9. *Synthetic Antimalarials. Part XI. The Effect of Variation of Substituents in Derivatives of Mono- and Di-alkylpyrimidines.*

By R. Hull, (Miss) B. J. Lovell, H. T. Openshaw, and A. R. Todd.

Following the discovery that certain 2-amino-4-dialkylaminoalkylamino-5 : 6-dialkylpyrimidines have marked antimalarial activity (Hull, Lovell, Openshaw, Payman, and Todd, Part III, *J.*, 1946, 357) a more extended investigation has been made of the effects of variation of substituents in compounds of this type. In addition several other series of simple mono- and di-methylpyrimidine derivatives bearing amino- and dialkylaminoalkylamino-substitutents have been synthesised; a number of the individual substances have been found to be active against *P. gallinaceum* in chicks.

In Part III (*loc. cit.*) the preparation of a number of derivatives of mono- and di-alkylpyrimidines containing as additional substituents an amino- and a dialkylaminoalkylamino-group was described. The discovery that marked antimalarial activity was possessed by substituted 5 : 6-dimethylpyrimidines of type (I) encouraged us to extend our study of such simple pyrimidine derivatives in the hope both of finding therapeutically useful compounds, and of discovering some connection between antimalarial activity and the chemical structure of the substances. In particular, we wished, if possible, to obtain further evidence bearing on the hypothesis advanced in Part III that interference with an adenosine-containing enzyme system might be responsible for the biological activity of this group of substances. The effect of some variations in the nature of the basic side chain (R″) and of the alkyl groups (R, R′) in pyrimidines of type (I) has already been described. In the present paper we describe some further modifications of the type structure (I), and also several other series of pyrimidine derivatives having different orientations of amino-, alkyl, and dialkylaminoalkylamino-substituents.

It has already been shown that a 5-alkyl group is necessary to promote activity in compounds of type (I). The presence of a 6-substituent in (I), however, is not essential; thus 2-amino-4-β-diethylaminoethylamino-5-methylpyrimidine (I; R = H, R′ = Me, R″ = $[CH_2]_2{\cdot}NEt_2$) and *2-amino-4-γ-diethylaminopropylamino-5-methylpyrimidine* (I; R = H, R′ = Me, R″ = $[CH_2]_3{\cdot}NEt_2$) were both highly active against *P. gallinaceum* in chicks at a dose of 80 mg./kg. Substitution of a phenoxy-group for the methyl group in these compounds (I; R = H, R′ = OPh, R″ = $[CH_2]_2{\cdot}NEt_2$ or $[CH_2]_3{\cdot}NEt_2$) reduced, but did not entirely destroy, the activity. A bromo-substituent at the 5-position was not capable of conferring activity; the 5-bromo-2-amino-4-dialkylaminoalkylamino-6-methylpyrimidines (I; R = Me, R′ = Br, R″ = $[CH_2]_2{\cdot}NEt_2$ or $[CH_2]_3{\cdot}NEt_2$) were inactive at a dose of 120 mg./kg. Other variations of type (I) included the replacement of the 6-methyl group by an amino-group, a chlorine atom, or a second diethylaminoethyl group. The antimalarial activity of the compounds is given in Table I.

The compounds mentioned above were prepared from the corresponding substituted 4-chloropyrimidines by the general method described in Part III (*loc. cit.*). *4-Chloro-2-amino-5-methylpyrimidine* was obtained by the interaction of phosphoryl chloride and 2-amino-4-hydroxy-5-methylpyrimidine (Johnson and Clapp, *Amer. Chem. J.*, 1904, **32**, 130). The similar replacement by chlorine of the hydroxy-group of *2-amino-4-hydroxy-5-phenoxypyrimidine* gave unsatisfactory results, and to overcome this difficulty the substance was acetylated. Instead of the expected 2-acetamido-compound, a *substance*, $C_{24}H_{20}O_5N_6$, was obtained; treatment of this with phosphoryl chloride, however, gave *4-chloro-2-acetamido-5-phenoxypyrimidine*. After condensation with the appropriate diamine, the acetyl group was removed by hydrolysis. When treated with an excess of β-diethylaminoethylamine in the usual manner, *4-chloro-5-bromo-2-amino-6-methylpyrimidine* suffers partial replacement of the bromine atom, but by interaction with an equimolecular quantity of the amine the chlorine atom alone is replaced. The 2 : 6-diamino-4-dialkylaminoalkylaminopyrimidines (I; R = NH_2, R′ = H) were obtained by the interaction of equimolecular quantities of 4-chloro-2 : 6-diaminopyrimidine (Büttner, *Ber.*, 1903, **36**, 2227) and the appropriate diamine; when excess of diamine was used 2-amino-4 : 6-bis(dialkylaminoalkylamino)pyrimidines were obtained, the structure of the products being proved by an independent preparation of one of them from 4-chloro-2-amino-6-β-diethylaminoethylaminopyrimidine (Curd *et al.*, forthcoming publication) and β-diethylaminoethylamine.

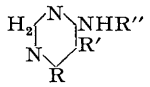
Of the six possible isomerides (II—VII) of the type structure (I), representatives of five (II—VI) are described in this paper; in addition, some monomethylpyrimidines (types VIII and IX) allied to (II) and (III) have been studied. The results of biological tests against *P.*

TABLE I.

Antimalarial Activity of Derivatives of 2-Aminopyrimidine (Type I).

Substituents at positions. 4.	5.	6.	Dose (mg./kg.).	Activity.
$NH\cdot[CH_2]_2\cdot NEt_2$	Me	H	160	++
			80	++
			40	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Me	H	160	Toxic
			80	++
			40	+
$NH\cdot[CH_2]_2\cdot NEt_2$	OPh	H	120	+
			60	±
$NH\cdot[CH_2]_3\cdot NEt_2$	OPh	H	240	Toxic
			120	±
			40	−
$NH\cdot[CH_2]_2\cdot NEt_2$	Br	Me	120	−
			80	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Br	Me	120	−
			80	−
$NH\cdot[CH_2]_2\cdot NEt_2$	H	NH_2	240	−
$NH\cdot[CH_2]_3\cdot NEt_2$	H	NH_2	240	Toxic
			120	−
$NH\cdot[CH_2]_2\cdot NEt_2$	H	$NH\cdot[CH_2]_2\cdot NEt_2$	160	±
			40	−
$NH\cdot[CH_2]_2\cdot NEt_2$	Me	NH_2	80	Toxic
			40	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Me	NH_2	80	Toxic
			40	−
$NH\cdot[CH_2]_2\cdot NEt_2$	Me	Cl	160	Toxic
			80	−
$NH\cdot[CH_2]_3\cdot NEt_2$	Me	Cl	160	Toxic
			40	Toxic
			20	−

gallinaceum in chicks carried out with these substances are shown in Table II. It will be seen that only among compounds of type (III) was marked activity observed; one of them,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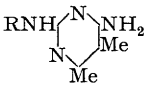
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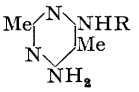
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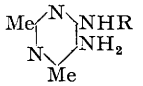
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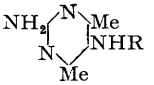
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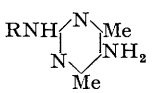
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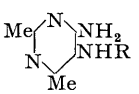
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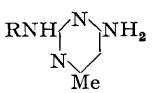
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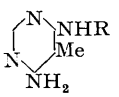

(IX.)

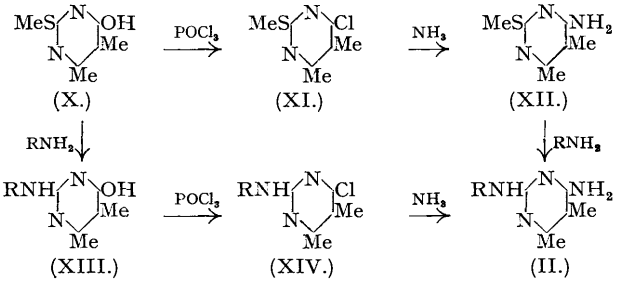
4-*amino*-6-γ-*diethylaminopropylamino*-2 : 5-*dimethylpyrimidine* (III; R = $[CH_2]_3\cdot NEt_2$) is the most active of all the simple pyrimidines we have prepared, appreciable activity being observed at a dose of 20 mg./kg. It is difficult to make any generalisations about structure and antimalarial activity on the basis of results so far obtained but it is interesting that the most active compounds we have prepared have structures which are compatible with the hypothetical mode of action tentatively advanced by us in Part III (*loc. cit.*). It is clearly impossible to argue the validity of any concept of action based on interference with the synthesis or functioning of enzyme components in the absence of extensive biological investigations, but there would seem to be some justification for its retention at present as a basis for further work. The weak activity shown by (V; R = $[CH_2]_2\cdot NEt_2$) is of some interest in connection with the views on the relation between structure and plasmodial action originally advanced by Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) and recently modified by Curd and Rose (Part X; *J.*, 1946, 729). It is difficult to formulate any *o*- or *p*-quinonoid tautomer of (V) involving the basic side chain.

The starting point for the synthesis of compounds of type (II) was 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (X), readily obtained by the interaction of ethyl α-methylacetoacetate with *S*-methyl*iso*thiourea; the substance had previously been prepared (Chi and Kao, *J. Amer. Chem. Soc.*, 1936, **58**, 769) by methylation of the 2-thiol compound. In the first route investigated (X) was converted through 4-*chloro*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (XI) into

TABLE II.

Type.	R.	Dose (mg./kg.).	Activity.
III	$[CH_2]_2 \cdot NEt_2$	80	++
		40	++
III	$[CH_2]_3 \cdot NEt_2$	80	++
		40	++
		20	+
III	$[CH_2]_3 \cdot NMe_2$	160	++
		80	+
II	$[CH_2]_2 \cdot NEt_2$	160	−
II	$[CH_2]_3 \cdot NEt_2$	80	±
		40	−
II	$[CH_2]_3 \cdot NBu^{\alpha}_2$	80	Toxic
		40	−
VIII	$[CH_2]_2 \cdot NEt_2$	160	Toxic
		80	−
VIII	$[CH_2]_3 \cdot NEt_2$	160	Toxic
		80	−
VIII	$[CH_2]_3 \cdot NBu^{\alpha}_2$	80	Toxic
		40	+
		20	−
VIII	$[CH_2]_3 \cdot NMe_2$	160	±
		80	−
IV	$[CH_2]_2 \cdot NEt_2$	160	−
IV	$[CH_2]_3 \cdot NEt_2$	160	−
IV	$[CH_2]_3 \cdot NBu^{\alpha}_2$	80	Toxic
V	$[CH_2]_2 \cdot NEt_2$	160	+
		80	−
IX	$[CH_2]_3 \cdot NEt_2$	120	−
IX	$[CH_2]_2 \cdot NEt_2$	160	Toxic
		80	−

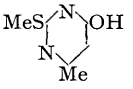
4-amino-2-methylthio-5 : 6-dimethylpyrimidine (XII); the second step was accompanied by some loss of methylthiol with formation of 2 : 4-diamino-5 : 6-dimethylpyrimidine. The substance (XII) when heated with γ-diethylaminopropylamine gave the desired *product* (II; $R = [CH_2]_3 \cdot NEt_2$). Analogous reactions with other dialkylaminoalkylamines proved unsatisfactory, however, and an alternative route was therefore employed. The substance (X) reacted smoothly with amines to form 2-dialkylaminoalkylamino-4-hydroxy-5 : 6-dimethylpyrimidines (XIII), which were converted through the chloro-compounds (XIV) into the desired products (II).



With one exception, the corresponding derivatives (VIII) of 6-methylpyrimidine were prepared from 4-hydroxy-2-methylthio-6-methylpyrimidine by the second route mentioned in the preceding paragraph; the intermediate chloro-compounds have been described in Part VI of this series (Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370). In the case where $R = [CH_2]_3 \cdot NMe_2$ the yields obtained by this method proved to be unsatisfactory and the first method was successfully employed. *4-Amino-2-methylthio-6-methylpyrimidine* (XVI) was readily obtained by amination of the 4-chloro-compound (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 435), and on heating with dimethylaminopropylamine it gave an almost theoretical yield of the desired product (VIII; $R = [CH_2]_3NMe_2$).

Variation in the reactivity of 2-methylthiopyrimidines towards amines has been noted previously; thus Curd and Rose (Part I, *J.*, 1946, 343) found that 2-methylthio-4 : 6-dimethylpyrimidine reacted only sluggishly with aniline at a high temperature, whereas 4-hydroxy-2-methylthio-6-methylpyrimidine (XV) reacted readily and completely at a much lower temperature and they attributed this difference in behaviour to the tautomeric character

of (XV). It is clear from the fact that (XVI) is less reactive than (XV) in this sense that this view requires some expansion, but available data are insufficient to permit a wholly satisfactory explanation on theoretical grounds.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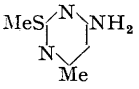
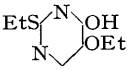
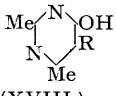

(XVI.)


(XVII.)

It appears from the present work that the reactivity of the 2-methylthio-group is also adversely affected by a methyl group at C_5. A similar effect was noted by Johnson and Heyl (*Amer. Chem. J.*, 1907, **38**, 237) who found that, whereas 4-hydroxy-2-ethylthiopyrimidine reacted readily with aniline at 100°, the 5-ethoxy-derivative (XVII) reacted only slowly at 200°. An *o–p*-directive group at C_5 will tend to increase the electron-availability at the *p*-position (C_2) and thus diminish the ease of attack by an amine.

Substances of type (III) were prepared in the usual manner from 4-chloro-6-amino-2 : 5-dimethylpyrimidine (Huber and Hölscher, *Ber.*, 1938, **71**, 92) and the appropriate amines. The related derivatives (IX) of 5-methylpyrimidine were prepared by a similar series of reactions. 4 : 6-*Dihydroxy*-5-*methylpyrimidine*, obtained by the condensation of formamidine with ethyl methylmalonate, was converted through 4 : 6-*dichloro*-5-*methylpyrimidine* into 4-*chloro*-6-*amino*-5-*methylpyrimidine* which was treated with dialkylaminoalkylamines in the usual manner.

5-Amino-2 : 6-dimethylpyrimidines carrying a basic side chain at C_4 (type IV) were prepared by interaction of the appropriate amines and 4-chloro-5-amino-2 : 6-dimethylpyrimidine (XIX; R = H). 5-Amino-4-hydroxy-2 : 6-dimethylpyrimidine (XVIII; R = NH_2) was conveniently obtained by hydrogenation of 5-benzeneazo-4-hydroxy-2 : 6-dimethylpyrimidine (XVIII; R = PhN_2) (Andersag and Westphal, *Ber.*, 1937, **70**, 2035) using a palladised barium sulphate catalyst, but the direct conversion of the former into 4-chloro-5-amino-2 : 6-dimethylpyrimidine (XIX; R = H) by means of phosphoryl chloride (cf. Andersag and Westphal, *loc. cit.*) gave, in our experience, only a very poor yield. Since it seemed probable that this was due to the reactivity of the 5-amino-group, the effect of protecting this group prior to chlorination was investigated. Attempts to replace the hydroxyl group of the benzeneazo-compound (XVIII; R = PhN_2) by chlorine were unsuccessful. The chlorination of 5-*acetamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NHAc), however, proceeded readily with phosphoryl chloride and dimethylaniline (Baddiley and Topham, *J.*, 1944, 678); the resulting 4-*chloro*-5-*acetamido*-2 : 6-*dimethylpyrimidine* (XIX; R = Ac) reacted readily with γ-diethylaminopropylamine, but on attempting to remove the acetyl group by hydrolysis the product (XX; R = $[CH_2]_3{\cdot}NEt_2$) cyclised to 9-γ-*diethylaminopropyl*-2 : 6 : 8-*trimethylpurine* (XXI; R = $[CH_2]_3{\cdot}NEt_2$). Treatment of (XIX; R = Ac) with other dialkylaminoalkylamines gave a mixture of the corresponding pyrimidine (XX) and purine (XXI) derivatives. The purines (XXI) were devoid of antimalarial activity. It therefore appeared essential to remove the protecting acetyl group before reaction with the amine was carried out. Attempts to achieve this by hydrolysis under a variety of conditions met with little success; either the substance was unaffected or the chlorine atom was simultaneously removed. The difficulty was finally overcome by employing a formyl in place of an acetyl group for protection. 5-*Formamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NH·CHO) was treated with phosphoryl chloride and dimethylaniline and the resulting 4-*chloro*-5-*formamido*-2 : 6-*dimethylpyrimidine* (XIX; R = CHO) was hydrolysed with cold concentrated hydrochloric acid to give 4-chloro-5-amino-2 : 6-dimethylpyrimidine.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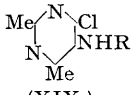
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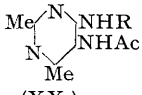
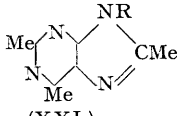
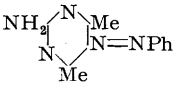

(XX.)

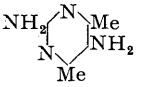

(XXI.)

The introduction of a 5-amino-group into the pyrimidine nucleus by reduction of a 5-benzeneazo-group seemed to offer a suitable approach to the preparation of derivatives of 2 : 5-diaminopyrimidine such as (V) and (VI). Since direct coupling of a pyrimidine with a diazonium compound requires the presence of groups capable of taking part in a prototropic change in at least two positions adjacent to the nuclear nitrogen atoms (Lythgoe, Todd, and Topham, *J.*, 1944, 315), the azo-group could not be introduced directly in the present case. 2-*Amino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (XXII) was readily prepared, however, by the

condensation of benzeneazoacetylacetone (Bülow *et al.*, *Ber.*, 1902, **35**, 2188) with guanidine; on catalytic hydrogenation 2 : 5-*diamino*-4 : 6-*dimethylpyrimidine* (XXIII) was obtained. Alkylation of the diamine with β-diethylaminoethyl chloride afforded (V; R = $[CH_2]_2NEt_2$). That alkylation occurred at the 5-amino-group is shown by the non-identity of the product with 5-amino-2-β-diethylaminoethylamino-4 : 6-dimethylpyrimidine (VI; R = $[CH_2]_2{\cdot}NEt_2$), the synthesis of which is described below.



(XXII.)



(XXIII.)

Several methods of approach to the synthesis of compounds of type (VI) were excluded by the failure of benzeneazoacetylacetone to condense under a variety of conditions with urea, thiourea, *S*-methyl*iso*thiourea, or β-diethylaminoethylguanidine. The last-named compound, obtained as the *hydriodide* by the interaction of *S*-methyl*iso*thiourea hydriodide with β-diethylaminoethylamine, also failed to give the expected product (XIII; R = $[CH_2]_2{\cdot}NEt_2$) on reaction with ethyl α-methylacetoacetate. The substance (VI; R = $[CH_2]_2{\cdot}NEt_2$) was finally obtained by applying the method employed by Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 736) for the alkylation of 2-aminopyrimidines. 2-Amino-5-benzeneazo-4 : 6-dimethylpyrimidine (XXII) was converted into its sodium salt by treatment with sodamide in toluene; reaction with β-diethylaminoethyl chloride then gave 2-β-*diethylaminoethylamino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine*, which on catalytic hydrogenation yielded the desired compound (VI).

Attempts to prepare compounds of type (VII) by the alkylation of 4 : 5-diamino-2 : 6-dimethylpyrimidine (Andersag and Westphal, *loc. cit.*) led to unsatisfactory results. The diamine reacted with dialkylaminoalkyl chlorides, but the products could not be obtained in an analytically pure condition and gave no crystalline derivatives. A similar result was obtained when β-diethylaminoethyl chloride was brought into reaction with 5-amino-4-hydroxy-2 : 6-dimethylpyrimidine and treatment of the impure reaction product with phosphoryl chloride gave none of the desired chloropyrimidine (XIX; R = $[CH_2]_2{\cdot}NEt_2$).

Experimental.

2-*Amino*-4-*hydroxy*-5-*methylpyrimidine*.—A mixture of ethyl formate (200 g.; 2·7 mols.) and ethyl propionate (255 g.; 2·5 mols.) was added dropwise to a well stirred suspension of powdered sodium (52·5 g.; 2·3 atoms) in anhydrous ether (1250 c.c.) during 3 hours. After being left overnight the crude ethyl sodio-α-formylpropionate was collected, washed with ether, and suspended in alcohol (1 l.). Guanidine hydrochloride (159 g.; 1·65 mols.) was added and the mixture stirred for 3 hours at room temperature, refluxed for 4 hours, and set aside overnight. The solid was collected and the filtrate evaporated; the residue and the solid were combined, dissolved in warm water and made alkaline with sodium hydroxide. The cooled, filtered solution was acidified with acetic acid and the product collected and crystallised from water. 2-Amino-4-hydroxy-5-methylpyrimidine (36·5 g.; 17%) formed colourless needles, m. p. 277—279°. Johnson and Clapp (*loc. cit.*) give m. p. 320—321°. Payman (M.Sc. Thesis, Manchester University, 1943, p. 86) gives m. p. 278—280° (Found: C, 48·0; H, 5·5; N, 33·0. Calc. for $C_5H_7ON_3$: C, 48·0; H, 5·6; N, 33·6%).

4-*Chloro*-2-*amino*-5-*methylpyrimidine*.—A mixture of 2-amino-4-hydroxy-5-methylpyrimidine (5 g.) and phosphoryl chloride (30 c.c.) was refluxed for 45 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on ice and left for 24 hours. On making alkaline with ammonia, keeping the temperature below 10°, 4-*chloro*-2-*amino*-5-*methylpyrimidine* (3·95 g.; 68%) precipitated as a colourless solid, m. p. 177—180°. Recrystallisation from alcohol gave colourless needles, m. p. 184—185° (Found: C, 42·2; H, 4·3; N, 29·3. $C_5H_6N_3Cl$ requires C, 41·8; H, 4·2; N, 29·3%).

2-*Amino*-4-β-*diethylaminoethylamino*-5-*methylpyrimidine*.—4-Chloro-2-amino-5-methylpyrimidine (3·5 g.) was treated with β-diethylaminoethylamine (11·4 g.) by the general method described in Part III (*loc. cit.*). The product (4·7 g.; 87%) distilled at 170° (bath temp.)/3 × 10^{-4} mm. as a viscous straw-coloured oil. The *dipicrate* formed yellow prisms from alcohol, m. p. 195—196° (Found: C, 41·0; H, 3·7; N, 22·4. $C_{11}H_{21}N_5,2C_6H_3O_7N_3$ requires C, 40·5; H, 3·9; N, 22·6%).

2-*Amino*-4-γ-*diethylaminopropylamino*-5-*methylpyrimidine*.—A mixture of 4-chloro-2-amino-5-methylpyrimidine (4 g.) and γ-diethylaminopropylamine (14·5 g.) was refluxed for 5 hours. The *product*, isolated in the usual manner, distilled at 185—210° (bath temp.)/4 × 10^{-4} mm. as an oil which crystallised on standing with anhydrous ether for 5 days. Recrystallisation from light petroleum (b. p. 60—80°) gave colourless needles, m. p. 70—71° (Found: C, 60·8; H, 9·7; N, 29·4. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%).

2-*Amino*-4-*hydroxy*-5-*phenoxypyrimidine*.—A mixture of ethyl formate (37 g.; 0·5 mol.) and ethyl phenoxyacetate (90 g.; 0·5 mol.) was added dropwise to a cooled and stirred suspension of powdered sodium (11·5 g.; 0·5 mol.) in anhydrous ether (250 c.c.) during 45 minutes. After standing overnight, the crude ethyl sodio-α-formyl-α-phenoxyacetate was collected, washed with ether and added to a

mixture of guanidine hydrochloride (47·8 g.; 0·5 mol.) and alcoholic sodium ethoxide (from 11·5 g. of sodium and 200 c.c. of alcohol). The mixture was refluxed for 5 hours and cooled, the precipitate collected, and the filtrate evaporated to dryness. The combined solids were dissolved in warm water, filtered, cooled, and acidified with acetic acid. The precipitate, m. p. 247—250°, was purified by redissolving in alkali (charcoal) and reprecipitating with acetic acid: the resulting *2-amino-4-hydroxy-5-phenoxypyrimidine* (56 g.; 55%), recrystallised from water, gave colourless prisms, m. p. 255—256° (Found: C, 59·2; H, 4·8; N, 20·9. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

4-Chloro-2-amino-5-phenoxypyrimidine.—A mixture of finely powdered 2-amino-4-hydroxy-5-phenoxypyrimidine (5 g.) and phosphoryl chloride (30 c.c.) was refluxed for 15 minutes. Worked up in the usual manner the solid product (4·4 g.) had m. p. 134—137°. A specimen purified by sublimation in a vacuum and recrystallisation from alcohol yielded *4-chloro-2-amino-5-phenoxypyrimidine* as needles, m. p. 157·5° (Found: C, 54·4; H, 3·2; N, 18·7. $C_{10}H_8ON_3Cl$ requires C, 54·2; H, 3·6; N, 18·9%).

Acetylation of 2-Amino-4-hydroxy-5-phenoxypyrimidine.—A mixture of the pyrimidine (3 g.), acetic anhydride (1·53 c.c.), and anhydrous pyridine (15 c.c.) was refluxed for 2 hours. Alcohol (7 c.c.) was added to the cooled mixture and the solid (2·05 g.), m. p. 239—240°, which separated was collected and washed with alcohol. Recrystallisation from alcohol–pyridine gave colourless needles, m. p. 239—240° (Found: C, 60·6; H, 4·7; N, 18·3; *M* (Rast), 478. $C_{24}H_{20}O_5N_6$ requires C, 60·9; H, 4·2; N, 17·9%; *M*, 472). The *substance* was soluble in hot water, alcohol, and pyridine. It dissolved in cold aqueous sodium hydroxide and was reprecipitated unchanged on acidification.

4-Chloro-2-acetamido-5-phenoxypyrimidine.—The above substance (13·3 g.) was refluxed with phosphoryl chloride (80 c.c.) for 15 minutes. The product (13·5 g.), isolated in the usual manner, was an orange solid, m. p. 148—153°. After recrystallising twice from alcohol (charcoal), *4-chloro-2-acetamido-5-phenoxypyrimidine* formed almost colourless needles, m. p. 163° (Found: C, 55·0; H, 3·7; N, 15·7. $C_{12}H_{10}O_2N_3Cl$ requires C, 54·7; H, 3·8; N, 15·9%).

2-Amino-4-β-diethylaminoethylamino-5-phenoxypyrimidine.—A mixture of 4-chloro-2-acetamido-5-phenoxypyrimidine (1·5 g.) and β-diethylaminoethylamine (2·65 g.) was refluxed for 5 hours and excess of diamine removed under reduced pressure. The residual oil was refluxed with dilute hydrochloric acid (30 c.c. of 10%) for 6 hours. The cooled solution was made alkaline and the liberated oil isolated by extraction with ether. *2-Amino-4-β-diethylaminoethylamino-5-phenoxypyrimidine* (1·52 g.; 89%) distilled at 200° (bath temp.)/10^{-4} mm. as a yellow viscous oil, and then crystallised from benzene–light petroleum in colourless platelets, m. p. 114—115° (Found: C, 63·8; H, 7·5; N, 23·6. $C_{16}H_{23}ON_5$ requires C, 63·8; H, 7·6; N, 23·2%).

2-Amino-4-γ-diethylaminopropylamino-5-phenoxypyrimidine.—Prepared from 4-chloro-2-acetamido-5-phenoxypyrimidine (1·1 g.) and γ-diethylaminopropylamine (2·18 g.) in the manner described above, *2-amino-4-γ-diethylaminopropylamino-5-phenoxypyrimidine* distilled at 250° (bath temp.)/10^{-4} mm. as a yellow, viscous oil (1·3 g.; 98%), which crystallised from benzene–light petroleum as fine needles, m. p. 130·5—131° (Found: C, 65·0; H, 7·9; N, 22·3. $C_{17}H_{25}ON_5$ requires C, 64·8; H, 7·9; N, 22·2%).

5-Bromo-2-amino-4-hydroxy-6-methylpyrimidine.—Bromine (17 c.c.; 0·34 mol.) was added dropwise to a stirred suspension of 2-amino-4-hydroxy-6-methylpyrimidine (40 g.; 0·32 mol.) in acetic acid (350 c.c.) during 30 minutes. After a further 30 minutes the pale yellow hydrobromide, m. p. 250° (decomp.) (93 g.; 100%), was collected and dried at 100°. Recrystallisation from water hydrolysed the salt, giving 5-bromo-2-amino-4-hydroxy-6-methylpyrimidine, m. p. 250° (decomp.) (Found: C, 29·4; H, 2·8; N, 20·4. Calc. for $C_5H_6ON_3Br$: C, 29·4; H, 2·9; N, 20·6%). Jaeger (*Annalen*, 1891, **262**, 367) prepared the substance but gave no m. p.

4-Chloro-5-bromo-2-amino-6-methylpyrimidine.—A mixture of the above hydroxypyrimidine hydrobromide (93 g.) and phosphoryl chloride (465 c.c.) was refluxed for 5 hours. The product (58 g.; 79%), isolated in the usual manner, was a yellow solid, m. p. 190—198°. On recrystallisation from alcohol, *4-chloro-5-bromo-2-amino-6-methylpyrimidine* formed colourless needles, m. p. 206—207° (Found: C, 26·8; H, 2·5; N, 19·4. $C_5H_5N_3ClBr$ requires C, 27·0; H, 2·2; N, 18·9%).

5-Bromo-2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine.—A mixture of 4-chloro-5-bromo-2-amino-6-methylpyrimidine (2·23 g.; 0·01 mol.), β-diethylaminoethylamine (1·17 g.; 0·01 mol.) and β-ethoxyethanol (20 c.c.) was refluxed for 5 hours. After removal of the solvent under reduced pressure the product was isolated in the usual manner. *5-Bromo-2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine* (2·4 g.; 80%) distilled at 200° (bath temp.)/10^{-2} mm. as a yellow viscous oil (Found: C, 44·0; H, 6·5; N, 23·3. $C_{11}H_{20}N_5Br$ requires C, 43·7; H, 6·6; N, 23·2%).

5-Bromo-2-amino-4-γ-diethylaminopropylamino-6-methylpyrimidine.—4-Chloro-5-bromo-2-amino-6-methylpyrimidine (5 g.; 0·022 mol.) and γ-diethylaminopropylamine (11·7 g.; 0·089 mol.) were heated together under reflux for 6 hours. The product (6·5 g.; 91·5%), isolated in the usual manner, distilled at 220—235° (bath temp.)/2 × 10^{-4} mm. as a yellow viscous oil which slowly crystallised. On recrystallisation from light petroleum, *5-bromo-2-amino-4-γ-diethylaminopropylamino-6-methylpyrimidine* formed colourless needles, m. p. 105·5—107° (Found: C, 45·6; H, 7·0; N, 22·3. $C_{12}H_{22}N_5Br$ requires C, 45·5; H, 6·9; N, 22·1%).

4-Chloro-2:6-diaminopyrimidine.—4:6-Dichloro-2-aminopyrimidine (70 g.), prepared by the interaction of 2-amino-4:6-dihydroxypyrimidine (Michael, *J. pr. Chem.*, 1894, **49**, 35) and phosphoryl chloride as indicated by Büttner (*loc. cit.*), was heated with alcoholic ammonia (420 c.c., saturated at 0°) in an autoclave at 150° for 3 hours. The solid was collected, combined with the residue obtained by evaporating the filtrate, and recrystallised from water (charcoal), giving colourless needles (51·5 g.; 84%), m. p. 196·5—197·5° (Büttner gives m. p. 198°).

2:6-Diamino-4-β-diethylaminoethylaminopyrimidine.—A solution of 4-chloro-2:6-diaminopyrimidine (5·78 g.; 0·04 mol.) and β-diethylaminoethylamine (4·45 g.; 0·043 mol.) in dry pyridine (13 c.c.) was refluxed for 16 hours and worked up in the usual way. The chloroform solution of the crude product on standing deposited unchanged 4-chloro-2:6-diaminopyrimidine (0·62 g.), which was removed; distillation of the filtrate gave 2:6-diamino-4-β-diethylaminoethylaminopyrimidine (5·5 g.; 62%), b. p. 270° (bath temp.)/10^{-3} mm., as a pale yellow oil. The *dipicrate*, rosettes of needles from water, had

m. p. 204—206° (Found : C, 39·0; H, 4·1; N, 25·0. $C_{10}H_{20}N_6,2C_6H_3O_7N_3$ requires C, 38·7; H, 3·8; N, 24·6%).

2 : 6-*Diamino*-4-*γ*-*diethylaminopropylaminopyrimidine*.—This, prepared in a similar manner, was a viscous yellow oil, b. p. 250° (bath temp.)/10^{-3} mm.; the *dipicrate* formed rosettes of needles from water, m. p. 202—203° (Found : C, 39·5; H, 4·3; N, 24·1. $C_{11}H_{22}N_6,2C_6H_3O_7N_3$ requires C, 39·6; H, 4·0; N, 24·1%).

2-*Amino*-4 : 6-*bis*-(*β*-*diethylaminoethylamino*)*pyrimidine*.—(*a*) 4-Chloro-2 : 6-diaminopyrimidine (6·5 g.; 0·045 mol.) and *β*-diethylaminoethylamine (20·8 g.; 0·18 mol.) were heated under reflux for 6 hours. Isolation of the product in the usual manner gave a brown viscous oil (9·25 g.), b. p. 230° (bath temp.)/10^{-3} mm., which on extraction with light petroleum yielded a colourless, hygroscopic, waxy solid, m. p. 45—47°. Recrystallisation from light petroleum raised the m. p. of the *compound* to 58—60° (Found : C, 59·6; H, 10·5; N, 30·1. $C_{16}H_{33}N_7$ requires C, 59·5; H, 10·2; N, 30·3%). The picrate had m. p. 177·5—178·5°.

(*b*) 4-Chloro-2-amino-6-*β*-diethylaminoethylaminopyrimidine (1·0 g.; 0·004 mol.) (Curd, *et al.*, forthcoming publication) was treated with *β*-diethylaminoethylamine (0·95 g.; 0·008 mol.) at 150° for 6 hours. The product, distilled at 260° (bath temp.)/5×10^{-3} mm. and twice crystallised from light petroleum, was a hygroscopic, waxy solid, m. p. 51—55°. The picrate had m. p. 178°, undepressed in admixture with the picrate obtained by method (*a*).

2-*Amino*-4 : 6-*bis*-(*γ*-*diethylaminopropylamino*)*pyrimidine*.—Prepared from 4-chloro-2 : 6-diaminopyrimidine (5·0 g.; 0·034 mol.) and *γ*-diethylaminopropylamine (17·0 g.; 0·13 mol.) by method (*a*) above, the *substance* was a brown viscous oil (5·65 g.), b. p. 270° (bath temp.)/4×10^{-4} mm., which could not be obtained crystalline. It was redistilled for analysis (Found : C, 62·1; H, 10·6; N, 28·2. $C_{18}H_{37}N_7$ requires C, 61·6; H, 10·5; N, 27·9%).

4 : 6-*Dichloro*-2-*amino*-5-*methylpyrimidine*.—The following modification of the method of Gerngross (*Ber.*, 1905, **38**, 3394) gave satisfactory results. To a solution of sodium ethoxide (4·0 mols.) in alcohol (1300 c.c.) were added successively guanidine hydrochloride (191 g.; 2·0 mols.) and ethyl methylmalonate (348 g.; 2·0 mols.). After the mixture had been refluxed for 2 hours and left overnight, the precipitated sodium salt was collected, combined with the residue obtained by evaporating the filtrate, dissolved in warm water, and treated with charcoal. The filtered solution was acidified with acetic acid, and the precipitated 2-amino-4 : 6-dihydroxy-5-methylpyrimidine (243 g.; 86%), m. p. > 300°, was collected, washed with water and dried at 100°. A mixture of this (125 g.) and phosphoryl chloride (500 c.c.) was refluxed for 45 minutes, excess of reagent removed by distillation, and the residue poured on ice and left overnight. The product (129 g.), precipitated by addition of ammonia with cooling, was collected and dried at 100°; m. p. 227—237°. Sublimation in a vacuum gave 94 g., m. p. 243·5—246°; washing with water and then methanol raised the m. p. to 245—248° (Gerngross, *loc. cit.*, gives m. p. 249°). Yield, 89 g.; 56·5%.

4-*Chloro*-2 : 6-*diamino*-5-*methylpyrimidine*.—This was prepared from 4 : 6-dichloro-2-amino-5-methylpyrimidine in 87% yield by the method of Gerngross (*loc. cit.*).

2 : 6-*Diamino*-4-*β*-*diethylaminoethylamino*-5-*methylpyrimidine*.—Prepared in the usual manner the *base* distilled at 250° (bath temp.)/10^{-4} mm. as a viscous, straw-coloured oil (yield 88%), which crystallised on trituration with dry ether at 0°. Recrystallisation from benzene–light petroleum gave rosettes of colourless needles, m. p. 102° (Found : C, 55·0; H, 9·2; N, 35·2. $C_{11}H_{22}N_6$ requires C, 55·5; H, 9·2; N, 35·3%).

2 : 6-*Diamino*-4-*γ*-*diethylaminopropylamino*-5-*methylpyrimidine*.—A viscous yellow oil, b. p. 250—270° (bath temp.)/10^{-2} mm. (yield, 81%), which was converted by trituration with ether to a hygroscopic, waxy solid. The *bis*-3 : 5-*dinitrobenzoate* formed needles from aqueous alcohol, m. p. 213° (Found : C, 45·8; H, 4·8; N, 20·2. $C_{12}H_{24}N_6,2C_7H_4O_6N_2$ requires C, 46·2; H, 4·7; N, 20·7%).

4-*Chloro*-2-*amino*-6-*β*-*diethylaminoethylamino*-5-*methylpyrimidine*.—A solution of 4 : 6-dichloro-2-amino-5-methylpyrimidine (8·9 g.; 0·05 mol.) and *β*-diethylaminoethylamine (5·8 g.; 0·05 mol.) in pyridine (25 c.c.) was refluxed for 15 hours, pyridine removed by distillation, and the residue dissolved in dilute hydrochloric acid. The product was liberated by the addition of solid sodium hydroxide, keeping the temperature below 10°, and extracted with chloroform. After distillation at 250° (bath temp.)/10^{-4} mm. and crystallisation from ethyl acetate–light petroleum, 4-*chloro*-2-*amino*-6-*β*-*diethylaminoethylamino*-5-*methylpyrimidine* (7·1 g.; 55%) formed colourless needles, m. p. 99—101° (Found : C, 50·8; H, 7·6; N, 27·2. $C_{11}H_{20}N_5Cl$ requires C, 51·3; H, 7·8; N, 27·2%).

4-*Chloro*-2-*amino*-6-*γ*-*diethylaminopropylamino*-5-*methylpyrimidine*.—A mixture of 4 : 6-dichloro-2-amino-5-methylpyrimidine (8·9 g.; 0·05 mol.), *γ*-diethylaminopropylamine (6·5 g.; 0·05 mol.), and glacial acetic acid (2·85 c.c.; 0·05 mol.) was heated at 110° for 4 hours and at 130° for a further 2 hours. After cooling, the mixture was diluted with ice-water (40 c.c.) and made alkaline with ammonia. After 2 days, a small amount of unchanged dichloropyrimidine was removed by filtration and the *product* precipitated as a colourless solid (10·3 g.; 76%), m. p. 112—114°, by adding solid sodium hydroxide. Recrystallisation from ethyl acetate gave colourless needles, m. p. 121—122° (Found : C, 53·0; H, 8·0; N, 25·8. $C_{12}H_{22}N_5Cl$ requires C, 53·0; H, 8·1; N, 25·8%).

4-*Hydroxy*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (X).—*S*-Methyl*iso*thiourea hydriodide (21·7 g.; 0·1 mol.) was added to alcoholic sodium ethoxide (from 4·6 g. of sodium and 250 c.c. of alcohol), followed after 10 minutes by ethyl *α*-methylacetoacetate (14·4 g.; 0·1 mol.). Next day, the alcohol was removed under reduced pressure and the residue dissolved in water. The solution was made just acid by adding hydrochloric acid, and the colourless precipitate was collected, washed with water, and recrystallised from alcohol giving colourless plates (10·3 g.; 61%), m. p. 227—229° (Chi and Kao, *loc. cit.*, give m. p. 225—227°) (Found : C, 49·5; H, 6·1; N, 16·5. Calc. for $C_7H_{10}ON_2S$: C, 49·4; H, 5·9; N, 16·5%).

4-*Chloro*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (XI).—A mixture of 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (11 g.) and phosphoryl chloride (150 c.c.) was warmed on the steam-bath for 5 minutes, excess of phosphoryl chloride removed under reduced pressure, and the residue poured on ice; the white precipitate was recrystallised from aqueous alcohol. 4-*Chloro*-2-*methylthio*-5 : 6-*dimethyl*-

pyrimidine (11·2 g.; 92%) formed colourless needles, m. p. 35—36° (Found: C, 44·1; H, 4·5; N, 14·7. $C_7H_9N_2ClS$ requires C, 44·6; H, 4·8; N, 14·8%).

4-*Amino*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (XII).—The above chloro-compound (2·05 g.) was dissolved in excess of saturated anhydrous alcoholic ammonia and the solution was heated in an autoclave at 115—125° for 6 hours. Ammonium chloride was removed by filtration and the filtrate evaporated to dryness. Recrystallised from hot water (charcoal) the residue gave 4-*amino*-2-*methylthio*-5 : 6-*dimethylpyrimidine* (0·9 g.; 50%) as colourless prisms, m. p. 158—159·5° (Found: C, 49·7; H, 6·3; N, 24·8. $C_7H_{11}N_3S$ requires C, 49·7; H, 6·5; N, 24·9%).

4-*Amino*-2-*γ*-*diethylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—A mixture of 4-amino-2-methylthio-5 : 6-dimethylpyrimidine (5·6 g.; 0·033 mol.) and γ-diethylaminopropylamine (8·6 g.; 0·066 mol.) was heated in an autoclave at 200—210° for 22 hours. After removal of excess of amine by distillation, the residue was distilled at 5×10^{-4} mm. (bath temp. 170—175°). The distillate, a pale yellow, viscous oil, contained sulphur. On heating at 100°/10^{-4} mm. for several hours, some unchanged methylthio-compound sublimed; the remainder of the starting material was removed by two further distillations, the first fractions of distillate being rejected. The final *product* (3·25 g.; 39%) was a viscous oil which did not crystallise (Found: C, 61·4; H, 9·7; N, 27·7. $C_{13}H_{25}N_5$ requires C, 62·1; H, 10·0; N, 27·9%). The *bis*-3 : 5-*dinitrobenzoate* separated from alcohol as pale yellow prisms, m. p. 210—212° (Found: C, 47·4; H, 4·7; N, 18·6. $C_{13}H_{25}N_5,2C_7H_4O_6N_2$ requires C, 48·0; H, 4·9; N, 18·7%).

2-*β*-*Diethylaminoethylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine*.—A mixture of 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (5·7 g.; 0·033 mol.) and β-diethylaminoethylamine (4·3 g.; 0·036 mol.) was heated under reflux in an oil-bath at 160—170° for 3 hours. The product distilled at 240—250° (bath temp.)/4 × 10^{-3} mm. as a pale yellow oil (7·75 g.; 98%). It crystallised on trituration with light petroleum; on recrystallisation from the same solvent, 2-*β*-*diethylaminoethylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine* had m. p. 86·5—88° (Found: C, 60·5; H, 9·6; N, 23·9. $C_{12}H_{22}ON_4$ requires C, 60·5; H, 9·2; N, 23·5%).

4-*Chloro*-2-*β*-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine*.—A mixture of the above hydroxypyrimidine (7·0 g.) and phosphoryl chloride (20 c.c.) was heated gradually to boiling; a vigorous reaction then occurred. After 5 minutes the mixture was cooled rapidly and poured on ice. Worked up in the usual manner 4-*chloro*-2-*β*-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine* (6·15 g.; 81%) distilled at 140—150° (bath temp.)/2 × 10^{-4} mm. as a pale yellow oil which rapidly solidified. A sample was further purified by sublimation at 90°/10^{-4} mm. and had m. p. 46·5—47·5° (Found: C, 55·6; H, 8·0; N, 22·1. $C_{12}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; N, 21·8%).

4-*Amino*-2-*β*-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine*.—(*a*) A solution of the above chloropyrimidine (5·5 g.) in excess of saturated alcoholic ammonia was heated in an autoclave at 180—190° for 3 hours. The crude product distilled at 180—190° (bath temp.)/8 × 10^{-3} mm. as a nearly colourless viscous oil which rapidly crystallised. On recrystallisation from benzene, 4-*amino*-2-*β*-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine* (2·45 g.; 49%) was obtained as colourless prisms, m. p. 130—131·5° (Found: C, 60·9; H, 9·5; N, 29·3. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%).

(*b*) 4-Amino-2-methylthio-5 : 6-dimethylpyrimidine (0·85 g.; 0·005 mol.) and β-diethylaminoethylamine (2·3 g.; 0·02 mol.) were mixed and heated in an autoclave at 190—200° for 22 hours. Distillation of the crude product gave a thick yellow oil, b. p. 200° (bath temp.)/2 × 10^{-3} mm., which rapidly solidified, melted indefinitely at about 140°, and appeared to be a mixture of starting material and the desired product. After recrystallising five times from benzene the final product (0·15 g.) had m. p. 130—131° and was identical with that obtained by method (*a*).

2-*γ*-*Di*-n-*butylaminopropylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine*.—4-Hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (5·7 g.; 0·033 mol.) was heated with γ-di-*n*-butylaminopropylamine (7·7 g.; 0·041 mol.) at 160—170° for three hours, and the product purified by distillation. It distilled at 260—280° (bath temp.)/2 × 10^{-4} mm. as a pale yellow oil, which slowly solidified (9·9 g.; 96%). The *dipicrate*, crystallised from ethyl alcohol, had m. p. 199—202° (Found: C, 45·6; H, 4·8; N, 19·0. $C_{17}H_{32}ON_4,2C_6H_3O_7N_3$ requires C, 45·4; H, 5·0; N, 18·3%)

4-*Chloro*-2-*γ*-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—The above hydroxypyrimidine (6·5 g.) was refluxed with phosphoryl chloride (15 c.c.) for 5 mins., and ethyl acetate was used in place of ether for the extraction of the product. The product distilled at 185—190° (bath temp.)/4 × 10^{-3} mm. as a colourless mobile oil which did not crystallise. The *dipicrate* crystallised from alcohol as bright yellow needles, m. p. 167·5—168·5° (Found: C 44·3; H 4·6; N 18·0. $C_{17}H_{31}N_4Cl,2C_6H_3O_7N_3$ requires C, 44·4; H, 4·7; N, 17·8%).

4-*Amino*-2-*γ*-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—The above chloropyrimidine (3·3 g.) was heated with alcoholic ammonia at 200° for 4 hours and the product was isolated in the usual manner. 4-*Amino*-2-*γ*-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine* (2·3 g.; 74%) distilled at 210—220° (bath temp.)/2 × 10^{-3} mm. as a viscous yellow oil which did not crystallise (Found: C, 66·2; H, 10·3; N, 22·8. $C_{17}H_{33}N_5$ requires C, 66·5; H, 10·7; N, 22·8%). The *dipicrate* formed yellow prisms from alcohol, m. p. 167—169° (depressed to 145° on admixture with the dipicrate of the corresponding chloropyrimidine) (Found: C, 46·0; H, 5·3; N, 19·9. $C_{17}H_{33}N_5,2C_6H_3O_7N_3$ requires C, 45·5; H, 5·1; N, 20·1%).

2-*γ*-*Dimethylaminopropylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine*.—Prepared from 4-hydroxy-2-methylthio-5 : 6-dimethylpyrimidine (4·25 g.; 0·025 mol.) and γ-dimethylaminopropylamine (2·8 g.; 0·028 mol.) in the usual manner, 2-*γ*-*dimethylaminopropylamino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine* distilled at 230—235° (bath temp.)/2 × 10^{-2} mm. as a pale yellow oil (5·4 g.; 97%) which set to a waxy solid. A specimen was crystallised from light petroleum as a colourless powder, m. p. 113·5—115° (Found: C, 52·7; H, 8·8; N, 22·7. $C_{11}H_{20}ON_4,1\frac{1}{2}H_2O$ requires C, 52·6; H, 9·2; N, 22·3%).

4-*Chloro*-2-*γ*-*dimethylaminopropylamino*-5 : 6-*dimethylpyrimidine*.—The above hydroxypyrimidine (16·8 g.) was treated with phosphoryl chloride (40 c.c.) in the usual manner. The *product* distilled at 150—155° (bath temp.)/2 × 10^{-2} mm. as a colourless oil (10 g.; 55%) which rapidly solidified. A

specimen was sublimed at 80—90°/10^{-4} mm. and had m. p. 36—38° (Found : C, 54·4; H, 8·0; N, 22·4. $C_{11}H_{19}N_4Cl$ requires C, 54·4; H, 7·8; N, 23·1%).

4-Amino-2-γ-dimethylaminopropylamino-5 : 6-dimethylpyrimidine.—The foregoing chloropyrimidine (3·0 g.) was treated with alcoholic ammonia in the usual manner; chloroform was used in place of ether for extracting the product, which distilled at 180—190° (bath temp.)/2 × 10^{-3} mm. as a yellow viscous oil (0·8 g.; 28%) and did not crystallise. The *tartrate* crystallised from 95% alcohol as colourless needles, m. p. 168—171° (Found : C, 44·2; H, 7·3; N, 17·5. $C_{11}H_{21}N_5,C_4H_6O_6,2H_2O$ requires C, 44·0; H, 7·6; N, 17·1%).

4-Amino-2-dialkylaminoalkylamino-6-methylpyrimidines (VIII).—The appropriate 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidine (Part VI, *loc. cit.*) was treated with excess of alcoholic ammonia in an autoclave at 180—190° for 3 hours (in the case of the γ-dibutylaminopropylamino-compound, at 200—210° for 5 hours), and the product was isolated in the usual manner. The *compound* (VIII; R = $NEt_2{\cdot}[CH_2]_2$) solidified after distillation and was crystallised from anhydrous benzene; the other *products* were viscous oils. The *bis*-3 : 5-*dinitrobenzoates* were crystallised from alcohol. The properties and analyses of the substances are recorded in Table III. The preparation of 4-chloro-2-γ-dimethylaminopropylamino-6-methylpyrimidine and its reaction with ammonia both gave poor yields, and the method described below was therefore preferred.

TABLE III.

4-Amino-2-dialkylaminoalkylamino-6-methylpyrimidines (VIII).

Compound.	M. p.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Required, %. C.	Required, %. H.	Required, %. N.
VIII, R = $NMe_2{\cdot}[CH_2]_3$	—	$C_{10}H_{19}N_5$	56·7	8·9	—	57·4	9·1	—
,, dinitrobenzoate	223—225°	$C_{10}H_{19}N_5,2C_7H_4O_6N_2$	46·0	4·6	19·3	45·5	4·3	19·9
VIII, R = $NEt_2{\cdot}[CH_2]_2$	98—100	$C_{11}H_{21}N_5$	59·3	9·6	31·8	59·2	9·4	31·4
VIII, R = $NEt_2{\cdot}[CH_2]_3$	—	$C_{12}H_{23}N_5$	60·7	9·6	—	60·8	9·7	—
,, dinitrobenzoate	218—220	$C_{12}H_{23}N_5,2C_7H_4O_6N_2$	47·4	4·8	18·6	47·2	4·7	19·0
VIII, R = $NBu_2{\cdot}[CH_2]_3$	—	$C_{16}H_{31}N_5$	66·2	10·4	23·5	65·5	10·6	23·9
,, dinitrobenzoate	200—202	$C_{16}H_{31}N_5,2C_7H_4O_6N_2$	50·1	5·4	17·3	50·2	5·4	17·6

4-Amino-2-methylthio-6-methylpyrimidine (XVI).—A solution of 4-chloro-2-methylthio-6-methylpyrimidine (4 g.) (Wheeler and McFarland, *loc. cit.*) in excess of concentrated alcoholic ammonia was heated in an autoclave at 125—135° for 5½ hours. Excess of ammonia and alcohol were removed by distillation and the residue was dissolved in hot water. On cooling, *4-amino-2-methylthio-6-methylpyrimidine* (2·6 g.; 74%) separated as colourless plates, m. p. 132—134°, raised on recrystallisation to 133·5—135° (Found : C, 46·2; H, 5·7; N, 26·8. $C_6H_9N_3S$ requires C, 46·5; H, 5·8; N, 27·1%).

4-Amino-2-γ-dimethylaminopropylamino-6-methylpyrimidine.—A mixture of 4-amino-2-methylthio-6-methylpyrimidine (2 g.) and γ-dimethylaminopropylamine (2·6 g.) was heated in an autoclave at 160—170° for 14 hours. 4-Amino-2-γ-dimethylaminopropylamino-6-methylpyrimidine distilled at 180—200° (bath temp.)/10^{-4} mm. as a pale yellow viscous oil (2·5 g.; 93%), which did not crystallise. The bis-3 : 5-dinitrobenzoate, crystallised from alcohol, formed hygroscopic pale yellow needles, m. p. 223—225°, undepressed by material obtained by the previous method.

6-Amino-4-dialkylaminoalkylamino-2 : 5-dimethylpyrimidines (Type III).—Prepared from 4-chloro-6-amino-2 : 5-dimethylpyrimidine (Huber and Hölscher, *loc. cit.*) and the appropriate amines by the general method described in Part III (*loc. cit.*), and crystallised from light petroleum or benzene–light petroleum. The properties and analyses of these *substances* are given in Table IV.

TABLE IV.

6-Amino-4-dialkylaminoalkylamino-5-methyl- and -2 : 5-dimethyl-pyrimidines (*Types* III *and* IX).

Compound. Type.	R.	Appearance.	M. p.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Required, %. C.	Required, %. H.	Required, %. N.
III	$[CH_2]_2{\cdot}NEt_2$	Needles	82—82·5°	$C_{12}H_{23}N_5$	60·4	9·6	30·1	60·8	9·7	29·5
III	$[CH_2]_3{\cdot}NMe_2$	Waxy,* hygroscopic	89—91	$C_{11}H_{21}N_5$	—	—	—	—	—	—
III	$[CH_2]_3{\cdot}NEt_2$	Needles	99—99·5	$C_{13}H_{25}N_5$	62·0	10·3	27·3	61·2	9·9	27·9
IX	$[CH_2]_2{\cdot}NEt_2$	Needles	95·5—96·5	$C_{11}H_{21}N_5$	58·9	9·0	31·4	59·2	9·4	31·4
IX	$[CH_2]_3{\cdot}NEt_2$	Needles	93—94	$C_{12}H_{23}N_5$	61·1	9·5	29·2	60·8	9·7	29·5

* *Bis*-3 : 5-*dinitrobenzoate*, needles from alcohol, m. p. 207·5—209° (Found : C, 46·7; H, 4·8; N, 19·8. $C_{11}H_{21}N_5,2C_7H_4O_6N_2$ requires C, 46·4; H, 4·5; N, 19·5%).

4 : 6-*Dihydroxy-5-methylpyrimidine.*—Formamidine hydrochloride (42 g.; 0·525 mol.) and diethyl methylmalonate (91 g.; 0·525 mols.) were added successively to alcoholic sodium ethoxide (from 24·5 g. of sodium and 360 c.c. of alcohol) at 20—25°. After being kept overnight, the mixture was refluxed for 1 hour, cooled, and filtered. The collected solid was combined with the residue obtained by evaporation of the filtrate, dissolved in warm water (650 c.c.), cooled, and acidified to litmus with acetic acid; 4 : 6-*dihydroxy-5-methylpyrimidine* (39·5 g.; 61%) then separated. Recrystallised from water it formed colourless prisms, which decomposed from 320° (Found : C, 48·0; H, 4·8; N, 22·2. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·8; N, 22·2%).

4 : 6-*Dichloro*-5-*methylpyrimidine*.—A mixture of 4 : 6-dihydroxy-5-methylpyrimidine (39 g.) and phosphoryl chloride (200 c.c.) was refluxed for 40 minutes, a clear solution being obtained. On working up 4 : 6-*dichloro*-5-*methylpyrimidine* (34 g.; 66%) crystallised from water in colourless needles, m. p. 56·5—57·5° (Found: C, 36·6; H, 2·4; N, 16·5. $C_5H_4N_2Cl_2$ requires C, 36·8; H, 2·4; N, 17·2%).

4-*Chloro*-6-*amino*-5-*methylpyrimidine*.—A mixture of 4 : 6-dichloro-5-methylpyrimidine (16·3 g.) and alcoholic ammonia (115 c.c., saturated at 0°) was heated at 140° for 3 hours. After evaporation, the residue was crystallised from water; 4-*chloro*-6-*amino*-5-*methylpyrimidine* separated as colourless needles, m. p. 237—238° (Found: C, 42·3; H, 4·4; N, 29·6. $C_5H_6N_3Cl$ requires C, 41·8; H, 4·2; N, 29·3%).

6-*Amino*-4-*dialkylaminoalkylamino*-5-*methylpyrimidines* (Type IX).—Prepared from the above chloropyrimidine in the usual manner, and crystallised from benzene–light petroleum. The properties and analyses of the *compounds* are given in Table IV.

5-*Formamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NH·CHO).—5-Amino-4-hydroxy-2 : 6-dimethylpyrimidine (13·5 g.) (Andersag and Westphal, *loc. cit.*) was dissolved in 98% formic acid (75 c.c.), and the solution refluxed for 15 minutes. Excess of formic acid was removed under reduced pressure and the solid residue was dissolved in water. The aqueous solution was evaporated to dryness under reduced pressure and the operation repeated twice to effect complete removal of formic acid. The product was recrystallised from alcohol (charcoal); 5-*formamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (14·8 g.; 92%) formed colourless, felted needles, m. p. 238—239° (decomp.) (Found: C, 50·2; H, 5·4; N, 24·8. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4; N, 25·1%).

4-*Chloro*-5-*formamido*-2 : 6-*dimethylpyrimidine* (XIX; R = CHO).—5-Formamido-4-hydroxy-2 : 6-dimethylpyrimidine (9 g.) was finely powdered and added to ice-cold phosphoryl chloride (75 c.c.). Dimethylaniline (20 c.c.) was now added to the mixture in portions of 3—4 c.c. with constant shaking; the solid gradually dissolved with evolution of heat and the temperature was kept below 50° by external cooling. When all the solid had dissolved, the brown solution was poured on ice with continual stirring. The resulting clear yellow solution was cooled in an ice-salt mixture and made alkaline by cautious addition of aqueous ammonia, the temperature being kept below 20°. The alkaline liquor was extracted five times with ethyl acetate and the extracts dried and evaporated under reduced pressure. The residue, a mixture of the desired product with dimethylaniline, was treated with cold light petroleum, which precipitated a light yellow solid. Recrystallisation from benzene (charcoal) gave 4-*chloro*-5-*formamido*-2 : 6-*dimethylpyrimidine* (4·5 g.; 45%) as colourless needles, m. p. 158—159·5° (Found: C, 45·0; H, 4·3; N, 22·7. $C_7H_8ON_3Cl$ requires C, 45·2; H, 4·3; N, 22·6%).

4-*Chloro*-5-*amino*-2 : 6-*dimethylpyrimidine* (XIX; R = H).—A solution of 4-chloro-5-formamido-2 : 6-dimethylpyrimidine (3·75 g.) in ice-cold concentrated hydrochloric acid was kept at room temperature for 30 minutes. The solution was cooled in an ice-salt bath and crushed ice was added followed by aqueous ammonia, the temperature being kept below 10°. The bulky white precipitate was collected and recrystallised from a small volume of water (charcoal), giving fine colourless needles (2·7 g.; 85%), m. p. 79—80°, undepressed in admixture with a specimen prepared (in 5% yield) by the method of Andersag and Westphal (*loc. cit.*).

5-*Amino*-4-*dialkylaminoalkylamino*-2 : 6-*dimethylpyrimidines* (IV).—The following substances were prepared by the interaction of 4-chloro-5-amino-2 : 6-dimethylpyrimidine and the appropriate amines, by the general method described in Part III (*loc. cit.*):

5-*Amino*-4-γ-*diethylaminopropylamino*-2 : 6-*dimethylpyrimidine* distilled at 170° (bath temp.)/2×10^{-3} mm. as a yellow oil which soon solidified and was recrystallised from light petroleum. Colourless hygroscopic solid, m. p. 68—70° (yield, 78%) (Found: C, 61·8; H, 9·8; N, 28·0. $C_{13}H_{25}N_5$ requires C, 62·1; H, 9·9; N, 27·8%).

5-*Amino*-4-β-*diethylaminoethylamino*-2 : 6-*dimethylpyrimidine* distilled at 170—180° (bath temp.)/10^{-3} mm. as a pale yellow oil which rapidly crystallised. Recrystallisation from anhydrous benzene–petrol afforded colourless irregular platelets, m. p. 95—96° (yield, 64%) (Found: C, 61·1; H, 9·9; N, 29·5. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%).

5-*Amino*-4-γ-*di*-n-*butylaminopropylamino*-2 : 6-*dimethylpyrimidine*, b. p. 230—240° (bath temp.)/0·25 mm., was a pale yellow oil which crystallised slowly (yield, 80%) (Found: C, 66·1; H, 11·0; N, 22·3. $C_{17}H_{33}N_5$ requires C, 66·4; H, 10·8; N, 22·8%).

5-*Acetamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (XVIII; R = NHAc).—A solution of 5-amino-4-hydroxy-2 : 6-dimethylpyrimidine (6·2 g.) in acetic anhydride (220 c.c.) was heated on the steam-bath for 30 minutes, then evaporated to dryness under reduced pressure. The residue was added to crushed ice and the resulting clear solution evaporated under reduced pressure. The residue was recrystallised from alcohol, 5-*acetamido*-4-*hydroxy*-2 : 6-*dimethylpyrimidine* (7 g.; 88%) being obtained as a felted mass of colourless needles, m. p. 275° (decomp.), readily soluble in cold water (Found: N, 23·2. $C_8H_{11}O_2N_3$ requires N, 23·2%).

4-*Chloro*-5-*acetamido*-2 : 6-*dimethylpyrimidine* (XIX; R = Ac).—Finely powdered 5-acetamido-4-hydroxy-2 : 6-dimethylpyrimidine (20 g.) was added to phosphoryl chloride (200 c.c.) with shaking. Dimethylaniline (40 c.c.) was added gradually to the mixture with constant shaking, the temperature being kept at 50—60° by cooling in ice; the pyrimidine slowly dissolved. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on ice. The resulting clear solution was made alkaline with ammonia, the temperature being maintained below 15° during neutralisation, and the liberated product was isolated by extracting five times with chloroform. The extract was dried, evaporated, and the residue recrystallised from benzene (charcoal). 4-*Chloro*-5-*acetamido*-2 : 6-*dimethylpyrimidine* (11·0 g.; 54%) separated as colourless prisms, m. p. 141—142° (Found: C, 48·5; H, 5·1; N, 20·7. $C_8H_{10}ON_3Cl$ requires C, 48·1; H, 5·0; N, 21·0%).

5-*Acetamido*-4-γ-*diethylaminopropylamino*-2 : 6-*dimethylpyrimidine*.—4-Chloro-5-acetamido-2 : 6-dimethylpyrimidine (5 g.; 0·025 mol.) was treated with γ-diethylaminopropylamine (13 g.; 0·1 mol.) by the usual procedure, special care being taken to keep the aqueous solution cool during isolation of the product. 5-*Acetamido*-4-γ-*diethylaminopropylamino*-2 : 6-*dimethylpyrimidine* (6 g.; 74%) distilled at

150—160° (bath temp.)/10^{-4} mm. as a pale yellow mobile oil (Found: C, 59·8; H, 8·7; N, 23·1. $C_{15}H_{27}ON_5$ requires C, 61·4; H, 9·2; N, 23·9%). The *flavianate*, prepared in alcoholic solution, and crystallised thrice from alcohol and once from water, formed bright yellow needles, m. p. 160° after sintering at 98° (Found: C, 47·8; H, 5·7; N, 15·6. $C_{15}H_{27}ON_5,C_{10}H_6O_8N_2S,H_2O$ requires C, 47·9; H, 5·6; N, 15·7. Found in material dried at 100° in a vacuum: C, 48·8; H, 6·0; N, 15·7. $C_{15}H_{27}ON_5,C_{10}H_6O_8N_2S$ requires C, 49·4; H, 5·4; N, 16·1%).

9-*γ-Diethylaminopropyl*-2 : 6 : 8-*trimethylpurine*.—A solution of the foregoing material (5·5 g.) in 30% sulphuric acid (30 c.c.) was heated on the steam-bath for 2 hours; the cooled solution was made alkaline with sodium hydroxide and the liberated oil isolated by extraction with ether. 9-*γ-Diethylaminopropyl*-2 : 6 : 8-*trimethylpurine* distilled at 140—150° (bath temp.)/10^{-4} mm. as a hygroscopic, pale yellow, mobile oil (Found: C, 64·7; H, 9·3. $C_{15}H_{25}N_5$ requires C, 65·5; H, 9·1%). The *dipicrate* formed pale yellow plates from alcohol, m. p. 187—188° (Found: C, 51·7; H, 5·0; N, 22·5. $C_{15}H_{25}N_5,2C_{10}H_8O_5N_4$ requires C, 52·3; H, 5·1; N, 22·7%)

9-*β-Diethylaminoethyl*-2 : 6 : 8-*trimethylpurine*.—The product obtained from the interaction of 4-chloro-5-acetamido-2 : 6-dimethylpyrimidine (9 g.; 0·045 mol.) and β-diethylaminoethylamine (21 g.; 0·18 mol.) was a pale yellow oil, b. p. 130—140° (bath temp.)/2 × 10^{-3} mm., giving analytical results suggesting it to be a mixture of the expected pyrimidine and the derived purine. It was dissolved in 30% sulphuric acid (40 c.c.) and the solution heated for 3 hours on the steam-bath. On isolation in the usual manner, 9-*β-diethylaminoethyl*-2 : 6 : 8-*trimethylpurine* (9·0 g.; 76%) distilled at 130—135° (bath temp.)/2 × 10^{-3} mm. as a pale yellow mobile oil (Found: C, 65·0; H, 9·3; N, 26·7. $C_{14}H_{23}N_5$ requires C, 64·3; H, 8·8; N, 26·8%). The *flavianate* crystallised from alcohol in clusters of bright yellow needles, m. p. 248° (decomp.) (Found: C, 50·0; H, 5·1; N, 17·5. $C_{14}H_{23}N_5,C_{10}H_6O_8N_2S$ requires C, 50·1; H, 5·0; N, 17·0%).

9-*γ-Diethylamino-α-methyl*-n-*butyl*-2 : 6 : 8-*trimethylpurine*.—The product of interaction of 4-chloro-5-acetamido-2 : 6-dimethylpyrimidine (1 g.) and γ-diethylamino-α-methyl-*n*-butylamine (4·9 g.) was treated in the manner described in the previous paragraph. 9-*γ-Diethylamino-α-methyl*-n-*butyl*-2 : 6 : 8-*trimethylpurine* (1·3 g.; 85%), b. p. 150—155° (bath temp.)/10^{-4} mm., was an almost colourless oil, from which no crystalline derivative could be obtained (Found: C, 67·1; H, 9·8; N, 22·4. $C_{17}H_{29}N_5$ requires C, 67·6; H, 9·6; N, 23·1%).

2-*Amino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (XXII).—Alcoholic sodium ethoxide (from 5·75 g. of sodium and 100 c.c. of alcohol) was added slowly, with stirring, to a solution of guanidine hydrochloride (23·9 g.; 0·25 mol.) and benzeneazoacetylacetone (51 g.; 0·25 mol.) (Bülow *et al.*, *loc. cit.*) in absolute alcohol (400 c.c.). After 20 days at room temperature the precipitate was collected, washed with water to remove sodium chloride, and crystallised from alcohol. 2-*Amino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (33 g.; 58·5%) formed bright orange plates, m. p. 228—230° (Found: C, 63·4; H, 5·9; N, 30·8. $C_{12}H_{13}N_5$ requires C, 63·5; H, 5·7; N, 30·8%).

2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine* (XXIII).—A solution of the above azo-compound (5 g.) in absolute alcohol was shaken with hydrogen at 90° under a pressure of 75 atmospheres in the presence of palladised barium sulphate until absorption ceased (3 hours). After filtration, the solution was evaporated to dryness under reduced pressure. The residue was washed with ether to remove aniline, and recrystallised from alcohol giving the *compound* as colourless prisms (2·95 g.; 100%), m. p. 183·5—184·5°, which sublimed at 100° in a vacuum (Found: C, 51·8; H, 7·3; N, 40·9. $C_6H_{10}N_4$ requires C, 52·2; H, 7·2; N, 40·6%).

2-*Amino*-5-*β-diethylaminoethylamino*-4 : 6-*dimethylpyrimidine*.—A solution of 2 : 5-diamino-4 : 6-dimethylpyrimidine (8 g.) and β-diethylaminoethyl chloride (19·6 g., freshly distilled) in anhydrous pyridine (40 c.c.) was refluxed for 7 hours. Pyridine was removed under reduced pressure, the dark brown residue dissolved in water and made alkaline, and the precipitated oil isolated by means of ether and distilled. 2-*Amino*-5-*β-diethylaminoethylamino*-4 : 6-*dimethylpyrimidine* (3·6 g.; 26%), b. p. 140—150° (bath temp.)/2 × 10^{-4} mm., was obtained as a pale yellow oil which rapidly solidified and crystallised from light petroleum in colourless plates, m. p. 95—96·5° (Found: C, 60·6; H, 9·5; N, 29·5. $C_{12}H_{23}N_5$ requires C, 60·8; H, 9·7; N, 29·5%). The *dipicrate* crystallised from acetone as fine yellow needles, m. p. 187—189° (decomp.), depressed to 162—164° in admixture with the dipicrate of 5-amino-2-β-diethylaminoethylamino-4 : 6-dimethylpyrimidine (see below) (Found: N, 21·9. $C_{13}H_{23}N_5,2C_6H_3O_7N_3$ requires N, 22·2%).

2-*β-Diethylaminoethylamino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine*.—A suspension of sodamide (0·6 g.; 0·015 mol.) and 2-amino-5-benzeneazo-4 : 6-dimethylpyrimidine (1·1 g.; 0·005 mol.) in dry toluene (10 c.c.) was refluxed for 10 hours in a bath at 130°. Ammonia was evolved and the sodium salt of the aminopyrimidine separated. β-Diethylaminoethyl chloride (6·8 g.; 0·05 mol.) was added to the cooled mixture and refluxing was continued for a further 18 hours at 160—170°. The cooled mixture was shaken with dilute hydrochloric acid and the aqueous layer washed with ether and made alkaline. The red oil was isolated by means of ether and distilled at 140° (bath temp.)/10^{-3} mm. The distillate partially crystallised; recrystallisation from light petroleum gave 2-*β-diethylaminoethylamino*-5-*benzeneazo*-4 : 6-*dimethylpyrimidine* (0·95 g.; 58%) as microscopic red leaflets, m. p. 87—88° (Found: C, 66·3; H, 8·1; N, 26·1. $C_{18}H_{26}N_6$ requires C, 66·2; H, 8·0; N, 25·8%).

5-*Amino*-2-*β-diethylaminoethylamino*-4 : 6-*dimethylpyrimidine*.—A solution of the foregoing material (0·8 g.) in alcohol (25 c.c.) was shaken with hydrogen and platinic oxide at room temperature and pressure. Absorption of hydrogen was rapid and the resulting almost colourless solution was filtered and evaporated. The residue distilled at 160° (bath temp.)/2 × 10^{-3} mm. giving 5-amino-2-β-diethylaminoethylamino-4 : 6-dimethylpyrimidine (0·35 g.; 60%) as a yellow viscous oil. The *dipicrate* crystallised from alcohol in bright yellow needles, m. p. 185—186°, with slight charring from 176°. On admixture with aniline picrate (m. p. 181°) the m. p. was depressed to 151—153° (Found: C, 41·4; H, 4·3; N, 22·3. $C_{12}H_{23}N_5,2C_6H_3O_7N_3$ requires C, 41·5; H, 4·2; N, 22·2%).

β-Diethylaminoethylguanidine Hydriodide.—A solution of *S*-methyl*iso*thiourea hydriodide (33 g.; 0·15 mol.) and β-diethylaminoethylamine (18 g.; 0·155 mol.) in alcohol (150 c.c.) was refluxed on the

steam-bath for 2 hours, methylthiol being evolved. The solution was evaporated to dryness and the syrupy residue dissolved in a little water and treated with a slight excess of hydriodic acid (*d* 1·7). After evaporation to dryness the residue was dissolved in warm alcohol and ether added to incipient turbidity. On cooling, *β-diethylaminoethylguanidine dihydriodide* (31·1 g.; 50%) separated as colourless plates, m. p. 136—139°; two further crystallisations raised the m. p. to 140—142° (Found: C, 20·7; H, 4·6; N, 13·7. $C_7H_{20}N_4,2HI$ requires C, 20·3; H, 4·8; N, 13·5%).

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