## 678. *Polypurines. Part I. Some Symmetrical αω-Di-9-purinylethanes and -hexanes.*

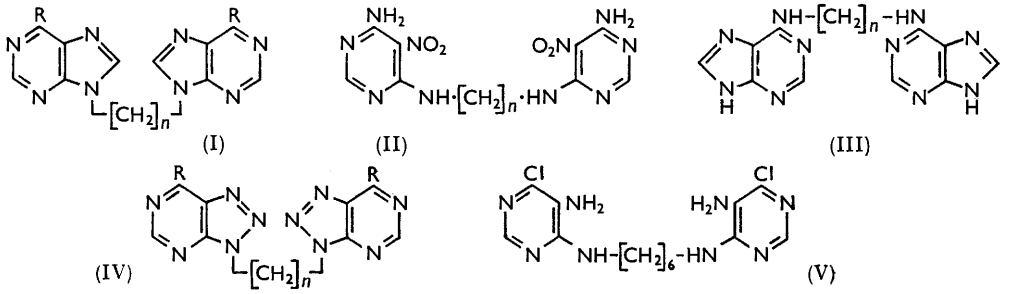
By J. H. Lister.

The preparation is described of like pairs of 6-substituted purines and 8-aza-purines linked together at the 9-position with di- and hexa-methylene chains. The two routes followed allow the synthesis of a wide range of 6-substituted bis-purines.

One aspect of the chemotherapeutic attack on malignant growth is the search for a means of interrupting the production of certain nucleic acids which may be characteristic for the tumour cell. The Watson–Crick hypothesis for DNA postulates a twin helical structure in which certain of the purine and pyrimidine bases in each helix are cross-linked by hydrogen bonds. These bonds will be momentarily broken at the time of replication and it has been suggested [1] that one possible means of stopping further replication " might be to use synthetic polymers with the object of blocking the . . . polynucleotide chains by attachment either through covalent or hydrogen bonds, so as to prevent polynucleotide synthesis on the . . . template." In the study reported here, which is part of a group programme carried out by Timmis and his co-workers,[2] this working hypothesis has been elaborated by supposing that purines and pyrimidines, similar to those occurring naturally, joined in linear fashion might be effective for this purpose. Therefore, as a step towards the synthesis of larger units the preparation of derivatives comprising two like purine molecules linked at the 9-position with polymethylene chains has been carried out. The choice of the 9-position, for the di- and hexa-methylene bridges, was made so as to conform structurally with the naturally occurring nucleotides. So far few di-purinyl derivatives of this kind have been reported. Taylor [3] and his co-workers have prepared the di-2-adeninyl-methane and -butane analogues, and Rose [4] a di-(6-dimethylamino-8-aza-9-purinyl)hexane.

[1] Todd, First Jephcott Lecture, *Brit. Med. J.*, 1959, *ii*, p. 521.
[2] Lister, Leese, and Timmis, *British Empire Cancer Campaign Annual Report*, 1958, **36**, p. 10.
[3] Taylor, Vogel, and Cheng, *J. Amer. Chem. Soc.*, 1959, **81**, 2442.
[4] Rose, *J.*, 1954, 4116.

The purines (I) were prepared from 4,6-dichloro-5-nitropyrimidine by either of two routes, the choice of which was governed by the group required in the 6-position. For the adenine and hypoxanthine derivatives the dichloronitropyrimidine was monoaminated, then condensed with the appropriate diamine. The bisnitropyrimidines (II) so formed



were reduced catalytically and cyclised to the bisadenines (I; $n = 2$ and 6, R = $NH_2$) with formamide and hydrochloric acid. Alkaline digestion of the purines was then made to remove any of the isomeric 6-adeninylalkanes (III) formed.

Conversion of the adenine into the hypoxanthine derivatives (I; $n = 2$ and 6, R = OH) involved treatment with warm nitrous acid. The corresponding 8-aza-adenines (IV; $n = 2$ and 6, R = $NH_2$) were obtained from the 4,5,6-triaminopyrimidines and cold nitrous acid and, like the adenine derivatives, were transformed by warm nitrous acid into the hypoxanthine analogues (IV; $n = 2$ and 6, R = OH). From 4-chloro-6-dimethylamino-5-nitropyrimidine, these methods gave the 6-dimethylaminopurine (I; $n = 2$, R = $NMe_2$) and the azapurine (IV; $n = 2$, R = $NMe_2$).

The above route was convenient only for purines substituted at the 6-position with hydroxyl, primary amino-, and tertiary amino-groups; secondary amino-groups would have given rise to mixed products on ring closure. As the 6-secondary amino-purines were required this necessitated having the appropriate 6-chloropurine intermediates. Whilst it is possible that the hypoxanthines described above could have been converted into the required chloropurines the following simpler route to these compounds was used.

Reduction of 4,6-dichloro-5-nitropyrimidine with hydrogen and Raney nickel was found to be preferable to the method [5] using alkaline ferrous sulphate. The resulting 5-aminopyrimidine was condensed with hexamethylenediamine, giving the bispyrimidine

*Ultraviolet spectra* (*values in parentheses are for* $10^{-3}$ ε).

| | pH 1 | | pH 13 | |
|---|---|---|---|---|
| Substance | $\lambda_{max.}$ | $\lambda_{min.}$ | $\lambda_{max.}$ | $\lambda_{min.}$ |
| (I; $n = 2$, R = $NH_2$) ..... | 258(24·6) | 232(6·07) | 258(21·0) | 230(4·74) |
| (I; $n = 2$, R = $NMe_2$) ..... | 267(29·2) | 233(3·86) | 272(27·8) | 237(3·51) |
| (I; $n = 6$, R = H) ..... | 264(11·3) | 232(3·2) | 265(14·5) | 223(2·3) |
| 9-Methylpurine [7] ..... | 262(5·5) | ~232(~1·9) [a] | 264(7·9) | <230(~1·6) [b] |
| (IV; $n = 2$, R = $NMe_2$) ..... | 268(16·5) | 236(4·08) | 294(12·1) | 241(2·47) |

[a] In water at pH 0. [b] In water at pH 8·5.

(V) which was then cyclised with acetic anhydride–ethyl orthorformate to the chloropurine (I; $n = 6$, R = Cl). With furfurylamine and dimethylamine this readily afforded the 6-amino-compounds, and the mercapto-derivative (I; $n = 6$, R = SH) which was obtained on treatment with thiourea was readily *S*-methylated. Hydrolysis of the chloropurine with dilute mineral acid gave a product identical with the hypoxanthine (I; $n = 6$, R = OH), as shown by analysis and infrared spectra.

[5] Brown, *J. Appl. Chem.*, 1954, **4**, 72.

Attempts to prepare the parent bis-purine (I; $n = 6$, R = H) by catalytic hydrogenation of the chloropurine or by dethiolation of the mercaptopurine were not successful. However, catalytic dechlorination of the diamine (V) was smooth, and ring closure of the product with acetic anhydride–ethyl orthoformate gave the purine.

Comparison of the ultraviolet absorption spectra of some of the bispurines (Table) with those of corresponding simple 9-substituted purines [6] reveals little change in the wavelengths at which maximum absorption occurs, but a general raising of the extinction values, in some cases to nearly double, shows the additive effect of the two bases.

## Experimental

Analyses are by Mr. P. R. W. Baker, Wellcome Research Laboratories, Beckenham.

The following examples illustrate the general procedure (see Tables 1—3).

1,6-*Di*-(4-*amino*-5-*nitro*-6-*pyrimidinylamino*)*hexane* (II).—4-Amino-6-chloro-5-nitropyrimidine (7 g.) in dioxan (15 ml.) was added in one portion to hexamethylenediamine (2·5 g.)

TABLE 1. αω-*Di*-(6-*pyrimidinylamine*)*alkanes* (II *and* V).

| 4-Subst. | 5-Subst. | *n* | M. p. | Solvent | Found (%) C | H | N | Formula | Required (%) C | H | N | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $NH_2$ | $NO_2$ | 2 | >350° | 2N-HCl | 32·2 | 3·9 | 36·7 | $C_{10}H_{12}N_{10}O_4,2H_2O$ | 32·3 | 4·3 | 37·6 | 86 |
| $NMe_2$ | $NO_2$ | 2 | 195—197 | Bu$^n$OH | 42·9 | 5·0 | 35·9 | $C_{14}H_{20}N_{10}O_4$ | 42·9 | 5·1 | 35·7 | 78 |
| $NH_2$ | $NO_2$ | 6 | 262—263 | H·CO·$NMe_2$ | 43·1 | 5·5 | 35·9 | $C_{14}H_{20}N_{10}O_4$ | 42·9 | 5·1 | 35·7 | 90 |
| $NMe_2$ [4] | $NO_2$ | 6 | 142—144 | Bu$^n$OH | 49·4 | 6·8 | 30·2 | $C_{18}H_{28}N_{10}O_4,\frac{1}{2}$BuOH | 48·9 | 6·5 | 30·0 | — |
| $NH_2$ | $NH_2$ | 2 | 290 * | 2N-HCl | 28·6 | 5·1 | 32·7 | $C_{10}H_{16}N_{10},4HCl$ | 28·5 | 4·8 | 33·2 | 62 |
| $NMe_2$ | $NH_2$ | 2 | 205—206 | $H_2O$ | 50·4 | 6·9 | 42·3 | $C_{14}H_{24}N_{10}$ | 50·6 | 7·3 | 42·2 | 76 |
| $NH_2$ | $NH_2$ | 6 | 234—236 | HCl–NaOH | 50·1 | 7·4 | 41·6 | $C_{14}H_{24}N_{10}$ | 50·6 | 7·3 | 42·2 | 91 |
| H | $NH_2$ | 6 | 226—228 | EtOH | 55·2 | 7·3 | 36·8 | $C_{14}H_{22}N_8$ | 55·6 | 7·3 | 37·1 | 38 |
| Cl [a] | $NH_2$ | 6 | 230—232 | Aq.EtOH | 45·5 | 5·0 | — | $C_{14}H_{20}Cl_2N_8$ | 45·3 | 5·4 | — | 47 |

[a] Cl: Found, 18·4. Required, 19·1%. * With decomp.

TABLE 2. αω-*Di*-(9-*purinyl*)*alkanes* (I).

| 6-Subst. | *n* | M. p. | Solvent | Found (%) C | H | N | Formula | Required (%) C | H | N | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 6 | 144—146° | $COMe_2$ | 59·7 | 5·6 | 34·2 | $C_{16}H_{18}N_8$ | 59·6 | 5·6 | 34·8 | 35 |
| $NH_2$ | 6 | 254—255 * | H·CO·$NH_2$ | 54·8 | 6·0 | 39·8 | $C_{16}H_{20}N_{10}$ | 54·5 | 5·7 | 39·8 | 81 |
| $NMe_2$ | 6 | 226—227 | EtOH | 58·8 | 6·8 | 34·7 | $C_{20}H_{28}N_{10}$ | 58·8 | 6·9 | 34·3 | 77 |
| NH·$C_5H_5O$ | 6 | 163—165 | EtOH | 60·8 | 5·6 | 27·3 | $C_{26}H_{28}N_{10}O_2$ | 60·9 | 5·5 | 27·3 | 73 |
| OH | 6 | 295 * | $H_2O$ | 53·7 | 5·2 | 32·6 | $C_{16}H_{18}N_8O_2$ | 54·2 | 5·1 | 31·6 | 70 |
| SH [a] | 6 | 330—334 * | NaOH–AcOH | 49·1 | 4·6 | 28·9 | $C_{16}H_{18}N_8S_2$ | 49·7 | 4·7 | 29·0 | 91 |
| SMe | 6 | 151—153 | MeOH | 52·0 | 5·5 | 27·3 | $C_{18}H_{22}N_8S_2$ | 52·2 | 5·4 | 27·0 | 85 |
| Cl [b] | 6 | 167—170 | Aq.MeOH | 48·7 | 4·0 | 28·5 | $C_{16}H_{16}Cl_2N_8$ | 49·1 | 4·1 | 28·7 | 41 |
| $NH_2$ | 2 | >350 | $NH_4$·OH–HCl | 48·3 | 3·8 | 47·1 | $C_{12}H_{12}N_{10}$ | 48·6 | 4·1 | 47·3 | 48 |
| $NMe_2$ | 2 | 226—227 | EtOH | 54·5 | 5·5 | 39·4 | $C_{16}H_{20}N_{10}$ | 54·5 | 5·7 | 39·8 | 85 |
| OH | 2 | >350 | Aq.AcOH | 45·4 | 4·0 | 35·1 | $C_{12}H_{10}N_8O_2,H_2O$ | 45·6 | 3·8 | 35·4 | 33 |

[a] S: Found 16·0. Required 16·6%. [b] Cl: Found 17·9%. Required 18·1%. * With decomp.

TABLE 3. αω-*Di*-(8-*aza*-9-*purinyl*)*alkanes* (IV).

| 6-Subst. | *n* | M. p. | Solvent | Found (%) C | H | N | Formula | Required (%) C | H | N | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $NH_2$ | 6 | 318—320 * | $H_2O$–AcOH | 46·9 | 4·9 | 46·2 | $C_{14}H_{18}N_{12}$ | 47·4 | 5·1 | 47·4 | 96 |
| OH | 6 | 256—258 | $H_2O$ | 46·8 | 4·1 | 39·0 | $C_{14}H_{16}N_{10}O_2$ | 47·2 | 4·5 | 39·3 | 45 |
| $NMe_2$ [4] | 6 | 183—184 | Bu$^n$OH | 52·7 | 6·7 | 40·05 | $C_{18}H_{26}N_{12}$ | 52·7 | 6·35 | 41·0 | — |
| $NH_2$ | 2 | >350 | HCl–NaOH | 39·6 | 3·5 | 55·7 | $C_{10}H_{10}N_{12},\frac{1}{2}H_2O$ | 39·7 | 3·5 | 55·5 | 75 |
| OH | 2 | 343 * | Aq.H·CO·$NH_2$ | 39·7 | 3·1 | 47·2 | $C_{10}H_8N_{10}O_2$ | 40·0 | 2·7 | 46·7 | 91 |
| $NM_2$ | 2 | 291—292 | n-$C_5H_{11}$·OH | 47·6 | 4·8 | 47·8 | $C_{14}H_{18}N_{12}$ | 47·4 | 5·1 | 47·4 | 83 |

* With decomp.

and triethylamine (7 g.) in dioxan (20 ml.). Immediate precipitation occurred and the mixture was stirred for 30 min., then water (80 ml.) was added and the product filtered off (8·6 g.). Recrystallisation from dimethylformamide gave the *bisnitropyrimidine*.

[6] Lister and Timmis, *J.*, 1960, 327.

1,6-*Di*-(4,5-*diamino*-6-*pyrimidinylamino*)*hexane*.—The above nitropyrimidine (13·6 g.) in 2N-hydrochloric acid (200 ml.) was hydrogenated to completion over 5% palladium–charcoal (8 g.), with heating by an infrared lamp. After removal of the catalyst the solution was basified with ammonia solution (*d* 0·88) and cooled, giving the *bistriamine* as a cream crystalline precipitate (10·5 g.).

1,6-*Di*-9′-*adeninylhexane* (I; $n = 6$, R = H).—A suspension of the triamine (3·5 g.) in formamide (20 ml.) and hydrochloric acid (*d* 1·16; 5 ml.) was heated at 175° for 30 min. A crystalline precipitate was formed on cooling and this was washed with 2N-sodium hydroxide (10 ml.) to remove the 6-isomer. The product (3 g.), 1,6-*di*-9′-*adeninylhexane*, was obtained as a microcrystalline solid from formamide.

1,6-*Di*-9′-*hypoxanthinylhexane* (I; $n = 6$, R = OH).—(*a*) A solution of the diadeninylhexane (0·5 g.) in water (20 ml.) and sulphuric acid (*d* 1·84, 1·5 ml.) was heated to 50° and sodium nitrite (2 g.) in water (5 ml.) added dropwise. The solution was boiled for 5 min., cooled, and brought to pH 4 with 2N-ammonia. The precipitate was crystallised (carbon) from water, giving the *bishypoxanthine* (0·35 g.) as a cream powder. (*b*) 1,6-Di-(6-chloropurinyl)hexane (0·25 g.) was boiled with 0·2N-hydrochloric acid (15 ml.) for 2 hr., then evaporated to dryness. The residue was taken up in N-sodium hydroxide (7 ml.) and reprecipitated with acetic acid. The product (0·11 g.), on recrystallisation from water, was identical with that obtained by the other method.

1,6-*Di*-(5-*amino*-4-*chloro*-6-*pyrimidinylamino*)*hexane* (V).—5-Amino-4,6-dichloropyrimidine (6·6 g.) in dioxan (75 ml.) containing triethylamine (8 ml.) was heated under reflux for 22 hr. with hexamethylenediamine (3·4 g.). Removal of the solvent and trituration of the residue with a little water gave the crude *bispyrimidine* (3·5 g.) which crystallised when its ethanolic solution was treated with water.

1,6-*Di*-(5-*amino*-4-*pyrimidinylamino*)*hexane*.—A solution of the preceding chloropyrimidine (1·45 g.) in ethanol (150 ml.) was hydrogenated over 5% palladium–charcoal (0·8 g.). The crude hydrochloride remaining after removal of catalyst and solvent was taken up in the minimum of water and treated with 10N-sodium hydroxide. There was a crystalline precipitate (0·45 g.) of the *bisdiaminopyrimidine*. Further recrystallisation was from ethanol.

1,6-*Di*-(6-*chloro*-9-*purinyl*)*hexane* (I; $n = 6$, R = Cl).—The chlorodiamine (5·65 g.) was heated with ethyl orthoformate (50 g.) and acetic anhydride (38 g.) for 2 hr. The residue left on evaporation was taken up in methanol (25 ml.), and hot water (170 ml.) was added, causing the *bischloropurine* to crystallise slowly.

1,6-*Di*-(6-*mercapto*-9-*purinyl*)*hexane* (I; $n = 6$, R = SH).—The bischloropurine (1 g.) in ethanol (20 ml.) and thiourea (0·38 g.) were heated under reflux for 90 min. The residue, after removal of solvent, was taken up in 2N-sodium hydroxide (8 ml.) and reprecipitated with acetic acid (0·78 g.). The *bisthiopurine* was purified by further reprecipitations.

Methylation was carried out in N-alkali at 10° with dimethyl sulphate. The *bismethylthiopurine* (I; $n = 6$, R = SMe) which separated crystallised from aqueous methanol.

1,6-*Di*-(6-*furfurylamino*-9-*purinyl*)*hexane* (I; $n = 6$, R = $NH{\cdot}C_5H_5O$).—The *bischloropurine* (0·5 g.) was suspended in water (10 ml.) and heated with furfurylamine (0·6 g.) for 1 hr. On cooling, the *furfurylaminopurine* (0·5 g.) was filtered off and crystallised from ethanol.

1,2-*Di*-(6-*dimethylamino*-8-*aza*-9-*purinyl*)*ethane* (IV; $n = 2$, R = $NMe_2$).—1,6-Di-(5-amino-4-dimethylamino-6-pyrimidinylamino)ethane (0·25 g.) in acetic acid (1 ml.) and water (2 ml.) was treated dropwise with sodium nitrite (0·1 g.) in water (1 ml.). The precipitated solid on crystallisation from pentyl alcohol gave the *bis*-8-*azapurine* (0·22 g.) as yellow needles.

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[7] Mason, *J.*, 1954, 2071; Bendich, Russell, and Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 6073.