Purine Studies. Part XX.[1] Methylation and Reduction of 2,8-Dioxo-, 2,8-Diamino-, and 2-Amino-8-oxo-purines, and the Stereochemistry of their 1,4,5,6-Tetrahydro-derivatives †

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Methylation of 1.7-dihydro-9*H*-purine-2.8-dione. 2 8-diaminopurine. and 2-amino-7.9-dihydropurin-8-one in neutral medium gave 3.7.8.9-tetrahydro-1.3.9-trimethyl-2.8-dioxo-2*H*-purinium iodide. 2.8-diamino-1.7.9-trimethyl-9*H*-purinium di-iodide. and 2-amino-7.9-dihydro-7-methylpurin-8-one respectively. Methylation of the 2.8-dione and its 1-methyl derivative in alkaline medium in each case provided a 1 : 1 mixture of 1.7-dihydro-1.3.7-trimethyl-3*H*- and 1.7-dihydro-1.7.9-trimethyl-9*H*-purine-2.8-dione. which on further methylation in neutral medium gave 3.7.8.9-tetrahydro-1.3.7.9-tetramethyl-2.8-dioxo-2*H*-purinium iodide. Methylation of 1.7-dihydro-7-methyl-9*H*-purine-2.8-dione. obtained by nitrosation of 2-amino-7.9-dihydro-7-methylpurin-8-one. in alkaline medium gave a 1 : 9 mixture of the above trimethylpurinediones. The methylation patterns were established by reduction. hydrolytic cleavage. methylation with CD_3I. and mass and ^1H n.m.r. spectral comparisons.

Reduction of these and related methylated purines with sodium borohydride produced 1.3.7-. 1.3.9-. and 1.7.9-trimethyl- and 1.3.6.9- and 1.3.7.9-tetramethyl-*cis*-perhydropurine-2.8-diones. and 1.7.9-trimethyl- and 1.6.7.9-tetramethyl-*cis*-2.8-diamino-4.5.6.9-tetrahydro-1*H*-purinium salts. Tafel's purone (perhydropurine-2.8-dione) and 2.8-diamino-4.5.6.9-tetrahydro-1*H*-purine were formed by electrolytic reduction of the respective purines. and had the *cis*-configuration at C-4 and C-5. similar to the above reduced purines. as shown by the patterns of ^1H n.m.r. signals. and spectral comparisons with *cis*-perhydrocyclopenta[*d*]pyrimidin-2-one and *cis*-2-amino- 4.4a.5.6.7.7a-hexahydro-3*H*-cyclopenta[*d*]pyrimidine.

SAXITOXIN (1) is a potent neurotoxin produced by the dinoflagellate *Gonyaulax catanella*,[2] and is responsible for 'red tides' and for the toxicity of shell fish that concentrate the toxin. Rapoport and his co-workers[3] proposed a 2,8-diamino-1,4,5,6-tetrahydropurine structure with a three-carbon bridge between C-5 and N-3, but this was recently revised by Schantz and his co-workers[4] to the formula (1) from an *X*-ray analysis of the bis-*p*-bromobenzenesulphonate salt. We began a study of simple analogues of saxitoxin for biological evaluation and for an investigation of the chemistry of purines in which the 4,5-double bond is reduced. The syntheses, properties, and stereochemistry of compounds related to 1,7-dihydro-9*H*-purine-2,8-dione are described here, together with those of the related 2,8-diaminopurines and 2-amino-7,9-dihydropurin-8-one.

Only a few 2,8-disubstituted 1,4,5,6-tetrahydropurines are known.[5] Tafel[6] reported the preparation of 'purone' and some of its *N*-methyl derivatives by electrolytic reduction of uric acid and some of its methyl derivatives in strong sulphuric acid. He proposed the

† *Editorial note.* The purines in this paper have been named in accord with I.U.P.A.C. recommendations.

[1] Part XIX, D. J. Brown and L. Stephenson, *Austral. J. Chem.*, in the press.

[2] V. E. Ghazarossain, E. J. Schantz, H. K. Schnoes, and F. M. Strong, *Biochem. Biophys. Res. Comm.*, 1974, **59**, 1219, and references therein.

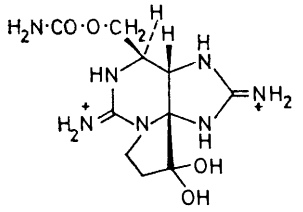
[3] J. L. Wong, R. Oesterlin, and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 7344.

[4] E. J. Schantz, V. E. Ghazarossain, H. K. Schnoes, F. M. Strong, J. P. Springer, J. O. Pezzanite, and J. Clardy, *J. Amer. Chem. Soc.*, 1975, **97**, 1238; J. Borner, W. E. Thiessen, H. A. Bates, and H. Rapoport, *ibid.*, p. 6008.

[5] J. H. Lister, 'Fused Pyrimidines. Part II. Purines,' ed. D. J. Brown, Wiley–Interscience, New York, 1971; I. Butula, *Annalen*, 1969, **729**, 73.

[6] J. Tafel, *Ber.*, 1901, **34**, 258.

structure (2; $R^1 = R^2 = R^3 = R^4 = H$) for purone, which was formed together with 5,6-dihydro-5-ureidouracil (3; $R^1 = R^2 = R^3 = R^4 = H$), but he did not indicate the stereochemistry at the bridgehead carbon atoms. Our intentions were to determine the stereochemistry of Tafel's purone and to prepare related purines of known stereochemistry. We first synthesized *cis*-perhydrocyclopenta[*d*]pyrimidin-2-one (4) for ^1H n.m.r. spectral comparison. This was prepared by cyclization of 2-ureidomethylenecyclopentanone to 1,5,6,7-tetrahydrocyclopenta[*d*]pyrimidin-2-one, followed by catalytic hydrogenation. The overall yield (8%) of the perhydro-compound (4) was considerably lower than the yield (88%) of *cis*-perhydroquinazolin-2-one from 2-ureidocyclohexanone,[7,8] and the difference is attributed to the greater difficulty in the intramolecular cyclization of 2-ureidomethylenecyclopentanone, as compared with the cyclohexanone. Chlorination of perhydrocyclopenta[*d*]pyrimidin-2-one with phosphoryl chloride followed by amination, by a procedure used previously,[9] provided the corresponding 2-amino-4,4a,5,6,7,7a-hexahydro-3*H*-cyclopenta[*d*]pyrimidine (5). The *cis*-stereochemistry at the bridgehead carbon atoms in (4) and (5) is consistent with the coupling constants between the two C-4 and the bridgehead C-4a protons. Both are less than 5 Hz, whereas J values for a *trans*-fused system would have at least one value larger than



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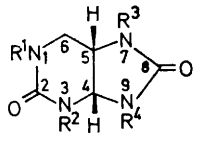

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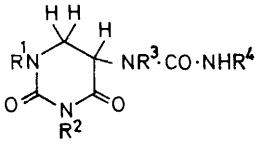

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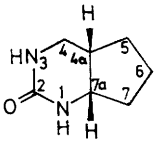
10 Hz. There was no evidence for the presence of the *trans*-isomers in any of these preparations.

Initial attempts to reduce 1,7-dihydro-9*H*-purine-2,8-dione with sodium or lithium borohydride were unsuccessful, probably owing to the formation of stable anions. Catalytic reduction in acid medium, on the other hand, proceeded with absorption of 1 mol. equiv. of hydrogen and 5,6-dihydro-5-ureidouracil (3; $R^1 = R^2 = R^3 = R^4 = H$) was isolated. The latter reaction, together with the properties of 3,7,8,9-tetrahydro-1,3,9-trimethyl-2,8-dioxo-2*H*-purinium iodide (6; R = H), prepared by methylation of 1,7-dihydro-9*H*-purine-2,8-dione in dimethylformamide, were described by us in a preliminary report,[10] and the full experimental details are reported here. In order to establish the stereochemistry of Tafel's purone we repeated the electrolytic reduction



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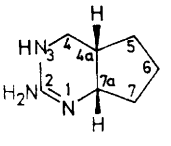

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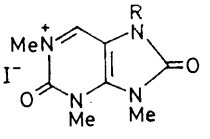


(6)

of uric acid in 29.4N-sulphuric acid and obtained a 3 : 1 mixture of purone and 5,6-dihydro-5-ureidouracil. A similar ratio of products was obtained in the electrolytic reduction of 1,7-dihydro-9*H*-purine-2,8-dione, suggesting that the latter is an intermediate in the reduction of uric acid. The ^1H n.m.r. spectrum of our purone is consistent with Tafel's structure and the small vicinal J values (*ca.* 2.8 Hz) between the two C-6 protons and the proton at C-5 (bridgehead) provided evidence for the *cis*-stereochemistry (2; $R^1 = R^2 = R^3 = R^4 = H$) [*cf.* the spectrum of (4) (Table)].

In an endeavour to prepare other 2,8-dioxoperhydropurines we studied the reduction of 3,7,8,9-tetrahydro-1,3,9-trimethyl-2,8-dioxo-2*H*-purinium iodide (6; R = H) with sodium borohydride. Unlike 1,7-dihydro-9*H*-purine-2,8-dione, the iodide cannot form stable anions. The reduction proceeded *via* the intermediate 1,3,6,7,8,9-hexahydro-derivative (7), as demonstrated by the ^1H n.m.r. spectrum of the solution. However, attempts to isolate this hexahydro-derivative led to a ready hydrolytic C(4)–N(9) ring cleavage, and 1,3-dimethyl-5,6-dihydro-5-*N'*-methylureidouracil (3; $R^1 = R^2 = R^4 =$ Me, $R^3 = H$) was isolated. This product was identical with that obtained in the catalytic reduction reported earlier.[10] Cleavage of the same bond also occurred at a neutral pH value and at the lower pH values necessary to decompose the excess of sodium borohydride. In methanol at high pH (*ca.* 9), on the other hand, the hexahydro-compound is relatively more stable. In the presence of an excess of reducing agent the reduction proceeds to completion and 1,3,9-trimethylperhydropurine-2,8-dione (2; $R^1 = R^2 = R^4 =$ Me, $R^3 = H$) is formed in high yields. The ^1H n.m.r. spectrum of the solution before isolation of the perhydropurine shows that only one product is formed, and the coupling constants ($J_{4.5}$ 9.5, $J_{5.6}$ 2.5, $J_{5.6'}$ 2.0, $J_{6.6'}$ 13.0 Hz) are consistent with the *cis*-fused structure (2). 3,7,8,9-Tetrahydro-1,3,7,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide (6; R = Me) (see below) reacted

[7] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1971, 1812.
[8] W. L. F. Armarego and P. A. Reece, *J.C.S. Perkin I*, 1974, 2314.
[9] W. L. F. Armarego and P. A. Reece, *J.C.S. Perkin I*, 1975, 1470.
[10] W. L. F. Armarego and P. A. Reece, *Tetrahedron Letters*, 1975, 423.

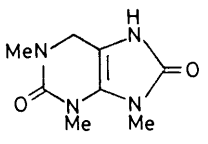
in the same manner and provided 1,3,7,9-tetramethyl-*cis*-perhydropurine-2,8-dione (2; $R^1 = R^2 = R^3 = R^4 =$ Me) in high yields.

The reduction of the iodide (6; R = H) with sodium borohydride in deuterium oxide proceeded as in water (above) except that a deuterium atom was completely incorporated at C-5 of the perhydropurine (2; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H) formed, and clearly showed that hydride attack on the trimethyl iodide (6; R = H) occurred at the electrophilic centres C-4 and C-6, and at C-4 in the hexahydro-derivative (7). This is in agreement with the mode of hydrolysis of (7) to the ureido-compound (3; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H), which must involve nucleophilic attack of water or OH^- ions at C-4 followed by ring cleavage. We made use of this property in attempts to introduce a side chain at C-4 [see saxitoxin (1)]. Reactions of the crude hexahydro-derivative (7) with nucleophiles such as cyanide, malononitrile, and diethyl malonate under a variety of conditions, however, have so far been unsuccessful; 1,3-dimethyl-5,6-dihydro-5-*N'*-methylureidouracil was isolated in each case. Similar attempts with the iodides (6; R = H) and (6; R = Me) or the 4-acetoxy-derivative (8; $R^1 = R^2 = R^4 =$ Me, $R^2 =$ H) [obtained from the corresponding ureido-compound (3; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H) in boiling acetic anhydride] also resulted in C(4)–N(9) bond cleavage to the corresponding derivatives (9) and (3), respectively. In an attempt to introduce a nitromethyl group at C-4 by a method found satisfactory in the quinazoline series,[9] a concentrated solution of the enamine (7) in methanol was fused with nitroacetic acid. The major product was the ureido-derivative (3; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H), but a new product was formed in 25% yield. Its elemental analysis, mass spectrum, and ^{1}H n.m.r. data were consistent with the molecular formula $C_9H_{10}N_4O_3$. The ^{1}H n.m.r. spectrum of this product and of the related product from the 1,3,9-tris(trideuteriomethyl) derivative, prepared from the tris(trideuteriomethyl) derivative of (7), are in agreement with the structure 5-methoxy-1,3,9-trimethylperhydropurine-2,8-dione (10),

^{1}H N.m.r. spectra of *cis*-perhydropurines (δ values; Me_4Si internal standard) [a]

Perhydropurine-2,8-dione	H-4	H-5	H-6	H-6′	NH	NCH_3	Other H	Solvent
Unsubstituted	5.28 (d, $J_{4.5}$ 8.9)	4.40 (dt, $J_{4.5}$ 8.9, $J_{5.6}$ 2.8)	3.37 (m)					D_2O [b]
4-AcO		4.30 (dd, $J_{5.6}$ 4.7, $J_{5.6'}$ 7.5) [d]	3.40 (dd, $J_{5.6}$ 4.7, $J_{6.6'}$ 13.5)	3.72 (dd, $J_{5.6'}$ 7.5, $J_{6.6'}$ 13.5)	11.72br (s), 11.49br (s), 8.84br (s), 7.68br (s)		2.06 (Ac)	$(CD_3)_2SO$
1,3,9-Me_3	4.93 (d, $J_{4.5}$ 9.5)	4.21 (dq, $J_{4.5}$ 9.5, $J_{5.6}$ 2.5, $J_{5.6'}$ 2.0)	3.44 (dd, $J_{5.6}$ 2.5, $J_{6.6'}$ 13.0)	3.04 (dd, $J_{5.6'}$ 2.0, $J_{6.6'}$ 13.0)	6.46br (s)	3.05 (s), 2.89 (s) [e]		$CDCl_3$ [b]
4-AcO-1,3,9-Me_3		4.68 (dd, $J_{5.6'}$ 5.0, $J_{5.6}$ 5.5)	4.10 (dd, $J_{5.6}$ 5.5, $J_{6.6'}$ 14.1)	3.77 (dd, $J_{5.6'}$ 5.0, $J_{6.6'}$ 14.1)		3.06 (2 × s), 3.07 (2 × s), 2.56 (s)	2.02 (s), [f] 2.12 (s) (Ac)	$CDCl_3$
1,3,7-Me_3	5.10 (dd, $J_{4.NH}$ 1.4, $J_{4.5}$ 9.2)	3.98 (dq, $J_{4.5}$ 9.2, $J_{5.6}$ 2.8. $J_{5.6'}$ 2.5)	3.47 (dd, $J_{5.6}$ 2.8, $J_{6.6'}$ 17.0)	3.18 (dd, $J_{5.6'}$ 2.5, $J_{6.6'}$ 17.0)	6.85br (d, $J_{NH.4}$ 1.4)	2.93 (s), 2.79 (s), 2.72 (s)		$CDCl_3$ [b]
1,7,9-Me_3	4.88 (dd, $J_{4.NH}$ 2.3, $J_{4.5}$ 9.2)	3.85 (dd, $J_{4.5}$ 9.2, $J_{5.6}$ 3.0)	3.47 (dd, $J_{5.6}$ 3.0, $J_{6.6'}$ 13.5)	3.22 (dd, $J_{5.6'}$ 3.0, $J_{6.6'}$ 13.5)	6.72br (d, $J_{NH.4}$ 2.3)	2.94 (s), 2.80 (s) [e]		$CDCl_3$ [b]
1,3,7,9-Me_4	4.81 (d, $J_{4.5}$ 9.5)	3.90 (dq, $J_{4.5}$ 9.5, $J_{5.6}$ 2.8, $J_{5.6'}$ 2.3)	3.34 (dd, $J_{5.6}$ 2.8, $J_{6.6'}$ 13.8,	3.06 (dd, $J_{5.6'}$ 2.3, $J_{6.6'}$ 13.8)		2.97 (s), 2.86 (s), [e] 2.75 (s)		$CDCl_4$
1,3,6,9-Me_4	4.90 (d, $J_{4.5}$ 9.8)	4.08 (dq, $J_{NH.5}$ 1.0, $J_{4.5}$ 9.8, $J_{5.6}$ 2.7)	3.47 (dq, $J_{5.6}$ 2.7, $J_{6.CH3}$ 7.0)		5.88br (d, $J_{NH.5}$ 1.0)	3.07 (s), 2.92 (s), 2.89 (s)	1.32 (d, $J_{Me.6}$ 7.0, 6-Me)	$CDCl_3$ [c]

[a] J Values in Hz; J_{gem} values are assumed negative. [b] 60 MHz at 35 °C. [c] 100 MHz at 35 °C. [d] After D_2O addition. [e] Two signals superimposed. [f] Two conformers.



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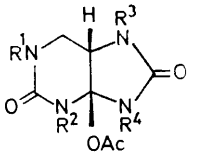

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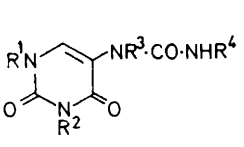

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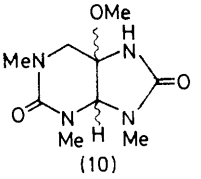
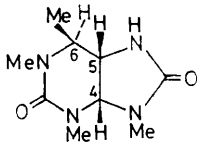


(10)

i.e. H-4 and the two 6-protons were not coupled, but provided no evidence for the stereochemistry at the bridgehead positions. Contrary to the above, this reaction probably proceeded by nucleophilic attack at C-5 (instead of C-4) which may have been caused by the strongly acidic medium.

Methylation of 1,7-dihydro-6-methyl-9*H*-purine-2,8-dione in neutral medium (MeI–Me_2N·CHO) gave 3,7,8,9-

tetrahydro-1,3,6,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide exclusively. This methylation pattern is identical with that of 1,7-dihydro-9*H*-purine-2,8-dione under the same conditions,[10] and was established by the similarity of its reactions with those of the trimethyl compound (6; R = H), by the observation of a coupling constant between N*H* and Me in the product of alkaline hydrolysis (1,3,6-trimethyl-5-*N'*-methylureidouracil), and an N(7)H,H-5 coupling constant in the sodium borohydride reduction product [1,3,6,9-tetramethyl-*cis*-perhydropurine-2,8-dione (11)]. The reduction of 3,7,8,9-tetrahydro-1,3,6,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide with sodium borohydride proceeded slowly, but *via* the intermediate enamine (12) (as observed by ^{1}H n.m.r.), unlike that of the 6-unsubstituted iodide (6; R = H) in which the intermediate enamine (7) was involved. Further reduction of the intermediate (12) gave only one perhydropurine (11). The relative configuration at C-6 in (11) is the same as in saxitoxin, *i.e.* (4*R**,5*S**,6*S**), and is supported by the stereochemistry of hydride attack at C-6 in the intermediate (12), *i.e.* from the face opposite to that of



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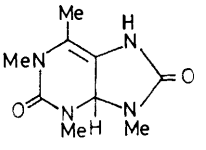
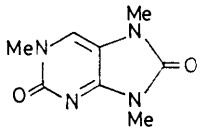


(12)

the C-4 hydrogen atom, and the ^{1}H n.m.r. coupling constants between C-5 and C-6 (*J* 2.7 Hz; *cf.* purone). In contrast, electrolytic reduction of 3,7,8,9-tetrahydro-1,3,6,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide gave an equal mixture of (11) and its C-6 epimer.

The methylation of 1,7-dihydro-9*H*-purine-2,8-dione in alkaline medium followed a different course. The reaction gave consistently a 1 : 1 mixture of two trimethyl derivatives (clearly discernible by n.m.r.) as free bases (*cf.* the methylation in dimethylformamide). Similar methylation of 1,7-dihydro-1-methyl-9*H*-purine-2,8-dione also gave a 1 : 1 mixture of these trimethyl derivatives. Johns [11] reported that only one trimethyl derivative was formed from the latter reaction and proposed that it was 1,7-dihydro-1,7,9-trimethyl-9*H*-purine-2,8-dione (13). Further methylation of the mixture of free bases in neutral medium (MeI–Me_2N·CHO) gave one 3,7,8,9-tetrahydro-1,3,7,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide (6; R = Me), which undergoes ring cleavage to the ureidouracil (9; $R^1 = R^2 = R^3 = R^4$ = Me) on basification (see above). Of the four possible trimethyl derivatives, *viz.* 1,3,7- (14), 1,7,9- (13), 1,3,9-, and 3,7,9-, only the first two can be considered for this mixture. The 1,3,9-trimethyl derivative is excluded on the evidence that the free base undergoes ready C(4)–N(9) bond cleavage in basic medium [see (6; R = H)], and the 3,7,9-trimethyl derivative cannot be formed because 1,7-dihydro-1-methyl-9*H*-purine-2,8-dione yields a mixture of the same methyl derivatives. The latter also suggests that N-1 is the first site of methylation of 1,7-dihydro-9*H*-purine-2,8-dione. The mixture was separated by fractional recrystallization from acetone. The more soluble isomer (colourless) was 1,7-dihydro-1,3,7-trimethyl-3*H*-purine-2,8-dione (14); it gave 3,7,8,9-tetrahydro-1,3,7-tri-



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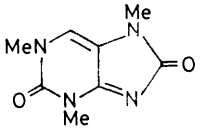


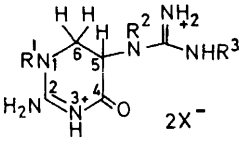
(14)

methyl-2,8-dioxo-9-trideuteriomethyl-2*H*-purinium iodide on methylation with CD_3I (Me_2N·CHO), which was cleaved to 1,3-dimethyl-5-(*N*-methyl-*N'*-trideuteriomethylureido)uracil (9; $R^1 = R^2 = R^3$ = Me, $R^4 = CD_3$), in the n.m.r. spectrum of which none of the observed three *N*-methyl signals was a doublet [*cf.* the spectrum of (9; $R^1 = R^2 = R^3 = R^4$ = Me) in which the *N'*-methyl signal is a doublet owing to coupling with N'H]. The least soluble isomer (yellow) is consequently 1,7-dihydro-1,7,9-trimethyl-9*H*-purine-2,8-dione (13), and further methylation of a mixture of (13) and (14) with CD_3I gave the corresponding trideuteriomethyltrimethyl iodide, which provided the ureido-compound (9; $R^1 = R^3 = R^4$ = Me, $R^2 = CD_3$), in the n.m.r. spectrum of which one of the three methyl signals (*N'*-Me) is a doublet. On the basis of physical properties, Johns' trimethyl compound was incorrectly identified, and should be 1,7-dihydro-1,3,7-trimethyl-3*H*-purine-2,8-dione. The two trimethyl derivatives, (13) and (14), are slowly reduced with sodium borohydride to 1,7,9- and 1,3,7-trimethyl-*cis*-perhydropurine-2,8-dione respectively.

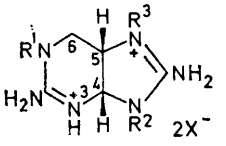
Catalytic reduction of 2,8-diaminopurine in 5N-hydrochloric acid (PtO_2) proceeded slowly with absorption of 1 mol. equiv. of hydrogen, and the product was isolated as a dihydrochloride and as a dipicrate. Elemental analysis and i.r. and ^{1}H n.m.r. spectra indicated that it was 2-amino-5-guanidino-1,4,5,6-tetrahydro-4-oxopyrimidinium dichloride (15; $R^1 = R^2 = R^3$ = H, X = Cl). Attempts to alter the work-up conditions in order to isolate 2,8-diamino-1,6-dihydropurine were unsuccessful, as were attempts to cyclise the ureidopyrimidine (15). The ready hydrolytic C(4)–N(9) bond cleavage in this series is similar to the one previously observed with 1,7-dihydro-9*H*-purine-2,8-dione. Electrolytic reduction of 2,8-diaminopurine in aqueous 10M-sulphuric acid at high current density gave a 3 : 2 : 1 mixture of 2,8-diamino-4,5,6,9-tetrahydro-1*H*-purinium sulphate (16; $R^1 = R^2 = R^3$ = H, 2X = SO_4), the amino-guanidino-oxopyrimidinium sulphate (15; $R^1 = R^2 = R^3$ = H, 2X = SO_4), and 2-amino-5-guanidino-5,6-dihydropyrimidinium sulphate (17; 2X = SO_4). Although the amino-guanidino-oxopyrimidine can be removed from the mixture, because of the insolubility of its sulphate salt, we were unable to separate the

[11] C. O. Johns, *J. Biol. Chem.*, 1914, **17**, 1.

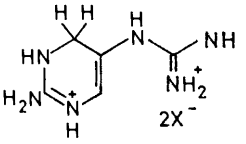
purine from the pyrimidine (17). The ^{1}H n.m.r. spectrum of the latter mixture showed clearly the H-4 signals of the purine and confirmed that the configuration at the bridgehead atoms C-4 and C-5 in 2,8-diamino-4,5,6,9-tetrahydro-1*H*-purinium sulphate is *cis*. The pattern of signals is similar to that observed in the *cis*-perhydropurine-2,8-diones (2), and is consistent with the pattern found in 2-amino-4,4a,5,6,7,7a-hexahydro-3*H*-cyclopenta[*d*]pyrimidine (5).



(15)



(16)

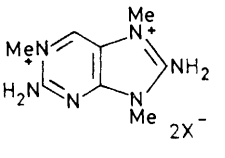


(17)

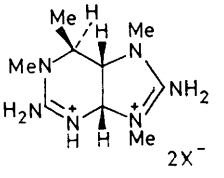
Methylation of 2,8-diaminopurine in neutral medium (MeI–Me_2N·CHO) gave a trimethyldiaminopurinium di-iodide. The structure of this salt, 2,8-diamino-1,7,9-trimethyl-9*H*-purinium di-iodide (18; X = I), was deduced from the following data. Catalytic reduction in water proceeded smoothly, and as in the case of 2,8-diaminopurine, one double bond was reduced and the product underwent hydrolytic C(4)–N(9) bond cleavage to furnish 2-amino-5-*NN'*-dimethylguanidino-1,4,5,6-tetrahydro-1-methyl-4-oxopyrimidinium di-iodide (15; $R^1 = R^2 = R^3$ = Me, X = I). The ^{1}H n.m.r. spectrum of the dipicrate clearly revealed two separate NH_2 signals and two separate NH signals, in support of the structure (15; $R^1 = R^2 = R^3$ = Me, X = picrate). Also, the fragmentation pattern in the mass spectrum showed a loss of $MeNH^{+\cdot}$, as in the fragmentation of the ureido-compound (3; $R^1 = R^2 = R^4$ = Me, R^3 = H). The reduction of the trimethyldiaminopurinium di-iodide (18; X = I) with sodium borohydride gave only one product, 2,8-diamino-4,5,6,9-tetrahydro-1,7,9-trimethyl-1*H*-purine (16; $R^1 = R^2 = R^3$ = Me), which was isolated as the dihydrochloride and as the dipicrate. The pattern of signals for H-4, H-5, and H-6 is consistent with *cis*-fusion between the rings, and further showed that H-4 was coupled with N(3)*H*. The presence of two NH_2 signals confirms the lack of methylation at the exocyclic nitrogen atoms. Attempts to convert these diaminopurines into the respective purine-2,8-diones, several of which are described in this work, by nitrosation or hydrolysis gave complex mixtures of unidentified products.

Methylation of 2,8-diamino-6-methylpurine also gave a tetramethyl di-iodide, which, by analogy with the above, should be 2,8-diamino-1,6,7,9-tetramethylpurine. This is supported by the ^{1}H n.m.r. properties of the product from reduction with sodium borohydride: (4*R**,5*S**,6*S**)-2,8-diamino-1,5,6,7-tetrahydro-1,6,7,9-tetramethyl-4*H*-purinium dipicrate (19; X = picrate). The spectrum clearly showed two separate NH_2 signals, a coupling between N-3 and H-4 (J 4.7 Hz), and general similarity of signal patterns and chemical shifts to those of the above trimethyl derivative (16; $R^1 = R^2 = R^3$ = Me). The stereochemistry at C-6 in the salt (19) is similar to the one observed in the purinedione (11) (the pattern of signals and values of J are similar).

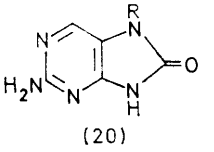
Substantial quantities of 2,8-diaminopurine were required for the above studies and a convenient synthesis was needed. The preparation by desulphurization of 2,8-diaminopurine-6-thione [12] was unsatisfactory in our hands. We also attempted the amination of 2,8-bismethylsulphonylpurine, but it was difficult to substitute the second methylsulphonyl group after the first one was displaced. Amination of 2-amino-8-methylthiopurine was slow at 120 °C, and the diamine was accompanied by an unidentified product. The conversion of 6-substituted 2,4,5-triaminopyrimidines into 6-substituted 2,8-diaminopurines with cyanogen bromide has been reported but no experimental details were provided.[13] We found that this was the most satisfactory method for preparing 2,8-diaminopurine (from 2,4,5-triaminopyrimidine) after obtaining the optimum



(18)



(19)



(20)

conditions, and we also synthesized 6-methyl- and 6-hydroxymethyl-2,8-diaminopurine in this way.

We extended our studies to 2-amino-7,9-dihydropurin-8-one and found that catalytic reduction in 5N-hydrochloric acid proceeded as in the above examples and gave 2-amino-5,6-dihydro-5-ureidopyrimidin-4-(3*H*)-one, identified by its physical properties. Methylation of 2-amino-7,9-dihydropurin-8-one in neutral medium, in contrast to the above examples, however, stops at the monomethyl stage and provides the free base. Treatment of 2-amino-7,9-dihydropurin-8-one and its monomethyl derivative with nitrous acid provided 1,7-dihydro-9*H*-purine-2,8-dione and its methyl derivative, respectively. The methyl derivative was not the 1-

[12] A. F. Lewis, A. G. Beaman, and R. K. Robins, *Canad. J. Chem.*, 1963, **41**, 1807.

[13] J. L. Wong, M. S. Brown, K. Matsumoto, R. Oesterlin, and H. Rapoport, *J. Amer. Chem. Soc.*, 1971, **93**, 4633.

methyl [14] (see above) or the 9-methyl derivative [14] (by direct i.r. comparison with an authentic sample kindly provided by Dr. D. J. Brown), and was different from the 1,7-dihydro-3-methyl-9*H*-purine-2,8-dione reported.[14] The product of methylation was the previously unknown 2-amino-7,9-dihydro-7-methylpurin-8-one (20; R = Me), and this was further confirmed by methylation of 2-amino-7,9-dihydropurin-8-one with a 1 : 1 mixture of methyl and trideuteriomethyl iodides. The mixture of monomethyl derivatives formed was converted into the corresponding mixture of monomethylated purinediones, and further methylated with dimethyl sulphate in alkaline medium. This gave a 9 : 1 mixture of 1,7-dihydro-1,9-dimethyl-7-trideuteriomethyl-9*H*- and 1,7-dihydro-1,3-dimethyl-7-trideuteriomethyl-3*H*-purine-2,8-diones, which were identified with the compounds (13) and (14) respectively by their n.m.r. spectra, and provided proof that the original methylation occurred at N-1 or N-7. The mixture was methylated further (MeI–Me_2N·CHO) to give one trimethyl-2,8-dioxomono(trideuteriomethyl)purinium iodide, which was readily cleaved by alkali to the tetraalkyl-5-ureidouracil (9; $R^1 = R^2 = R^4 = Me$, $R^3 = CD_3$). The n.m.r. data of this compound showed conclusively that the trideuteriomethyl group was on N-7 of the purines since the chemical shift of the 7-methyl group in 3,7,8,9-tetrahydro-1,3,7,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide is as assigned above. From the n.m.r. spectra of the latter iodide (6; R = Me), 3,7,8,9-tetrahydro-1,3,9-trimethyl-7-trideuteriomethyl-, 3,7,8,9-tetrahydro-1,3,7-trimethyl-9-trideuteriomethyl-, and 3,7,8,9-tetrahydro-1,7,9-trimethyl-3-trideuteriomethyl-2,8-dioxo-2*H*-purinium iodides, all the methyl signals of the iodide (6; R = Me) were assigned.

The approximate minimal lethal doses for male mice (mg kg^{-1}; intraperitoneal injection in sterile 0.9N-saline solution) for *cis*-perhydropurine-2,8-dione (2; $R^1 = R^2 = R^3 = R^4 = H$) and its 4-acetoxy- (8; $R^1 = R^2 = R^3 = R^4 = H$) and 1,3,9-trimethyl (2; $R^1 = R^2 = R^4 = Me$, $R^3 = H$) derivatives, a 1 : 1 mixture of *cis*-2,8-diamino-4,5,6,9-tetrahydro-1*H*-purinium (16; $R^1 = R^2 = R^3 = H$, $2X = SO_4$) and 2-amino-5-guanidino-1,4,5,6-tetrahydro-4-oxopyrimidinium sulphates (15; $R^1 = R^2 = R^3 = H$, $2X = SO_4$), *cis*-2,8-diamino-1,4,5,6-tetrahydro-1,7,9-trimethylpurinium dichloride (16; $R^1 = R^2 = R^3 = Me$, X = Cl), 2-amino-5-guanidino-1,4,5,6-tetrahydro-4-oxopyrimidinium dichloride (15; $R^1 = R^2 = R^3 = H$, X = Cl), 2,8-diamino-1,7,9-trimethyl-9*H*-purinium di-iodide (18; X = I), 2-amino-4,4a,5,6,7,7a-hexahydro-3*H*-cyclopenta[*d*]pyrimidine (5), and 2-amino-4,5-dihydroimidazole were >500, >100, >500, 400, 300, >500, 170, and 120, respectively.

EXPERIMENTAL

Elemental analyses were determined by the Australian National University Analytical Services Unit. I.r. spectra (KBr discs) were measured on a Perkin-Elmer 21 and a Unicam SP 1000 spectrometer; band assignments are tentative. ^1H N.m.r. spectra were measured on a Varian T60A spectrometer unless otherwise stated; *J* values are in Hz. All extracts were dried over Na_2SO_4 and evaporations were carried out below 30 °C and at *ca.* 18 mmHg.

2-*Ureidomethylenecyclopentanone*.—2-Hydroxymethylenecyclopentanone (22.4 g) [15] was added to a solution of urea (14.4 g, 1.1 mol. equiv.) in hot acetic acid (30 ml) and the mixture set aside for 2 days. The precipitated solid was collected and recrystallized from water to give pure 2-*ureidomethylenecyclopentanone* (11.5 g 37%), m.p. 264° (Found: C, 54.4; H, 6.7; N, 18.1. $C_7H_{10}N_2O_2$ requires C, 54.5; H, 6.5; N, 18.2%); $\nu_{max.}$ 3 280 (NH str.), 1 717 (CO), 1 690 (urea CO), 1 590 (C=C), and 1 520 cm^{-1} (NH bend); δ[$(CD_3)_2SO$] 8.82 (d, NH, *J* 12.0), 7.57 (d, C=CH, *J* 12.0), 4.40br (m, NH_2), and 1.7—2.3 (m, 3-, 4-, and 5-H_2).

cis-*Perhydrocyclopenta*[d]*pyrimidin*-2-*one* (4).—2-Ureidomethylenecyclopentanone (3.08 g) in N-sodium hydroxide (60 ml) was refluxed for 4 min. The mixture was cooled, neutralized with concentrated hydrochloric acid, and evaporated. Extraction of the residue with boiling ethanol, followed by evaporation of the extracts, gave crude 1,5,6,7-tetrahydrocyclopenta[*d*]pyrimidin-2-one. This oily solid was dissolved in water and extracted with chloroform. The aqueous layer was evaporated and the residue dissolved in acetic acid (100 ml) containing sulphuric acid (*d* 1.81; 3 drops); platinum oxide (750 mg) was added and the mixture was hydrogenated at 4.4 atm and 20 °C for 3 h. Filtration and evaporation gave a residue which was extracted with boiling chloroform. Evaporation extracts gave cis-*perhydrocyclopenta*[d]*pyrimidin*-2-*one* (215 mg, 8%), m.p. 195—196.5° (from C_6H_6) (Found: C, 59.6; H, 8.4; N, 19.5. $C_7H_{12}N_2O$ requires C, 59.9; H, 8.6; N, 19.9%); $\nu_{max.}$ 3 300 (NH str.), 1 675 (CO), and 1 530 cm^{-1}; δ($CDCl_3$) 5.98 (s, NH), 5.76 (s, NH), 3.73br (m, H-7a), 3.40 (dd H-4*eq*, $J_{4.4'}$ 11.0, $J_{4a.4eq}$ 4.5), 3.07 (dd H-4*ax*, $J_{4.4'}$ 11.0, $J_{4a.4ax}$ 5.0), 2.24 (m, H-4a), and 1.6—2.1 (m, carbocyclic H). The *picrate* had m.p. 156° (from C_6H_6) (Found: C, 42.5; H, 4.2; N, 18.7. $C_{13}H_{15}N_5O_8$ requires C, 42.3; H, 4.1; N 19.0%); $\nu_{max.}$ 3 435, 3 270 (NH str.), and 1 690 cm^{-1} (CO).

2-*Amino*-4,4a,5,6,7,7a-*hexahydro*-3H-*cyclopenta*[d]*pyrimidine* (5).—Compound (4) (215 mg) in phosphoryl chloride (15 ml) containing phosphorus pentachloride (320 mg, 1 mol. equiv.) was heated at 130 °C for 2.5 h in a sealed tube. Volatile material was removed and the residue treated with liquid ammonia (50 ml) containing sodamide (62 mg, 1 mol. equiv.) and set aside overnight. The product was dissolved in water (20 ml) and acidified (pH 6.0), and the aqueous solution was extracted with chloroform (3 × 20 ml). The aqueous layer was evaporated and dried leaving the crude *hydrochloride* of (5) (134 mg, 50%) as a hygroscopic solid; $\nu_{max.}$ 3 330 (NH str.), and 1 665 and 1 635 cm^{-1} (guanidino); δ(D_2O) 3.72 (m, H-7a), 3.40 (dd, H-7, $J_{4',4a}$ 4.5, $J_{4,4'}$ 13.0), 3.08 (dd, H-4, $J_{4.4a}$ 5.0, $J_{4.4'}$ 13.0), and 1.2—2.7 (carbocyclic H). The *picrate* had m.p. 155—156° (from water) (Found: C, 42.8; H, 4.5; N, 22.7. $C_{13}H_{16}N_6O_7$ requires C, 42.4; H, 4.4; N, 22.8%); $\nu_{max.}$ 3 425 (NH str.), and 1 665 and 1 634 cm^{-1} (guanidino).

3,7,8,9-*Tetrahydro*-1,3,9-*trimethyl*-2,8-*dioxo*-2H-*purinium Iodide* (6; R = H).—1,7-Dihydro-9*H*-purine-2,8-dione [16] (1 g) was finely ground and suspended in dimethylformamide (100 ml) containing methyl iodide (3 ml), and the mixture was heated on a steam-bath for 6 h. The solvent

[14] D. J. Brown, *J. Appl. Chem.*, 1959, **9**, 203.
[15] C. Ainsworth, *Org. Synth.*, 1959 **39**, 27.
[16] A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060.

was evaporated off and the residue triturated with acetone to give the *iodide* (1.7 g, 80%), m.p. >360° (from MeOH) (Found: C, 30.0; H, 3.6; N, 17.0. $C_8H_{11}IN_4O_2$ requires C, 29.8; H, 3.4; N, 17.4%); $\nu_{max.}$ 1 770, 1 710, 1 696, 1 626, and 1 552 cm^{-1}; $\lambda_{max.}(H_2O)$ 226 (ε 22 800) and 340 nm (10 800); δ(D_2O) 8.20 (s, H-6), 3.93 (s, NMe), 3.72 (s, NMe), and 3.64 (s, NMe). The *picrate* had m.p. >300° (Found: C, 39.6; H, 3.4; N, 22.8. $C_{15}H_{15}N_7O_9$ requires C, 39.7; H, 3.1; N, 23.1%). Prolonged heating of the mixture gave the same product contaminated with substantial amounts of tetramethylammonium iodide.

1,7-Dihydro-9*H*-purine-2,8-dione (200 mg) was similarly treated with trideuteriomethyl iodide and gave the 1,3,9-*tristrideuteriomethyl analogue* (310 mg, 69%); δ(D_2O) 8.18 (H-6).

Benzylation of 1,7-*Dihydro*-9H-*purine*-2,8-*dione*.—The purinedione (500 mg) in dimethylformamide (50 ml) containing benzyl bromide (5 ml) was heated under reflux for 12 h. The solvent was evaporated off and the residue triturated with acetone to give a dibenzyl derivative (452 mg, 41%), m.p. 340° (Found: C, 68.1; H, 5.1; N, 17.1. $C_{19}H_{18}N_4O_2$ requires C, 68.3; H, 5.4; N, 16.8%); δ[$(CD_3)_2SO$] 7.91 (s H-6), 7.39br (s, aromatic H), 5.12 (s, benzyl CH_2), and 4.93 (s, benzyl CH_2). This compound could not be methylated further with methyl iodide in dimethylformamide but could be methylated with dimethyl sulphate and aqueous N-sodium hydroxide to give a dibenzyl monomethyl purinedione (77%); δ($CDCl_3$) 7.33 (s, aromatic H), 5.12 (s, benzyl CH_2), 4.98 (s, benzyl CH_2), and 3.15 (s, NMe). The orientation of substituents was not investigated further.

1,7-*Dihydro*-1,7,9-*trimethyl*-9H- *and* 1,7-*Dihydro*-1,3,7-*trimethyl*-3H-*purine*-2,8-*dione* [(13) *and* (14)].—1,7-Dihydro-1-methyl-9*H*-purine-2,8-dione [14,17] (1 g) in aqueous N-sodium hydroxide (12.1 ml, 2.05 mol. equiv.) was stirred with dimethyl sulphate (1.54 g, 2.1 mol. equiv.) until the mixture became acidic. The solution was basified with aqueous ammonia, evaporated, and extracted with boiling chloroform. Evaporation of the extracts gave a 1 : 1 mixture (by n.m.r.) of the 1,7,9- and 1,3,7-trimethyl derivatives (1.11 g, 95%) (Found: C, 49.1; H, 5.2; N, 29.1. $C_8H_{10}N_4O_2$ requires C, 49.5; H, 5.2; N, 28.9%), which could not be separated by t.l.c. However, four recrystallizations from acetone gave yellow crystals of the 1,7,9-*trimethyl isomer* (13) (101 mg), m.p. 241—242°; $\nu_{max.}$ 1 740, 1 692, 1 638, and 1 599 cm^{-1}; δ($CDCl_3$) 7.17 (s, H-6), 3.56 (s, NMe), 3.33 (s, NMe), and 3.31 (s, NMe). The mother liquors were combined and evaporated and the residue recrystallized from ethanol (3 ×) to give the 1,3,7-*trimethyl isomer* (14) (57 mg), m.p. 235—238°; $\nu_{max.}$ 1 678, 1 580, and 1 517 cm^{-1}; $\lambda_{max.}(H_2O)$ 223 (ε 13 400), 257 (4 000), and 321 nm (8 800); δ($CDCl_3$) 6.63 (s, H-6), 3.64 (s, NMe), 3.53 (s, NMe), and 3.25 (s, NMe).

Similarly, methylation of 1,7-dihydro-9*H*-purine-2,8-dione (1 g) with dimethyl sulphate (4.4 g, 5.3 mol. equiv.) and aqueous N-sodium hydroxide (21 ml, 2.1 mol. equiv.) gave an identical 1 : 1 mixture of 1,7,9- and 1,3,7-trimethyl derivatives (1.25 g; quant.).

3,7,8,9-*Tetrahydro*-1,3,7,9-*tetramethyl*-2,8-*dioxo*-2H-*purinium Iodide* (6; R = Me).—The mixture of trimethylpurines (13) and (14) (388 mg) in dimethylformamide (50 ml) containing methyl iodide (5 ml) was heated under reflux on a steam-bath for 1 h. The solvent was removed and the residue triturated with acetone as before to give the *iodide* (410 mg, 61%), m.p. 217° (from MeOH) (Found: C, 32.0; H, 4.3; N, 16.2. $C_9H_{13}IN_4O_2$ requires C, 32.2; H, 3.9; N, 16.6%); $\nu_{max.}$ 3 460 (NH str.), 1 763 and 1 705 (CO), 1 620, and 1 549 cm^{-1}; $\lambda_{max.}(H_2O)$ 229 (ε 23 400) and 343 nm (11 400); δ(D_2O) 8.26 (s, H-6), 3.86 (s, 3-Me), 3.75 (s, 9-Me), 3.66 (s, 7-Me), and 3.35 (1-Me).

Treatment of the trimethylpurinedione (14) with trideuteriomethyl iodide in dimethylformamide as above gave the 9-*trideuteriomethyl analogue*, δ(D_2O) 8.32 (s, H-6), 3.91 (s, NMe), 3.66 (s, NMe), and 3.32 (s, NMe).

2,8-*Diamino*-1,7,9-*trimethyl*-9H-*purinium Di-iodide* (18; X = I).—2,8-Diaminopurine (1 g), treated with methyl iodide in dimethylformamide (100 ml) at 100 °C for 2.5 h as above, gave the *di-iodide* (18; X = I) (1.66 g, 60%), m.p. >200° (decomp.) (Found: C, 21.7; H, 3.4; N, 18.9. $C_8H_{14}I_2N_6$ requires C, 21.4; H, 3.1; N, 18.7%); $\lambda_{max.}(H_2O)$ 230 (ε 58 000) and 321 nm (9 200); δ(D_2O) 8.48 (s, H-6), 3.90 (s, NMe), 3.65 (s, NMe), and 3.63 (s, NMe).

2,8-*Diamino*-1,6,7,9-*tetramethylpurinium Di-iodide*.—2,8-Diamino-6-methylpurine (328 mg) in dimethylformamide (50 ml) containing an excess of methyl iodide, was heated at 100 °C under reflux for 4 h as above, gave the *di-iodide* (310 mg, 34%), m.p. 306° (decomp.) (from methanol) (Found: C, 23.1; H, 3.7; N, 17.8. $C_9H_{16}I_2N_6$ requires C, 23.4; H, 3.5; N, 18.2%); δ(D_2O) 3.72 (s, NMe), 3.70 (s, NMe), 3.40 (s, NMe), and 2.83 (s, CMe).

5,6-*Dihydro*-5-*ureidouracil* (3; $R^1 = R^2 = R^3 = R^4 =$ H).—1,7-Dihydro-9*H*-purine-2,8-dione [16] (500 mg) in aqueous 5N-hydrochloric acid (100 ml) containing platinum oxide (100 mg) was hydrogenated at 1 atm until 1 mol. equiv. of hydrogen was consumed (3—4 h) (no further uptake occurred). Filtration and evaporation, followed by recrystallization from water, gave the ureido-compound (340 mg, 60%), m.p. 215° (lit.,[6] 212—213°) (Found: C, 34.8; H, 4.9; N, 32.3. Calc. for $C_5H_8N_4O_3$: C, 34.9; H, 4.7; N, 32.6%); *m/e* 172 (M^+), 155, 129, 112, and 100; $\nu_{max.}$ 3 440, 3 360 and 3 320 (NH), 1 780 and 1 713 (CO), 1 575, and 1 430 cm^{-1}; δ[$(CD_3)_2SO$] 7.76 (s, NH), 6.02 (t, NH, *J* 7.0), 5.59 (s, NH_2), 4.05 (t, H-5, $J_{5.6}$ 5.0), and 3.30 (t, H-6, $J_{5.6}$ 5.0); δ(D_2O) 4.30 (t, H-5, $J_{5.6}$ 5.0) and 3.53 (d, H-6, $J_{5.6}$ 5.0); δ(2N-NaOD) 3.42 (s, H-6); δ(N-DCl) 4.37 (dd, $J_{5.6}$ 5.5, $J_{5.6'}$ 7.0) and 3.5 (m, H-6, AB of ABX).

5,6-*Dihydro*-1,3-*dimethyl*-5-N′-*methylureidouracil* (3; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H).—3,7,8,9-Tetrahydro-1,3,9-trimethyl-2,8-dioxo-2*H*-purinium iodide (6; R = Me) (200 mg) in water (25 ml) containing platinum oxide (100 mg) was catalytically hydrogenated at 1 atm and 20 °C for 1 h as above. The residue left after evaporation was extracted with ethanol and the extracts were concentrated, whereupon the *ureido-compound* (87 mg, 65%) crystallized from solution; m.p. 218° (Found: C, 44.3; H, 6.8; N, 25.4. $C_8H_4N_4O_3$,0.15H_2O requires C, 44.1; H, 6.6; N, 25.7%); *m/e* 214 (M^+), 184 (M^+ — MeNH), 156, 141, 127, 114, 101, 58, 44, 30, and 28; $\nu_{max.}$ 1 761 and 1 720 (CO), 1 635, 1 558, and 1 483 cm^{-1}; δ($CDCl_3$) 6.90br (s, NH), 4.75br (m, MeN*H*), 4.23 (m, H-5, X of ABX), 3.75 (m, H-6, AB of ABX), 3.00 (s, NMe), 2.90 (s, NMe), and 2.80 (d, *Me*NH, *J* 4.5); δ(D_2O) 4.55 (t, H-5, $J_{5.6}$ 4.0), 3.84 (d, H-6, $J_{5.6}$ 4.0), 3.10 (s, NMe), 3.04 (s, NMe), and 2.82 (s, NMe).

5-(NN′-*Dimethylureido*)-5,6-*dihydro*-1,3-*dimethyluracil* (3; $R^1 = R^2 = R^3 = R^4 =$ Me).— 3,7,8,9-Tetrahydro-1,3,7,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide (168 mg) was reduced catalytically as above to give the *ureido-compound* (80 mg, 70%), m.p. 122—124° (sublimed at 160° and 0.07

[17] C. O. Johns, *J. Biol. Chem.*, 1912, **11**, 393.

mmHg) (Found: C, 47.0; H, 7.2; N, 24.4. $C_9H_{16}N_4O_3$ requires C, 47.4; H, 7.1; N, 24.6%); $\nu_{max.}$ 3 405 (NH str.), 1 767, 1 709, and 1 635 cm^{-1}; $\delta(CDCl_3)$ 4.66br (m, N*H*Me), 3.78 (m, H-5 and H-6), 2.99 (s, NMe), 2.95 (s, NMe), 2.86 (s, NMe), and 2.75 (d, NH*Me*, $J_{Me,NH}$ 3.0).

2-*Amino*-5-*guanidino*-1,4,5,6-*tetrahydro*-4-*oxopyrimidinium Dipicrate* (15; $R^1 = R^2 = R^3 = H$, X = *picrate*).—2,8-Diaminopurine (400 mg) in aqueous 5N-hydrochloric acid (25 ml) containing platinum oxide (100 mg) was hydrogenated at 4.6 atm and 20 °C for 4 h. Filtration and evaporation gave the *pyrimidinium dichloride* (630 mg, quant.) as a hygroscopic gum; $\delta(D_2O)$ 4.69 (t, H-5, $J_{5.6}$ 5.0) and 3.96 (d, H-6, $J_{5.6}$ 5.0). The *dipicrate* had m.p. 227.5—228° (from water) (Found: C, 32.3; H, 3.0; N, 26.3. $C_{17}H_{16}N_{12}O_{15}$ requires C, 32.5; H, 2.7; N, 26.7%); $\nu_{max.}$ 1 780, 1 711, 1 680, and 1 635 cm^{-1}.

2-*Amino*-5-NN′-*dimethylguanidino*-1,4,5,6-*tetrahydro*-1-*methyl*-4-*oxopyrimidinium Dipicrate* (15; $R^1 = R^2 = R^3 =$ Me, X = *picrate*).—The di-iodide (18; X = I) (500 mg) in water (20 ml) containing platinum oxide (200 mg) was hydrogenated at 1 atm and 20 °C for 2 h. Filtration and evaporation gave the *pyrimidinium di-iodide* (497 mg, quant.) as a hygroscopic solid; *m/e* 254 (M^+ — NHMe), 139, and 128; $\nu_{max.}$ 1 771, 1 682, 1 646, and 1 611 cm^{-1}; $\delta(D_2O)$ 4.74 (t H-5, $J_{5.6}$ 6.0), 3.94 (d, H-6, $J_{5.6}$ 6.0), 3.28 (s, 2 × NMe), and 3.15 (s, NMe). The *dipicrate* had m.p. 190° (from methanol) (Found: C, 36.2; H, 3.4; N, 25.0. $C_{20}H_{22}N_{12}O_{15}$ requires C, 35.8; H, 3.3; N, 25.1%); $\delta[(CD_3)_2SO]$ 9.60br (s, NH), 8.67 (s, picrate H), 8.07 (d, NH, *J* 2.0), 7.43 (s, 2 × NH_2), 4.63 (m, H-5), 3.80 (m, H-6), 3.10 (s, 2 × NMe), and 3.05 (s, NMe).

2-*Amino*-3,4,5,6-*tetrahydro*-4-*oxo*-5-*ureidopyrimidinium Picrate*.—2-Amino-7,9-dihydropurin-8-one [14] (655 mg) in aqueous 5N-hydrochloric acid (50 ml) containing platinum oxide was hydrogenated at 4.6 atm and 20 °C for 24 h as before, and gave the *pyrimidinium chloride* (734 mg, 98%) as a hygroscopic gum; $\delta(D_2O)$ 4.16 (t, H-5, $J_{5.6}$ 5.0), 3.35 (d, H-6, $J_{5.6}$ 5.0), 3.02 (d, H-6′, $J_{5.6'}$ 5.0). The *picrate* had m.p. 221° (from methanol; another form of the picrate was discarded) (Found: C, 33.1; H, 3.1; N, 27.8. $C_{11}H_{12}N_8O_9$ requires C, 33.0; H, 3.0; N, 28.0%); $\nu_{max.}$ 3 465, 3 410, 3 380 and 3 210 (NH str.), 1 737, 1 694, and 1 642 cm^{-1}; $\delta[(CD_3)_2SO]$ 8.58 (s, picrate H), 7.54 (s, NH_2), 6.43 (d, NH, *J* 7.5), 5.83 (s, NH_2), 4.56 (m, H-5), 3.66 (dd, H-6, $J_{5.6}$ 7.5, $J_{6.6'}$ 12.5), 3.34 (t, H-6′ $J_{5.6'}$ 12.5, $J_{6.6'}$ 12.5); the H-5 signal became a dd ($J_{5.6}$ 7.5, $J_{5,6'}$ 12.5) on D_2O addition.

4-*Acetoxy*-cis-*perhydropurine*-2,8-*dione* (8; $R^1 = R^2 = R^3 = R^4 =$ H).—The ureidopyrimidine (3; $R^1 = R^2 = R^3 = R^4 =$ H) (1.1 g) in acetic anhydride (20 ml) was refluxed for 20 min and cooled, and the crystalline solid was filtered off and dried at 110 °C giving the *acetoxyperhydropurine* (645 mg, 48%), m.p. 295° (sublimed at 280° and 0.03 mmHg) (Found: C, 39.0; H, 4.9. $C_7H_{10}N_4O_4$ requires C, 39.3; H, 4.7%); *m/e* 214 (M^+), 185, 171, 142, 129, 112, 103, and 100; $\nu_{max.}$ 1 730 (ester CO), 1 670 (CO), and 1 540 cm^{-1}; $\delta[(CD_3)_2SO]$ 11.72 (s, NH), 11.49 (s, NH), 8.84 (d, NH, *J* 6.0), 7.68 (s, NH), 4.30 [dd (after D_2O addn.), H-5, $J_{5.6}$ 4.7, $J_{5,6'}$ 7.5], 3.72 (dd, H-6, $J_{5.6}$ 4.7, $J_{6.6'}$ 13.5), 3.40 (dd, H-6′, $J_{5.6'}$ 7.5 $J_{6.6'}$ 13.5), and 2.06 (s, Me); δ(N-DCl) 4.22 (m, H-5), 3.53 (m, H-6), and 1.93 (s, Me).

This compound (43 mg) in 2N-sodium hydroxide (2 ml) under reflux for 1 h gave the ureidopyrimidine (3; $R^1 = R^2 = R^3 = R^4 =$ H) (quant.).

Cyclization of the 5,6-dihydro-1,3-dimethyl-5-*N*′-methylureidouracil (3; $R^1 = R^2 = R^4 =$ Me $R^3 =$ H) (20 mg) in refluxing acetic anhydride (2 ml) gave 4-*acetoxy*-1,3,9-*trimethyl*-cis-*perhydropurine*-2,8-*dione* (8; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H) (22 mg) as a glassy solid which could not be sublimed or recrystallized; *m/e* 241 (M^+ — Me), 198, 184, 156, 143, and 114; $\nu_{max.}$ 1 720 (CO), 1 645, and 1 455 cm^{-1}; $\delta(CDCl_3)$ 4.68 (dd, H-5, $J_{5.6}$ 5.0, $J_{5,6'}$ 5.5), 4.10 (dd, H-6, $J_{5.6}$ 5.5, $J_{6,6'}$ 14.1), 3.77 (dd, H-6′ $J_{5,6'}$ 5.0 $J_{6.6'}$ 14.1), 3.06 (4 × s, 2 × NMe, 2 conformers), 2.56 (s, NMe), and 2.02 and 2.12 (2 × s, Ac, 2 conformers).

5-(NN′-*Dimethylureido*)-1,3-*dimethyluracil* (9; $R^1 = R^2 = R^3 = R^4 =$ Me).—The tetramethyl iodide (6; R = Me) (336 mg) in water (2 ml) was treated with sodium hydroxide (45 mg, 1.1 mol. equiv.) and the solution evaporated. The residue was extracted with chloroform and the extracts were evaporated to give the *ureido-compound* (212 mg, 94%), m.p. 198—200° (from benzene–methanol, 5 : 1) (Found: C, 47.7; H, 6.2; N, 24.8. $C_9H_{14}N_4O_3$ requires C, 47.8; H, 6.2; N, 24.8%); $\nu_{max.}$ 1 704 and 1 658 (CO), 1 640, and 1 536 cm^{-1}; $\lambda_{max.}(H_2O)$ 206 (ε 8 000) and 275 nm (5 800); $\delta(CDCl_3)$ 7.48 (s, H-6), 3.43 (s, NMe), 3.37 (s, NMe), 3.19 (s, NMe), and 2.86 (d, MeNH, $J_{Me,NH}$ 5.0).

Similarly the 9-trideuteriomethyl iodide (27 mg) gave 1,3-dimethyl-5-(*N*-methyl-*N*′-trideuteriomethylureido)-uracil (9; $R^1 = R^2 = R^3 =$ Me, $R^4 = CD_3$) (18 mg, 97%), $\delta(CDCl_3)$ 7.45 (s, H-6), 3.42 (s, NMe), 3.35 (s, NMe), and 3.17 (s, NMe).

1,3-*Dimethyl*-5-N′-*methylureidouracil* (9; $R^1 = R^2 = R^4 =$ Me, $R^3 =$ H).—The iodide (6; R = H) (220 mg) in water (5 ml) was treated with aqueous 2N-sodium hydroxide (0.5 ml, 1.5 mol. equiv.). Fine needles of the *uracil* (81 mg, 57%) crystallized out, and were collected and washed with water; m.p. 235 and 332° (from EtOH) (Found: C, 45.3; H, 6.0; N, 26.2. $C_8H_{12}N_4O_3$ requires C, 45.3; H, 5.7; N, 26.4%); *m/e* 212 (M^+); $\lambda_{max.}(H_2O)$ 208 (ε 9 400) and 277 nm (6 400); $\nu_{max.}$ 3 430 and 3 320 (NH), 1 705 (CO), 1 670 (urea CO), 1 627, and 1 567 cm^{-1}; $\delta[(CD_3)_2SO]$ 8.17 (s, H-6), 7.78 (s, NH), 6.65br (m, NH), 3.33 (s, NMe), 3.24 (s, NMe), and 2.63 (d, *Me*NH, $J_{Me,NH}$ 4.0); the product was identical with an authentic sample prepared by fusion of 5-amino-1,3-dimethyluracil (155 mg) [18] with *NN*′-dimethylurea (348 mg, 4 mol. equiv.) at 200 °C for 1 h. The residue was dissolved in boiling water and the solution cooled to give the uracil.

1,3,6-*Trimethyl*-5-N′-*methylureidouracil*.— 3,7,8,9-Tetrahydro-1,3,6,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide (200 mg) was treated with sodium hydroxide (1.1 mol. equiv.) as before and gave the *ureido-compound* (69 mg, 50%) (sublimed at 300° and 0.05 mmHg without melting) (Found: C, 47.9; H, 6.4; N, 24.6. $C_9H_{14}N_4O_3$ requires C, 47.8; H, 6.2; N, 24.8%); $\nu_{max.}$ 3 335 and 3 305 (NH str.), 1 699, 1 648, and 1 579 cm^{-1}; $\lambda_{max.}(H_2O)$ 206 (ε 11 200) and 273 nm (9 200); $\delta(CDCl_3)$ 3.45 (s, NMe), 3.37 (s, NMe), 2.80 (d, NHMe, $J_{NH,Me}$ 5.0), and 2.30 (s, CMe).

The Electrolytic Cell.—The cell (*cf.* Tafel [6]) consisted of a lead beaker (cathode) immersed in an ice-bath. The anode was essentially a large cold finger made of lead through which a cold stream of brine (−5 °C) flowed. The anode solution (generally aqueous 21N-sulphuric acid) was separated from the cathode solution (10% w/w solution of uric acid in aqueous 25.8N-sulphuric acid) by a porous clay pot. The latter was made from brick-clay fired at 800 °C for 48 h. Pots made from other finer clays were not sufficiently

[18] W. Pfleiderer and E. Liedek, *Annalen*, 1958, **612**, 184.

porous and the resistance to the current flow was too great. Similarly, the use of more viscous, concentrated sulphuric acid (*e.g.* >30N) also increased the resistance of the circuit because of the collection of gas bubbles on the surface of the electrodes. The current was supplied by a variable-voltage battery charger.

Electrolytic Reductions.—(a) *Of* 1,7-*dihydro*-9H-*purine*-2,8-*dione* (2; $R^1 = R^2 = R^3 = R^4 = H$). The purine (1 g) in 25.8N-sulphuric acid (15 ml) was reduced electrochemically (2 A, 8 V at <10 °C for 2 h; reduction complete by u.v.). The mixture was diluted with ice and water (45 g) and treated with barium carbonate (45 g) with stirring. This mixture was then worked up as before to give a residue which was recrystallized from water (2.5 ml) and gave 5-ureidoperhydropyrimidine-2,4-dione (3; $R^1 = R^2 = R^3 = R^4 = H$). The mother liquors were triturated with methanol to give *cis*-perhydropurine-2,8-dione (401 mg, 40%), identical with 'purone' prepared by Tafel,[6] $\nu_{max.}$ 3 300 (NH), 1 710, 1 656 (CO), 1 530, 1 465, 1 322, and 1 266 cm^{-1}.

(b) *Of uric acid.* Uric acid (2.5 g) in aqueous 25.8N-sulphuric acid (25 ml) was electrochemically reduced (3 A, 8 V at 5—8 °C for 4.25 h; reduction shown to be complete by u.v.). The mixture (3 : 1) was worked up as above to give the *cis*-perhydropurine-2,8-dione (800 mg, 34%), identical with the above sample.

In a second reduction, uric acid (15 g) in aqueous 29.4N-sulphuric acid (150 ml) was electrolysed at 4.5 A for 8 h at 20—24 °C. The acid mixture (3 : 1) was diluted with ice and water (370 ml) and treated with barium carbonate (750 g) in portions and then stirred until effervescence ceased. The still acidic mixture was filtered and the filtrate neutralized with aqueous barium hydroxide and filtered. The filtrate was evaporated to 10 ml to allow crystallization of the ureidotetrahydropyrimidine (1.8 g, 11%), identical with the above sample.

(c) *Of* 2,8-*diaminopurine*. 2,8-Diaminopurine (1 g) in 10M-sulphuric acid (15 ml) was reduced with 4.0 A (8 V) for 1.5 h at 5—8 °C. The mixture was worked up as above to give a residue (800 mg) containing the *cis*-tetrahydropurine (16; $R^1 = R^2 = R^3 = H$, $2X = SO_4$), the guanidinotetrahydropyrimidine (15; $R^1 = R^2 = R^3 = H$, $2X = SO_4$), and the *dihydro-compound* (17) (3 : 2 : 1). The sulphate (15; $R^1 = R^2 = R^3 = H$, $2X = SO_4$) was easily removed by recrystallization from water and had spectral properties identical with those described before. The tetrahydropurine could not be separated from compound (17) by recrystallization or by preparation of the mixture of dipicrates and recrystallization. Only the H-4 signal of the tetrahydropurine ($J_{4.5}$ 8.5) could be clearly seen in the n.m.r. spectra.

The same mixture of products was obtained from electrolytic reduction of 2,8-diaminopurin-6-ol.[19,20]

1,3,9-*Trimethyl*-cis-*perhydropurine*-2,8-*dione* (2; $R^1 = R^2 = R^4 = Me$, $R^3 = H$).—3,7,8,9-Tetrahydro-1,3,9-trimethyl-2,8-dioxo-2*H*-purinium iodide (6; R = H) (200 mg) in water (10 ml) was treated with sodium borohydride (284 mg, 13 mol. equiv.) and the mixture set aside overnight. The aqueous solution was evaporated to dryness and the residue extracted with hot chloroform (100 ml). Evaporation of the extracts gave the hygroscopic *perhydropurine* (113 mg, 92%), m.p. 138° (from benzene) (Found: C, 47.0; H, 7.4; N, 27.4. $C_8H_{14}N_4O_2,0.33H_2O$ requires C, 47.0; H, 7.2; N, 27.4%); $\nu_{max.}$ 3 250 (NH str.), 1 673 and 1 663 (CO), and 1 519 cm^{-1}.

When an aqueous or methanolic solution of the trimethyl iodide (6; R = H) was treated with sodium borohydride (2 mol. equiv.), and the n.m.r. spectrum immediately determined, the spectrum of 1,3,6,7,8,9-hexahydro-derivative (7) was observed: $\delta(D_2O)$ 4.27 (s, H-6), 3.34 (s, NMe), 3.26 (NMe), and 2.94 (s, NMe). This intermediate was rapidly (5—10 min) converted into 1,3-dimethyl-5-*N'*-methylureidoperhydropyrimidine-2,4-dione (3; $R^1 = R^2 = R^4 = Me$, $R^3 = H$) on adjustment of the pH to 6—7 or on attempted isolation.

Reduction with sodium borohydride of the purine iodide (6; R = H) in D_2O gave the 5-deuterioperhydropurine, $\delta(D_2O)$ 4.90 (s, H-4), 3.37 (d, H-6, $J_{6.6'}$ 13.0), and 3.00 (d, H-6', $J_{6.6'}$ 13.0).

1,3,7,9-*Tetramethyl*-cis-*perhydropurine*-2,8-*dione* (2; $R^1 = R^2 = R^3 = R^4 = Me$).— 3,7,8,9-Tetrahydro-1,3,7,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide (168 mg) was reduced as above to give the *perhydropurine* (85 mg, 80%), m.p. 159—161° (from C_6H_6) (Found: C, 51.1; H, 7.2; N, 26.7. $C_9H_{16}N_4O_2$ requires C, 50.9; H, 7.6; N, 26.4%); $\nu_{max.}$ 1 700 and 1 656 (CO), and 1 509 cm^{-1}.

When a methanolic solution of the same iodide was treated with sodium borohydride, the n.m.r. spectrum of the 1,3,6,7,8,9-hexahydro-derivative was observed: $\delta(D_2O)$ 4.64 (s, H-6), 3.40 (s, NMe), 3.33 (s, NMe), 3.20 (s, NMe), and 3.00 (s, NMe). Again this intermediate readily gave 5-(*NN'*-dimethylureido)-1,3-dimethylperhydropyrimidine-2,4-dione; the hexahydropurine could not be isolated.

1,7,9-*Trimethyl*-cis-*perhydropurine*-2,8-*dione* (2; $R^1 = R^3 = R^4 = Me$, $R^2 = H$).—1,7-Dihydro-1,7,9-trimethyl-9*H*-purine-2,8-dione (13) (30 mg) in water (1 ml) was treated with sodium borohydride (38 mg) as above to give the *perhydropurine* (35 mg, quant.), m.p. 125—126° (from C_6H_6) (Found: C, 48.6; H, 7.1; N, 28.0. $C_8H_{14}N_4O_2$ requires C, 48.5; H, 7.1; N, 28.3%); $\nu_{max.}$ 3 242 (NH str.), 1 715 and 1 690 (CO), 1 653, and 1 532 cm^{-1}.

1,3,7-*Trimethyl*-cis-*perhydropurine*-2,8-*dione* (2; $R^1 = R^2 = R^3 = Me$, $R^4 = H$).— 1,7-Dihydro-1,3,7-trimethyl-3*H*-purine-2,8-dione (14) (30 mg) was treated as above to give the *perhydropurine* (23 mg, 75%), m.p. 183—184° (from C_6H_6) (Found: C, 48.4; H, 6.8; N, 28.1. $C_8H_{14}N_4O_2$ requires C, 48.5; H, 7.1; N, 28.3%); $\nu_{max.}$ 3 303 (NH str.), 1 716 and 1 690 (CO), 1 657, 1 515, and 1 417 cm^{-1}.

(4*R**,5*S**,6*S**)-1,3,6,9-*Tetramethyl*-cis-*perhydropurine*-2,8-*dione* (11).—1,7-Dihydro-6-methyl-9*H*-purine-2,8-dione [21] (1 g) was methylated with methyl iodide in dimethylformamide as for 1,7-dihydro-9*H*-purine-2,8-dione to give the *trimethylpurinium iodide* (1.7 g, 85%), $\delta(D_2O)$ 3.93 (s, NMe), 3.70 (s, NMe), 3.60 (s, NMe), and 2.57 (s, 6-Me); $\lambda_{max.}(H_2O)$ 226 (ε 24 000) and 338 nm (10 700), containing a small amount of dimethyl impurity which was removed by recrystallization from ethanol.

The purinium iodide (200 mg) in water (5 ml) was treated with sodium borohydride (300 mg, 13 mol. equiv.) and set aside for 24 h. Evaporation and extraction with chloroform gave the cis-*perhydropurine* (99 mg, 79%), m.p. 178° (from C_6H_6) (Found: C, 50.7; H, 7.5; N, 26.1. $C_9H_{16}N_4O_2$ requires C, 50.9; H, 7.6; N, 26.4%); $\nu_{max.}$ 3 245 (NH str.), 1 694, 1 668, and 1 509 cm^{-1}. Reduction of the iodide in deuterium oxide with sodium borohydride gave the 5-

[19] R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.

[20] J. R. Spies and T. H. Harris, *J. Amer. Chem. Soc.*, 1939, **61**, 351.

[21] C. O. Johns, *Amer. Chem. J.*, 1909, **41**, 58.

deuterio-compound, δ(D_2O) 5.11 (s, H-4), *ca.* 3.5 (q, H-6, $J_{6,Me}$ 7.0), 3.25 (s, NMe), 3.01 (s, NMe), 2.97 (s, NMe), and 1.30 (d, 6-Me, $J_{Me,6}$ 7.0).

Reduction of the iodide (45 mg) in methanol with sodium borohydride occurred rapidly (by n.m.r. spectra), and evaporation and extraction gave 1,3,4,7-*tetrahydro*-1,3,6,9-*tetramethyl*-9H-*purine*-2,8-*dione* (12) (28 mg, 78%), δ($CDCl_3$) 5.75br (s, NH), 4.93 (q, H-4, $J_{4,Me}$ 1.8), 3.07 (s, NMe), 2.98 (s, NMe), 2.97 (s, NMe), 1.87 (d, 6-Me, $J_{Me,4}$ 1.8), which decomposed (24 h).

cis-2,8-*Diamino*-4,5,6,9-*tetrahydro*-1,7,9-*trimethyl*-1H-*purinium Dipicrate* (16; $R^1 = R^2 = R^3$ = Me, X = *picrate*).—The di-iodide (18; X = I) (200 mg) in water (1 ml) was treated with sodium borohydride (51 mg, 3 mol. equiv.) and set aside for 15 min. The solution was brought to pH 6 with hydrochloric acid and treated with an excess of picric acid to give the cis-*tetrahydropurinium dipicrate* (370 mg, quantitative), m.p. 223—224° (from MeOH–H_2O, 9 : 1) (Found: C, 36.9; H, 3.3; N, 25.8. $C_{20}H_{22}N_{12}O_{14}$ requires C, 36.7; H, 3.4; N, 25.7%); δ[$(CD_3)_2SO$] 8.63 (s, picrate H), 8.30 (s, NH_2), 7.71 (s, NH_2), 5.22 (dd, H-4, $J_{4,5}$ 10.0, $J_{4,NH}$ 1.8), 4.48 (dt, H-5, $J_{4,5}$ 10.0, $J_{5,6}$ 2.3), 3.59 (d, H-6, $J_{5,6}$ 2.3), 3.00 (s, NMe), 2.92 (s, NMe), and 2.87 (s, NMe).

The dipicrate was passed through an Amberlite IR-400 (OH^-) column (2 × 20 cm) in ethanol. The eluates were acidified with methanolic hydrogen chloride and evaporated to give the *dihydrochloride* (16; $R^1 = R^2 = R^3$ = Me, X = Cl) (100 mg, 90%) as a hygroscopic solid; $\nu_{max.}$ 1 675, 1 640, 1 607, and 1 569 cm^{-1}; δ(D_2O) 5.63 (d, H-4, $J_{4,5}$ 9.8), 4.57 (dt, H-5, $J_{4,5}$ 9.8, $J_{5,6}$ 2.3), 3.71 (d, H-6, $J_{5,6}$ 2.3), 3.15 (s, NMe), and 3.02 (s, 2 × NMe).

Reduction of the iodide (18) in D_2O with sodium borohydride as above gave 2,8-*diamino*-5-*deuterio*-1,7,9-*trimethyl*-cis-*perhydropurinium dipicrate*, m.p. 225° (from MeOH) (Found: C, 36.3; H + D, 3.6; N, 25.2. $C_{20}H_{21}DN_{12}O_{14}$ requires C, 36.6; H + D, 3.5; N, 25.6%); $\nu_{max.}$ 3 400 and 3 200 (NH str.), 1 664, 1 630, 1 610, 1 569, and 1 551 cm^{-1}; δ[$(CD_3)_2SO$] 8.63 (s, picrate H), 5.31 (s, H-4), 3.68br (s, H-6), 3.09 (s, NMe), and 2.98 (s, 2 × NMe).

(4*R**,5*S**,6*S**)-cis-2,8-*Diamino*-1,6,7,9-*tetramethyl*-4,5,6,7-*tetrahydro*-1H-*purinium Dipicrate* (19; X = *picrate*).—2,8-Diamino-1,6,7,9-tetramethylpurinium di-iodide (100 mg) in water (1 ml) was treated with sodium borohydride (100 mg, 12.4 mol. equiv.) and set aside overnight. The solution was neutralized with hydrochloric acid and treated with picric acid as before. The *picrate* (110 mg, 76%) had m.p. 270° (decomp.) (from water) (Found: C, 38.2; H, 4.0; N, 25.0. $C_{21}H_{24}N_{12}O_{14}$ requires C, 38.2; H, 3.6; N, 25.1%); δ[$(CD_3)_2SO$] 8.70br (m, NH), 8.67 (s, picrate H), 8.50br (s, NH_2), 7.85br (s, NH_2), 5.32 (dd, H-4, $J_{NH,4}$ 3.5, $J_{4,5}$ 8.5), 4.40 (dd, H-5, $J_{4,5}$ 8.5, $J_{5,6}$ 4.7), 4.10 (dq, H-6, $J_{5,6}$ 4.7, $J_{6,Me}$ 6.8), 3.07 (s, NMe), 3.00 (s, NMe), 2.90 (s, NMe), and 1.20 (d, CMe, $J_{Me,6}$ 6.8).

5-*Methoxy*-1,3,9-*trimethylperhydropurine*-2,8-*dione* (10).—A concentrated solution of 1,6,7,9-tetrahydro-1,3,9-trimethyl-3*H*-purine-2,8-dione (7) in methanol was prepared by addition of sodium borohydride (300 mg) 3,7,8,9-tetrahydro-1,3,9-trimethyl-2,8-dioxo-2*H*-purinium iodide (6; R = H) (322 mg) in methanol (100 ml), followed by evaporation to *ca.* 2 ml. The mixture was then treated with nitroacetic acid [9] (1 g), heated at 50—70 °C until effervescence ceased, then evaporated; the residue was extracted with chloroform. Evaporation of the extracts left an oil which was a mixture of the methoxy-compound and 5,6-dihydro-1,3-dimethyl-5-*N'*-methylureidouracil (3; $R^1 = R^2 = R^4$ = Me, R^3 = H). This was chromatographed on preparative alumina thin-layer plates ($CHCl_3$ containing 2% MeOH), and the major band with R_F 0.4 was removed and extracted with boiling $CHCl_3$–MeOH (1 : 1) to give the 5-*methoxy-compound* (52 mg, 23%), m.p. 122° (sublimed at 170° and 0.1 mmHg) (Found: C, 47.5; H, 7.1. $C_9H_{16}N_4O_3$ requires C, 47.4; H, 7.1%); *m/e* 228 (M^+), 213, 196, 158, and 128; $\nu_{max.}$ 3 485 and 3 300 (NH str.), 1 715 and 1 659 (CO), and 1 516 cm^{-1}; δ($CDCl_3$) 6.67 (s, NH), 4.63 (s, H-4), 3.27 (s, OMe), 3.47 (d, H-6, $J_{6,6'}$ 12.5), 3.02 (d, H-6′, $J_{6,6'}$ 12.5), 3.07 (s, NMe), 2.93 (s, NMe), and 2.90 (s, NMe).

Similarly, the 1,3,9-tristrideuteriomethyl analogue gave 1,3,9-*tristrideuteriomethyl*-5-*methoxyperhydropurine*-2,8-*dione*; δ($CDCl_3$) 5.90br (s, NH), 4.57 (s, H-4), 3.45 (d, H-6, $J_{6,6'}$ 12.5), and 3.00 (d, H-6′, $J_{6,6'}$ 12.5).

Attempted reactions of nitroacetic acid with the purine iodides (6), with *cis*-4-acetoxyperhydropurine-2,8-dione (8; $R^1 = R^2 = R^3 = R^4$ = H), and with the ureido-compound (3; $R^1 = R^2 = R^3 = R^4$ = H) were unsuccessful; starting material was recovered in each case.

2,8-*Diaminopurine*.—(a) *From* 2,4,5-*triaminopyrimidine*.[12] The triaminopyrimidine (12.5 g) and cyanogen bromide (26 g, 2.5 mol. equiv.) in methanol (1 l) were refluxed for 4 h. The solvent was evaporated off and the residue in hot water (50 ml) was basified with aqueous ammonia, treated with charcoal, and filtered. Refrigeration of the filtrate precipitated the diaminopurine (7.1 g, 47%), m.p. 296° (lit.,[19] 296°); pK_a 1.52 and 6.05.

(b) *From* 2-*amino*-8-*methylthiopurine*.[12] The methylthiopurine (3.6 g) in 14N-ammonia (8.6 ml) and water (8.6 ml) containing traces of copper-bronze and copper acetate was heated in a sealed tube at 170 °C for 48 h. The solution was then boiled with charcoal, filtered, and evaporated and the residue extracted with boiling methanol (50 ml), leaving 2,8-diaminopurine (1.25 g, 39%), m.p. 296° (lit.,[19] 296°).

2,8-*Diamino*-6-*methylpurinium Sulphate*.—2,4,5-Triamino-6-methylpyridine (1.39 g), cyanogen bromide (2.6 g, 2.5 mol. equiv.), and methanol (100 ml) were refluxed for 12 h. The product was passed through an Amberlite IR-400 (OH^-) column in water. The eluates were evaporated to 10 ml, treated with charcoal, boiled, filtered, and cooled giving the diaminopurine (460 mg, 30%), m.p. 320° (from water); δ(D_2O) 2.38 (s, Me); δ[$(CD)_3SO$] 7.53br (2 × NH_2) and 2.40 (s, Me). A sample was converted into the *sulphate* by recrystallization from aqueous 2N-sulphuric acid; m.p. 270° (Found: C, 27.4; H, 4.1; N, 31.8. $C_6H_{10}N_6O_4S$ requires C, 27.5; H, 3.8; N, 32.0%); $\lambda_{max.}$(H_2O) 231 (ε 19 600), 263 (7 900), and 309 nm (8 100).

2,4,5-*Triamino*-6-*hydroxymethylpyrimidine*.—2,4,5-Triamino-6-ethoxycarbonylpyrimidine [22] (30 g) in methanol (1 l) was treated with sodium borohydride (74.5 g, 13 mol. equiv.) in portions; the mixture was set aside for 5 h and then refluxed for 1 h. The solution was neutralized with methanolic hydrogen chloride and filtered. The filtrate was passed through an Amberlite IR-400 (OH^-) column (4 × 50 cm) in methanol. Evaporation of part of the methanol gave the crystalline *triaminopyrimidine* (20.1 g, 85%), m.p. 183—185° (decomp.), *m/e* 155 (M^+), 137, 126, and 109; δ[$(CD_3)_2SO$] 6.01 (s, NH_2), 5.18 (s, NH_2), 4.27 (s, CH_2·OH), and 3.69 (s, NH_2). Recrystallization from aqueous 5N-sulphuric acid gave the *sulphate*, decomp.

[22] J. Clark and G. R. Ramage, *J. Chem. Soc.*, 1958, 2821.

>200° (Found: C, 22.8; H, 4.5; N, 27.0. $C_5H_9N_5O,H_2SO_4,H_2O$ requires C, 22.9; H, 4.6; N, 26.7%).

2,8-*Diamino*-6-*hydroxymethylpurine*.—The triamino-6-hydroxymethylpyrimidine (above) (15.5 g) and cyanogen bromide (26.0 g, 2.5 mol. equiv.) in methanol (1 l) were refluxed for 4 h as before to give crude 2,8-diamino-6-hydroxymethylpurine (8.3 g, 46%); δ(D_2O) 4.90 (s, CH_2OH) [lit.,[13] δ(D_2O) 4.90 (s, CH_2OH)].

2-*Amino*-7,9-*dihydro*-7-*methylpurin*-8-*one* (20; R = Me). —2-Amino-7,9-dihydropurin-8-one [14] (151 mg) was methylated with methyl iodide in dimethylformamide (100 °C; 2 h) to give 2-*amino*-7,9-*dihydro*-7-*methylpurin*-8-*one hydroiodide* (230 mg, 79%), m.p. 289° (from water) (Found: C, 24.0; H, 3.4; N, 22.9. $C_6H_5IN_5O,0.5H_2O$ requires C, 23.9; H, 3.0; N, 23.2%); δ(D_2O) 7.98 (s, H-6) and 3.82 (s, NMe).

The above iodide in water (0.5 ml) was brought to pH 7 with aqueous sodium hydroxide to give the free base, m.p. 300° (Found: C, 39.6; H, 5.2; N, 38.2. $C_6H_7N_5O$ requires C, 39.3; H, 5.0; N, 38.2%); $\nu_{max.}$ 3 340 and 3 165 (NH str.), 1 678, 1 645, 1 583, and 1 550 cm^{-1}; δ[$(CD_3)_2SO$] 7.07 (s, H-6), 7.02br (s, NH_2), and 3.45 (s, NMe).

Similarly, the 7-trideuteriomethyl analogue (20; R = CD_3) (76%) was prepared by using trideuteriomethyl iodide.

1,7-*Dihydro*-9H-7-*methylpurine*-2,8-*dione*.— 2-Amino-7,9-dihydro-7-methylpurin-8-one (20; R = Me) (500 mg) in aqueous 2N-hydrochloric acid (25 ml) was treated in portions with sodium nitrite (750 mg) over 4 h at 20 °C. The solution was then neutralized with aqueous ammonia and evaporated to 5 ml, whereupon the *dioxopurine* precipitated (350 mg, 71%), m.p. 350° (from water) (Found: C, 38.8; H, 4.0; N, 30.1. $C_6H_6N_4O_2,H_2O$ requires C, 39.1; H, 4.4; N, 30.4%); $\nu_{max.}$ 3 480 and 3 260 (NH str.), 1 665, 1 536, and 1 500 cm^{-1}; δ(2N-DCl) 8.27 (s, H-6) and 4.18 (s, NMe). The 7-trideuteriomethyl compound was similarly prepared by using trideuteriomethyl iodide. Methylation of the dione (100 mg) in aqueous sodium hydroxide (1.2 ml, 2 mol. equiv.) gave a mixture of trialkylpurines with spectral properties identical with those of the 1,7-dihydro-1,3,7- and -1,7,9-trimethylpurine-2,8-diones except for the absence of the 7-methyl signal.

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