177. *New Potential Chemotherapeutic Agents. Part VII. Experiments on the Synthesis of 8-Aminopurines.*

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With the possibility that the synthesis of potential adenine inhibitors might lead to a plasmodicidal compound, the preparation of basically-substituted purines related to adenine, *e.g.* (II; R = NH·$[CH_2]_3$·NEt_2), has been investigated. The principal intermediates obtained in this research are the previously unknown purines (V; R = NHPh) and (VI; R = OH), and the triazole (IX; R = Me), but only in (VI; R = OH), the methylthio-group of which does not react with amines, was it possible to replace the 6-hydroxyl group by a basic substituent. The arylcarbamides (IV; R = SH) and (IV; R = NH_2) were resistant to cyclisation, but the derivative (IV; R = OH) was successfully converted into (V; R = NHPh), which was also directly obtained from the hydrochloride of (III) and phenylcyanamide in boiling butanol, possibly through the *O*-butyl ether (IV; R = O·C_4H_9).

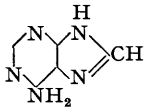
IN its application to antimalarial compounds, the current theory as to the mode of action of the more specific chemotherapeutic agents was first expressed by Oesterlin (*Klin. Woch.*, 1936, **15**, 1719), who suggested that the activity of mepacrine and pamaquin arose from their easy reduction to dihydro-derivatives, a property which enabled them to inhibit some riboflavin-containing enzyme essential to the metabolism of the parasite. The close structural resemblance of these drugs to riboflavin is in agreement with this idea, and the ability, not only of mepacrine but also of some of the newer pyrimidine antimalarials (see Curd and Rose, *J.*, 1946, 343 *et seq.*), to function as riboflavin antagonists has recently been experimentally demonstrated in nutritional investigations with *Lactobacillus casei* by Madinaveitia (*Biochem. J.*, 1946, **40**, 373).

If, as these observations seem to imply, antimalarial action is dependent on the inhibition of well-known enzymes, it should also be possible, by means of suitably constituted reagents, to arrest the growth of the plasmodia by interfering with the synthesis or utilisation of other co-enzyme constituents, for example, the purines adenine and guanine. Such a hypothesis has, in fact, lately been propounded by Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1946, 360) to account for the antimalarial properties of certain 5-methylpyrimidines, which these authors consider may be due to blocking of the purine biosynthesis by the 5-substituent. From considerations similar to those advanced by Todd and his colleagues (*loc. cit.*), it occurred to us that useful results might follow from the preparation of purine bases as potential antimalarial agents, and we were for a time engaged in the synthesis of appropriately substituted compounds related to adenine (I).

The derivatives of (I) considered most likely to possess biological activity were those incorporating the characteristic dialkylaminoalkylamino- side chain and the chlorinated or methoxylated aniline residue typical of what may be termed the riboflavin antimalarials. Of the several possible arrangements of these presumably essential components about the adenine, or somewhat more readily obtainable 2-methyladenine, nucleus, that shown as (II; R = NH·$[CH_2]_3$·NEt_2) was selected as the first objective. Although the project has made some progress, its full development has been hindered by unexpected difficulties, the nature of which is indicated in the following account of the experiments.

With 4 : 5-diamino-6-hydroxy-2-methylpyrimidine (III) as the starting point, the sequence of reactions in the proposed synthesis of (II; R = NH·$[CH_2]_3$·NEt_2) was (i) formation of the 5-*p*-chlorophenylthiocarbamido-derivative; (ii) its cyclisation to 8-*p*-chloroanilino-6-hydroxy-2-methylpurine (II; R = OH); (iii) replacement of the 6-hydroxyl group by chlorine, giving

(II; R = Cl); and (iv) substitution of the chlorine by a diethylaminopropylamino-group. Since there was no reason to suppose that the necessary conditions would be appreciably affected by slight variations in structure, the reactions were for the most part investigated with the anilino- rather than the *p*-chloroanilino-derivatives.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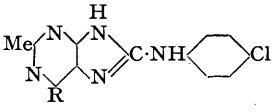
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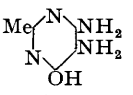
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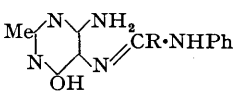
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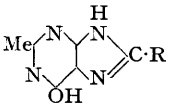
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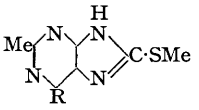
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The action of ammonium phenyldithiocarbamate on the diaminopyrimidine (III) in aqueous solution at 100° gave the *5-phenylthiocarbamido*-derivative (IV; R = SH), but the latter remained unchanged on attempted ring-closure in boiling water, and with lead hydroxide in refluxing ethanol or *iso*amyl alcohol. Methylation to the potentially more reactive methylthio-compound (IV; R = SMe) could not be accomplished. However, prolonged heating of (IV; R = SH) with pyridine effected cyclisation, but with the elimination of aniline, so that the product was *6-hydroxy-8-mercapto-2-methylpurine* (V; R = SH). The constitution of this compound was confirmed by means of an independent synthesis from the diamine (III) by fusion with thiourea, and also by the formation of *6-hydroxy-8-methylthio-2-methylpurine* (V; R = SMe) on treatment with methyl iodide in aqueous sodium hydroxide. Unfortunately, the methylthio-derivative could not be utilised for the synthesis of the 8-anilinopurine (V; R = NHPh), or even of (V; R = NH·$[CH_2]_3$·NEt_2), since it failed to react with either aniline or γ-diethylaminopropylamine.

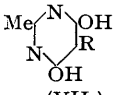
In order to permit of the use of other methods of ring-closure to the required base (V; R = NHPh), the original scheme was modified by substituting as an intermediate *4-amino-5-(N'-phenylcarbamido)-6-hydroxy-2-methylpyrimidine* (IV; R = OH), which was prepared from (III) by the action of phenyl *iso*cyanate in boiling toluene. Treatment of the carbamidopyrimidine with both phosphoryl chloride and phosphorus pentachloride under various conditions did not succeed in giving any purifiable substance, but with phosphorus trichloride in refluxing toluene a product having the composition of the required *8-anilino-6-hydroxy-2-methylpurine* (V; R = NHPh) was obtained. Since there is also a possibility of reaction between the substituents at the 5- and the 6-position, which would result in the formation of 6-amino-8-hydroxy-9-phenyl-2-methylpurine, the synthesis did not provide definite proof of the constitution of the new base. Moreover, the product exhibited an unexpected stability towards chlorinating agents, a property which could be interpreted as a further manifestation of the inertness of the 8-substituent already encountered in the analogous 8-methylthiopurine (V; R = SMe). Accordingly, a method was designed for the synthesis of (V; R = NHPh) which would leave the structure of the final product in no doubt. This involved the preparation of the guanidine (IV; R = NH_2) which was effected by prolonged heating of (III), in the form of its hydrochloride, with phenylcyanamide in refluxing ethanol. The condensation was repeated with p-*chlorophenylcyanamide*, both guanidines being further identified by their *hydrochlorides* and *picrates*, but in no circumstances could the cyclisation of either guanidine be achieved. Nevertheless, the product (V; R = NHPh) was ultimately obtained when attempting to accelerate the reaction of phenylcyanamide with the pyrimidine (III) by using boiling butanol instead of ethanol as solvent. The base gave a dihydrated *hydrochloride* and was in every respect identical with the substance already prepared from (IV; R = OH), the constitution of which is thus established.

The derivative (IV; R = NH_2) could not be detected in the reaction product, and together with the fact that it failed to cyclise under similar conditions, it is fairly certain that the guanidine is not an intermediate in the cyclisation. It is possible to suggest an explanation for the variation of product with solvent if the likely supposition is made that a preliminary step is the formation from the cyanamide of an imino-ether, Ph·NH·C(:NH)·O-alkyl. Two alternatives are then possible in the subsequent condensation with the pyrimidine 5-amino-group: (i) elimination of alcohol, giving the guanidine (IV; R = NH_2); or (ii) loss of ammonia, a reaction

similar to that introduced by Schmidt (*Ber.*, 1914, **47**, 2548) for the preparation of *N*-substituted imino-ethers, giving (IV; R = O-alkyl). Normally, guanidine formation would be expected to occur, but when O-alkyl is the comparatively inert butoxy-group, formation of the substituted imino-ether (IV; R = O·C_4H_9) would take precedence, the final ring-closure to (V; R = NHPh), a reaction of the amidine type, being facilitated by the favourable spatial configuration of the molecule.

Since the anilinohydroxypurine (V; R = NHPh) was highly resistant to attack by chlorinating agents, further progress in the direction of (II; R = dialkylaminoalkylamino-) was impossible. Shortly afterwards, Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 1271) reported similar difficulties in attempting to convert guanine hydrochloride into 6-chloro-2-aminopurine. These results are surprising, particularly when compared with those from later experiments on the methylthiopurine (V; R = SMe). Under the conditions used by Baddiley and Topham (*J.*, 1944, 678) for the preparation of trichloropyrimidine from barbituric acid, *viz.*, heating with phosphoryl chloride and dimethylaniline, the only isolable product was a small yield of 6-N-*methylanilino*-8-*methylthio*-2-*methylpurine* (V; R = NMePh), but, with phosphoryl chloride alone, no difficulty was experienced in obtaining the 6-*chloro*-8-*methylthio*-2-*methylpurine* (VI; R = Cl). Heating the latter in toluene with γ-diethylaminopropylamine gave the corresponding basically-substituted purine (VI; R = NH·$[CH_2]_3$·NEt_2) which was isolated as the *hydrochloride*. The necessary γ-diethylaminopropylamine was prepared by reduction of β-diethylaminopropionitrile in ammoniacal methanol over Raney nickel, and was characterised by its picrate, *picrolonate*, and *flavianate*.

In connexion with other work on purine analogues, 5-amino-4 : 6-dihydroxy-2-methylpyrimidine (VII; R = NH_2) was required; this we proposed to prepare from 4 : 6-dihydroxy-2-methylpyrimidine (VII; R = H) *via* the 5-nitroso-derivative. Both the nitrosation of (VII;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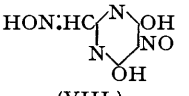
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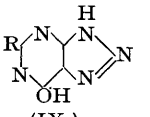
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R = H) and its reaction with *p*-chlorobenzenediazonium chloride have been described by Lythgoe, Todd, and Topham (*J.*, 1944, 315) but no attempt was made to isolate the products. On repeating these reactions, 5-p-*chlorobenzeneazo*-4 : 6-*dihydroxy*-2-*methylpyrimidine* (VII; R = N_2·C_6H_4·Cl) was obtained and characterised, but the bright green solid which separated on adding nitrous acid to the pyrimidine (VII; R = H) proved to be a dinitroso-compound, and not the expected derivative (VII; R = NO). In view of the reactivity of the 2-methyl group in certain hydroxypyrimidines, *e.g.*, 4-hydroxy-2-methylpyrimidine, which is oxidised by nitrous acid to 4-hydroxypyrimidine-2-carboxylic acid (Huber and Hölscher, *Ber.*, 1938, **71**, 87), the product appeared to be 5-*nitroso*-4 : 6-*dihydroxy*-2-iso*nitrosomethylpyrimidine* (VIII). The considerably increased yield obtained on using a second equivalent of nitrite supported this view, which was confirmed by reduction of the derivative to the corresponding *diamine*.

From the diaminopyrimidine (III) the triazolopyrimidine (IX; R = Me) was prepared by the action of nitrous acid, and was isolated as a hydrated double *salt*, $C_5H_5ON_5$,$C_5H_4ON_5Na$. As with the purine (V; R = NHPh), attempts to replace the 6-hydroxyl group by chlorine were unsuccessful. Roblin, Lampen, English, Cole, and Vaughan (*J. Amer. Chem. Soc.*, 1945, **67**, 290) subsequently described the antibacterial activity of the lower homologue (IX; R = H), and when tested *in vitro* against *Staph. aureus* by the method of Heatley (*Lancet*, 1941, **2**, 177), the 2-methyltriazole (IX; R = Me) was found to possess comparable activity.

Hydrochlorides of the amine (VI; R = NH·$[CH_2]_3$·NEt_2), and of the guanidine (IV; R = NH_2) and the analogous *p*-chloro-compound were tested against *P. gallinaceum* infections in chicks. The tests were kindly carried out by Miss I. M. Tonkin, National Institute of Medical Research, London, N.W. 3, who reports that none of the compounds has antimalarial activity.

Experimental.

4-Amino-5-(*N'-phenylthiocarbamido*)-6-*hydroxy*-2-*methylpyrimidine* (IV; R = SH).—4 : 5-Diamino-6-hydroxy-2-methylpyrimidine monohydrate (Traube, *Annalen*, 1923, **43**, 287) (5 g., 1 mol.) in aqueous sodium hydroxide (1·43 g., 1·13 mol., in 25 c.c.), and a solution of ammonium phenyldithiocarbamate (*Org. Synth.*, **6**, 72) (6·65 g., 1·13 mol.) in water (25 c.c.), were heated on a steam-bath for 6 hours. The precipitate, together with a further quantity of solid obtained by the addition of acid, was collected and purified by dissolving in 2N-sodium hydroxide. The *phenylthiocarbamide* (6·6 g., 76%) obtained on acidifying the filtered solution was crystallised from a large volume of boiling water, and formed

colourless microscopic tablets, m. p. >310° (Found: C, 52·5; H, 5·0; S, 10·8. $C_{12}H_{13}ON_5S$ requires C, 52·4; H, 4·7; S, 11·6%). The compound was insoluble in organic solvents, but dissolved readily in aqueous sodium hydroxide forming a mono-sodium salt and a more soluble di-sodium salt. It was not affected either by heating in boiling water for 48 hours, or on treatment with freshly prepared lead hydroxide in refluxing ethanol or *iso*amyl alcohol for 24 hours.

6-*Hydroxy*-8-*mercapto*-2-*methylpurine* (V; R = SH).—(*a*) The phenylthiocarbamide (IV; R = SH) (5 g.) was heated in boiling pyridine (50 c.c.) for 36 hours, and the solid collected and dissolved in 2N-sodium hydroxide. The micro-crystalline pale fawn powder obtained on acidification passed through filter paper, even after heating to 100°, and the product was accordingly isolated by centrifugation, and washed with water and ethanol. The resulting 6-*hydroxy*-8-*mercapto*-2-*methylpurine*, a light brown powder (2·7 g., 81%), m. p. >310°, which was very sparingly soluble in water and organic solvents, was purified by precipitation from its aqueous alkaline solution with acid (Found: C, 39·4; H, 3·7; S, 17·4. $C_6H_6ON_4S$ requires C, 39·5; H, 3·3; S, 17·6%). It gave both a mono- and a di-sodium salt, the former being sparingly soluble.

(*b*) When 4:5-diamino-6-hydroxy-2-methylpyrimidine (5 g.) and excess of thiourea (10 g.) were fused over a flame for 30 minutes, the mixture frothed and evolved ammonia. After cooling, the mercaptopurine was extracted with dilute alkali, the purified product (4·95 g., 86%) being identical in appearance, solubilities, etc., with that from reaction (*a*) (Found: S, 17·0%).

6-*Hydroxy*-8-*methylthio*-2-*methylpurine* (V; R = SMe).—6-Hydroxy-8-mercapto-2-methylpurine (5 g.) in excess of 2N-sodium hydroxide was shaken at room temperature with methyl iodide (4·0 g., 1·1 mol.) for 20 minutes. On neutralisation, the *methylthiopurine* (4·3 g., 81%) separated in pale fawn needles, m. p. >310°. The methyl ether is more soluble than the parent compound (V; R = SH), dissolving in both acids and alkalis and crystallising well from water (Found: C, 42·7; H, 4·4; N, 28·8; S, 16·4. $C_7H_8ON_4S$ requires C, 42·9; H, 4·1; N, 28·6; S, 16·3%).

On heating with aniline or γ-diethylaminopropylamine the methylthiopurine was either largely unchanged or, under extreme conditions, suffered decomposition.

4-*Amino*-5-(N′-*phenylcarbamido*)-6-*hydroxy*-2-*methylpyrimidine* (IV; R = OH).—4:5-Diamino-6-hydroxy-2-methylpyrimidine (7 g., 1 mol.), dried at 140°/0·6 mm. over phosphoric oxide, was heated with phenyl *iso*cyanate (7 g., 1·17 mol.) in boiling toluene (100 c.c.) for 8 hours. The colourless solid product (11·5 g., 88·8%), which was very sparingly soluble in organic solvents, water, and acids, but readily soluble in alkalis, was crystallised from a large volume of boiling water. The pure *phenylcarbamidopyrimidine* formed colourless microscopic rhombs, m. p. >305° (Found: C, 55·2; H, 5·0; N, 26·5. $C_{12}H_{13}O_2N_5$ requires C, 55·6; H, 5·0; N, 27·0%).

Heating the derivative (2 g.) with phosphoryl chloride (10 c.c.), followed by removal of halide under reduced pressure, dissolution of the residue in ethanol, and precipitation with water, gave an uncrystallisable solid (1·2 g.) devoid of halogen. Prolonged treatment with phosphoryl chloride or phosphorus pentachloride in toluene gave inseparable mixtures of partly chlorinated products.

8-*Anilino*-6-*hydroxy*-2-*methylpurine* (V; R = NHPh).—(*a*) 4-Amino-5-(N′-phenylcarbamido)-6-hydroxy-2-methylpyrimidine (5 g.) in toluene (100 c.c.) was treated with phosphorus trichloride (1·8 g., 2 mol.), and the mixture refluxed for 10 hours. The solid was collected and purified by precipitation from its aqueous solution by addition of a large excess of concentrated hydrochloric acid. The purine (V; R = NHPh) was thus obtained as a sparingly soluble *hydrochloride* (4·6 g., 80·4%), crystallising in minute pale cream-coloured plates, m. p. >310° (Found: C, 46·2; H, 5·3; Cl, 12·0. $C_{12}H_{11}ON_5,HCl,2H_2O$ requires C, 46·0; H, 5·1; Cl, 11·3%. Found, after drying at 100°: C, 50·0; H, 4·9. $C_{12}H_{11}ON_5,HCl,\frac{1}{2}H_2O$ requires C, 50·2; H, 4·5%).

(*b*) 4:5-Diamino-6-hydroxy-2-methylpyrimidine hydrochloride (5 g.) and phenylcyanamide were refluxed in dry *n*-butanol for 25 hours. The cooled product was filtered, thus giving a fawn solid (6 g.), which was extracted with hot water (300 c.c.). The undissolved halogen-free product (2·3 g., 33·5%) was soluble in alkalis and sparingly soluble in organic solvents. It was purified by adding a large excess of hydrochloric acid to its alkaline solution; the hydrochloride, m. p. >310°, then separated in minute almost colourless plates (Found: C, 45·7; H, 5·1; N, 22·2; Cl, 11·1%. Found after drying at 100°: C, 50·0; H, 4·5%).

Evaporation of the solution from the hot water extraction gave only unchanged diaminopyrimidine hydrochloride. Yields from the above condensation varied considerably and were sometimes extremely small. Several attempts were made to obtain the 6-chloro-derivative from the purine (V; R = NHPh) using phosphorus chlorides, but only resinous products were obtained.

4-*Amino*-5-(N′-*phenylguanidino*)-6-*hydroxy*-2-*methylpyrimidine* (IV; R = NH_2).—Finely divided 4:5-diamino-6-hydroxy-2-methylpyrimidine hydrochloride (1·5 g.) and excess of phenylcyanamide (2 g.) were heated in boiling ethanol (60 c.c.) for 30 hours. The resulting solid (2·2 g., 83%) was collected and the guanidine purified as *hydrochloride* by crystallisation from dilute hydrochloric acid, from which the salt separated as small colourless plates, m. p. 295° (decomp.), soluble in alkali, very sparingly soluble in organic solvents (Found: C, 45·5; H, 5·5; N, 26·5; Cl, 11·6. $C_{12}H_{14}ON_6,HCl,H_2O$ requires C, 46·1; H, 5·4; N, 26·8; Cl, 11·4%. Found after drying at 100°: C, 47·2; H, 5·3. $C_{12}H_{14}ON_6,HCl,\frac{1}{2}H_2O$ requires C, 47·4; H, 5·3%).

On treating a solution of the pure hydrochloride with aqueous sodium picrate, the very sparingly soluble *picrate* separated as thick, minute yellow prisms, m. p. 270° (decomp.) (Found: C, 42·8; H, 3·9. $C_{12}H_{14}ON_6$, $C_6H_3O_7N_3,H_2O$ requires C, 42·7; H, 3·8%. Found after drying at 100°: C, 43·8; H, 3·9. $C_{12}H_{14}ON_6,C_6H_3O_7N_3$ requires C, 44·3; H, 3·5%).

Attempted ring-closure to (V; R = NHPh) by heating alone, or in high boiling solvents, or with concentrated hydrochloric acid, was unsuccessful.

p-*Chlorophenylcyanamide*.—To *p*-chlorophenylthiourea (Stolle, *J. pr. Chem.*, 1932, **134**, 282) (18·5 g., 1 mol.) and lead acetate (50 g., 1·5 mol.) in water (200 c.c.) at 90° a solution of potassium hydroxide (25 g., 4 mol.) in water (50 c.c.) was added. The mixture was shaken during 15 minutes' heating on a steam-bath, and, after removal of lead sulphide, the clear solution was cooled and acidified with acetic acid. p-*Chlorophenylcyanamide* separated as a colourless solid (9·4 g., 61%), insoluble in water, very

soluble in the common organic solvents, and crystallising from aqueous ethanol in long silky colourless needles, m. p. 107° (Found : C, 55·0; H, 3·2; Cl, 24·1. $C_7H_5N_2Cl$ requires C, 55·0; H, 3·3; Cl, 23·3%).

4-*Amino*-5-(N′-p-*chlorophenylguanidino*)-6-*hydroxy*-2-*methylpyrimidine*.—Finely powdered 4 : 5-diamino-6-hydroxy-2-methylpyrimidine hydrochloride (5 g.) and excess of *p*-chlorophenylcyanamide (10 g.) were refluxed in ethanol for 30 hours. The crystalline guanidine was collected and purified as the *dihydrochloride* by precipitation from an alkaline solution with hydrochloric acid. The salt formed a colourless microcrystalline powder, m. p. 302° (decomp.), virtually insoluble in organic solvents (Found : C, 39·4; H, 4·1; Cl, 29·4. $C_{12}H_{13}ON_6Cl,2HCl$ requires C, 39·4; H, 4·1; Cl, 29·8%).

The *picrate*, which was precipitated from aqueous solutions of the hydrochloride and sodium picrate, crystallised from ethanol in minute yellow prisms, m. p. 268° (decomp.) (Found : C, 39·9; H, 3·6; N, 23·6. $C_{12}H_{13}ON_6Cl,C_6H_3O_7N_3,H_2O$ requires C, 40·2; H, 3·3; N, 23·4%).

6-N-*Methylanilino*-8-*methylthio*-2-*methylpurine* (VI; R = NMePh).—6-Hydroxy-8-methylthio-2-methylpurine (3 g.) was refluxed for 3 hours with phosphoryl chloride (3·2 c.c.) and dimethylaniline (2 c.c.). The dark liquid was poured on ice, and after 1 hour the water layer was decanted and the residual tarry product triturated with a little ethanol. The crystalline residue (0·9 g., 22%) was the 6-methylanilinopurine *hydrochloride*, which separated from alcohol–ether as a grey microcrystalline powder, m. p. 270—271° (decomp.), soluble in water, ethanol, and acetone, insoluble in ether (Found : C, 52·5; H, 6·2; Cl, 10·4. $C_{14}H_{15}N_5S,HCl,C_2H_6O$ requires C, 52·2; H, 6·0; Cl, 9·7%).

6-*Chloro*-8-*methylthio*-2-*methylpurine* (VI; R = Cl).—6-Hydroxy-8-methylthio-2-methylpurine (3 g.) was refluxed for 3 hours with excess of phosphoryl chloride. The thick black syrup remaining after evaporation was treated with sodium carbonate (2 g.), water (*ca.* ½ c.c.), and toluene (50 c.c.), and the mixture heated to boiling. The hot toluene solution was decanted, and on cooling it deposited the *chloropurine* (1·75 g., 53%) in long colourless silky needles. The product was easily soluble in ethanol and almost insoluble in water. Crystallised from toluene, the pure compound had m. p. 231° (Found : C, 39·8; H, 3·5; Cl, 16·9. $C_7H_7N_4ClS$ requires C, 39·2; H, 3·3; Cl, 16·6%).

γ-*Diethylaminopropylamine* (cf. Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725).—Reduction of β-diethylaminopropionitrile (Holcomb and Hamilton, *ibid.*, 1942, **64**, 1309) (15 g.) in ammoniacal methanol (150 c.c. saturated at 0°) at 100°/100 atm. for 20 minutes gave γ-diethylaminopropylamine (12·3 g., 82%), b. p. 175°. It was identified by the picrate, m. p. 192° (decomp.) (literature 194°); the *picrolonate*, m. p. 261° (decomp.), a microcrystalline powder, very sparingly soluble in hot alcohol (Found : C, 49·4; H, 5·4. $C_7H_{18}N_2,2C_{10}H_8O_5N_4$ requires C, 49·2; H, 5·4%); and the *flavianate*, yellow-orange, felted needles, m. p. 260° (decomp.), readily soluble in hot ethanol (Found : C, 45·8; H, 5·3. $C_7H_{18}N_2,C_{10}H_6O_8N_2S$ requires C, 46·0; H, 5·4%).

6-γ-*Diethylaminopropylamino*-8-*methylthio*-2-*methylpurine* (VI; R = NH·[CH$_2$]$_3$·NEt$_2$).—The hydroxypurine (VI; R = OH) (5 g.) was chlorinated as before, and the product remaining after removing excess of phosphoryl chloride was heated with γ-diethylaminopropylamine (5 g., 1·5 mol.) in boiling toluene (75 c.c.) for 10 hours. The solvent was evaporated under reduced pressure and the tarry residue extracted with ethanol (150 c.c.). Dry hydrogen chloride was passed into the extract and the volume reduced to 50 c.c. on a steam-bath. On cooling, the purine *hydrochloride* (14·5 g., 80%) separated as brown tablets, soluble in water, alcohol, and acetone; when recrystallised from ethanol–ether it formed colourless prisms, m. p. 243° (Found : C, 44·0; H, 6·9; N, 22·1; Cl, 19·2; S, 8·0. $C_{14}H_{24}N_6S,2HCl$ requires C, 44·1; H, 6·8; N, 22·1; Cl, 18·6; S, 8·4%).

On treating the above alcoholic extract with picric acid, the sparingly soluble *picrate* was obtained, which crystallised from alcohol as a monohydrate in yellow needles, m. p. 110° (decomp.) (Found : C, 40·3; H, 4·3; N, 21·0. $C_{14}H_{24}N_6S,2C_6H_3O_7N_3,H_2O$ requires C, 39·8; H, 4·1; N, 21·4%).

5-p-*Chlorobenzeneazo*-4 : 6-*dihydroxy*-2-*methylpyrimidine* (VII; R = N_2·C_6H_4·Cl) (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—A solution of *p*-chlorobenzenediazonium chloride, from *p*-chloroaniline (25 g.), in excess of hydrochloric acid was slowly added to 4 : 6-dihydroxy-2-methylpyrimidine (25 g.) in 2N-sodium carbonate (100 c.c.) containing excess of sodium acetate. The precipitated pale yellow solid (39·9 g., 76%) was collected and dried at 100°. The *pyrimidine* was sparingly soluble in organic solvents, but was crystallised from a large volume of ethanol, forming yellow needles, m. p. >310°, which dissolved in alkali to an orange solution (Found : C, 50·0; H, 3·5. $C_{11}H_9O_2N_4Cl$ requires C, 49·9; H, 3·4%).

5-*Nitroso*-4 : 6-*dihydroxy*-2-*isonitrosomethylpyrimidine* (VIII) (cf. Lythgoe, Todd, and Topham, *loc. cit.*).—Sodium nitrite (5·5 g., 2 mol.) was added to the pyrimidine (VII; R = H) (5 g., 1 mol.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) dissolved in 2N-sodium hydroxide, and the mixture treated with excess of hydrochloric acid. A dark green solid immediately separated, which was collected and washed with alcohol and ether. The *dinitrosopyrimidine* (6·4 g., 89%) became grey at 100° but did not melt below 310° (Found : C, 32·2; H, 2·5. $C_5H_4O_4N_4$ requires C, 32·6; H, 2·2%). It was insoluble in organic solvents, but dissolved in aqueous alkali from which it was precipitated by acid. Repeated dissolution in alkali destroyed the characteristic green colour, and the pyrimidine was better purified through the *sodium* salt. This separated on the addition of alcohol to its aqueous solution as a bright green microcrystalline powder, m. p. >310°, containing water of crystallisation (Found : C, 21·5; H, 2·6; N, 19·9. $C_5H_2O_4N_4Na_2,2\frac{1}{2}H_2O$ requires C, 22·0; H, 2·6; N, 20·5%. Found after drying at 100° : C, 24·1; H, 1·4. $C_5H_2O_4N_4Na_2,H_2O$ requires C, 24·4; H, 1·6%).

5-*Amino*-4 : 6-*dihydroxy*-2-*aminomethylpyrimidine*.—The nitroso-compound (VIII) (11·5 g.) was added to aqueous ammonia (50 c.c. of 17%) saturated with hydrogen sulphide at 0°. After a few seconds the green colour disappeared, and a yellow solid was deposited, probably an ammonium salt. This was dissolved in hot water, and on acidifying with concentrated hydrochloric acid the diamine *hydrochloride* separated as a light pink powder (6·1 g., 42·6%), with decomposition point 200° (Found : C, 26·3; H, 4·8. $C_5H_8O_2N_4,2HCl$ requires C, 26·2; H, 4·4%).

Both the hydrochloride and the free base are very soluble in water, sparingly soluble in organic solvents. Heating the base with water led to decomposition with elimination of ammonia.

5 : 6-(4 : 5-*Triazolo*)-4-*hydroxy*-2-*methylpyrimidine* (IX; R = Me).—The diaminopyrimidine (III) (5 g.), dissolved in excess of hydrochloric acid, was treated at 0° with aqueous sodium nitrite (2·2 g. in 10 c.c.), and after 10 minutes the solution was carefully neutralised with solid sodium hydrogen carbonate.

The precipitated solid (3 g., 50%) crystallised from water in long plates, m. p. 310°, soluble in aqueous alkali and acid, and was found on analysis to consist of the triazolopyrimidine acid sodium salt *trihydrate* (Found: C, 31·4; H, 4·3; N, 37·0; Na, 6·1. $C_5H_5ON_5,C_5H_4ON_5Na,3H_2O$ requires C, 31·7; H, 4·0; N, 37·0; Na, 6·1%). The compound was remarkably resistant to chlorinating agents, being almost quantitatively recovered even after fusion with phosphorus pentachloride.

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