62. *Potential Anti-purines. Part III.*[1] *Some 9-Dialkylamino-alkyl-purines and -8-azapurines.*

By J. H. Lister and G. M. Timmis.

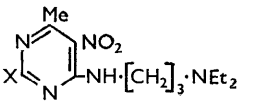
The synthesis is described of purines and 8-azapurines substituted at the 9-position with ω-dialkylaminoalkyl groups. Some related ω-hydroxy- and ω-amino-alkylpurines are included. Absorption spectra are recorded and discussed.

Antimalarial compounds of the mepacrine and chloroquine types, which are derivatives of acridine and quinoline respectively, have been shown [2] readily to penetrate the cell and to be localised on the nucleic acid. An essential feature of the structure of these antimalarials is a basic side chain, and since interference at some stage of the biosynthesis of nucleic acid may be an essential requisite in the chemotherapy of the malignant cell, we have prepared purines and 8-azapurines bearing such side chains in the hope that these derivatives would be readily assimilated into the cell. By analogy with the naturally occurring nucleosides we have also attached 2-hydroxyethyl and 3-hydroxypropyl groups at the 9-position of the purine.

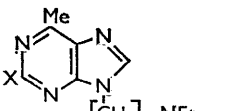
Two series of purines were prepared, both having a two- or three-carbon chain at the 9-position terminating in a basic or a hydroxyl group.

In the first series, based upon 6-methylpyrimidine, the purines were usually liquids or low-melting solids and the intermediates were unstable. The other series, being derivatives of adenine, had higher melting points, and the intermediates were more stable; in this series the corresponding 8-azapurines were also prepared.

6-*Methylpurines.*—Condensing 2 equivalents of 3-diethylaminopropylamine with 2,4-dichloro-6-methyl-5-nitropyrimidine in ether gave a solution containing 2-chloro-4-3′-diethylaminopropylamino-6-methyl-5-nitropyrimidine (I; X = Cl). This compound was not isolated but was caused to react at the 2-position with an excess of an amine, yielding



(I)



(II)

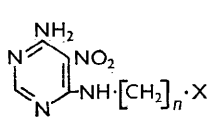
the nitropyrimidines (I; X = NH·$[CH_2]_3$·NEt_2 and X = NH_2). On catalytic reduction over Raney nickel these gave gums: the 5-amino-2-diethylaminopropylaminopyrimidine was isolated as the tripicrate, and the 2,5-diamino-derivative was purified by distillation. Ring closure with formamide in the presence of hydrochloric acid gave the purines (II; X = NH·$[CH_2]_3$·NEt_2) as a viscous oil and (II; X = NH_2) as a low-melting solid, both somewhat hydrated.

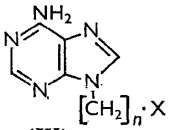
Adenine Derivatives.—These were prepared similarly, from 4-amino-6-chloro-5-nitropyrimidine in ethanol (see Table 1). In the case of compound (III; $n = 2$, X = NH_2) the addition procedure was reversed, the chloropyrimidine being added to an ethanolic solution of ethylenediamine. Reduction was smoothly accomplished in ethanol with hydrogen and Raney nickel to the 4,5,6-triaminopyrimidines (Table 2), which were light-sensitive and unstable. These gave the corresponding purines (IV) (Table 3) on treatment with formamide and hydrochloric acid.

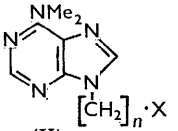
A few derivatives of 6-dimethylaminopurine were also made, these being analogues of the base of Puromycin. By starting with 4-chloro-6-dimethylamino-5-nitropyrimidine [3] and using the above conditions 9-diethylaminopropyl-6-dimethylaminopurine

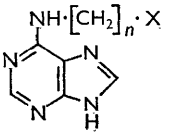
[1] Part II, Leese and Timmis, *J.*, 1958, 4107.
[2] Parker and Irvin, *J. Biol. Chem.*, 1952, **199**, 897.
[3] Rose, *J.*, 1954, 4116.

(V; $n = 3$, X = NEt_2) was obtained as a distillable oil. The hydroxyethylpurine (V; $n = 2$, X = OH) was formed as its acetate after ring closure with an ethyl orthoformate–acetic anhydride mixture and recovered therefrom by treatment with aqueous alkali. Attempts to prepare the aminoethylpurine (V; $n = 2$, X = NH_2) were not successful as the initial condensation of ethylenediamine with the nitropyrimidine gave only the ethylenediamine derivative (VII). The alkali-treatment used during the isolation of the majority of the purines removed the risk of contamination by the isomeric 6-(substituted amino)purines (VI) which could have been formed by the alternative ring closure across the two primary amino-groups.


(III)

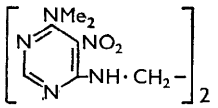

(IV)

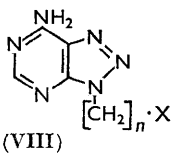

(V)

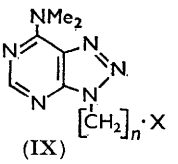

(VI)

The action of thionyl chloride on the hydroxyethyl- and hydroxpropyl-purine (IV; $n = 2$ and 3 respectively, X = OH) gave the chloroalkyl derivatives (IV; $n = 2$ and 3, X = Cl) which were of interest as possible cytotoxic agents in view of their relation to the " nitrogen mustards."

From the above 4,5-diaminopyrimidine intermediates 8-azapurines (Table 4) were obtained by the action of cold nitrous acid, namely, (VIII; $n = 3$, X = NMe_2 and NEt_2; $n = 2$ and 3, X = OH) and (IX; $n = 3$, X = NEt_2; $n = 2$, X = OH).


(VII)


(VIII)


(IX)

The ultraviolet absorption spectra of aqueous solutions confirmed the structures of the above adenine derivatives. There was no change in the curves between pH 7 and 12, a single peak in the region 260—261 mμ being exhibited, but at lower pH a slight shift to shorter wavelengths was observed. This indication of the lack of an anionic centre is reminiscent of the behaviour of 9-methyladenine [4] under the same conditions. On the other hand, the isomeric 6-dialkylaminoalkylaminopurines have been reported [5] and show similar spectra to those of 6-methylaminopurine [6] which absorbs at higher wavelengths than the 9-substituted isomers. The anionic centre is apparent in the similar spectra at pH 2 and 7 and in the shift to longer wavelengths in alkaline solution.

The spectra of the 8-aza-adenines are likewise unaltered curves between pH 7 and pH 12, but the maxima are at much longer wavelengths (278 mμ) than those of the corresponding adenines. At lower pH the region of maximum absorption is at shorter wavelengths (262—263 mμ) and is close to that of the above adenines.

For both the purines and the azapurines replacement of the 6-amino- by a dimethylamino-group generally moves the peaks to longer wavelengths.

Experimental

Analyses are by Mr. P. R. W. Baker, Beckenham.

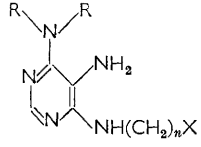
2,4-Bis-3'-diethylaminopropylamino-6-methyl-5-nitropyrimidine (I; X = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$). —To a solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (10 g.) in ether (150 ml.) was added

[4] Robins and Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490.
[5] Skinner, Shive, Ham, Fitzgerald, and Eakin, *ibid.*, 1956, **78**, 5097.
[6] Mason, *J.*, 1954, 2071.

TABLE 1. *Pyrimidines, as* (III) *but with* NH_2 *varied.*

4-Subst.	X	*n*	M. p.	Solvent	Found (%) C	H	N	Formula	Required (%) C	H	N	Yield (%)
NH_2	NH_2	2	195—197°	H_2O	36·6	5·2	42·0	$C_6H_{10}O_2N_6$	36·4	5·1	42·4	88
NH_2	NMe_2	3	156—157	H_2O	45·0	6·7	35·0	$C_9H_{16}O_2N_6$	45·0	6·7	35·0	63
NH_2	NEt_2	3	127—128	EtOH	49·5	7·4	31·2	$C_{11}H_{20}O_2N_6$	49·2	7·4	31·2	98
NMe_2	NEt_2	3	174—176 (picrate)	Aq. EtOH	43·0	5·0	—	$C_{13}H_{24}O_2N_6,C_6H_3O_7N_3$	43·4	5·2	—	—
NH_2	OH	2	212—213	H_2O	36·4	4·7	34·8	$C_6H_9O_3N_5$	36·2	4·6	35·2	92
NMe_2	OH	2	127	EtOH	42·0	5·6	31·0	$C_8H_{13}O_3N_5$	42·3	5·8	30·8	88
NH_2	OH	3	175—176	H_2O	39·5	5·0	32·6	$C_7H_{11}O_3N_5$	39·4	5·2	32·9	97

TABLE 2. *Triamines formed by reduction of the 5-nitro-group in the pyrimidines of Table* 1.



4-Subst.	X	*n*	M. p.	Solvent	Found (%) C	H	N	Formula	Required (%) C	H	N	Yield (%)
NH_2	NH_2	2	270°	Aq. PrOH	29·9	5·7	34·8	$C_6H_{12}N_6,2HCl$ [a]	29·9	5·8	34·9	—
NH_2	NMe_2	3	120—122	EtAc	51·5	8·5	40·1	$C_9H_{18}N_6$	51·4	8·6	40·0	97
NH_2	NEt_2	3	123—125	CCl_4	54·3	8·7	34·2	$C_{11}H_{22}N_6,\frac{1}{4}H_2O$	54·5	9·3	34·6	76
NMe_2	NEt_2	3	85—88	Pet [b]	56·7	9·7	30·4	$C_{13}H_{26}N_6,\frac{1}{2}H_2O$	56·7	9·9	30·6	—
NH_2	OH [c]	2	127—128	Dioxan	42·3	6·9	40·6	$C_6H_{11}ON_5$	42·6	6·6	41·4	98
NMe_2	OH	2	119—120	C_6H_6	48·8	7·6	35·4	$C_8H_{15}ON_5$	48·7	7·7	35·5	93
NH_2	OH	3	136—137	Dioxan	46·0	7·1	37·8	$C_7H_{13}ON_5$	45·9	7·2	38·2	99

[a] Found: Cl, 29·0. Required: Cl, 29·4%. [b] Light petroleum (b. p. 60—80°). [c] Picrate, m. p. 206° (Found: C, 36·2; H, 3·5; N, 27·7. $C_6H_{11}ON_5,C_6H_3O_7N_3$ requires C, 36·2; H, 3·5; N, 28·15%).

TABLE 3. *Purines* (IV) *and* (V).

6-Subst.	X	*n*	M. p.	Solvent	Found (%) C	H	N	Formula	Required (%) C	H	N	Yield (%)
NH_2	NH_2	2	219—221°	Dioxan	47·2	5·85	46·7	$C_7H_{10}N_6$	47·2	5·7	47·2	—
NH_2	NMe_2	3	135—136	C_6H_6	50·9	7·5	35·1	$C_{10}H_{16}N_6,H_2O$	50·4	7·6	35·3	57
					54·9	7·8	—	$C_{10}H_{16}N_6$	54·5	7·3	—	—
NH_2	NEt_2 [a]	3	122—123	EtOAc	57·9	7·7	33·9	$C_{12}H_{20}N_6$	58·0	8·1	33·9	63
NMe_2	NEt_2 [b]	3	(173—178°/0·8 mm.)	—	61·1	8·5	30·0	$C_{14}H_{24}N_6$	60·8	8·75	30·4	73
NH_2	OH	2	236—238	DMF [c]	46·8	5·3	38·6	$C_7H_9ON_5$	46·9	5·1	39·1	33
NMe_2	OH	2	135—136	EtOH–Et_2O	52·0	6·1	33·2	$C_9H_{13}ON_5$	52·1	6·3	33·8	—
NMe_2	OAc [d]	2	93—94	C_6H_{12} [e]	53·6	5·9	27·7	$C_{11}H_{15}O_2N_5$	52·95	6·1	28·1	58
NH_2	OH	3	194—198	EtOH	49·6	5·9	—	$C_8H_{11}ON_5$	49·7	5·7	—	54
NH_2	Cl	2	203—205	EtOH	42·5	3·9	35·6	$C_7H_8N_5Cl$ [f]	42·6	4·1	35·5	—
NH_2	Cl	3	187—189	MeOH	42·4	4·9	30·3	$C_8H_{10}N_5Cl,H_2O$ [g]	41·8	5·3	30·5	

[a] *Dipicrate*, m. p. 225° (Found: C, 40·9; H, 3·6; N, 23·3. $C_{12}H_{20}N_6,2C_6H_3O_7N_3$ requires C, 40·8; H, 3·7; N, 23·8%). [b] *Dipicrate*, m. p. 157° (Found: C, 43·1; H, 4·3; N, 23·0. $C_{14}H_{24}N_6,2C_6H_3O_7N_3$ requires C, 42·5; H, 4·1; N, 22·9%). [c] Dimethylformamide. [d] Ac: Found 17·3, required 17·6%. [e] Cyclohexane. [f] Cl: Found 17·6, required 17·9%. [g] Cl: Found 15·4, required 15·4%.

3-diethylaminopropylamine (30 g.) with stirring. Next morning the ether layer was shaken with water and dried (Na_2SO_4). Removal of the ether left a mobile orange oil which crystallised (18 g.). It was dissolved in ether, filtered through charcoal and Filtercel, and recovered, affording the *product* as pale yellow prisms, m. p. 37—39° (Found: C, 57·4; H, 9·3; N, 25·0. $C_{19}H_{37}O_2N_7$ requires C, 57·7; H, 9·4; N, 24·8%).

5-*Amino*-2,4-*bis*-3′-*diethylaminopropylamino*-6-*methylpyrimidine*.—The above product (18 g.) in ethanol was hydrogenated over Raney nickel until the uptake was completed. Removal of the catalyst and solvent left a low-melting wax (14·5 g.). It did not crystallise but with saturated ethanolic picric acid gave the *tripicrate*, m. p. 142° (from ethanol) (Found: C, 42·75; H, 4·9; N, 20·7. $C_{19}H_{39}N_7,3C_6H_3O_7N_3$ requires C, 42·2; H, 4·6; N, 21·3%).

9-3′-*Diethylaminopropyl*-2-3′-*diethylaminopropylamino*-6-*methylpurine* (II; X = $NH\cdot[CH_2]_3\cdot NEt_2$).—The preceding pyrimidine (14 g.) was heated in formamide (20 ml.) and hydrochloric acid (*d* 1·16; 5 ml.) at 175—180° for 30 min. After cooling, the solution was treated with 10N-sodium hydroxide and ether extracted, the extracts, after drying ($MgSO_4$), were evaporated, and the residual dark oil was distilled at reduced pressure. Redistillation gave the *purine* (5 g.), b. p. 216—218°/0·5 mm. (Found: C, 62·6; H, 9·7; N, 26·1. $C_{20}H_{37}N_7,\frac{1}{2}H_2O$ requires C, 62·5; H, 10·0; N, 25·5%).

Analogous compounds were similarly prepared. The *purines* (IV; $n = 3$, X = NMe_2 and NEt_2) were recovered by adding concentrated sodium hydroxide solution to the reaction

TABLE 4. *Azapurines* (VIII) *and* (IX).

					Found (%)				Required (%)			Yield
6-Subst.	X	*n*	M. p.	Solvent	C	H	N	Formula	C	H	N	(%)
H	NMe_2	3	172—173°	$COMe_2$	48·6	6·9	44·3	$C_9H_{15}N_7$	48·8	6·8	44·3	67
H	NEt_2	3	161—162	$COMe_2$	53·3	7·4	39·7	$C_{11}H_{19}N_7$	53·0	7·7	39·3	99
Me	NEt_2	3	(167—168°/ 0·1 mm.)	—	55·3	8·0	34·4	$C_{13}H_{23}N_7,\frac{1}{4}H_2O$	55·4	8·4	34·8	65
H	OH	2	253—254	H_2O	40·0	4·5	46·2	$C_6H_8ON_6$	40·0	4·5	46·6	74
Me	OH	2	139—140	C_6H_6	46·2	5·8	40·0	$C_8H_{12}ON_6$	46·2	5·8	40·4	54
H	OH	3	214—215	H_2O	43·5	5·1	42·9	$C_7H_{10}ON_6$	43·3	5·2	43·4	69

TABLE 5. pH *and absorption maximum* (mμ).

Substance	pH	$\lambda_{max.}$	$10^{-3}\varepsilon$	Substance	pH	$\lambda_{max.}$	$10^{-3}\varepsilon$
Adenine derivatives				*Purine derivatives*			
9-Methyl [4]	1	261	14·6	9-3′-Diethylaminopropyl-6-dimethylamino	2	268	16·4
	11	262	11·9		7—12	277	16·1
9-3′-Dimethylaminopropyl	2	259	13·7	9-2′-Hydroxyethyl-6-dimethylamino	2	268	14·2
	7—12	261	13·8		7—12	277	14·7
9-3′-Diethylaminopropyl	2	258	14·5	6-Methylamino [6]	2—7	266—267	~16·0
	7—12	261	14·4				
9-2′-Aminoethyl	2	257	12·1		12	273	~16·0
	7—12	261	12·6				
9-3′-Hydroxypropyl	2	259	14·6	*8-Aza-adenine derivatives*			
	7—12	261	14·6	9-3′-Dimethylaminopropyl	2	263	14·7
9-2′-Hydroxyethyl	2	258	12·8		7—12	278	11·3
	7—12	260	12·9	9-3′-Diethylaminopropyl	2	263	10·2
9-3′-Chloropropyl	2	259	13·9		7—12	278	9·8
	7—12	261	14·3	9-3′-Hydroxypropyl	2	263	12·2
9-2′-Chloroethyl	2	258	14·1		7—12	278	11·6
	7—12	261	14·1	9-2′-Hydroxyethyl	2	262	12·0
					7—12	278	11·0
				8-Azapurine derivatives			
				9-3′-Diethylaminopropyl-6-dimethylamino	2	274	17·0
					7—12	297	23·7
				9-2′-Hydroxyethyl-6-dimethylamino	2	273	14·0
					7—12	295	14·0

mixture; and (IV; $n = 2$, X = NH_2) by similar addition after evaporation and treatment with a little water; but (IV; $n = 2$ and 3, X = OH) crystallised from the reaction mixture. These products are in Table 3.

2,5-*Diamino*-4-3′-*diethylaminopropylamino*-6-*methylpyrimidine*.—To a cooled, stirred solution

of 2,4-dichloro-6-methyl-5-nitropyrimidine (9·6 g.) in ether was added dropwise 3-diethylaminopropylamine (12 g.). After 1 hr. the solution was evaporated to small bulk and an excess of ethanol saturated with ammonia added, after which the solution was heated under reflux for 1 hr. Removal of the ethanol left a red oil which was hydrogenated in ethanol to completion over Raney nickel. After removal of the solvent the residual oil was distilled under reduced pressure (b. p. 214—220°/2·5 mm.); recrystallisation of the distillate (1·2 g.) from ether gave the *triaminopyrimidine* as needles, m. p. 123—125° (Found: C, 56·9; H, 9·8; N, 33·8. $C_{12}H_{24}N_6$ requires C, 57·1; H, 9·6; N, 33·3%).

2-*Amino*-9-3′-*diethylaminopropyl*-6-*methylpurine* (II; X = NH_2).—The triaminopyrimidine (1 g.) was heated in formamide (5 ml.) with hydrochloric acid (*d* 1·16; 0·5 ml.) at 175° for 30 min., then cooled. An excess of saturated ethanolic picric acid was added, giving the *dipicrate* (2·15 g.), m. p. 208—210° (from water) (Found: C, 41·5; H, 3·8; N, 23·2. $C_{13}H_{22}N_6,2C_6H_3O_7N_3$ requires C, 41·7; H, 3·9; N, 23·2%).

The free *base* was obtained by treating the picrate with cold, concentrated sodium hydroxide solution and extracting the whole with ether. It had m. p. 53—54° (Found, on material dried at 40°: C, 58·6; H, 8·7; N, 32·1. $C_{13}H_{22}N_6,\frac{1}{4}H_2O$ requires C, 58·5; H, 8·5; N, 31·5%).

6-*Dimethylamino*-9-2′-*hydroxyethylpurine* (V; *n* = 2, X = OH) (see Table 3).—The appropriate triamine (1 g.) in ethyl orthoformate (14 g.) and acetic anhydride (10 g.) was heated under reflux for 1 hr. After evaporation, the residue was dissolved in hot benzene and reprecipitated with light petroleum (b. p. 40—60°), then recrystallised from cyclohexane, giving 9-2′-*acetoxyethyl*-6-*dimethylaminopurine* (0·73 g., 85%) as needles, m. p. 93—94°.

This derivative (0·25 g.) was heated in ethanol (4 ml.) and 2N-sodium hydroxide (5 ml.) at 40° for 25 min. and the whole was evaporated. The residue was extracted with hot ethyl acetate, the combined extracts were evaporated, and the residual oil was rubbed with ether, giving an off-white solid. Crystallisation from ethanol–ether gave 6-*dimethylamino*-9-2′-*hydroxyethylpurine* as prisms, m. p. 135—136°.

9-2′-*Chloroethyladenine* (IV; *n* = 2, X = Cl) (*see* Table 3).—9-2′-Hydroxyethyladenine (0·85 g.) and thionyl chloride (10 ml.) were heated on a water-bath for 30 min. Removal of the thionyl chloride and crystallisation of the residue from the minimum of ethanol gave 9-2′-*chloroethyladenine hydrochloride* as yellow laths (0·85 g., 77%), m. p. 221—223° (Found: C, 35·6; H, 4·1; N, 29·9. $C_7H_8N_5Cl,HCl$ requires C, 35·9; H, 3·9; N, 29·9%).

The base was obtained as a crystalline precipitate on treatment of an aqueous solution of the hydrochloride with sodium carbonate solution. Recrystallisation from ethanol gave colourless prisms of 9-2′-*chloroethyladenine*, m. p. 203—205°.

8-*Azapurines* (see Table 4).—The preparation of 9-3′-*dimethylaminopropyl*-8-*aza-adenine* (VIII; *n* = 3, X = NMe_2) is given as an example of the general method.

Sodium nitrite (2·6 g.) in water (15 ml.) was added dropwise to a stirred solution of 4,5-diamino-6-3′-dimethylaminopropylaminopyrimidine (5·5 g.) in acetic acid (50 ml.). The solution was then brought to pH 7 by means of ammonia solution, and the precipitate was filtered off and dried. Crystallisation from acetone gave 9-3′-dimethylaminopropyl-8-aza-adenine (3·9 g., 67%) m. p. 172—173°

We are indebted to Dr. E. M. F. Roe for light-absorption data and to Mr. J. M. Johnson for technical assistance. This work was supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, June 24th*, 1959.]