136. *New Potential Chemotherapeutic Agents. Part VI. Derivatives of* 1 : 3-*Diaza-acridine.*

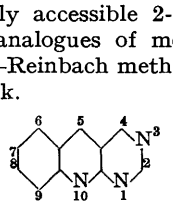
By F. E. King and T. J. King.

A series of dihydroxypyrimidines has been prepared with basic substituents at the 2- or the 4-position. In general, these were obtained from 2 : 4 : 6-trichloropyrimidine, with which the simple aliphatic amines gave isomeric dichloroaminopyrimidines. Hydrolysis of the chlorine in these compounds was conveniently carried out through the intermediate aminodibenzyloxy-derivatives, which were then debenzylated by catalytic hydrogenation.

The resulting aminodihydroxypyrimidines were condensed with *o*-aminobenzaldehyde; those with primary or secondary 2-amino-groups gave 2-amino-4-hydroxy-1 : 3-diaza-acridines (II; R = amino, R′ = OH). In the 4-amino-series, only the 4-guanidino-compound led to a basically substituted diaza-acridine; in the other condensations investigated, through hydrolysis of the basic side chains, the product was invariably 2 : 4-dihydroxy-1 : 3-diaza-acridine (II; R = R′ = OH).

Reference has already been made (Part V, J., 1946, 681) to the interest, from the standpoint of chemotherapy, of compounds having a structural resemblance to riboflavin : mepacrine, acriflavine, and several other aminoacridines are examples of substances which may derive their biological activity from this connexion. Closely related to acridine, but having more features in common with the ring-system present in riboflavin, is another heterocyclic nucleus, (I), usually known as quinolino-2′ : 3′-4 : 5-pyrimidine, but more concisely designated 1 : 3-diaza-acridine. Compounds of this series have so far received little attention, and the literature records but one example, *i.e.*, the dihydroxy-derivative (II; R = R′ = OH). This was prepared by Conrad and Reinbach (*Ber.*, 1901, **34**, 1341) from *o*-aminobenzaldehyde and barbituric acid, a method apparently capable of adaptation to the synthesis of various other derivatives of the nucleus. Attempts have now been made to extend it to the preparation of 1 : 3-diaza-acridines with basic side-chains. The experiments outlined in the present paper concern diaza-acridines substituted at the 2- or the 4-position, as these can be derived from

relatively accessible 2- or 4-substituted pyrimidines. The 5-aminodiaza-acridines, through which analogues of mepacrine would be available, obviously cannot be obtained by the Conrad–Reinbach method, and it is hoped that a later publication will deal with this aspect of the work.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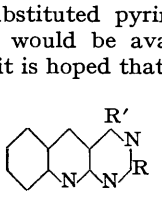
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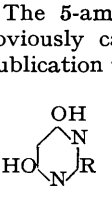
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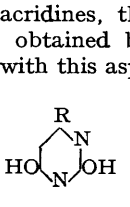
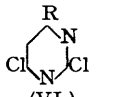

(IV.)

Initially, interest centred on derivatives containing the dialkylaminoalkylamine type of substituent, *e.g.* (II; R = NH·[CH_2]$_3$·NEt_2, R′ = OH). The heterocyclic component necessary for the synthesis of this diaza-acridine is 2-*γ-diethylamino*-n-*propylamino*-4 : 6-*dihydroxypyrimidine* (III; R = NH·[CH_2]$_3$·NEt_2), which was obtained from 2-mercaptobarbituric acid (III; R = SH) by heating with γ-diethylamino-*n*-propylamine and lead hydroxide, or analogously, omitting the hydroxide, from the 2-methylthio-compound (III; R = SMe). The latter can be prepared from thiobarbituric acid and methyl sulphate in good yield (cf. Wheeler and Jamieson, *Amer. Chem. J.*, 1904, **32**, 345) if the methylation is carried out in sodium bicarbonate solution.

The synthesis of the isomeric pyrimidine (IV, R = NH·[CH_2]$_3$·NEt_2) was more difficult. Thus, the action of γ-diethylaminopropylamine on the ureide $EtO_2C·CH_2·CO·NH·CO·NH_2$ gave barbituric acid, and not the derivative $Et_2N·[CH_2]_3·NH·CO·CH_2·CO·NH·CO·NH_2$ (V), which might have cyclised to the required pyrimidine with phosphoryl chloride. An alternative route to (V) was unsuccessful, through failure of the *amido-ester* $Et_2N·[CH_2]_3·NH·CO·CH_2·CH_2·CO_2Et$ to condense with urea, and the interaction of the corresponding *amidine* $Et_2N·[CH_2]_3·NH·C(:NH)·CH_2·CO_2Et$ with ethyl carbamate—based on a synthesis of barbituric acid ("Friedländer," 1906, **8**, 1113)—gave complex products. Eventually, the required 4-*γ-diethylaminopropylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = NH·[CH_2]$_3$·NEt_2) was obtained by starting from 2 : 4 : 6-trichloropyrimidine, which was prepared from barbituric acid by the method of Baddiley and Topham (*J.*, 1944, 678).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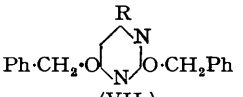
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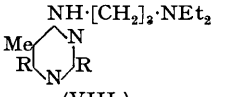
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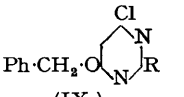
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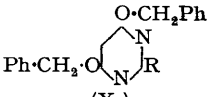

(X.)

On adding γ-diethylaminopropylamine to a solution of the trichloropyrimidine in acetone, a crystalline *hydrochloride* separated in high yield. Analyses of this salt and of the *picrate* and *picrolonate* proved them to be derivatives of a dichlorodiethylaminopropylaminopyrimidine, which was later shown to be (VI; R = NH·[CH_2]$_3$·NEt_2), the basic substituent having entered the 4- (or equivalent 6-) position. In an attempt to convert it into the required dihydroxy-derivative, the compound was submitted to alkaline hydrolysis, but no alkali soluble product was obtained. On the other hand, concentrated hydrochloric acid at 100° led to the formation of a monochloro-base, isolated as a *hydrochloride*, which, on account of the greater reactivity of the 2-chlorine atom, is believed to be 6-chloro-4-γ-diethylaminopropylamino-2-hydroxy-pyrimidine [for a discussion relevant to this point, see Basford, Curd, and Rose (*J.*, 1946, 713].

Finally, the dichloroamine was converted into the related aminodibenzyloxypyrimidine (VII; R = NH·[CH_2]$_3$·NEt_2) so that an attempt might be made to remove the benzyl groups by hydrogenation. This method of hydrolysis does not seem previously to have been employed in the pyrimidine series, and a preliminary investigation was therefore carried out with 2 : 4 : 6-*tribenzyloxypyrimidine*, which was prepared from the trichloropyrimidine and sodium benzyloxide in boiling toluene. Hydrolysis of the benzyloxy-groups with sodium in liquid ammonia was unsuccessful, but, on hydrogenation over palladised charcoal, barbituric acid was obtained in excellent yield. When applied to (VII; R = NH·[CH_2]$_3$·NEt_2), the catalytic reduction method readily afforded a basically-substituted dihydroxypyrimidine which, being isomeric but not identical with that already prepared from 2-thio- or 2-methylthio-barbituric acid, was thus shown to be the 4-diethylaminopropylaminodihydroxy-compound (IV; R = NH·[CH_2]$_3$·NEt_2). The product coupled with *p*-chlorobenzenediazonium chloride, and an attempt was made to use the resulting p-*chlorobenzeneazopyrimidine* for a synthesis of 9-γ-diethyl-aminopropylxanthine, but, owing to the extreme readiness with which the intermediate diaminopyrimidine oxidised in the air, this intention was not realised.

The pyrimidine (IV; R = NH·[CH_2]$_3$·NEt_2) was tested for anti-malarial properties, but it

showed no activity against *P. gallinaceum* in chicks. However, in view of the activity of certain basically-substituted 5-methylpyrimidines—a property not apparent in lower homologues from which the methyl group is omitted (Hall, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357)—the 5-methyl analogue of (IV; R = NH·[CH_2]$_3$·NEt_2) was also synthesised. 2 : 4 : 6-Trichloro-5-methylpyrimidine combined with γ-diethylaminopropylamine to give a *hydrochloride*, presumably, by analogy with the previous condensation, a salt of 2 : 6-*dichloro*-4-*amino*-5-*methylpyrimidine* (VIII; R = Cl). From the derived *dibenzyloxy*-compound (VIII; R = O·CH_2·Ph), 4-γ-diethylamino-2 : 6-dihydroxy-5-methylpyrimidine (VIII, R = OH) was obtained by catalytic reduction, and characterised by a *picrate* and *picrolonate*. Like the pyrimidine (IV; R = NH·[CH_2]$_3$·NEt_2), when tested in a similar manner the product (VIII; R = OH) was found to have no antimalarial activity.

Before going on to the synthesis of the diethylaminopropylaminodiaza-acridines from the new pyrimidines, the preparation of some simpler aminodihydroxypyrimidines was first investigated, including 2-*methylamino*- and 2-*dimethylamino*-4 : 6-*dihydroxypyrimidine*, and 4-*methylamino*-, 4-*dimethylamino*-, and 4-*guanidino*-2 : 6-*dihydroxypyrimidine*.

The isomeric dichloromethylaminopyrimidines have already been prepared and oriented (Winkelmann, *J. pr. Chem.*, 1927, **115**, 292). Of these, the 2 : 6-dichloro-4-methylamino-compound (VI; R = NHMe) was directly converted into the corresponding *dibenzyloxy*-derivative (VII; R = NHMe), but the 4 : 6-dichloropyrimidine gave first 4-*chloro*-2-*methylamino*-6-*benzyloxypyrimidine* (IX; R = NHMe), and further heating with the sodium benzyloxide was necessary to obtain the 2-*methylamino*-4 : 6-*dibenzyloxypyrimidine* (X; R = NHMe). Catalytic reduction of the isomeric dibenzyloxypyrimidines occurred without difficulty to give the methylaminodihydroxy-compounds (III and IV; R = NHMe). Both are mentioned in patent literature (see *Chem. Zentr.*, 1938, I, 2790; II, 3163) but neither their preparation nor properties have been described.

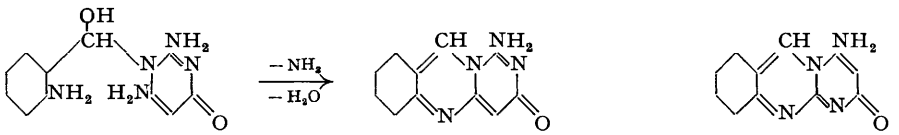
The action of dimethylamine on trichloropyrimidine in aqueous ethanol also gave two products of very markedly different solubilities, of which the sparingly soluble isomer, by analogy with the monomethylamine series, is regarded as the *dichloro*-4-*dimethylamino*-compound (VI; R = NMe_2). Both the 2-*dimethylamino*-4 : 6-*dichloropyrimidine* and its isomer (VI; R = NMe_2) gave *dibenzyloxypyrimidines* (VII and X; R = NMe_2), but from the somewhat less reactive 2 : 6-dichloro-compound it was possible to obtain an intermediate *monochloro-benzyloxypyrimidine* (IX; R = NMe_2).

Addition of trichloropyrimidine to guanidine in ethanol solution gave an oily product, apparently a mixture of dichloroethoxy- and chlorodiethoxy-pyrimidine, an unexpected result which may be connected with the high basicity of guanidine. With acetone as solvent, a dichloromonoguanidinopyrimidine separated, and as it is characteristic of the 4-amino-compounds in this series to be the less-soluble isomers, it was tentatively assigned the constitution (VI; R = NH·C[:NH]·NH_2). However, as in the trichloropyrimidine–diethylaminopropylamine condensation, none of the isomeric 2-guanidino-compound was found in the acetone residues. In the reaction with sodium benzyloxide in toluene a sparingly soluble product crystallised which is probably 6-*chloro*-4-*guanidino*-2-*benzyloxypyrimidine*. The dibenzyloxy-derivative formed on prolonged reaction and characterised by its *picrate*, was hydrogenated to give 4-*guanidino*-2 : 6-*dihydroxypyrimidine* (IV; R = NH·C[:NH]·NH_2). Its extremely sparing solubility in ethanol, in which respect it evidently differs from the 2-guanidinopyrimidine synthesised from ethyl malonate and diguanidine (Rackmann, *Annalen*, 1910, **376**, 176), is further evidence in support of its constitution and that of the dichloro-compound from which it is derived.

With the exception of the pyrimidine (IV; R = NH·C[:NH]·NH_2) the behaviour of the foregoing amino-compounds when condensed with *o*-aminobenzaldehyde conformed to the structures which have been assigned to them. The reaction conditions were first explored with 2- and 4-aminodihydroxypyrimidine and 2 : 4-diamino-6-hydroxypyrimidine. The condensations were carried out in aqueous solution, but, without the addition of acid, the pyrimidine 5-position is insufficiently activated for reaction to occur. With the addition of dilute hydrochloric acid, no difficulty was experienced in obtaining from malonylguanidine (III; R = NH_2) the expected 2-*amino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II; R = NH_2, R′ = OH), which was isolated first as a *hydrochloride*. On the other hand, in condensations involving the 4-amino-series of hydroxypyrimidines, mineral acid cannot be used owing to hydrolysis of the amino-group (see Conrad, *Annalen*, 1905, **340**, 312), and the reaction of 4-amino-2 : 6-dihydroxy-pyrimidine with *o*-aminobenzaldehyde was therefore carried out in aqueous acetic acid. The product exhibited the characterstic diaza-acridine fluorescence, but investigation showed it to

consist of 2 : 4-dihydroxy-1 : 3-diaza-acridine (II; R = OH, R′ = OH), indicating the loss at some stage of the reaction of a molecule of ammonia. In view of the mild conditions, hydrolysis of the aminopyrimidine was unlikely, and it therefore appeared that ring-closure had occurred by loss of the 4-amino-group as ammonia in preference to the elimination of the hydroxyl at the 6-position. In order to demonstrate the possibility of such a reaction mechanism, *o*-aminobenzaldehyde was treated under similar conditions with 4 : 6-diamino-2-hydroxy- and 2 : 4 : 6-triamino-pyrimidine, but in neither case could any condensation be induced.

Elimination of ammonia also occurred in the reaction between 2 : 4-diamino-6-hydroxypyrimidine and *o*-aminobenzaldehyde, which gave a deep yellow, sparingly soluble compound. This had the molecular composition of the aminohydroxydiaza-acridines, but was clearly different from the base (II; R = NH_2, R′ = OH) already prepared from malonylguanidine. On the other hand, it appeared incredible that the new substance could be the isomeric 4-amino-2-hydroxydiaza-acridine, since its formation would have necessitated the loss of the stable 2-amino-group of the pyrimidine while retaining the more readily hydrolysable 4-substituent. It is much more probable that, the pyrimidine 5-position being insufficiently active, the primary reaction of the aldehyde group is to combine with one of the two hetero atoms forming a carbinol (XI). Ring-closure, by extrusion of ammonia, would then lead to a



(XI.) (XII.) (XIII.)

new type of diaza-acridine, and of the two possible products (XII) and (XIII), preference is given to 4-*amino*-2-*keto*-3 : 12-*diaza*-2 : 12-*dihydroacridine* (XII) (or its 2-hydroxy-4-imino-tautomer) which would be obtained by removal of the more labile 4-amino-group. A further alternative, in which the 2- and 4-substituents of (XII) are interchanged, can also be dismissed since the initial carbinol formation is unlikely to take place with the nuclear amido-nitrogen in preference to that which is part of an amidine structure.

Condensation of 2-methylamino-4 : 6-dihydroxypyrimidine with *o*-aminobenzaldehyde gave the expected 2-*methylamino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II; R = NHMe, R′ = OH), but, as anticipated from the behaviour of the corresponding primary amine (IV; R = NH_2), the isomeric 4-methylaminodihydroxypyrimidine, by undergoing loss of methylamine, yielded the dihydroxydiaza-acridine (II, R = R′ = OH). The two dimethylaminodihydroxypyrimidines, in which triketo-tautomerism is excluded by the tertiary nature of the amino-groups, both failed to react with the aldehyde, and it is of interest in this connexion that the 4-dimethylamino-group in the pyrimidine (IV; R = NMe_2) is not hydrolysed by boiling hydrochloric acid. Somewhat remarkably, in view of previous failures to synthesis 4-aminodiaza-acridines, the 4-guanidinodihydroxypyrimidine easily condensed with *o*-aminobenzaldehyde in 25% acetic acid, to give the 4-*guanidinohydroxydiaza-acridine* (II, R = OH, R′ = NH·C[:NH]·NH_2), which was further characterised by the *hydrochloride* and *picrate*. It is suggested that this exceptional result can be interpreted in terms of the enhanced stability conferred on the guanidino kation by resonance.

Finally, the diethylaminopropylaminodihydroxypyrimidines were condensed with aminobenzaldehyde, the 2-isomer affording 2-*γ-diethylaminopropylamino*-4-*hydroxy*-1 : 3-*diaza-acridine*. Tested in the form of a *meconate*, it proved inactive against *P. gallinaceum* infections in chicks. Condensation of the 4-aminopyrimidine (IV; R = NH·$[CH_2]_3$·NEt_2) was accompanied by loss of the basic side-chain, the product once more being the diaza-acridine (II; R = R′ = OH).

The possibility of introducing amino-groups into the benzene ring of the diaza-acridines was considered, and for this purpose 2 : 4-dinitrobenzaldehyde, which gave with barbituric acid a *benzylidene* derivative, was prepared. The 4-nitro-2-amino-aldehyde obtained by ferrous hydroxide reduction condensed with barbituric acid to give 8-*nitro*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*, but this compound is so sparingly soluble that it has not been possible to bring about reduction of the 8-nitro-group.

Through the kindness of Dr. E. P. Abraham of the Sir William Dunn School of Pathology, Oxford, the above diaza-acridines were examined for antibacterial properties. With the exception of the 2-amino-4-hydroxy-derivative, which is slightly active, none of them showed antibacterial activity when tested *in vitro* against *Staph. aureus*. For the antimalarial tests

recorded above we are indebted to Miss I. M. Tonkin, National Institute of Medical Research, London, N.W.3.

Experimental.

2-γ-Diethylaminopropylamino-4 : 6-dihydroxypyrimidine (III; R = NH·[CH_2]$_3$·NEt_2).—(*a*) Mercaptor barbituric acid (5 g.), γ-diethylaminopropylamine (4·5 g., 1·5 mol.), and freshly prepared lead hydroxide (*ca.* 2 mols.) were heated in refluxing *iso*amyl alcohol for 15 hours. The hot solution was filtered and evaporated under reduced pressure, giving a friable mass (6·5 g., 78%), which was identified as the amine (III; R = NH·[CH_2]$_3$·NEt_2) by its picrolonate (below).

(*b*) Mercaptobarbituric acid (14·4 g.) in aqueous sodium bicarbonate (8·4 g. in 200 c.c. of water) was shaken at room temperature with methyl sulphate (12·6 g.); after 30 minutes the sulphate had dissolved and a crystalline solid had separated. This was collected, washed with water, alcohol, and ether, and identified as 4 : 6-dihydroxy-2-methylthiopyrimidine (10·4 g., 72%) (cf. Wheeler and Jamieson, *loc. cit.*).

Without further purification the methylated pyrimidine (10 g., 1 mol.) was gradually heated to 180° with γ-diethylaminopropylamine (3·9 g., 0·95 mol.); the nearly solid mass then became gummy and methylthiol was evolved. After 30 minutes reaction ceased, and the mixture was cooled, dissolved in ethanol (70 c.c.), filtered to remove unchanged pyrimidine, and evaporated under reduced pressure. The product (13 g., 92%) was soluble in water and ethanol, sparingly soluble in ether. Its hydrochloride, oxalate, and picrate were oily, but the *picrolonate*, prepared in acetone, crystallised after 24 hours at 0°. It separated from *cyclo*hexanone–ether as a hydrate in microscopic yellow tablets, m. p. 235° (decomp.) (Found: C, 47·7; H, 5·5; N, 20·9. $C_{11}H_{20}O_2N_4$,$C_{10}H_8O_5N_4$,H_2O requires C, 48·3; H, 5·7; N, 21·4%. Found after drying at 100°: C, 48·9; H, 5·5; loss, 1·85. $C_{11}H_{20}O_2N_4$,$C_{10}H_8O_5N_4$,$\frac{1}{2}H_2O$ requires C, 49·1; H, 5·6; loss, 1·7%. Found after drying at 150°: C, 49·8; H, 5·4. $C_{11}H_{20}O_2N_4$,$C_{10}H_8O_5N_4$ requires C, 50·0; H, 5·6%).

Carbethoxyacet-(N-γ-diethylaminopropyl)amide.—Solutions of carbethoxyacetyl chloride (6 g., 1 mol.) and γ-diethylaminopropylamine (5·2 g., 1 mol.) in dry ether were gradually mixed at 0°. The orange oil which had separated was treated, after decantation of the ether, with aqueous sodium carbonate, and the liberated base taken up in chloroform. By distillation the *amido-ester* was obtained as a colourless oil (5·85 g., 60%), b. p. 115°/0·05 mm. (Found: C, 59·3; H, 9·9; N, 12·2. $C_{12}H_{24}O_3N_2$ requires C, 59·0; H, 9·8; N, 11·5%). When it was heated with sodium ethoxide and urea in ethanol for 6 hours, a thick black oil was obtained, distillation of which gave no recognisable new product.

An attempt to prepare the corresponding acid from ethyl carboxyacetate and γ-diethylaminopropylamine was unsuccessful, and hydrolysis of the amido-ester with aqueous alcoholic potassium hydroxide (1 mol.) at room temperature gave an oil, which on treatment with picrolonic acid gave only the γ-diethylaminopropylamine salt.

Carbethoxyacet-(N-γ-diethylaminopropyl)amidine.—Ethyl α-carbethoxyacetiminate hydrochloride (6 g., 1 mol.) in ethanol (100 c.c.) was treated with γ-diethylaminopropylamine (4·2 g., 1 mol.) at room temperature. Heat was evolved, and after 12 hours the solvent was evaporated under reduced pressure to give a colourless oil, from which the *picrolonate*, prepared in acetone solution, was obtained without further crystallisation in an analytically pure condition as yellow prisms, m. p. 125—130° (Found: C, 48·6; H, 5·5; N, 19·0; loss on drying at 100°, 2·8. $C_{12}H_{25}O_2N_3$,$2C_{10}H_8O_5N_4$,H_2O requires C, 48·7; H, 5·7; N, 19·5; loss, 2·3%).

Attempts to condense the amidine with ethyl carbamate in the presence of sodium ethoxide gave complex oily products. The only crystalline derivative obtained from these oils was γ-diethylaminopropylamine picrolonate. Later, when the properties of the desired compound (IV; R = NH·[CH_2]$_3$·NEt_2) were known it became certain that it could not have been present in the reaction mixture.

2 : 4 : 6-*Tribenzyloxypyrimidine.*—To powdered sodium (1·15 g., 1 mol.) under toluene (100 c.c.), benzyl alcohol (11 g., 2 mols.) was added, and after the initial vigorous reaction had subsided the mixture was heated under reflux until no more sodium remained (2 hours). When trichloropyrimidine (3 g., 1 mol.) in toluene (10 c.c.) was cautiously added, the thick mass of sodium benzyloxide rapidly disappeared and sodium chloride was deposited. After refluxing for 1 hour, the solution was cooled and shaken with water to remove sodium chloride and any remaining alcohol, and the toluene was evaporated under reduced pressure. The residual oil solidified on trituration with ethanol to give 2 : 4 : 6-*tribenzyloxypyrimidine* (4·1 g., 63%) which crystallised in long silky needles, m. p. 62—64°, soluble in alcohols, ether, and acetone, insoluble in water (Found: C, 75·3; H, 5·6; N, 6·9. $C_{25}H_{22}O_3N_2$ requires C, 75·4; H, 5·5; N, 7·0%).

Treatment with sodium in liquid ammonia gave a mixture of products from which no pure compound was obtained.

Barbituric Acid.—Tribenzyloxypyrimidine (2 g.) dissolved in acetic acid (40 c.c.) was hydrogenated at atmospheric pressure and temperature over palladised charcoal (0·1 g.). Reduction was complete in 2 hours, and on evaporating the filtered solution barbituric acid (0·54 g., 84%) was obtained and identified by its melting point and that of its benzylidene derivative.

2 : 6-*Dichloro-4-γ-diethylaminopropylaminopyrimidine* (VI; R = NH·[CH_2]$_3$·NEt_2).—By the method of Baddiley and Topham (*loc. cit.*), using pure dry barbituric acid and gently warming the reaction mixture until the solid passed into solution, trichloropyrimidine was obtained pure after one distillation in up to 83% yield. γ-Diethylaminopropylamine (13 g., 1 mol.) in acetone (50 c.c.) was cautiously added to an acetone solution of trichloropyrimidine (18 g., 1 mol., in 100 c.c.); the reaction vessel must be cooled during addition to prevent loss by frothing. On cooling, and with vigorous scratching, the product separated as a crystalline mass. After 1 hour the solid was collected and washed with cold acetone (yield 22·6 g., 72%); by concentrating the mother liquors a further crop (4·1 g., total yield 85%) was obtained. Crystallisation from acetone gave the *hydrochloride* in colourless large glistening rhombs, m. p. 149° (Found: C, 42·2; H, 6·1; N, 18·1. $C_{11}H_{18}N_4Cl_2$,HCl requires C, 42·1; H, 6·0; N, 17·6%). Aqueous solutions of the hydrochloride and sodium picrate gave the *picrate*, separating from ethanol in

bright yellow shining prisms, m. p. 162° (Found : C, 40·3; H, 4·4; Cl, 13·9. $C_{11}H_{18}N_4Cl_2,C_6H_3O_7N_3$ requires C, 40·3; H, 4·2; Cl, 14·0%). An alcoholic solution of the hydrochloride with *picrolonic* acid gave the *picrolonate*, which crystallised from *n*-propanol in yellow prisms, m. p. 164° (Found : Cl, 13·1. $C_{11}H_{18}N_4Cl_2,C_{10}H_8O_5N_4$ requires Cl, 13·1%).

Experiments on the hydrolysis of the dichloroaminopyrimidine by heating with aqueous alcoholic potassium hydroxide gave only alkali-insoluble products. These, on treatment with picric acid, gave mixed salts, among them the above picrate, m. p. 162°, but nothing corresponding to a dihydroxypyrimidine derivative could be isolated.

6-*Chloro*-4-*γ*-*diethylaminopropylamino*-2-*hydroxypyrimidine*.—The above dichloro-compound (3·1 g.) was digested on a steam-bath with concentrated hydrochloric acid (10 c.c.) for 12 hours. Evaporation of the solvent gave a residue consisting of a *dihydrochloride* (2·5 g., 76%), very soluble in water, sparingly so in alcohol and acetone. It separated from boiling ethanol in colourless platelets, m. p. 253° (decomp.) (Found : C, 39·6; H, 6·4; N, 16·7; Cl, 31·8. $C_{11}H_{19}ON_4Cl,2HCl$ requires C, 39·8; H, 6·3; N, 16·9; Cl, 32·1%). An aqueous solution of the hydrochloride treated with alcoholic picric acid gave the *picrate*, very sparingly soluble in ordinary solvents, and crystallising from a large volume of boiling water in small compact yellow tablets, m. p. 209° (decomp.) Found : C, 41·5; H, 4·5; Cl, 7·9. $C_{11}H_{19}ON_4Cl,C_6H_3O_7N_3$ requires C, 41·8; H, 4·5; Cl, 7·3%).

4-*γ*-*Diethylaminopropylamino*-2 : 6-*dibenzyloxypyrimidine* (VII; R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$).—To powdered sodium (1·4 g., 1 mol.) under toluene (100 c.c.), benzyl alcohol (13 g., 2 mol.) was added, and, when the sodium had reacted, 2 : 6-dichloro-4-*γ*-diethylaminopropylaminopyrimidine (6·25 g., 1 mol.) was introduced in 10 portions with shaking. The sodium benzyloxide rapidly disappeared with evolution of heat, after which the liquid was refluxed for 2 hours. After being washed with water, dried, and evaporated under reduced pressure, the toluene solution yielded a pale brown viscous oil which solidified on standing. Crystallisation from light petroleum gave the *benzyloxypyrimidine* (6·5 g., 80%) in colourless needles, m. p. 68° (Found : C, 71·0; H, 7·4; N, 13·3. $C_{25}H_{32}O_2N_4$ requires C, 71·4; H, 7·6; N, 13·3%). Its *dipicrate* was obtained from alcohol solution in large glistening prisms, m. p. 156° (Found : C, 50·1; H, 4·5; N, 16·0. $C_{25}H_{32}O_2N_4,2C_6H_3O_7N_3$ requires C, 50·6; H, 4·3; N, 16·0%).

4-*γ*-*Diethylaminopropylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$).—The crude benzyloxypyrimidine from 2 : 6-dichloro-4-*γ*-diethylaminopropylaminopyrimidine hydrochloride (12·5 g.), dissolved in acetic acid (75 c.c.), was hydrogenated over palladised charcoal at room pressure and temperature. After 4 hours, hydrogen uptake (1270 c.c., 71%) ceased, and the catalyst was removed and the solvent evaporated under reduced pressure. The product (10·2 g., 61%), a light brown oil, had partially crystallised after 1 month in a vacuum over potassium hydroxide, and was apparently the *acetate* (Found : C, 45·0; H, 8·0. $C_{11}H_{20}O_2N_4,3C_2H_4O_2$ requires C, 45·3; H, 7·8%). It was very hygroscopic, soluble in ethanol and acetone, insoluble in ether and light petroleum, and its alcoholic solution gave a *picrate* crystallising in small needles, m. p. 225° (decomp.) (Found : C, 43·4; H, 5·2; N, 20·5. $C_{11}H_{20}O_2N_4,C_6H_3O_7N_3$ requires C, 43·5; H, 4·9; N, 20·9%). From acetone the very sparingly soluble *picrolonate* was slowly deposited, which crystallised from dimethylformamide–ethanol in minute prisms, m. p. 186° (decomp.) (Found : C, 47·2; H, 5·8; N, 20·9. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4,2H_2O$ requires C, 46·7; H, 5·9; N, 20·8%. Found after drying at 100° : C, 48·3; H, 6·0; N, 21·5. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4,H_2O$ requires C, 48·2; H, 5·7; N, 21·4%. Found after drying at 130° : C, 49·7; H, 5·8. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4$ requires C, 50·0; H, 5·6%).

4-*γ*-*Diethylaminopropylamino*-5-*p*-*chlorobenzeneazo*-2 : 6-*dihydroxypyrimidine*.—*p*-Chlorobenzenediazonium chloride, from *p*-chloroaniline (1·6 g., 1 mol.), in excess of hydrochloric acid, was added to an aqueous solution (100 c.c.) of the pyrimidine (IV; R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$) (5 g., 1 mol.), and the mixture neutralised with sodium bicarbonate. After 24 hours at 0° a bright yellow sludge had separated, from which the supernatant liquid and washings were removed by centrifugation. The product was digested with ethanol (100 c.c.) to remove a bright red soluble impurity, and the sparingly soluble residue crystallised from a large volume of alcohol. The pure *azopyrimidine* (2·7 g., 57%), separated in yellow feathery needles, m. p. 151° (efferv.) (Found : C, 49·2; H, 6·35; N, 19·9. $C_{17}H_{23}O_2N_6Cl,2H_2O$ requires C, 49·2; H, 6·4; N, 20·3%. Found after drying at 100° : Cl, 8·95. $C_{17}H_{23}O_2N_6Cl,H_2O$ requires Cl, 8·95%). From the purified base and alcoholic picric acid, the *dipicrate*, m. p. 205° (decomp.), was obtained (Found : C, 41·2; H, 3·7. $C_{17}H_{23}O_2N_6Cl,2C_6H_3O_7N_3$ requires C, 41·6; H, 3·5%).

Catalytic reduction of the azo-compound over Raney nickel gave a product which very rapidly oxidised in air. Immediate treatment of the reduction mixture with formic acid followed by removal of the catalyst, evaporation, and heating to 180°, gave an intractable tar.

2 : 6-*Dichloro*-4-*γ*-*diethylaminopropylamino*-5-*methylpyrimidine* (VIII; R = Cl).—2 : 4 : 6-Trichloro-5-methylpyrimidine (19·7 g., 1 mol.), which was obtained from 5-methylbarbituric acid in 76% yield by the method of Baddiley and Topham, was dissolved in acetone (100 c.c.) and cautiously treated with an acetone solution of *γ*-diethylaminopropylamine (13 g. 1 mol., in 100 c.c.). On cooling to 0°, the *hydrochloride* (15·4 g., 41%) separated, and concentration of the solution gave a further quantity (6·5 g., 20%). The salt, which is easily soluble in ethanol and highly soluble in water, was recrystallised from acetone, and it then formed large glistening tablets, m. p. 193—195° (Found : C, 44·2; H, 6·5; Cl, 33·2. $C_{12}H_{20}N_4Cl_2,HCl$ requires C, 43·7; H, 6·4; Cl, 32·6%). Treated with aqueous sodium picrate, it gave a *picrate*, which crystallised from a large quantity of alcohol in long prisms, m. p. 163° (Found : C, 41·2; H, 4·4; N, 18·5. $C_{12}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 41·4; H, 4·4; N, 18·8%).

4-*γ*-*Diethylaminopropylamino*-2 : 6-*dibenzyloxy*-5-*methylpyrimidine* (VIII; R = $O{\cdot}CH_2Ph$).—2 : 6-Dichloro-4-*γ*-diethylaminopropylamino-5-methylpyrimidine hydrochloride (8·2 g.) was slowly added to a suspension of sodium benzyloxide (from 1·72 g. of sodium) in toluene (75 c.c.), which was then heated under reflux for 2 hours. When isolated from the solvent, the dibenzyloxy-compound was an uncrystallisable oil which in ethanol solution gave a *tripicrate* having m. p. 141—142° not raised by recrystallisation from *iso*amyl alcohol (Found : C, 47·2; H, 3·9; N, 16·4. $C_{26}H_{34}O_2N_4,3C_6H_3O_7N_3$ requires C, 47·1; H, 3·8; N, 16·3%).

4-*γ*-*Diethylaminopropylamino*-2 : 6-*dihydroxy*-5-*methylpyrimidine* (VIII; R = OH).—The unpurified benzyloxypyrimidine from the above reaction was hydrogenated in acetic acid (100 c.c.) over palladised

charcoal at room temperature and pressure. Absorption (952 c.c., 85%) ceased after 5 hours; the filtered solution was then evaporated. The residue (7·2 g.), which partially solidified on leaving in a vacuum desiccator for a month, consisted of the *triacetate* (Found: C, 48·4; H, 8·2; N, 12·3. $C_{12}H_{22}O_2N_4,3C_2H_4O_2,H_2O$ requires C, 48·8; H, 8·1; N, 12·7%). From the acetate a sparingly soluble *dipicrate* was obtained as yellow needles, m. p. 183—184° (decomp.), from *iso*amyl alcohol (Found: C, 40·5; H, 4·1; N, 19·2. $C_{12}H_{22}O_2N_4,2C_6H_3O_7N_3$ requires C, 40·4; H, 3·9; N, 19·7%). The *picrolonate* was a yellow microcrystalline powder, m. p. 223° (decomp.) (Found: C, 50·7; H, 5·6. $C_{12}H_{22}O_2N_4,C_{10}H_8O_5N_4$ requires C, 50·9; H, 5·8%).

4-*Chloro*-2-*methylamino*-6-*benzyloxypyrimidine* (IX; R = NHMe).—4 : 6-Dichloro-2-methylaminopyrimidine (Winkelmann, *loc. cit.*) (4·4 g., 1 mol.) was added to sodium benzyloxide (from 1·15 g. of sodium, 2 mols.) in toluene (150 c.c.), and after 1 hour at 100° the toluene was washed with water and evaporated. The residue, which solidified on trituration with alcohol, had no definite m. p., and presumably also contained the dibenzyloxypyrimidine (X; R = NHMe), but on crystallisation from ethanol 4-*chloro*-2-*methylamino*-6-*benzyloxypyrimidine* (1·7 g., 27·5%) was obtained as glistening colourless platelets, m. p. 120° (Found: N, 15·9; Cl, 14·9. $C_{12}H_{12}ON_3Cl$ requires N, 16·7; Cl, 14·2%).

2-*Methylamino*-4 : 6-*dibenzyloxypyrimidine* (X; R = NHMe).—When similar quantities of the reagents used in the foregoing preparation of the pyrimidine (IX, R = NHMe) were heated in vigorously refluxing toluene (50 c.c.) for 4 hours, a more soluble product was obtained, from which 2-*methylamino*-4 : 6-*dibenzyloxypyrimidine* (5·5 g., 61%) was obtained on crystallisation from ethanol as colourless, long radiating spikes, m. p. 101° (Found: C, 71·2; H, 5·8; N, 13·2. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 5·9; N, 13·1%).

2-*Methylamino*-4 : 6-*dihydroxypyrimidine* (III; R = NHMe).—The reduction of 2-methylamino-4 : 6-dibenzyloxypyrimidine (5·0 g.) in acetic acid (75 c.c.) using palladised charcoal required 8 hours; hydrogen uptake (630 c.c. 90%) had then ceased. The slowness of the reaction appeared to be due to separation of the sparingly soluble product. It was dissolved by heating, and the filtered solution on cooling gave 2-*methylamino*-4 : 6-*dihydroxypyrimidine* (1·9 g., 66·6%). It dissolved in aqueous alkali and mineral acid, and being sparingly soluble in ethanol and water, was recrystallised from acetic acid, separating in compact prisms, m. p. > 310° (Found: C, 39·4; H, 5·6; N, 22·4. $C_5H_7O_2N_3,\frac{1}{2}C_2H_4O_2,\frac{2}{3}H_2O$ requires C, 39·4; H, 5·8; N, 23·0%. Found after drying at 100°: C, 42·2; H, 4·9; loss, 21·2. $C_5H_7O_2N_3$ requires C, 42·5; H, 5·0; loss, 23·0%).

4-*Methylamino*-2 : 6-*dibenzyloxypyrimidine* (VII; R = NHMe).—2 : 6-Dichloro-4-methylaminopyrimidine (Winkelmann, *loc. cit.*) (6 g.) was heated with sodium benzyloxide (from 1·55 g. of sodium) in boiling toluene (75 c.c.) for 3 hours. After evaporation of the washed and dried solution, the residue of 4-*methylamino*-2 : 6-*dibenzyloxypyrimidine* (7·45 g., 69%), which was quite soluble in cold alcohol, ether and acetone, was recrystallised from ethanol, separating as large colourless leaflets, m. p. 118° (Found: C, 70·8; H, 5·8; N, 12·8. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 5·9; N, 13·1%).

4-*Methylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = NHMe).—4-Methylamino-2 : 6-dibenzyloxypyrimidine (6·45 g.), dissolved in acetic acid (60 c.c.), was almost completely hydrogenated with palladised charcoal catalyst under normal conditions within 2½ hours. Removal of catalyst and solvent gave the crystalline 4-*methylamino*-2 : 6-*dihydroxypyrimidine* (2·8 g., 98·8%), soluble in aqueous alkali and acid, very sparingly soluble in ethanol and water. It was recrystallised from acetic acid and formed minute tablets, m. p. 302° (decomp.) (Found: C, 42·8; H, 5·0; N, 30·2. $C_5H_7O_2N_3$ requires C, 42·5; H, 5·0; N, 29·8%).

2 : 6-*Dichloro*-4-*dimethylaminopyrimidine* (VI; R = NMe_2).—Trichloropyrimidine (15 g., 1 mol.) in ethanol (75 c.c.) was treated with aqueous dimethylamine (27 c.c. of 33%, 2·5 mol.); 2 : 6-*dichloro*-4-*dimethylaminopyrimidine* (7·5 g., 48%) slowly separated. The base was insoluble in water, sparingly soluble in cold acetone and alcohol, and crystallised from alcohol in long colourless needles, m. p. 113° (Found: C, 38·0; H, 3·8; Cl, 37·0. $C_6H_7N_3Cl_2$ requires C, 37·5; H, 3·6; Cl, 36·9%).

4-*Dimethylamino*-2 : 6-*dibenzyloxypyrimidine* (VII; R = NMe_2).—When 2 : 6-dichloro-4-dimethylaminopyrimidine (7 g.,) and sodium benzyloxide (from 1·68 g. of sodium) were refluxed in toluene (75 c.c.) for an hour, the *dibenzyloxypyrimidine* (VII; R = NMe_2) was obtained. Isolated in the usual way, it crystallised from ethanol in beautiful long needles (8·5 g., 69·5%), m. p. 79° (Found: C, 71·3; H, 6·6; N, 11·9. $C_{20}H_{21}O_2N_3$ requires C, 71·6; H, 6·3; N, 12·5%).

4-*Dimethylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = NMe_2).—The above dibenzyloxypyrimidine (7 g.) was completely hydrogenated over palladised charcoal in acetic acid (75 c.c.) under normal conditions within 4 hours. Removal of catalyst and solvent gave the *dihydroxy*-compound (IV; R = NMe_2), a sparingly soluble solid of amphoteric character, which crystallised from acetic acid in large colourless tablets (2·5 g., 77%), m. p. 320° (efferv.) (Found: C, 46·7; H, 6·0. $C_6H_9O_2N_3$ requires C, 46·5; H, 5·8%). After being boiled for 1 hour with dilute hydrochloric acid, the base was recovered unchanged on neutralisation.

4 : 6-*Dichloro*-2-*dimethylaminopyrimidine*.—When water (150 c.c.) was added to the alcoholic mother liquors from the preparation of 2 : 6-dichloro-4-dimethylaminopyrimidine (VI; R = NMe_2), an oil separated which solidified on scratching. It was very soluble in cold alcohol and acetone, but recrystallisation from aqueous ethanol gave the 2-*dimethylamino*-compound (5·5 g., 35%), m. p. 102—103° (Found: C, 37·9; H, 3·7; Cl, 37·6. $C_6H_7N_3Cl_2$ requires C, 37·5; H, 3·6; Cl, 36·9%).

4-*Chloro*-2-*dimethylamino*-6-*benzyloxypyrimidine* (IX; R = NMe_2).—4 : 6-Dichloro-2-dimethylaminopyrimidine (3·5 g., 1 mol.) and sodium benzyloxide (from 0·84 g. of sodium, 2 mols.), heated in toluene (50 c.c.) to 100° for an hour, gave, on isolation in the usual way, a solid residue from which the *monobenzyloxy*-compound (3·5 g., 73%) was obtained. It crystallised from alcohol in long colourless rods, m. p. 84° (Found: C, 59·0; H, 5·2; Cl, 13·9. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 5·3; Cl, 13·5%).

2-*Dimethylamino*-4 : 6-*dibenzyloxypyrimidine* (X; R = NMe_2).—When 4 : 6-dichloro-2-dimethylaminopyrimidine (7 g.) and sodium benzyloxide (from 1·68 g. of sodium) were heated in toluene (100 c.c.) under reflux for 3 hours, and the washed solution evaporated, an uncrystallisable oil (8·5 g., 69·5%) was obtained. Treatment with alcoholic picric acid gave the *picrate*, pure after one crystallisation from

ethanol; it formed yellow leaflets, m. p. 176° (Found: C, 55·7; H, 4·3. $C_{20}H_{21}O_2N_3,C_6H_3O_7N_3$ requires C, 55·3; H, 4·2%).

2-Dimethylamino-4 : 6-dihydroxypyrimidine (III, R = NMe_2).—2-Dimethylamino-4 : 6-dibenzyloxypyrimidine (6·5 g.) was hydrogenated in acetic acid solution (100 c.c.) over palladised charcoal under normal conditions during 5 hours. Evaporation of the filtered solution under reduced pressure gave the *dihydroxypyrimidine* (III, R = NMe_2), which crystallised from acetic acid in stout yellowish prisms (2·2 g., 73%), m. p. 320° (efferv.) Found: C, 46·0; H, 5·7; N, 27·9. $C_6H_9O_2N_3$ requires C, 46·5; H, 5·8; N, 27·1%). The pyrimidine was very sparingly soluble in water, but dissolved in aqueous acid and alkali.

2 : 6-Dichloro-4-guanidinopyrimidine [VI; R = NH·C(:NH)·NH_2].—Guanidine, prepared from guanidine hydrochloride (6 g., 2 mols.), in water (10 c.c.) was added to a solution of trichloropyrimidine (5·75 g., 1 mol.) in acetone (90 c.c.). Heat was evolved, and after 15 minutes a colourless crystalline solid separated, which was collected, washed with acetone, and dried. The *dichloroguanidinopyrimidine* (3·4 g., 53%), which was insoluble in water and very sparingly soluble in acetone and alcohol, crystallised from alcohol in long colourless needles, m. p. 325° (decomp., previous darkening) (Found: C, 29·5; H, 2·5; Cl, 34·4. $C_5H_3N_5Cl_2$ requires C, 29·1; H, 2·4; Cl, 34·5%). On adding water to the residual acetone solution, a further quantity (up to 43%) of the apparently identical product, having the same exceptionally high m. p., was obtained; there was no evidence that any significant amount of a 2-guanidino-compound was present in the solution.

6-Chloro-4-guanidino-2-benzyloxypyrimidine.—2 : 6-Dichloro-4-guanidinopyrimidine (2·1 g., 1 mol.) was heated with sodium benzyloxide (from 0·46 g. of sodium, 2 mols.) in toluene (50 c.c.) to 100° for 2 hours. The insoluble product was collected, washed with water, and crystallised from ethanol; the *6-chloro-4-guanidino-2-benzyloxypyrimidine* (1·7 g., 61%) was thus obtained in colourless needles, very sparingly soluble in cold toluene, m. p. 170° (Found: C, 51·8; H, 4·5. $C_{12}H_{12}ON_5Cl$ requires C, 51·9; H, 4·3%). Treatment with ethanolic picric acid gave a *picrate* which crystallised from *iso*amyl alcohol in small yellow prisms, m. p. 250° (decomp.) (Found: Cl, 7·3. $C_{12}H_{12}ON_5Cl,C_6H_3O_7N_3$ requires Cl, 7·0%).

4-Guanidino-2 : 6-dibenzyloxypyrimidine [VII; R = NH·C(:NH)·NH_2].—2 : 6-Dichloro-4-guanidinopyrimidine (5 g.) was heated with sodium benzyloxide (from 1·1 g. of sodium) in refluxing toluene (75 c.c.) for 8 hours. The semi-solid yellow oil (6·6 g., 78%), which was subsequently isolated, was difficult to recrystallise, and so the dibenzyloxypyrimidine was characterised by its *picrate*, which separated from *iso*amyl alcohol as microscopic prisms, m. p. 200° (Found: C, 51·5; H, 4·0; N, 19·8. $C_{19}H_{19}O_2N_5,C_6H_3O_7N_3$ requires C, 51·8; H, 3·8; N, 19·4%).

4-Guanidino-2 : 6-dihydroxypyrimidine [IV; R = NH·C(:NH)·NH_2].—Hydrogenation of the unpurified 4-guanidino-2 : 6-dibenzyloxypyrimidine (4·1 g.) in acetic acid (125 c.c.) over palladised charcoal ceased in 5 hours, by which time a finely divided solid had separated. This dissolved on heating, and after filtration the solvent was removed under reduced pressure. The crude solid, which was very sparingly soluble in water, ethanol, and *iso*amyl alcohol, readily dissolved in hot acetic acid with which it formed a gel on cooling. The total product was finally treated with boiling water (1 l.), the insoluble fraction discarded, and the filtered solution evaporated. The residue (0·8 g., 38%) consisted of the *guanidinopyrimidine* [IV; R = NH·C(:NH)·NH_2], m. p. 300° (Found: C, 33·6; H, 4·4. $C_5H_7O_2N_5,\frac{1}{2}H_2O$ requires C, 33·7; H, 4·5%).

2-Amino-4-hydroxy-1 : 3-diaza-acridine (II; R = NH_2, R′ = OH).—A suspension of malonylguanidine (III, R = NH_2) (2 g., 1 mol.) and *o*-aminobenzaldehyde (cf. Bamberger, *Ber.*, 1927, **60**, 319) (3 g., 1·5 mols.) in water (100 c.c.) containing concentrated hydrochloric acid (5 c.c.), was heated on a steam-bath for 1 hour. The precipitated aldehyde polymer was removed and the solution cooled; the aminodiaza-acridine *hydrochloride* (2·7 g., 69·5%) then separated. The salt was quite readily hydrolysed in water and was recrystallised from boiling dilute hydrochloric acid, from which it separated in colourless long needles, m. p. > 310° (Found: C, 46·1; H, 4·3; Cl, 12·3. $C_{11}H_8ON_4,HCl,2H_2O$ requires C, 46·3; H, 4·6; Cl, 12·5%).

The action of sodium carbonate solution on the pure hydrochloride gave the microcrystalline *base* (II; R = NH_2, R′ = OH), m. p. > 310° (Found: C, 62·4; H, 3·6. $C_{11}H_8ON_4$ requires C, 62·2; H, 3·8%). It dissolves in sodium hydroxide to a pale yellow solution with a strong greenish-blue fluorescence.

2 : 4-Dihydroxy-1 : 3-diaza-acridine (II; R = R′ = OH).—4-Amino-2 : 6-dihydroxypyrimidine (IV; R = NH_2) (2 g.) and *o*-aminobenzaldehyde (3 g.) were heated in water (100 c.c.) containing concentrated hydrochloric acid (5 c.c.) for an hour. The solid which separated (yield 61%) was collected, washed with alcohol, and purified by precipitation from an alkaline solution with acetic acid. It was very sparingly soluble in water, the alcohols, and acetone, and did not combine with hydrochloric acid. In these properties it was identical with a specimen of 2 : 4-dihydroxy-1 : 3-diaza-acridine (II; R = R′ = OH) prepared from *o*-aminobenzaldehyde and barbituric acid (Conrad and Reinbach, *loc. cit.*) (Found: C, 61·4; H, 3·1; N, 19·3. Calc. for $C_{11}H_7O_2N_3$: C, 62·0; H, 3·3; N, 19·7%).

When the above condensation was repeated in 5% aqueous acetic acid, the compound (II; R = R′ = OH) was once more obtained. On crystallisation from boiling acetic acid the diaza-acridine formed an *acetate*, from which the solvent was expelled on heating to 100° in a vacuum. In this respect it further resembled the authentic diaza-acridine prepared from barbituric acid [Found: C, 57·2; H, 4·1; N, 15·1. $C_{11}H_7O_2N_3,C_2H_4O_2$ requires C, 57·2; H, 4·0; N, 15·4%. Found, after drying at 100°: C, 61·5; H, 3·6; loss 18·9. Found, with authentic specimen of (II; R = R′ = OH): loss, 22·4. $C_{11}H_7O_2N_3$ requires loss, 22·0%].

4-Amino-2-keto-3 : 12-diaza-2 : 12-dihydroacridine (XII).—2 : 4-Diamino-6-hydroxypyrimidine (3 g., 1 mol.) dissolved in water (100 c.c.) containing acetic acid (10 c.c.) was treated with *o*-aminobenzaldehyde (3 g., 1 mol.) in ethanol (10 c.c.). The solution was heated to boiling, and after 1 minute a dense yellow solid began to deposit. In 30 minutes the mixture was cooled, and the product (1·8 g., 35%) collected and crystallised from a large volume of acetic acid. The *diaza-acridine* (XII) was thus obtained as a very sparingly soluble bright yellow microcrystalline powder, m. p. > 330°, giving a

difficultly soluble sodium salt (Found: C, 59·9; H, 4·1; N, 25·4. $C_{11}H_8ON_4,\frac{1}{2}H_2O$ requires C, 59·7; H, 4·1; N, 25·4%). Solutions of the diaza-acridine exhibited a vivid blue fluorescence. The *hydrochloride* crystallised from dilute hydrochloric acid, in which it is very slightly soluble, in minute biscuit-coloured hexagonal plates, m. p. > 310° (Found: C, 53·0; H, 3·7; Cl, 14·5. $C_{11}H_8ON_4,HCl$ requires C, 53·1; H, 3·6; Cl, 14·3%).

2-*Methylamino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II, R = NHMe, R′ = OH).—A solution of 2-methylamino-4 : 6-dihydroxypyrimidine (1·4 g.) and *o*-aminobenzaldehyde (1·8 g.) in acetic acid (5 c.c.) and water (75 c.c.) was heated under reflux for 30 minutes. After the green aldehyde polymer had been removed by ether, the solution was neutralised with sodium bicarbonate, and the precipitated 2-*methylamino*-4-*hydroxydiaza-acridine* (1·4 g., 63·5%) obtained as stout pale yellow prisms, m. p. > 310° (Found: C, 57·6; H, 5·0. $C_{12}H_{10}ON_4,1\frac{1}{3}H_2O$ requires C, 57·6; H, 5·0%. Found, after drying at 100°: C, 63·5; H, 4·7. $C_{12}H_{10}ON_4$ requires C, 63·7; H, 4·4%). The diaza-acridine dissolves sparingly in organic solvents, easily in aqueous acids and alkali, and its solutions exhibit a marked green-blue fluorescence.

When the isomeric 4-methylaminodihydroxypyrimidine was similarly treated with *o*-aminobenzaldehyde, the product, recrystallised from acetic acid, was identified as the diaza-acridine (II; R = R′ = OH) (Found: C, 56·7; H, 4·2. Calc. for $C_{11}H_7O_2N_3,C_2H_4O_2$: C, 57·2; H, 4·0%).

4-*Guanidino*-2-*hydroxy*-1 : 3-*diaza-acridine* [II; R = NH·C(:NH)·NH$_2$, R′ = OH].—4-Guanidino-2 : 6-dihydroxypyrimidine (0·5 g.) and *o*-aminobenzaldehyde (0·5 g.) were heated in boiling 25% acetic acid (40 c.c.) for 30 minutes. On cooling, the diaza-acridine [II; R = NH·C(:NH)·NH$_2$, R′ = OH] separated as felted needles (0·6 g., 81%), m. p. > 310°, soluble in aqueous acid and alkali. The base was difficult to purify, but the *dihydrochloride*, m. p. > 310°, was readily crystallised from dilute hydrochloric acid, forming small cream coloured plates, and losing a molecule of hydrogen chloride on drying at 120° (Found: C, 40·3; H, 4·3; Cl, 19·4. $C_{12}H_{10}ON_6,2HCl,1\frac{1}{2}H_2O$ requires C, 40·7; H, 4·2; Cl, 20·0%. Found, after drying: C, 47·0; H, 4·2; loss, 12·2. $C_{12}H_{10}ON_6,HCl,H_2O$ requires C, 46·6; H, 4·2; loss, 12·5%). The compound was further characterised by the *picrate*, which separated from acetic acid in microscopic yellow tablets, m. p. 230° (decomp.) (Found: C, 42·4; H, 3·2. $C_{12}H_{10}ON_6,C_6H_3O_7N_3,1\frac{1}{2}H_2O$ requires C, 42·4; H, 3·2%. Found, after drying at 100°: C, 43·3; H, 3·0; loss, 3·1. $C_{12}H_{10}ON_6,C_6H_3O_7N_3,\frac{1}{2}H_2O$ requires C, 43·8; H, 2·8; loss, 3·5%).

2-*γ*-*Diethylaminopropylamino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II; R = NH·[CH$_2$]$_3$·NEt$_2$, R′ = OH).—2-*γ*-Diethylaminopropylamino-4 : 6-dihydroxypyrimidine (7·2 g.) and *o*-aminobenzaldehyde (5·4 g.) were heated to 100° in N-hydrochloric acid (100 c.c.) for 1 hour. The cooled, filtered solution was neutralised with sodium carbonate, and after 12 hours a small amount of flocculent precipitate was removed and the filtrate evaporated under reduced pressure. From the residue the crude diaza-acridine was removed as a reddish oil (7·1 g.) by extraction with absolute alcohol (100 c.c.). The only satisfactory derivative was the *meconate*, which separated as a highly crystalline pale yellow powder on adding excess alcoholic meconic acid. It had m. p. 180° (efferv.) not raised by crystallisation from aqueous ethanol, and was sparingly soluble in the alcohols and acetone, very soluble in water. From 15 c.c. of the alcoholic extract the amount of pure salt was 1·4 g., corresponding to a total yield of 4·9 g. (50·0%) of pure base (Found: C, 48·4; H, 5·7; N, 10·9. $C_{18}H_{23}ON_5,C_7H_4O_7,5H_2O$ requires C, 48·8; H, 6·0; N, 11·4%. Found, after drying at 100°: C, 53·0; H, 5·6; loss, 7·7. $C_{18}H_{23}ON_5,C_7H_4O_7,2\frac{1}{2}H_2O$ requires C, 52·7; H, 5·8; loss, 7·3%). The *picrate*, prepared from the base in ethanol, on boiling with a little acetone was obtained as an alcoholate, a microcrystalline powder, m. p. 222° (decomp.), not capable of further purification (Found: C, 51·7; H, 5·2; N, 18·5. $C_{18}H_{23}ON_5,C_6H_3O_7N_3,C_2H_6O$ requires C, 52·0; H, 5·3; N, 18·7%).

5-(2 : 4-*Dinitrobenzylidene*)*barbituric Acid*.—Barbituric acid (3·9 g., 1·5 mol.) was added to a suspension of 2 : 4-dinitrobenzaldehyde (3·9 g., 1 mol.) in boiling water (150 c.c.); in a few seconds a voluminous pale yellow precipitate of the *dinitrobenzylidene* compound (4·1 g., 71·5%) separated. It was very sparingly soluble in water and ethanol, and gave with sodium hydroxide solution a difficultly soluble sodium salt. The dinitrobenzylidene acid was recrystallised from much acetic acid, giving orange needles, m. p. > 310° (Found: C, 43·6; H, 2·3. $C_{11}H_6O_7N_4$ requires C, 43·1; H, 2·0%).

8-*Nitro*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*.—4-Nitro-2-aminobenzaldehyde (3·5 g., 1 mol.) in warm ethanol (75 c.c.) was added to a solution of barbituric acid (3·5 g., 1·3 mols.) in boiling water (250 c.c.); a copious precipitate rapidly appeared, and after 1 hour the *diaza-acridine* (3·5 g., 64·5%) was collected. It was very slightly soluble in the usual solvents, and was purified by crystallisation from a large volume of acetic acid as cream-coloured fluffy needles, m. p. > 310°, giving a sparingly soluble orange sodium salt (Found: C, 49·0; H, 3·0; N, 17·2. $C_{11}H_6O_4N_4,C_2H_4O_2$ requires C, 49·0; H, 3·1; N, 17·5%). In acetic acid the compound showed the blue fluorescence characteristic of the diaza-acridine nucleus.

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