{20}N_8,2{\cdot}1HCl,2H_2O$ [b] ‡	—	—	27·1	—	—	27·1
p-NH·C_6H_4·NH	4	89	NMe_2·CHO	293—295 *	$C_{16}H_{18}N_8$	60·1	5·5	35·0	59·7	5·6	34·75
m-NH·C_6H_4·NH	4	48	NMe_2·CHO–H_2O	179—180	$C_{16}H_{18}N_8,H_2O$ [c]	56·0	5·9	32·95	56·5	5·9	33·0
o-NH·C_6H_4·NH	4	67	NMe_2·CHO	282—284	$C_{16}H_{18}N_8$	60·2	5·6	34·9	59·7	5·6	34·75

[a] Solvent for recrystn. [b] Isolated as the hydrochloride (Found: Cl, 17·9. Required: 18·1%). [c] Found: H_2O, 5·7 Required: H_2O, 5·3%. [d] Crude.

* With decomp. ‡ See corresponding footnote in Table 1.

TABLE 3.

Bisquaternary salts.

Formula	*n* or Y	X	Method	Yield (%)	Solvent [a]	M. p.	Formula	Found (%) N	Found (%) Hal	Required (%) N	Required (%) Hal
IIa	2	I	1	39·5	H_2O	357—360° †	$C_{14}H_{28}N_8I_2$	20·1	45·5	19·7	45·2
			2	35·5							
IIa	2	Cl	6	53	MeOH–$COMe_2$	348—349 †	$C_{14}H_{28}Cl_2N_8,2H_2O$	27·2	17·7	27·0	17·1
IIa	5	I	4	48	H_2O–NaI	285—287 †	$C_{17}H_{30}I_2N_8,2{\cdot}5H_2O$	17·3	39·5	17·4	39·4
IIa	6	I	1	16·5	H_2O	257—259 †	$C_{18}H_{32}I_2N_8,H_2O$	17·6	40·5	17·7	40·2
IIa	7	I	4	64	MeOH–Et_2O	216—218	$C_{19}H_{34}I_2N_8,2H_2O$	16·9	38·5	16·85	38·2
IIa	8	I	1	46	EtOH	110—120, 270—271 *	$C_{20}H_{36}I_2N_8,3H_2O$	15·9	36·6	16·1	36·5
IIa	10	I	3	39 [b]	—	110—120,	*c*				
			4	93·5 [b]		240—242 *					
IIa	10	Cl	6	67·5	2N-HCl	290—291 †	$C_{22}H_{40}Cl_2N_8$	22·75	14·9	23·0	14·6
IIa	11	I	4	100 [b]	—	—	*c*				
IIa	11	Cl	6	53	EtOH–Et_2O	268—270 †‡	$C_{23}H_{42}Cl_2N_8,2{\cdot}5H_2O$ [d]	20·75	13·12	20·5	13·0
IIa	12	I	4	86 [b]	—	110—120, 262—264 *	*c*				
IIa	12	Cl	6	65·5	EtOH–$COMe_2$	279—281 †	$C_{24}H_{44}Cl_2N_8$ [e]	21·1	13·7	21·7	13·8
IIc	*p*-NH·C_6H_4·NH	I	5	76	H_2O	<360	$C_{18}H_{24}I_2N_8$	18·6	41·4	18·5	41·9
		$MeSO_3$	6	76·5	H_2O	<360	$C_{18}H_{24}N_8,2CH_3SO_3,H_2O$ [f]	20·0	—	20·0	—
IIb	—	I	3	64·5	H_2O	343—345 †	$C_{16}H_{26}I_2N_8$	19·3	43·1	19·2	43·4
		Cl	6	76	MeOH–$COMe_2$	360 †	$C_{16}H_{26}Cl_2N_8$	27·2	17·3	27·9	17·7

[a] Solvent for recrystn. [b] Yield of crude material. [c] Not analysed; converted directly into the chloride. [d] Found: H_2O, 8·1. Required: H_2O, 8·2%. [e] Found: C, 55·7; H, 8·6. Required: C, 55·9; H, 8·55%. [f] Found: S, 11·8. Required: S, 11·4%.

* Double m. p. † With decomp. ‡ Loss of H_2O at 70—100°.

and the solution was filtered and cooled. The hydrochloride was filtered off, washed with acetone, and dried at 90° to give white needles (22 g.) which did not melt below 360°.

Method 4: NN′-*di*(2-*amino*-6-*methylpyrimidin*-4-*yl*)-p-*phenylenediamine*. 2-Amino-4-chloro-6-methylpyrimidine (30 g.), *p*-phenylenediamine (11·25 g.), 2N-hydrochloric acid (42 ml.), and water (400 ml.) were refluxed for 1 hr. and then cooled. The hydrochloride was filtered off and dissolved in boiling water, and the solution was basified with 2N-sodium hydroxide. The base crystallised from dimethylformamide as prisms (37·5 g.), m. p. 283—285°.

Preparation of Quaternary Salts (*Table* 3).—*Method* 1: NN′-*di*-(2-*amino*-6-*methylpyrimidin*-4-*yl*)*hexamethylenediamine dimethiodide*. Hexamethylenediamine (2·0 g.), 2-amino-4-chloro-6-methylpyrimidine methiodide [5] (10·24 g.), and dry methanol (20 ml.) were heated in a sealed tube at 120° for 3 hr. The contents of 4 tubes were combined and evaporated to dryness *in vacuo*, and the residual gum was dissolved in cold water (*ca.* 80 ml.). After filtration from a trace of insoluble material the solution was heated to 90° and treated with potassium iodide (40 g.). The product crystallised on cooling and was filtered off, washed with a little water, and dried *in vacuo*, to give the crude dimethiodide (17·17 g., 40%), m. p. 235—245° (decomp.).

Method 2: 2-amino-4-chloro-6-methylpyrimidine methiodide and the appropriate diamine in 2-ethoxyethanol were stirred and heated under reflux at 140° for 3 hr. The product separated on cooling.

Method 3: This is similar to method 2, but phenol was used as solvent.

Method 4: NN′-*di*-(2-*amino*-6-*methylpyrimidin*-4-*yl*)*pentamethylenediamine dimethiodide*. 2-Amino-4-chloro-6-methylpyrimidine methiodide (30·0 g.) and pentamethylenediamine (5·0 g.) in water (120 ml.) were refluxed for 0·5 hr. During the first 0·25 hr. 2N-sodium hydroxide (52·5 ml.) was gradually added so as to maintain a solution just alkaline to phenolphthalein. Sodium iodide (25·0 g.) was added to the hot solution and, on cooling, an oil separated which rapidly crystallised to a mass of pale yellow needles which were washed with acetone. The product (30·5 g., 94·5%), m. p. 277—280° (decomp.), crystallised from aqueous sodium iodide, giving the pure dimethiodide.

Method 5: NN′-*di*-(2-*amino*-6-*methylpyrimidin*-4-*yl*)-p-*phenylenediamine dimethiodide*. *p*-Phenylenediamine (5·0 g.), 2-amino-4-chloro-6-methylpyrimidine methiodide (26·5 g.) with 2N-hydrochloric acid (50 ml.) and water (100 ml.) were refluxed for 1 hr., during which a solid separated. The solid was washed with acetone, to give the crude product (21·0 g., 77%), m. p. ⩽360°.

Method 6: the iodides were converted into the chlorides by heating them with a slight excess of silver chloride in water.

Methanesulphonates were similarly prepared, but only the theoretical amount of silver methanesulphonate was used.

NN′-*Di*-(2-*mercapto*-6-*methylpyrimidin*-4-*yl*)*ethylenediamine*.—2,4-Dimercapto-6-methylpyrimidine [2] (94 g.), ethylenediamine (21·6 ml.), and phenol (376 g.) were heated and stirred under reflux. Within 0·25 hr. a clear solution was obtained and hydrogen sulphide was evolved. After 2 hr. the mixture was cooled, diluted with ether (*ca.* 940 ml.), and filtered. The residual solid was extracted with warm 2N-hydrochloric acid (700 ml.), and the mixture was filtered and added dropwise to a stirred solution of sodium acetate (140 g.) in water (700 ml.). The gum which at first separated soon crystallised and was washed with water and ethanol, to give a granular yellow solid (64·5 g., 71%) which did not melt but blackened above 260°. It was further purified by again dissolving it in warm 2N-hydrochloric acid and precipitating it with sodium acetate. The *base* did not melt below 360° (Found: C, 45·0; H, 5·45; N, 25·9; S, 19·2; H_2O, 3·9. $C_{12}H_{16}N_6S_2,0{\cdot}75H_2O$ requires C, 44·8; H, 5·45; N, 26·1; S, 19·9; H_2O, 4·2%).

NN′-*Di*-(2-*methylthio*-6-*methylpyrimidin*-4-*yl*)*ethylenediamine*.—To the preceding dithiol (64·5 g.), dissolved in 2N-sodium hydroxide (645 ml.), was added methyl sulphate (51 ml.) during 40 min. The reaction was kept at 20—25° by gentle cooling and, after being stirred for a further 30 min., the solid which had separated was washed with water; recrystallisation from dimethylformamide gave the pure *base* (41·2 g., 58·5%) as cream needles, m. p. 275—277° (slight decomp.) (Found: C, 49·9; H, 6·2; N, 24·7; S, 18·7. $C_{14}H_{20}N_6S_2$ requires C, 50·0; H, 5·95; N, 25·0; S, 19·0%).

NN′-*Di*-(2-2′-*hydroxyethylamino*-6-*methylpyrimidin*-4-*yl*)*ethylenediamine*.—The preceding

[5] Ainley, Curd, Hepworth, Murray, and Vasey, *J.*, 1953, 59.

sulphide (27 g.), ethanolamine (27 ml.), and phenol (108 g.) were refluxed for 6 hr. The phenol was distilled out with steam, and the residual solution (*ca.* 70 ml.) was kept at 0° overnight. The solid was ground with 2N-sodium hydroxide, washed with water, and dried at 60°, to give the crude *base* (22 g., 75%), which melts at 85—90°, loses water, resolidifies, and remelts at 188°. Recrystallisation from aqueous ethanol gave the pure product as compact prisms (10·2 g., 35%), m. p. 187—189°.

NN′-*Diacetyl*-NN′-*di*-(2-*acetamido*-6-*methylpyrimidin*-4-*yl*)*ethylenediamine*.—A mixture of *NN*′-di-(2-amino-6-methylpyrimidin-4-yl)ethylenediamine (20 g.) and acetic anhydride (100 ml.) was refluxed for 30 min. The solution was cooled, and the pink solid which separated was filtered off, washed with a little ethanol, and dried at 90°, to give the crude product (19·0 g.), m. p. 229—232°. Recrystallisation from 50% aqueous ethanol gave the pure *acetyl derivative* as needles (14·1 g., 36·5%), m. p. 233—234° (Found: C, 54·2; H, 6·1; N, 25·0; Ac, 41·2. $C_{20}H_{26}N_8O_4$ requires C, 54·3; H, 5·9; N, 25·3; Ac, 38·9%).

NN′-*Di*-(4-*hydroxy*-6-*methylpyrimidin*-2-*yl*)*ethylenediamine Dihydrochloride*.—4-Hydroxy-6-methyl-2-methylthiopyrimidine [6] (60 g.), ethylenediamine (14 ml.), and phenol (180 g.) were refluxed for 3·5 hr. The cooled mixture was diluted with ether (500 ml.), and the solid was filtered off and refluxed with ethanol (500 ml.). The mixture was filtered, and the residue was dried at 90° to give the crude product (62 g.). This was dissolved in methanesulphonic acid (30 ml.) and water (270 ml.), and the solution was treated with charcoal and filtered. On addition of concentrated hydrochloric acid to the warmed filtrate the pure *hydrochloride* (44 g., 66%) separated and was washed with acetone; it had m. p. 323—325° (decomp.) (Found: C, 41·3; H, 5·4; Cl, 20·3; N, 24·0. $C_{12}H_{16}N_6O_2$,2HCl requires C, 41·3; H, 5·15; Cl, 20·3; N, 24·05%).

NN′-*Di*-(4-*chloro*-6-*methylpyrimidin*-2-*yl*)*ethylenediamine*.—The foregoing hydrochloride (43 g.) and phosphorus oxychloride (258 ml.) were refluxed for 3 hr. during which a clear solution was formed. After being cooled the solution was poured on ice and was then filtered from a trace of solid. The filtrate was basified with concentrated aqueous ammonia below 25°. The solid was washed with water and with ethanol, to give the crude product (24 g., 62%), m. p. 225—230°. The *chloro-compound* crystallised from 2-ethoxyethanol as colourless needles, m. p. 235—237° (Found: C, 46·6; H, 4·5; Cl, 22·7; N, 26·6. $C_{12}H_{14}Cl_2N_6$ requires C, 46·0; H, 4·5; Cl, 22·7; N, 26·8%).

NN′-*Di*-(4-*amino*-6-*methylpyrimidin*-2-*yl*)*ethylenediamine*.—Dry ammonia was passed during 8 hr. through a refluxing solution of *NN*′-di-(4-chloro-6-methylpyrimidin-2-yl)ethylenediamine (18·8 g.) in phenol (150·4 g.). The cooled solution was freed from phenol by steam-distillation; concentrated hydrochloric acid (10 ml.) was then added and the solution evaporated to dryness *in vacuo*. The hydrochloride was triturated with acetone, dissolved in water (117 ml.), and basified with 50% aqueous sodium hydroxide. The product separated and was crystallised from water (*ca.* 500 ml.), giving the pure *base* (12·4 g., 75%), m. p. 211—212°, as colourless needles (Found: C, 52·3; H, 7·1; N, 41·2. $C_{12}H_{18}N_8$ requires C, 52·5; H, 6·6; N, 40·9%).

NN′-*Di*-(4-*amino*-5-*nitropyrimidin*-2-*yl*)*ethylenediamine*.—This was prepared by method 1 from 4-amino-2-chloro-5-nitropyrimidine [7] (46 g.), ethylenediamine (9·7 ml.), and phenol (185 g.). The solid product was washed with water and dissolved in a mixture of concentrated hydrochloric acid (165 ml.) and water (215 ml.). The filtered solution was basified with concentrated aqueous ammonia (120 ml.). The buff solid was washed with water and ethanol and dried at 90°, to give the product (31·5 g., 71%) which did not melt below 360°. The *nitro-compound* could not be crystallised (Found: C, 35·6; H, 3·6; N, 40·75. $C_{10}H_{12}N_{10}O_4$ requires C, 35·75; H, 3·6; N, 41·6%).

NN′-*Di*-(2-*amino*-5,6-*dimethylpyrimidin*-4-*yl*)*ethylenediamine*.—This was similarly obtained from 2-amino-4-chloro-5,6-dimethylpyrimidine [8] (27·6 g.), ethylenediamine (6·5 ml.), and phenol (110·5 g.). It was purified by dissolution in warm N-hydrochloric acid (470 ml.), filtration, and basification whilst hot with concentrated aqueous ammonia. The *base* crystallised on cooling as white needles which were filtered off, washed with water, and dried at 90°, then having m. p. 299—300° (decomp.) (18 g., 69%) (Found: C, 55·8; H, 7·2; N, 37·2. $C_{14}H_{22}N_8$ requires C, 55·6; H, 7·3; N, 37·1%).

2-*Acetamido*-4-*hydroxy*-6-*methylpyrimidine*.—2-Amino-4-hydroxy-6-methylpyrimidine (90

[6] Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478.
[7] Brown, *J. Appl. Chem.*, 1952, **2**, 239.
[8] Schlenker, *Ber.*, 1901, **34**, 2812.

g.) in acetic anhydride (450 ml.) was refluxed for 1 hr. On cooling, a solid separated which was filtered off, washed with ethanol, and dried at 90°, to give the crude product (70 g., 58%), m. p. 218—221°. Crystallisation from ethanol gave the pure *acetamido-compound* as buff prisms, m. p. 220—221° (Found: C, 51·0; H, 5·5; N, 25·15. $C_7H_9N_3O_2$ requires C, 50·3; H, 5·4; N, 25·15%).

2-*Acetamido*-4-*chloro*-6-*methylpyrimidine*.—2-Acetamido-4-hydroxy-6-methylpyrimidine (65 g.) and phosphorus oxychloride (195 ml.) were refluxed for 10 min. The solution was cooled and poured on ice (*ca.* 1·5 kg.). The resulting solution was basified with concentrated aqueous ammonia and extracted with ether. Evaporation of the combined, dried, ethereal extracts gave a solid which was extracted with boiling water (*ca.* 300 ml.). The cooled aqueous extract deposited a solid (6·0 g.) which was filtered off and dried at 90°. It had m. p. 182—184°, undepressed on admixture with authentic 2-amino-4-chloro-6-methylpyrimidine. The aqueous mother-liquor was extracted with ether (3 × 50 ml.), and the combined extracts were dried and evaporated, giving a solid which crystallised from light petroleum (b. p. 60—80°) to give the pure *chloro-compound* (24·0 g.), m. p. 136·5—137° (Found: N, 22·5; Cl, 19·1. $C_7H_8ClN_3O$ requires N, 22·6; Cl, 19·1%).

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