417. *Polypurines. Part III.*[1] *Further Studies and Syntheses with αω-Dipurin-9-ylalkanes and Related Compounds.*

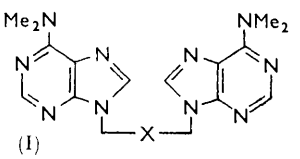
By J. H. Lister.

Analogues of 1,2-bis-(6-dimethylaminopurin-9-yl) ethane (CB 2685) have been made in an unsuccessful attempt to enhance the weak antitumour activity. A new cyclisation of 8-methylpurines and an efficient method of reducing chloro-5-nitropyrimidines are reported.

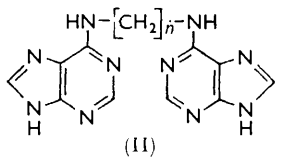
Because of the biological activity shown by the dipurin-9-ylethane (I; X = $[CH_2]_2$) (CB 2685),[2] which contains the purine portion of the antitumour antibiotic " puromycin," some related dipurinyl derivatives have now been made. It is relevant to this work that bispurines (II) have been reported,[3] of which the ethylenediamine derivative (II; $n = 2$) has cytostatic activity.

Two groups of compounds were prepared in order to try to associate some structural feature of the molecule with biological activity. In the first group the 6-dimethylaminopurine portion was retained but the length and nature of the chain were varied. In the second, the ethylene chain was present but a variety of purines was linked by it. A few bispurines in which both the chain length and the purine were altered will also be described.

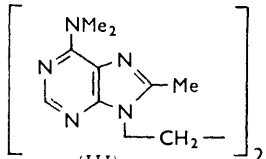
In the first series the chain was extended to three and four methylene units and varied to a branched chain analogue (·CHMe·CH_2·) by published methods.[2] No further extension of the chain length was considered although the hexamethylene derivative has already been prepared.[2] In one example the ethylene bridge was replaced by a *m*-phenylene group; this arrangement was shown by models to give the same spatial separation of the purines as in the ethylene-bridged derivative.



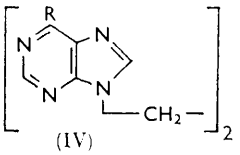
(I)



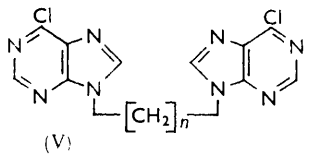
(II)



(III)



(IV)



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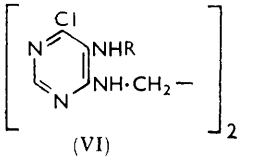


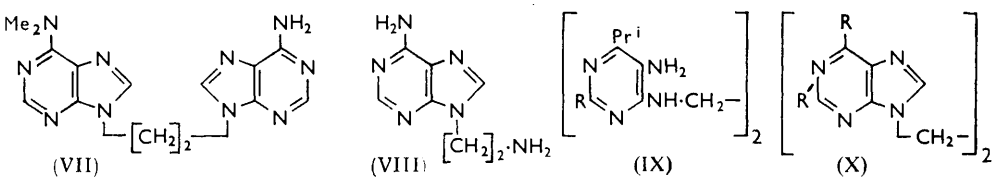
(VI)

In the second series the 8-methyl homologue (III) was originally prepared in poor yield by cyclisation of the corresponding bisaminopyrimidine in acetic anhydride. Later a nearly quantitative yield was obtained by using a mixture of *NN*-dimethylacetamide and phosphoryl chloride as cyclising agent—dimethylformamide and phosphoryl chloride were recently used to afford 8-unsubstituted purines.[4] Some 6-substituted purines were also synthesised. The diethylamino-homologue (IV; R = NEt_2) of CB 2685 could not be prepared by the route used for CB 2685 as the precursor, 4-chloro-6-diethylamino-5-nitropyrimidine, was not easily obtained. Also unsuccessful were attempts to replace directly the 6-amino-groups of the bisadenine (IV; R = NH_2) [2] by using diethylamine hydrochloride although this reaction has succeeded with adenine itself [5] and some aminopteridines [6] and -pyrimidines.[5] The final route to the required purine was by reaction

[1] Part II, Lister, *J.*, 1960, 3682.
[2] Lister, *J.*, 1960, 3394.
[3] Lettré and Ballweg, *Naturwiss.*, 1958, **45**, 364.
[4] Clark and Lister, *J.*, 1961, 5048.
[5] Whitehead and Traverso, *J. Amer. Chem. Soc.*, 1960, **82**, 3971.
[6] Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1648; Potter and Henshall, *J.*, 1956, 2000.

of diethylamine with the 6-chloropurine derivative (V; $n = 2$). This chloro-compound proved difficult to obtain initially as the standard cyclising reagent for chloropurines, triethyl orthoformate–acetic anhydride, when used with 1,2-di-(5-amino-4-chloropyrimidin-6-ylamino)ethane (VI; R = H) gave only the 5-acetamidopyrimidine (VI; R = Ac). This was confirmed by a comparison of the ultraviolet absorption spectrum with that of 5-acetamido-4-chloro-6-methylaminopyrimidine. The failure to effect cyclisation may be due to steric factors as the corresponding bischloropurine linked by a hexamethylene chain was readily obtained by this method. Ring closure of the 4,5-diaminopyrimidine was achieved with a good yield of purine (V; $n = 2$) by using *NN*-dimethylformamide and phosphoryl chloride.[4] This route was also used for the propane (V; $n = 3$) and butane (V; $n = 4$) homologues. Reaction of the chloropurine (V; $n = 2$) with diethylamine gave the diethylaminopurine (IV; R = NEt_2), and similarly obtained were the 6-alkylaminopurines (I; X = $[CH_2]_3$ and $[CH_2]_4$) and (IV; R = NHMe, NMe_2, and furfurylamino). The action of nitrous acid on the methylamine derivative (IV; R = NHMe) gave the *N*-nitrosomethylamino-derivative. The 6-mercaptopurine (IV; R = SH) was derived from the 6-chloropurine and thiourea, and with dimethyl sulphate it gave the methylthio-derivative (IV; R = SMe). Dehalogenation of the chloropyrimidine (VI; R = H) over palladium and cyclisation of the product gave the parent member (IV; R = H) of the series.

The unsymmetrical dipurinylethane (VII) was obtained (*a*) by condensing 9-2′-aminoethyladenine[7] (VIII) with 4-chloro-6-dimethylamino-5-nitropyrimidine followed by reduction and cyclisation in dimethylformamide, and (*b*) by interaction of 4-amino-6-2′-aminoethylamino-5-nitropyrimidine and 4-chloro-6-dimethylamino-5-nitropyrimidine and then simultaneous reduction and cyclisation of both pyrimidines.



By preparing the analogue of CB 2685, in which the 6-dimethylamino-group was replaced by an isopropyl group, a molecule possessing the same dimensional envelope but a less basic nature was obtained. 2,4-Dichloro-6-isopropyl-5-nitropyrimidine prepared by the standard route from 4-isopropyl-2-thiouracil,[8] was condensed with ethylene diamine and reduced to the 5-aminopyrimidine (IX; R = Cl). Catalytic reduction removed the halogen and the amine (IX; R = H) was converted into the purine (X; R = Pr^i, R′ = H) with acetic anhydride–triethyl orthoformate. The chloroamine (IX; R = Cl) was similarly cyclised to the 2-chloropurine (X; R = Pr^i, R′ = Cl) which resisted all attempts to dehalogenate it. The 2-dimethylaminopurine (X; R = Pr^i, R′ = NMe_2) was also prepared.

The above route was used to obtain the di-6-methylpurinylethane (X; R = Me, R′ = H) and its 2-chloro-derivative (X; R = Me, R′ = Cl), starting from 2,4-dichloro-6-methyl-5-nitrouracil, and also the 6-trifluoromethylpurine (X; R = CF_3, R′ = Cl) from 6-trifluoromethyluracil.[9]

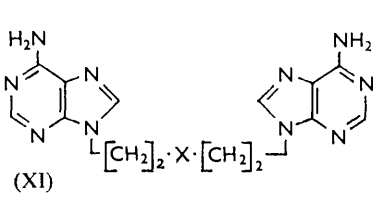
Some polyadeninyl derivatives were investigated. Interaction of diethylenetriamine and 4-amino-6-chloro-5-nitropyrimidine and subsequent reduction and cyclisation gave the bisadeninyl derivative (XI; X = >N·CHO) which with alkali was deformylated to

[7] Lister and Timmis, *J.*, 1960, 327.
[8] Anderson, Halverstadt, Miller and Roblin, *J. Amer. Chem. Soc.*, 1945, **67**, 2197.
[9] Miller, Dessert, and Anderson, *J. Amer. Chem. Soc.*, 1948, **70**, 500.

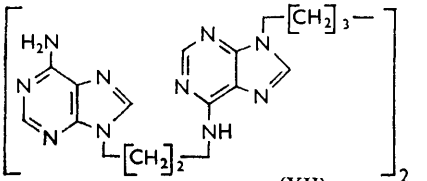
the parent (XI; X = >NH) in which the adenine groups were linked by a " nitrogen-mustard "-type chain. Two molecules of 9-2′-aminoethyladenine (VIII) were condensed with oxalyl chloride, producing the oxamide derivative (XI; X = HN·[CO]$_2$·NH).

Use has been made of the 9-2′-aminoethyladenine (VIII) to give the " tetra-adenine " (XII) by condensation with 1,6-di-(6-chloropurin-9-yl)hexane.[2] This chloropurine, with ethylenediamine, affords the " polyadenine " (XIII). All the adenine derivatives described above showed some degree of structural hydration.

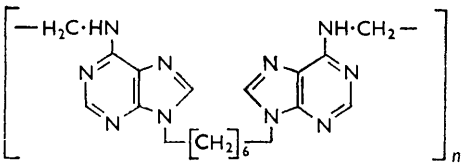
During the above work it was found that dichloro-5-nitropyrimidines were readily reduced, under mild conditions, by stannous chloride in ethanolic hydrochloric acid.



(XI)



(XII)



(XIII)

This procedure, previously used [10] only once in this series, gave good yields of 5-amino-4,6-dichloro- and 5-amino-2,4-dichloro-6-methyl-pyrimidine from their respective 5-nitropyrimidines. The method is quicker and simpler than the published methods involving catalytic hydrogenation [2] or alkaline ferrous sulphate.[11]

Experimental

Details of most of the *products* are given in the Tables.

1,2-*Bis*-(6-*dimethylamino*-8-*methylpurin*-9-*yl*)*ethane* (III).—(*a*) The 1,2-di-(5-amino-4-dimethylaminopyrimidin-6-ylamino)ethane [2] (2·1 g.) in acetic anhydride (25 ml.) was heated under reflux for 4 hr. After evaporation the residue was taken up in water (8 ml.) and treated with 10N-sodium hydroxide (4 ml.), and the buff precipitate (0·6 g., 25%) was filtered off and washed with acetic acid and water. Crystallisation from the minimum of ethanol (charcoal) gave the 8-*methylpurine derivative*, m. p. 240—241° (Found: C, 57·0; H, 6·4; N, 36·8. $C_{18}H_{24}O_{10}$ requires C, 56·8; H, 6·4; N, 36·8%).

(*b*) A mixture of 1,2-di-(5-amino-4-dimethylaminopyrimidin-6-ylamino)ethane (0·35 g.) in *NN*-dimethylacetamide (4 ml.) was treated with phosphoryl chloride (0·75 ml.) with cooling. After 2 hr. the mixture was evaporated and the residue treated with ice–water and made alkaline with ammonia solution. 1,2-Bis-(6-dimethylamino-8-methylpurin-9-yl)ethane (0·37 g., 92%) was obtained, identical in m. p. and infrared spectrum with the preceding specimen.

1,2-*Di*-(6-N-*methyl*-N-*nitrosoaminopurin*-9-*yl*)*ethane* (IV; R = NMe·NO).—1,2-Di-(6-methylaminopurin-9-yl)ethane (0·8 g.) in 2N-hydrochloric acid (20 ml.) was treated dropwise with sodium nitrite (0·35 g.) in water (5 ml.) and then brought to the b. p. The pH of the cooled solution was brought to 8 with ammonia solution. The *di*-N-*methyl*-N-*nitrosoaminopurine* which was precipitated crystallised from propan-1-ol (see Table 1).

1,2-*Di*-(4-*chloro*-5-*formamidopyrimidin*-6-*ylamino*)*ethane* (VI; R = CHO).—The di-5-aminopyrimidinylaminoethane (1·65 g.) was heated in 100% formic acid (5 ml.) on a water-bath for 20 min. After cooling, the *product* was filtered off and recrystallised (Table 1).

1,2-*Di*-(5-*formamido*-4-*methylaminopyrimidin*-6-*ylamino*)*ethane*.—This *amide* was prepared

[10] Bitterli and Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 835.
[11] Brown, *J. Appl. Chem.*, 1954, **4**, 72.

TABLE 1.

αω-Di(pyrimidin-6-ylamino)alkanes.

No.	Substituents 2-	4-	5-	X	M. p. (corr.)	Solvent §	Prep.*	Yield (%)
1	H	H	NH_2	$[CH_2]_2$	255—257°	Aq.H·CO·NMe_2	E	60
2	H	Cl	NH_2	$[CH_2]_2$	275—280	Aq.H·CO·NMe_2	C	49
3	H	Cl	NH·CHO	$[CH_2]_2$	250 †	Aq.H·CO·NMe_2	—	31
4	H	Cl	NH·Ac	$[CH_2]_2$	260 †	Aq.H·CO·NMe_2	—	45
5	H	Cl	NH_2	$[CH_2]_3$	104—106 †	Aq.Cell.	C	86
6	H	Cl	NH_2	$[CH_2]_4$	213—214	Aq.Cell.	C	83
7	H	Cl	NH_2	CHMe·CH_2	247—249	Dioxan	C	35
8	H	Me	NH_2	$[CH_2]_2$	300 †	Aq.H·CO·NMe_2	E	63
9	Cl	Me	NO_2	$[CH_2]_2$	234—236	AcOEt	A	48
10	Cl	Me	NH_2	$[CH_2]_2$	275 †	Aq.H·CO·NMe_2	B, C	26, 59
11	H	Pr^i	NH_2	$[CH_2]_2$	285 †	Aq.H·CO·NMe_2	E	79
12	Cl	Pr^i	NO_2	$[CH_2]_2$	238—240	Bu^nOH	A	67
13	Cl	Pr^i	NH_2	$[CH_2]_2$	265 †	Aq.Dioxan	B	96
14	NMe_2	Pr^i	NO_2	$[CH_2]_2$	195—197	Bu^nOH	D	96
15	Cl	CF_3	NH_2	$[CH_2]_2$	>300	Aq.Dioxan	C	54
16	H	NMe_2	NH·CHO	$[CH_2]_2$	210—212	MeOH	—	47
17	H	NMe_2	NO_2	$[CH_2]_3$	150—151	MeOH	A	62
18	H	NMe_2	NH_2	$[CH_2]_3$	139—141	H_2O	B	94
19	H	NMe_2	NO_2	$[CH_2]_4$	236—237	Aq.Dioxan	A	65
20	H	NMe_2	NH_2	$[CH_2]_4$	235—236	Aq.H·CO·NMe_2	B	58
21	H	NMe_2	NO_2	CHMe·CH_2	116—118	Pr^nOH	A	57
22	H	NMe_2	NH_2	CHMe·CH_2	201—202	Aq.MeOH	B	13
23	H	NMe_2	NO_2	*m*-C_6H_4	202—203	Aq.Dioxan	A	55
24	H	NMe_2	NO_2	NH(CH_2·CH_2–)$_2$	128—130	Pr^nOH	A	27
25	H	NH_2	NO_2	NH(CH_2·CH_2–)$_2$	221—222	Dioxan	A	82
26	H	NH_2	NH_2	NH(CH_2·CH_2–)$_2$	135 †‡	EtOH	B	—

* A, Condensation of 4-chloro-5-nitropyrimidine with the αω-diaminoalkane. B, Catalytic reduction of the di-5-nitropyrimidinylalkane. C, Condensation of the 5-amino-4-chloropyrimidine with the αω-diaminoalkane. D, Action of dimethylamine on the di-2-chloro-5-nitropyrimidinylalkane. E, Catalytic dechlorination with palladium–charcoal of the appropriate di-(2- or 4-chloro-5-aminopyrimidinyl)alkane. † With decomp. ‡ Picrate. § Cell. = Cellosolve (EtO·$[CH_2]_2$·OH).

No.	Found (%) C	H	N	Formula	Required (%) C	H	N
1	46·8	5·4	—	$C_{10}H_{14}N_8,\frac{1}{2}H_2O$	47·1	5·9	—
2	37·9	3·9	35·5	$C_{10}H_{12}Cl_2N_8$	38·1	3·8	35·6
3	39·2	3·0	30·2	$C_{12}H_{12}Cl_2N_8O_2$	38·8	3·3	30·2
4	42·4	4·0	28·2	$C_{14}H_{16}Cl_2N_8O_2$	42·1	4·0	28·1
5	37·5	4·9	32·5	$C_{11}H_{14}Cl_2N_8,H_2O$	38·0	4·7	32·3
6	42·5	4·7	32·4	$C_{12}H_{16}Cl_2N_8$	42·0	4·7	32·7
7	41·6	4·8	30·4	$C_{11}H_{14}Cl_2N_8,\frac{1}{2}C_4H_8O_2$	41·8	4·9	30·0
8	52·5	6·2	40·5	$C_{12}H_{18}N_8$	52·5	6·6	40·9
9	35·4	2·9	27·3	$C_{12}H_{12}Cl_2N_8O_4$	35·7	3·0	27·8
10	41·9	5·1	32·1	$C_{12}H_{16}Cl_2N_8$	42·0	4·7	32·7
11	57·7	7·6	33·9	$C_{16}H_{26}N_8$	58·2	7·9	33·9
12	41·4	4·2	23·8	$C_{16}H_{20}Cl_2N_8O_4$	41·8	4·4	24·4
13	47·9	6·0	28·3	$C_{16}H_{24}Cl_2N_8$	48·1	6·1	28·1
14	50·2	6·5	29·7	$C_{20}H_{32}N_{10}O_4$	50·4	6·8	29·4
15	34·0	2·8	25·4	$C_{12}H_{10}Cl_2F_6N_8$	33·9	2·3	24·8
16	49·4	6·2	36·2	$C_{16}H_{24}N_{10}O_2$	49·5	6·2	36·2
17	44·3	5·4	34·0	$C_{15}H_{22}N_{10}O_4$	44·3	5·5	34·5
18	51·8	7·3	40·0	$C_{15}H_{26}N_{10}$	52·0	7·6	40·4
19	45·9	5·6	32·9	$C_{16}H_{24}N_{10}O_4$	45·7	5·8	33·3
20	53·0	7·6	38·5	$C_{16}H_{28}N_{10}$	53·3	7·8	38·9
21	44·4	5·4	34·7	$C_{15}H_{22}N_{10}O_4$	44·3	5·5	34·5
22	51·9	7·4	39·9	$C_{15}H_{26}N_{10}$	52·0	7·6	40·4
23	49·3	4·6	—	$C_{18}H_{20}N_{10}O_4$	49·1	4·6	—
24	45·0	5·5	33·1	$C_{16}H_{25}N_{11}O_4,\frac{1}{2}C_3H_8O$	45·3	6·1	33·2
25	38·0	4·5	40·2	$C_{12}H_{17}N_{11}O_4$	38·0	4·5	40·6
26	35·6	3·6	—	$C_{12}H_{21}N_{11},3C_6H_3N_3O_7$	35·8	3·0	—

Cl analyses: No. 3, found 19·0, reqd. 19·1%; No. 4, found 17·8, reqd. 17·8%; No. 7, found 19·0, reqd. 19·0%; No. 9, found 17·5, reqd. 17·6%; No. 12, found 15·6, reqd. 15·4%.

TABLE 2.

αω-Dipurin-9-ylalkanes.

No.	Subst. 2-	Subst. 6-	X	M. p. (corr.)	Solvent	Prep.*	Yield (%)
1	H	H	$[CH_2]_2$	308—310°	Aq.H·CO·NMe_2	B	52
2	H	Cl	$[CH_2]_2$	284—286	Pr^nOH	C	82
3	H	Cl	$[CH_2]_3$	240—242	Aq.H·CO·NMe_2	C	55
4	H	Cl	$[CH_2]_4$	251—253	Aq.H·CO·NMe_2	C	58
5	H	Me	$[CH_2]_2$	207—208	Aq.H·CO·NMe_2	B	34
6	Cl	Me	$[CH_2]_2$	284—287	Bu^nOH	B	18
7	H	Pr^i	$[CH_2]_2$	184—186	Me_2CO	B	30
8	Cl	Pr^i	$[CH_2]_2$	211—213	EtOH	B	25
9	NMe_2	Pr^i	$[CH_2]_2$	136—137	Aq.EtOH	A	52
10	Cl	CF_3	$[CH_2]_2$	260 †	Aq.H·CO·NMe_2	C	88
11	H	NMe_2	$[CH_2]_3$	221—222	MeOH	A	73
12	H	NMe_2	$[CH_2]_4$	224—226	MeOH	A	70
13	H	NMe_2	$CHMe·CH_2$	160—161	AcOEt	A	26
14	H	NMe_2	*m*-C_6H_4	264—265	Dioxan	A	31
15	H	NEt_2	$[CH_2]_2$	165—166	Aq.EtOH	D	77
16	H	NH·Me	$[CH_2]_2$	285 †	Pr^nOH	D	85
17	H	NMe·NO	$[CH_2]_2$	210 †	Pr^nOH	—	66
18	H	NH·C_6H_5O	$[CH_2]_2$	253—255	EtO·$[CH_2]_2$·OH	D	92
19	H	SH	$[CH_2]_2$	>350 †	NaOH–AcOH	D	98
20	H	SMe	$[CH_2]_2$	219—221	EtOH	—	79
21	H	OH	$[CH_2]_3$	>350 †	NaOH–AcOH	E	—
22	H	NH_2	OHC·$N(CH_2·CH_2–)_2$	300 †	H_2O	A	—
23	H	NH_2	$NH(CH_2·CH_2–)_2$	260—261	H_2O	—	—

* A, H·CO·NH_2–HCl. B, H·$C(OEt)_3$–Ac_2O. C, H·CO·NMe_2–$POCl_3$. D, From 1,2-di-(6-chloropurin-9-yl)ethane. E, Acid hydrolysis of 1,3-di-(6-chloropurin-9-yl)propane. † With decomp.

No.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
1	54·3	3·8	41·8	$C_{12}H_{10}N_8$	54·1	3·8	42·1
2	43·5	2·6	33·6	$C_{12}H_8Cl_2N_8$	43·0	2·4	33·5
3	44·7	2·9	31·8	$C_{13}H_{10}Cl_2N_8$	44·7	2·9	32·1
4	46·5	3·3	30·6	$C_{14}H_{12}Cl_2N_8$	46·3	3·3	30·9
5	55·4	5·0	36·9	$C_{14}H_{14}N_8,\frac{1}{2}H_2O$	55·5	5·0	37·0
6	46·6	3·4	30·4	$C_{14}H_{12}Cl_2N_8$	46·3	3·3	30·9
7	61·4	6·4	32·0	$C_{18}H_{22}N_8$	61·7	6·3	32·0
8	51·7	4·9	26·4	$C_{18}H_{20}Cl_2N_8$	51·6	4·8	26·7
9	60·3	7·6	32·1	$C_{22}H_{32}N_{10}$	60·4	7·4	32·2
10	36·4	1·6	24·1	$C_{14}H_6Cl_2F_6N_8$	35·7	1·4	23·8
11	55·8	6·3	37·8	$C_{17}H_{22}N_{10}$	55·7	6·1	38·2
12	56·5	6·1	36·5	$C_{18}H_{24}N_{10}$	56·8	6·4	36·8
13	55·8	6·1	38·4	$C_{17}H_{22}N_{10}$	55·7	6·1	38·2
14	60·2	5·0	34·8	$C_{20}H_{20}N_{10}$	60·0	5·0	35·0
15	58·6	6·5	34·3	$C_{20}H_{28}N_{10}$	58·8	6·9	34·3
16	50·9	5·0	43·0	$C_{14}H_{16}N_{10},\frac{1}{2}H_2O$	50·5	5·1	42·0
17	45·5	4·4	41·4	$C_{14}H_{14}N_{12}O_2,\frac{1}{2}C_3H_8O$	45·2	4·4	40·8
18	57·7	4·6	30·2	$C_{22}H_{20}N_{10}O_2$	57·9	4·4	30·7
19	42·4	2·8	33·0	$C_{12}H_{10}N_8S_2,\frac{1}{2}H_2O$ ‡	42·5	3·3	33·0
20	46·8	3·9	31·2	$C_{14}H_{14}N_8S_2$	46·9	3·9	31·3
21	49·7	4·0	35·7	$C_{13}H_{12}N_8O_2$	50·0	3·9	35·9
22	47·8	4·7	41·1	$C_{15}H_{17}N_{11}O,\frac{1}{2}H_2O$	47·8	4·8	40·9
23	48·7	4·9	43·9	$C_{14}H_{17}N_{11},\frac{1}{2}H_2O$	48·3	5·2	44·2

‡ S: Found, 18·8. Required, 18·9%.

by heating the bis-5-aminopyrimidine derivative (1·2 g.) with 100% formic acid (8 ml.) for 90 min., then evaporating the solution to dryness and crystallising the residue (Table 1).

9-2′-(4-*Dimethylamino*-5-*nitropyrimidin*-6-*ylamino*)*ethyladenine*.—A suspension of 9-2′-aminoethyladenine [7] (1·7 g.) and 4-chloro-6-dimethylamino-5-nitropyrimidine (2 g.) in water (40 ml.) containing triethylamine (4 ml.) was heated under reflux for 2 hr. The residue obtained on evaporation was extracted with hot ethanol (250 ml.), and the extracts were concentrated to

50 ml. Recrystallisation from ethanol gave the lemon-yellow *product* (2·3 g., 70%), m. p. 245—248° (Found: C, 45·5; H, 4·6; N, 40·4. $C_{13}H_{16}N_{10}O_2$ requires C, 45·3; H, 4·7; N, 40·7%).

9-2′-(5-*Amino*-4-*dimethylaminopyrimidin*-6-*ylamino*)*ethyladenine*.—The above nitro-derivative (2·2 g.) in N-hydrochloric acid was hydrogenated over 5% palladium–charcoal. The solution was filtered, made alkaline with ammonia solution, and evaporated. Crystallisation of the residue from water gave the 5-*aminopyrimidine* (0·8 g., 40%) as colourless prisms, m. p. 266—268° (Found: C, 49·1; H, 5·4; N, 44·0. $C_{13}H_{18}N_{10}$ requires C, 49·6; H, 5·8; N, 44·5%).

1-(6-*Aminopurin*-9-*yl*)-2-(6-*dimethylaminopurin*-9-*yl*)*ethane* (VII).—The 5-aminopyrimidinyl derivative (0·7 g.) from the preceding preparation was cyclised in formamide (5 ml.) and concentrated hydrochloric acid (0·5 ml.) at 170°. On addition of water a crystalline *dipurinyl derivative* (0·6 g., 62%) was obtained. Purification was by precipitation from dilute acid with 10N-sodium hydroxide, giving an amorphous powder, m. p. 250° (Found: C, 50·7; H, 4·7; N, 42·1. $C_{14}H_{16}N_{10},\frac{1}{2}H_2O$ requires C, 50·5; H, 5·1; N, 42·0%).

1-(4-*Amino*-5-*nitropyrimidin*-6-*ylamino*)-2-(4-*dimethylamino*-5-*nitropyrimidin*-6-*ylamino*)-*ethane*.—A suspension of 4-amino-6-2′-aminoethylamino-5-nitropyrimidine (2·5 g.) and 4-chloro-6-dimethylamino-5-nitropyrimidine (2·5 g.) in water (100 ml.) containing triethylamine (6 ml.) was heated under reflux for 90 min. The precipitate obtained (3·2 g., 71%) on cooling was recrystallised from aqueous dioxan. The *bis*-5-*nitropyrimidine* had m. p. 237—239° (Found: C, 39·5; H, 4·3. $C_{12}H_{16}N_{10}O_4$ requires C, 39·6; H, 4·4%).

1-(5-*Amino*-4-*dimethylaminopyrimidin*-6-*ylamino*)-2-(4,5-*diaminopyrimidin*-6-*ylamino*)-*ethane*.—The bisnitropyrimidine derivative (3·2 g.) was hydrogenated in 2N-hydrochloric acid (100 ml.) over 5% palladium.charcoal (2 g.). After filtration and evaporating the hydrochloride (3·3 g.) obtained was treated with an excess of sodium hydroxide solution. The *bisdiaminopyrimidine derivative* was obtained as colourless needles, m. p. 232—234° from water (Found: C, 47·1; H, 6·2. $C_{12}H_{20}N_{10}$ requires C, 47·2; H, 6·6%).

NN′-*Di*-[2-(6-*aminopurin*-9-*yl*)*ethyl*]*oxamide* (XI; X = NH·CO·CO·HN).—A solution of 9-2′-aminoethyladenine (0·5 g.) in dry dioxan (40 ml.) containing a trace of pyridine was treated dropwise with oxalyl chloride (0·2 g.). After 30 min. at the b. p. the solution was cooled and triethylamine (5 ml.) was added. Evaporation, and washing of the residue with ethanol, gave the crude product (0·28 g., 48%). The *bispurine derivative*, m. p. 300°, was obtained pure by precipitation from acetic acid with ammonia solution (Found: C, 45·4; H, 4·8; N, 40·6. $C_{16}H_{18}N_{12}O_2,\frac{1}{2}H_2O$ requires C, 45·8; H, 4·6; N, 40·1%).

" *Tetra-adenine Derivative* " (XII).—9-2′-Aminoethyladenine (0·45 g.) and 1,6-di-(6-chloropurin-9-yl)hexane [2] (0·5 g.) in water (10 ml.) containing triethylamine (2 ml.) were heated under reflux for 2 hr. The *product* (0·75 g., 86%), m. p. 295° (decomp.), separated on cooling and was purified by precipitation from acetic acid by 2N-ammonia (Found: C, 52·4; H, 5·2; N, 39·6. $C_{30}H_{34}N_{20},H_2O$ requires C, 52·0; H, 5·2; N, 40·4%).

" *Polyadenine* " *Derivative* (XIII).—A suspension of 1,6-di-(6-chloropurin-9-yl)hexane (0·45 g.) in water (20 ml.) and triethylamine (4 ml.) was heated with ethylenediamine (0·08 g.) for 2·5 hr. After cooling, the *product* (0·38 g.) was filtered off and reprecipitated from acetic acid with 2N-ammonia. The material did not melt below 300° and was equilibrated with the atmosphere for analysis (Found: C, 55·1; H, 5·9; N, 34·7. $[C_9H_{11}N_5,\frac{1}{2}H_2O]_n$ requires C, 55·4; H, 6·1; N, 35·3%).

5-*Acetamido*-4-*chloro*-6-*methylaminopyrimidine*. — 5-Amino-4-chloro-6-methylaminopyrimidine [11] (0·8 g.) was kept at room temperature in acetic anhydride (20 ml.) for 2 hr. 5-*Acetamido*-4-*chloro*-6-*methylaminopyrimidine* (0·8 g., 78%), m. p. 232—234°, that separated was recrystallised from butan-1-ol (Found: C, 41·8; H, 4·4; N, 28·1. $C_6H_7ClN_4O$ requires C, 41·9; H, 4·5; N, 27·9%).

2,4-*Dichloro*-6-*isopropyl*-5-*nitrouracil*.—4-Isopropyluracil [12] was nitrated in 1 : 1 v/v sulphuric acid–nitric acid (*d* 1·5) at 7—10°. The product, obtained by pouring the mixture on ice, recrystallised from water, giving 4-*isopropyl*-5-*nitrouracil* (75%) as yellow prisms, decomp. >230° (Found: C, 42·1; H, 4·7; N, 20·8. $C_7H_9N_3O_4$ requires C, 42·2; H, 4·6; N, 21·1%). Chlorination, by the method of Baddiley and Topham,[13] gave 2,4-*dichloro*-6-*isopropyl*-5-*nitropyrimidine* (77%), m. p. 37°, distilled at 134—136°/12 mm. (Found: C, 35·6; H, 3·1; N, 17·7. $C_7H_7Cl_2N_3O_2$ requires C, 35·6; H, 3·0; N, 17·8%).

5-*Aminodichloropyrimidines*.—The dichloro-5-nitropyrimidines in ethanol were treated

[12] Evans, Jones, Palmer, and Stephens, *J.*, 1956, 4106.
[13] Baddiley and Topham, *J.*, 1944, 678.

with a solution of stannous chloride in hydrochloric acid.[10] The 5-aminopyrimidines were obtained in >80% yields.

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CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL,
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