663. *New Syntheses based on 5-Aminopyrimidines.*

By F. L. Rose.

A series of 5-aminopyrimidines (most of them substituted in position 2 by additional amine residues) has been prepared, and the similarity of the behaviour of the 5-amino-group to that in aromatic primary amines has been demonstrated. The 5-amino-group can be diazotised, but the presence of a 4(6)-mercapto-, -hydroxyl, or primary -amino-group leads to rapid formation, even under acid conditions, of pyrimidino-thiadiazoles, -oxadiazoles, and -triazoles, respectively. Ring-closure also occurs, most readily in the presence of caustic alkali, when alkyl groups are present in positions 4 and 6. The products are 1 : 2 : 4 : 6-tetra-azaindenes, isomeric with the purines, and one such compound, 5-amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene exhibits anti-tuberculous activity *in vivo*. The preparation of many homologues and analogues is described. The 5-amino-group exhibited normal behaviour towards acylating agents and in its reaction with dicyanimide and dicyandiamides from which a series of pyrimidyldiguanides was prepared.

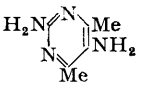
Many 5-aminopyrimidines have been prepared in the course of numerous researches in the purine and pteridine fields, but comparatively little work has been undertaken on the behaviour of these substances towards diazotisation, a property which they theoretically possess in common with 3-aminopyridines. Boarland and McOmie (*J.*, 1951, 1218) commented on the failure of 5-aminopyrimidine itself to give a diazonium compound when

treated with nitrous acid, but it has been found in these laboratories that the introduction of certain substituents into the pyrimidine ring leads to amines often capable of forming very stable diazonium salts. Initial attention was drawn to this influence when the properties of 2 : 5-diamino-4 : 6-dimethylpyrimidine (I), prepared by Todd and his co-workers for use in drug syntheses (*J.*, 1946, 357; 1947, 41), were studied in detail. When this substance was treated with nitrous acid at 20°, the 2-amino-group was unchanged, but the 5-amino-group was converted into a diazonium group, which only slowly decomposed, even when the solution was warmed.

A potential chemotherapeutic interest in this particular diazonium compound arose from the observation that the methyl groups were so activated (additively by the ring-nitrogen atoms and the diazonium group) that a form of internal coupling occurred under certain conditions to give (II) or (III) in a manner analogous to the production of indazoles from *o*-toluidines. The bicyclic system so formed was isomeric with that of the purine (IV), the 8 : 9-components of the glyoxaline ring of the latter having been transposed to yield the pyrazole analogue. Despite this re-arrangement, the new compound was physically and chemically very similar to the true purine in that it was amphoteric, exhibited marked fluorescence in solution at high dilution, and possessed very similar ultra-violet absorption.

Functional derivatives of various condensed pyrimidine systems have been studied during the last few years by several groups of workers, particularly as "purine antagonists." As a consequence, the triazolopyrimidine (V) (Roblin, Lampen, English, Cole, and Vaughan, *J. Amer. Chem. Soc.*, 1945, **67**, 290) and 2 : 6-diaminopurine have proved of experimental interest in the treatment of leukæmia. Dr. Walpole, in these laboratories, examined several compounds of type (III) against mouse leukæmia, including (XIII; $R^1 = NH_2$, $R^2 = OH$, $R^3 = H$) and the diamine (VI), analogous to the substances referred to, but was only able to detect marginal activity. On the other hand, (III) was found by Mr. J. Francis and Dr. A. R. Martin to exhibit marked action against tubercular infections in mice (method of Martin, *J. Path. Bact.*, 1946, **58**, 580). These results will be reported elsewhere in detail, but they clearly called for a thorough chemical investigation of the purine isomers, during which much new information on the properties of diazotisable aminopyrimidines came to light and is here recorded.

Only one example of a compound of type (III) appeared to be known. This arose from a study by Behrend (*Annalen*, 1888, **245**, 213) of the action of nitrous acid on 5-amino-6-methyluracil (VII), during which a compound was isolated that analysed as, and was given the structure (VIII). In support of this formulation it was pointed out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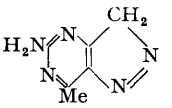
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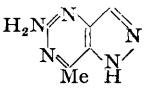
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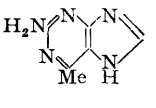
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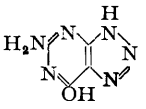
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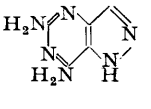
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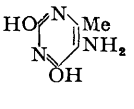
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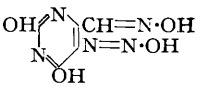
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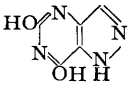
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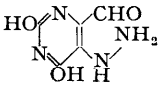
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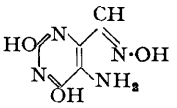
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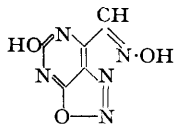

(XII)

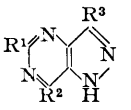
that reduction with stannous chloride gave (IX), with either the hydrazine (X) or the amino-oxime (XI) as the intermediate substance. Re-investigation of Behrend's work showed (VIII) to be a very stable compound, and moreover to be a hydrate from which water was removed in boiling dichlorobenzene but not in vacuum at 100°. The hydrate could be re-formed by crystallisation from water. The oxadiazole structure (XII) seemed

therefore more probable, and this type of substance is now known to be readily formed from 5-amino-6-hydroxypyrimidines. (It is not proposed to become involved here in the controversies about the precise structure of the oxides.) Behrend referred to (IX) as "iso-xanthine" but the use of the prefix in this connection is obviously undesirable and in the present communication this class of compound has been considered as derived from 1 : 2 : 4 : 6-tetra-azaindene. The first variations on the structure of (III) concerned the introduction of other substituents into positions 3, 5, and 7. Most of the preparations (XIII) had R^1 = basic group, but a few examples were made having hydrogen or methylthio in this position. As would be expected, the nature of the substituent R^2 in the parent diamine (XIV) markedly influenced the ease of formation of the pyrazole ring. With amino, alkylamino, hydroxy, or mercapto in this position the diazonium salt cyclised preferentially with these substituents, giving triazole, oxadiazole and thiadiazole rings respectively. Compounds of type (XIII) were successfully prepared directly from the diazotised (XIV), however, when R^2 was (in addition to alkyl) phenyl, dialkylamino, alkylthio, and carboxymethylthio. Conditions for optimum yield of the pyrazole derivatives were also dependent on the chemical characteristics of R^2. With the 4 : 6-dimethylpyrimidine (I) it was necessary to add the solution of the diazonium salt through a capillary tube below the surface of a rapidly stirred aqueous solution of an excess of sodium hydroxide. A less drastic basification, either by the slow addition of sodium hydroxide to the diazo-solution or the use of sodium carbonate or ammonia, always led to the formation of the azo-compound analysing as, and believed to be (XV). A similar behaviour was observed with (XIV; $R^1 = NH_2$, R^2 = Ph, R^3 = Me). Ring-closure using caustic alkali was also successful with (XIV; R^2 = dialkylamino) but compounds of this type were found to give even better yields when the acid solutions of the corresponding diazonium salts were kept for some time at laboratory temperature. Compound (XIV; $R^1 = NH_2$, R^2 = SMe, R^3 = Me) was also convertible into the tetra-azaindene in this manner, but in this instance only in low yield. Under such conditions the respective diazonium groups exhibited remarkable stability in that, unlike those derived from the 4 : 6-dialkylpyrimidines of type (I), there was little or no evolution of nitrogen. The rate at which ring-closure proceeded could be markedly increased by heat, again without noticeable decomposition, and indeed an almost quantitative yield of the tetra-azaindene (XIII; $R^1 = NH_2$, $R^2 = NMe_2$, R^3 = H) resulted simply when the acid solution of the parent diazonium compound was brought rapidly to the boil. In these reactions the presence of residual unchanged diazonium groups was detected by adding a drop of the solution to *m*-phenylenediamine or alkaline R-salt solution, characteristic soluble azo-coupling products being formed. The greater stability of the diazonium groups in the tertiary amino- and alkylthio-compounds, and the increased reactivity of the adjacent methyl group, could both be explained on the basis of the additional positive charge resulting from the assumed intermediate formation of the diazosulphonium and triazolinium ionic structures, (XVI) and (XVII) respectively. A salt of the former was isolated and analysed. By contrast, the diazonium salts derived from the corresponding 5-amino-4-methoxy- and -4-chloropyrimidines were relatively unstable. The solutions coupled with alkaline R-salt, but evolution of nitrogen occurred even in the presence of hydrochloric acid, and was very rapid on addition to caustic alkali. No tetra-azaindene (XIII; $R^1 = NH_2$, R^2 = OMe or Cl, R^3 = H) was isolated. A similar result was obtained on starting with 2 : 5-diamino-4-methylpyrimidine in an attempt to prepare (XIII; $R^1 = NH_2$, $R^2 = R^3$ = H), although chromatographic analysis of the final reaction mixture indicated the presence of a trace of a product similar in speed of travel and fluorescence to the methyl homologue (XIII; $R^1 = NH_2$, R^2 = Me, R^3 = H).

The preparation of compounds of type [XIII; R^2 = OH, NH_2, NHAlkyl, $N(Alkyl)_2$] was possible, by indirect means, by making use of the labile nature of the alkylthio-group in the tetra-azaindenes just discussed (XIII; R^2 = SAlkyl). A hydroxy-derivative (XIII; $R^1 = NH_2$, R^2 = OH, R^3 = H) resulted from oxidation of the corresponding methylthio-compound in hot glacial acetic acid with perhydrol, the methanesulphonate crystallising. Amine residues such as *iso*propylamino, piperidino, and morpholino, were introduced into the same position by heating the methylthio-tetra-azaindene with the

appropriate amine, usually under pressure at temperatures up to 150°. The diamine (VI) already referred to, was obtained in this way with ammonia.

Diazotisation and ring-closure of 4 : 6-dialkyl-5-aminopyrimidines in which the alkyl groups were different would clearly lead to mixture of two possible isomers. This has proved to be the case in the several examples examined. Thus (XIV; $R^1 = NH_2$, $R^2 =$ Me, $R^3 =$ Et) yielded (XIII; $R^1 = NH_2$, $R^2 = R^3 =$ Me) and (XIII; $R^1 = NH_2$, $R^2 =$ Et, $R^3 =$ H). Separation of the isomers depended on the marked difference in the



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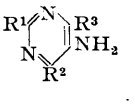

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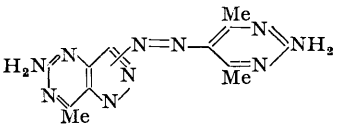

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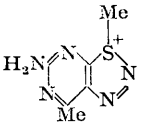

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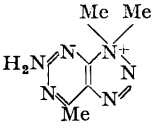

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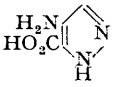

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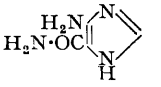


(XIX)

solubilities of the hydrochlorides, and structures were assigned on the basis of comparison of the ultra-violet absorption spectra with those of (III) and (XIII; $R^1 = NH_2$, $R^2 =$ Et, $R^3 =$ Me), the latter being the sole possible product from the diazotisation of (XIV; $R^1 = NH_2$, $R^2 = R^3 =$ Et) and regarded as typical of those tetra-azaindenes carrying an alkyl group (R^3) on the pyrazole ring. The relevant maxima and minima of ultra-violet absorption in 0·1N-sodium hydroxide are given in Table 1.

TABLE 1. *Positions of maxima and minima in the ultra-violet absorption spectra of certain tetra-azaindenes (solvent,* N*-sodium hydroxide).*

	Maxima (mμ)			Minima (mμ)	
(III)	231	284	343	258	309
(XIII; $R^1 = NH_2$, $R^2 =$ Et, $R^3 =$ Me)	236	289	358	262	314
(XIII; $R^1 = NH_2$, $R^2 =$ Et, $R^3 =$ H), m. p. 278—280°	228	284	338	257	311
(XIII; $R^1 = NH_2$, $R^2 =$ Me, $R^3 =$ Me), m. p. 327°	236	289	353	263	315
(IV)	224	268 *	301	242	345

* Point of inflexion.

The tetra-azaindene (XIII; $R^1 = NH_2$, $R^2 =$ Ph, $R^3 =$ H), obtained in good yield from the corresponding 2 : 5-diaminopyrimidine, was unusual in that, unlike the analogous alkyl compounds, it was markedly soluble in water as the free base, the solution again exhibiting intense fluorescence.

Some indication of the variety of substituents introduced into the 2-position of the pyrimidine ring has already been given (position R^1 in XIII). In greater detail these have included amino (already discussed), methylthio, methylamino, dimethylamino, ethylamino, *n*-propylamino, *iso*propylamino, *n*-butylamino, *iso*butylamino, *n*-amylamino, piperidino, guanidino, *p*-chlorophenylguanidino, and *p*-anisidino. In some instances, yields of the tetra-azaindenes were low. Special mention is necessary for compounds of type (XIII; $R^1 = H$). These were of particular interest in that with $R^2 =$ OH or NH_2, the products would be isomeric with hypoxanthine and adenine, respectively. So far, only the related (XIII; $R^1 = H$, $R^2 = NMe_2$, $R^3 = H$) has been prepared. Because of difficulties associated with the preparation of the parent 5-aminopyrimidine, the hydrogen was introduced into position R^1 in the ultimate reaction of the series by using the general method first employed by Mozingo, specifically, by heating the 2-methylthio-compound (XIII; $R^1 =$ SMe, $R^2 = NMe_2$, $R^3 = H$) with excess of Raney nickel, containing much occluded hydrogen, in boiling dimethylformamide. The intermediate methylthio-derivative was itself prepared in very good yield by heating the acid solution of the diazonium salt from (XIV; $R^1 =$ SMe, $R^2 = NMe_2$, $R^3 =$ Me) at 90° for a few minutes.

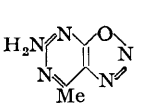
Attempts to replace the dimethylamino-group of (XIII; $R^1 = R^3 = H$, $R^2 = NMe_2$) by hydroxyl have failed. The only product of low solubility obtained by refluxing this

product with concentrated hydrochloric acid for some hours, was a diazotisable amino-acid which gave analyses for $C_4H_5O_2N_3$. This compound may be the aminopyrazolecarboxylic acid (XVIII) which might be expected to result from breakdown of the pyrimidine portion of the molecule. No rigid proof has, however, been sought. If the constitution adduced is correct, then this amino-acid is related structurally to 4-aminoglyoxaline-5-carboxyamide (XIX) formed by bacteria during sulphonamide bacteriostasis; this was initially isolated by Stetten and Fox (*J. Biol. Chem.*, 1945, **161**, 333), later shown to be constituted as formulated by Shive, Ackermann, Gordon, Getzendaner, and Eakin (*J. Amer. Chem. Soc.*, 1947, **69**, 725), and proposed as a possible precursor in purine biosynthesis. Because of this, (XVIII) was examined for antibacterial action, but was found to be devoid of activity. By contrast, (III) when refluxed with concentrated hydrochloric acid gave a good yield of the 5-hydroxy-compound (XIII; $R^1 = OH$, $R^2 = Me$, $R^3 = H$).

The therapeutic effect of (III) against tubercular infections led to the synthesis of a number of analogues containing a fused pyrimidine ring substituted by amino and methyl in the same manner. The corresponding purine (IV) has already been described by Gabriel and Colman (*Ber.*, 1901, **34**, 1249). The three compounds, (XX), (XXI), and (XXII), were prepared by diazotisation of the corresponding 5-amino-6-hydroxy-, 5 : 6-diamino-, and 5-amino-6-mercapto-pyrimidines. Ring-closure occurred spontaneously in the second and third instances when the acid diazonium solutions were kept for a few hours. In the case of (XX), the solution was made alkaline with ammonia, whereupon the oxadiazolopyrimidine crystallised.

Cook, Heilbron, and their co-workers (*J.*, 1949, 1064, 1069, 1071) have prepared a number of thiazolopyrimidines through ring-closure of thioureidothiazoles, and Falco and Hitchings (*J. Amer. Chem. Soc.*, 1950, **72**, 3203) have made similar compounds as functional derivatives of condensed pyrimidine systems and therefore potential antimicrobial agents. The two compounds (XXIII) and (XXIV), however, appear to be new. The former was synthesised when (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = SH$) was refluxed with formic acid, while the latter was obtained initially as the hydrochloride when a solution of (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = Cl$) in dilute hydrochloric acid was refluxed with potassium thiocyanate. The pteridine (XXV) resulted from the direct action of diacetyl on (XIV; $R^1 = R^3 = NH_2$, $R^2 = Me$) in aqueous solution at 80°, whereas the dihydroketothiazine (XXVI) was formed when the corresponding thioglycollic acid (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = S{\cdot}CH_2{\cdot}CO_2H$) was heated in dilute hydrochloric acid solution. Not one of these analogues of (III) exhibited therapeutic activity.

The availability of the many 5-aminopyrimidines prepared in the course of this research prompted a study of the properties, other than diazotisation followed by ring-closure, conferred by the amino-group in this position. The several reactions studied centred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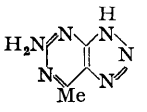
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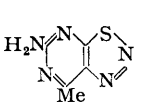
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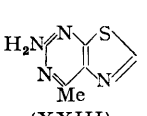
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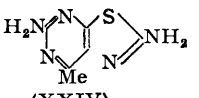
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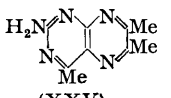
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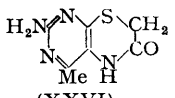
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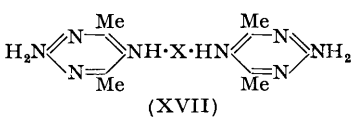
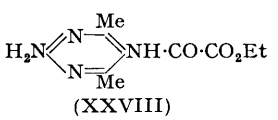

(XVII)


(XXVIII)

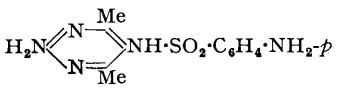
mainly round the simple diamine (I). This substance is itself unusual. Not only is it freely soluble in cold water (>20%), but the solutions exhibit a strong fluorescence even at high dilution. The monohydrochloride is less soluble than the base and does not fluoresce. Acetylation and benzoylation gave the 5-acyl derivatives, since the products

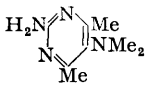
did not react with nitrous acid. Treatment with carbonyl chloride in aqueous solution in the presence of sodium acetate readily yielded the symmetrical urea (XXVII; X = CO), and treatment with ethyl malonate alone at 200° gave the malondiamide (XXVII; X = $CO{\cdot}CH_2{\cdot}CO$). Ethyl oxalate under reflux gave mainly the oxamic ester (XXVIII). The sulphanilamide derivative (XXIX) of (I) was prepared by the action on the latter of *p*-nitrobenzenesulphonyl chloride in the presence of aqueous sodium acetate, followed by reduction of the nitro-group. Condensation at the 5-amino-group under these conditions was again confirmed by the failure of the intermediate product to react with nitrous acid. The methylation of (I) was investigated, but not completely. Treatment with methyl iodide at 100° gave, amongst other things, a good yield of a dimethyl derivative. Since this compound was only sparingly soluble in water, but soluble in benzene, and since it was unaffected by treatment with nitrous acid, the 5-dimethylamino-structure (XXX) seemed the most probable.

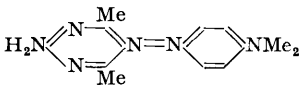
The behaviour of the diazo-compound from (I) under alkaline conditions has already been discussed. Coupling with an external end-component does occur, however, even under these conditions provided that the latter compound is sufficiently reactive (*e.g.*, β-naphthol). Where coupling is possible under acid conditions, concomitant ring-closure is avoided. Thus with dimethylaniline, a high yield of the phenylazopyrimidine (XXXI) was obtained. Normal diazo behaviour was also exhibited towards potassium iodide, with the formation of the 5-iodopyrimidine (XXXII).

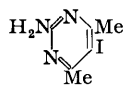
Finally, a series of diguanide derivatives of (I) was made, in which the 5-amino-group exhibited properties comparable to those of an aromatic primary amine. The pyrimidyldicyandiamide (XXXIII) was readily obtained from the diamine and dicyanimide, and this reacted with alkylamine salts to form the diguanides of type (XXXIV). Similar compounds were also obtained from the action of alkyldicyandiamides on the diamine in the manner worked out by Curd, Hendry, Kenny, Murray, and Rose (*J.*, 1948, 1630) in the proguanil series. Dr. D. G. Davey reported all the compounds made to be inactive against *P. gallinaceum* in the chick (method of Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 139).

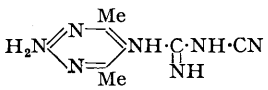
With regard to the preparation of the 5-aminopyrimidines recorded in this communication, the method worked out by Todd *et al.* (*loc. cit.*) for compound (I) was in many instances applicable, and required the condensation of a phenylazo-diketone, obtained usually in excellent yield from diazotised aniline, with a guanidine, giving 5-azopyrimidines of type (XXXV). Diguanides yielded the corresponding compound [XXXV; R^2 = H, R^1 = $C(:NH){\cdot}NH_2$]. The use of sodium ethoxide in dry ethanol, the condition employed by Todd *et al.* in the original synthesis, was found to be unnecessary. Aqueous-methanolic sodium hydroxide at 50° frequently gave better yields and in a shorter time. Reduction of (XXXV) to the 5-aminopyrimidines was by hydrogen and Raney nickel under pressure, and the yields were nearly quantitative. Of the preparations

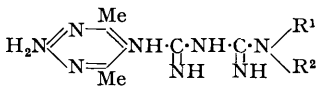

(XXIX)


(XXX)


(XXXI)


(XXXII)


(XXXIII)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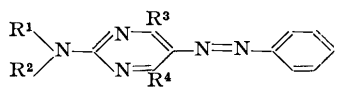
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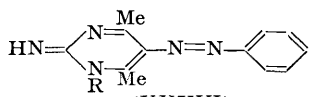
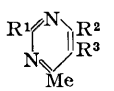

(XXXVI)


(XXXVII)

achieved in this way, that of compounds related to (XXXV; R^1 = H, R^2 = alkyl) alone seemed ambiguous. The possibility here existed that primary condensation of a monoalkylguanidine with a phenylazo-diketone might give rise exclusively, or additionally, to the

isomer (XXXVI) (cf. Majima, *Ber.*, 1908, **41**, 176). This possibility was largely excluded in the case of (XXXVI; R = Me), and by inference in other instances, by comparing the ultra-violet absorption of the final tetra-azaindene with that of (III) and (XIII; $R^1 = NMe_2$, $R^2 = Me$, $R^3 = H$). The spectra were all very similar.

The 5-amino-groups in (XIV; $R^1 = NH_2$, $R^3 = Me$, $R^2 = NMe_2$, SH, OMe, Cl, SMe, and $S{\cdot}CH_2{\cdot}CO_2H$) were introduced initially into the pyrimidine ring as nitro-groups, the intermediate used being the chloronitropyrimidine (XXXVII; $R^1 = NH_2$, $R^2 = Cl$, $R^3 = NO_2$). (XIV; $R^1 = NH_2$, $R^2 = SH$, $R^3 = Me$) was prepared directly from this compound by the action of excess of sodium sulphide which replaced the chlorine atom by the mercapto-group and also reduced the nitro- to an amino-group. The methylthio-derivative was obtained through the action of methanethiol on the same chloronitropyrimidine. The aminopyrimidine (XXXVII; $R^1 = SMe$, $R^2 = NMe_2$, $R^3 = NH_2$) required for conversion into (XIII; $R^1 = H$, $R^2 = NMe_2$, $R^3 = H$) was prepared by the reaction series (XXXVII; $R^1 = R^2 = Cl$, $R^3 = NO_2$) $\longrightarrow$ (XXXVII; $R^1 = Cl$, $R^2 = NMe_2$, $R^3 = NO_2$) $\longrightarrow$ (XXXVII; $R^1 = SH$, $R^2 = NMe_2$, $R^3 = NO_2$) $\longrightarrow$ (XXXVII; $R^1 = SMe$, $R^2 = NMe_2$, $R^3 = NO_2$), followed by catalytic reduction. 2 : 5-Diamino-4-methylpyrimidine (XIV; $R^1 = NH_2$, $R^2 = H$, $R^3 = Me$) was obtained by reduction of the aforementioned (XIV; $R^1 = NH_2$, $R^2 = Cl$, $R^3 = Me$) with zinc dust in boiling dilute aqueous sodium hydroxide.

Experimental

Tetra-azaindenes.

5-Amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene (III).—2 : 5-Diamino-4 : 6-dimethylpyrimidine (138 g., 1 mol.) in water (1 l.) and concentrated hydrochloric acid (225 c.c.) was diazotised at 5—10° by the slow addition of sodium nitrite (70 g.) in water (200 c.c.). The solution of the diazonium salt was added during ¾ hour, through a capillary and below the surface, to vigorously stirred 5N-sodium hydroxide (1100 c.c.), kept below 10° with external cooling. The azo by-products formed were destroyed by heating the solution at 80° for 20 minutes with sodium hydrosulphite (dithionite) (50 g.), and the crude *tetra-azaindene* (123 g.; m. p. 303—304°) precipitated by adding concentrated hydrochloric acid (about 350 c.c.) until neutral to litmus. It crystallised from dimethylformamide in straw-coloured needles, m. p. 301° (decomp.) (inserted at 290°) (Found: C, 48·35; H, 4·7; N, 46·6. $C_6H_7N_5$ requires C, 48·3; H, 4·7; N, 47·0%). Addition of acetone to a solution of the base in 2N-hydrochloric acid gave a crystalline *hydrochloride*, m. p. 253° (decomp.) (Found: C, 38·3; H, 4·2; N, 37·6; Cl, 18·65. $C_6H_7N_5$,HCl requires C, 38·8; H, 4·3; N, 37·7; Cl, 19·1%). The free base was only sparingly soluble in common organic solvents and water. Dilute solutions showed strong fluorescence. It dissolved readily in dilute aqueous sodium hydroxide, but not in sodium carbonate or dilute ammonia solution.

The *azo* by-product in this reaction was made in good yield by adding the diazotised aminopyrimidine to aqueous ammonia (or sodium carbonate) in place of the sodium hydroxide. It formed red-brown plates from acetic acid, which did not melt at <340° (Found: C, 48·6; H, 4·7; N, 45·8. $C_{12}H_{14}N_{10}$ requires C, 48·3; H, 4·7; N, 47·0%).

5-Hydroxy-7-methyl-1 : 2 : 4 : 6-tetra-azaindene.—This compound slowly separated as the free *base* when the above 5-amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene (4 g.) was heated under reflux for 20 hours with concentrated hydrochloric acid (10 c.c.). It crystallised from water in colourless needles, m. p. 339° (decomp.) (Found: C, 40·9; H, 5·35; N, 32·6. $C_6H_6ON_4$,1½H_2O requires C, 40·65; H, 5·1; N, 31·65%).

5-Amino-7-methylthio-1 : 2 : 4 : 6-tetra-azaindene.—2 : 5-Diamino-4-methyl-6-methylthiopyrimidine (68 g., 0·4 mol.) was diazotised (diazonium salt partly out of solution) and added to aqueous sodium hydroxide as described above for (III). The reaction mixture was heated to 50° and similarly decolorised with sodium dithionite. Caustic alkalinity was reduced by adding concentrated hydrochloric acid (75 c.c.) and finally removed with ammonium chloride (70 g.) in water (300 c.c.). The suspension was cooled and the crude *product* (32 g.) collected. It crystallised from 2-ethoxyethanol in pale yellow prisms, m. p. 269° (decomp.) (inserted at 260°) (Found: C, 40·45; H, 4·2; N, 36·7. $C_6H_7N_5S$ requires C, 39·75; H, 3·9; N, 38·7%). The *hydrochloride* crystallised from water and was not molten at 350° (Found: C, 32·05; H, 4·1; N, 31·6. $C_6H_7N_5S$,HCl,½H_2O requires C, 31·8; H, 3·95; N, 30·9%). Ring-closure also occurred when the diazonium salt was heated in acid solution at 80—85° for 1½ hours. There was little or no evolution of nitrogen, but unwanted by-products were separated by dissolving

TABLE 2. *5-Phenylazopyrimidines.*

Compound no.	Substituent in position 2	Reaction notes	Solvent *	M. p.	Formula	Found, % C	H	N	Required, % C	H	N
1	Me_2N	5 Days at 20—25°	Pet, A	99°	$C_{14}H_{17}N_5$	64·3	6·3	27·25	65·9	6·7	27·4
2	EtNH	,, ,,	Pet, B	122	$C_{14}H_{17}N_5$	64·1	6·0	27·2	65·9	6·7	27·4
3	Pr^nNH	3 Days at 37°	MeOH	136	$C_{15}H_{19}N_5$	67·3	6·7	26·4	66·9	7·1	26·0
4	Pr^iNH	7 Days at 20—25°	Aq. MeOH	75—76	$C_{15}H_{19}N_5$	67·25	6·9	26·45	66·9	7·1	26·0
5	Bu^nNH	3 Days at 37°	MeOH	89	$C_{16}H_{21}N_5$	67·0	7·1	25·0	67·85	7·4	24·75
6	Bu^iNH	,,	,,	104	$C_{16}H_{21}N_5$	67·6	7·2	25·7	67·85	7·4	24·75
7	n-$C_5H_{11}NH$	Solid NaOH used; 3 days at 37°	,,	92—93	$C_{17}H_{23}N_5$	68·55	7·95	23·65	68·7	7·7	23·6
8	$[CH_2]_5>N$	3 Days at 37°	BuOH	107	$C_{17}H_{21}N_5$	69·05	7·0	24·0	69·15	7·1	23·75
9	p-Cl·C_6H_4·NH	,,	EtOH	126—127	$C_{18}H_{16}N_5Cl$	64·25	4·8	20·3	64·0	4·75	20·75
10	p-MeO·C_6H_4·NH	,,	C_6H_6–Pet	128—130	$C_{19}H_{19}ON_5$	69·0	5·8	22·3	68·5	5·7	21·0
11	NH_2–C(=NH)–NH	From diguanide sulphate, 5 mins. at 70°, then 16 hours at 45°	BuOH	247—248	$C_{13}H_{15}N_7$	57·7	5·7	36·4	57·95	5·7	36·45

TABLE 3. *5-Aminopyrimidines.*

Compound no.	Substituent in position 2	4	6	Isolation †	Solvent *	M. p.	Formula	Found, % C	H	N	Required, % C	H	N
1	Me_2N	Me	Me	Steam; base	Pet, A	122°	$C_8H_{14}N_4$	57·7	8·1	33·55	57·85	8·45	33·75
2	EtHN	Me	Me	Steam; sulphate	EtOH	145	$C_8H_{14}N_4,H_2SO_4,H_2O$	34·75	5·65	19·4	34·05	6·4	19·85
				base	Pet, A	72	$C_8H_{14}N_4$	57·95	7·9	33·3	57·85	8·45	33·7
3	Pr^iHN	Me	Me	Steam; base	,,	101	$C_9H_{16}N_4$	58·9	8·2	31·05	60·0	8·9	31·1
4	Pr^nHN	Me	Me	Steam; base	Pet, B	98	$C_9H_{16}N_4$	60·0	9·2	31·95	60·0	8·9	31·1
5	Bu^nHN	Me	Me	Steam; sulphate	H_2O	150	$C_{11}H_{18}N_4,H_2SO_4,\frac{1}{2}H_2O$	39·7	7·0	19·35	39·9	7·0	18·6
6	Bu^iHN	Me	Me	Steam; sulphate	,,	150	$C_{10}H_{18}N_4,H_2SO_4,\frac{1}{2}H_2O$	39·5	7·0	17·65	39·9	7·0	18·6
7	n-C_5H_{11}·NH	Me	Me	Steam; sulphate	,,	143—144	$C_{10}H_{20}N_4,H_2SO_4$	42·1	7·15	18·2	43·15	7·2	18·3
8	$[CH_2]_5>N$	Me	Me	Steam; base	MeOH	160—162	$C_{11}H_{18}N_4$	64·5	8·5	27·85	64·1	8·7	27·2
9	p-Cl·C_6H_4·NH	Me	Me	Steam; base	PhMe	132	$C_{12}H_{13}N_4Cl$	58·35	5·35	22·7	57·95	5·25	22·55
10	p-MeO·C_6H_4·NH	Me	Me	Benzene	,,	119	$C_{13}H_{16}ON_4$	63·95	6·5	24·3	63·9	6·55	22·95
11	NH_2	Ph	Me	Steam; base	$COMe_2$	146	$C_{11}H_{12}N_4$	66·1	6·05	27·95	66·0	6·0	28·0
12	NH_2	Pr^n	Me	Steam; base	C_6H_6	114—116	$C_8H_{14}N_4$	57·5	8·0	34·85	57·85	8·45	33·75
13	NH_2	Et	Me	Steam; ether	PhMe	132	$C_7H_{12}N_4$	55·05	7·55	36·5	55·2	7·9	36·85
14	NH_2	Et	Et	Steam; excess of NaOH	C_6H_6	98	$C_8H_{14}N_4$	58·55	8·2	33·5	57·85	8·45	33·75

* Pet, A = light petroleum, b. p. 60—80°; B, b. p. 100—120°. † Steam = steam-distillation.

out the required tetra-azaindene in dilute aqueous sodium hydroxide. The product was obtained in a much smaller yield.

The diazonium salt was obtained in solid form by filtration of the cold diazonium suspension, and recrystallised from water without appreciable decomposition as large straw-coloured prisms which decomposed, without melting, at 180° (Found: C, 30·0; H, 4·4; N, 28·9; Cl^-, 14·7. $C_6H_8N_5SCl,1{\cdot}25H_2O$ requires C, 30·0; H, 4·4; N, 29·2; Cl^-, 14·8%). It coupled vigorously with *m*-phenylenediamine and alkaline R-salt.

5-Amino-7-hydroxy-1 : 2 : 4 : 6-tetra-azaindene.—The above 7-methylthio-compound (4·5 g.) was dissolved in hot acetic acid (40 c.c.) and perhydrol (15 c.c.) cautiously added. After continued heating at 90—95° for 1 hour the crystalline precipitate of *5-amino-7-hydroxy-1 : 2 : 4 : 6-tetra-azaindene methanesulphonate* was collected (4 g.). It crystallised slowly from water in pale yellow prisms, m. p. 370° (decomp.) (inserted at 360°) (Found: C, 28·8; H, 3·65; N, 27·95; S, 12·3. $C_5H_5ON_5,CH_3{\cdot}SO_3H$ requires C, 29·15; H, 3·65; N, 28·35; S, 12·95%).

5-Amino-7-benzylthio-1 : 2 : 4 : 6-tetra-azaindene.—2 : 5-Diamino-4-benzylthio-6-methylpyrimidine (6·2 g., 0·025 mol.) was diazotised and treated with sodium hydroxide in the manner described above. The resultant solution was treated with charcoal, and the *product* (2·25 g.) precipitated by an excess of ammonium chloride. Crystallised from chlorobenzene, it had m. p. 198° (Found: C, 56·0; H, 3·85; N, 26·65. $C_{12}H_{11}N_5S$ requires C, 56·05; H, 4·3; N, 27·1%).

5-Amino-1 : 2 : 4 : 6-tetra-azainden-7-ylthioacetic Acid.—2 : 5-Diamino-4-methyl-6-pyrimidylthioacetic acid (22 g., 0·1 mol.) in N-hydrochloric acid (250 c.c.) was diazotised and added as before to 2·5N-sodium hydroxide (200 c.c.) at 5°. Addition of excess of acetic acid precipitated the crude *tetra-azaindene* (5 g.). It was insoluble in organic solvents and did not melt. A pure specimen was prepared by adding dilute acetic acid to a solution in dilute aqueous ammonia (charcoal) (Found: C, 34·35; H, 3·95; N, 28·05. $C_7H_7O_2N_5S,H_2O$ requires C, 34·6; H, 3·7; N, 28·8%).

5 : 7-Diamino-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-7-methylthio-1 : 2 : 4 : 6-tetra-azaindene (5 g.) and ammonia (15 c.c.; *d* 0·88) were heated in a sealed tube at 150° for 16 hours. The free base (2·8 g.), m. p. 330° (decomp.), which crystallised on cooling was insoluble in organic solvents but fairly soluble in water. When added to dilute hydrochloric acid the sparingly soluble *hydrochloride* was formed which crystallised from water in infusible colourless rosettes (Found: C, 29·65; H, 4·55; N, 41·0. $C_5H_6N_6,HCl,H_2O$ requires C, 29·35; H, 4·4; N, 41·05%). The 7-benzylthiotetra-azaindene also gave the diamine under the same reaction conditions.

*5-Amino-7-iso*propylamino*-1 : 2 : 4 : 6-tetra-azaindene.*—5-Amino-7-methylthio-1 : 2 : 4 : 6-tetra-azaindene (10 g.) reacted similarly with *iso*propylamine (20 c.c.), and the residue after evaporation to dryness was extracted with dilute hydrochloric acid. The clarified suspension was treated with excess of sodium hydrogen sulphite solution. The product was obtained as the free *base* by dissolving the crystalline hydrogen sulphite, which separated, in dilute sodium hydroxide and adding excess of ammonium chloride. It crystallised from water in colourless prisms, m. p. 246° (Found: C, 47·25; H, 6·5; N, 41·5. $C_8H_{12}N_6,\frac{1}{2}H_2O$ requires C, 47·75; H, 6·45; N, 41·6%).

5-Amino-7-piperidino-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-7-benzylthio-1 : 2 : 4 : 6-tetra-azaindene (5 g.) and piperidine (5 c.c.) were heated under reflux for 4 hours. The semi-solid *product* left after treatment of the reaction mixture with benzene crystallised from dioxan in colourless prisms, m. p. 224° (decomp.) (Found: C, 54·45; H, 6·3; N, 37·35. $C_{10}H_{14}N_6$ requires C, 55·0; H, 6·4; N, 38·5%).

5-Amino-7-morpholino-1 : 2 : 4 : 6-tetra-azaindene.—Prepared similarly by using morpholine (5 g.), the *base* crystallised from water in slightly hydrated pale cream-coloured needles, m. p. 229—232° (Found: C, 47·4; H, 5·65; N, 36·95. $C_9H_{12}ON_6,0{\cdot}33H_2O$ requires C, 47·1; H, 5·6; N, 37·15%).

5-Amino-7-dimethylamino-1 : 2 : 4 : 6-tetra-azaindene.—(*a*) 2 : 5-Diamino-4-dimethylamino-6-methylpyrimidine (4·2 g.) in N-hydrochloric acid (100 c.c.) was diazotised and added to 3N-sodium hydroxide (70 c.c.) below 10°. Crystals of the sodium salt of the *product* began to separate, and after addition of 10N-sodium hydroxide (50 c.c.) they were collected and redissolved in hot water and the solution (charcoal) neutralised with acetic acid. The solid (4 g.) formed yellow crystals, m. p. 264° (decomp.), from dimethylformamide (Found: C, 42·75; H, 5·65; N, 42·25. $C_7H_{10}N_6,H_2O$ requires C, 42·85; H, 6·1; N, 42·85%).—(*b*) The diazo-solution similarly prepared from the diamine (2·7 g.) was kept at 95—100° for 10 minutes. After the colour reaction (yellow) given with *m*-phenylenediamine was no longer obtainable, excess of sodium acetate was added; the tetra-azaindene (2 g.), identical with the above, crystallised out.

7-*Methyl*-5-*methylamino*-1 : 2 : 4 : 6-*tetra-azaindene*.—The solution obtained by adding diazotised 5-amino-4 : 6-dimethyl-2-methylaminopyrimidine sulphate (25 g.) to 3N-sodium hydroxide (150 c.c.) was heated to 60° with the addition of sodium dithionite (3 g.), treated with charcoal, and filtered. The *product* (11·3 g.) separated when the filtrate was neutralised with hydrochloric acid, and was obtained as colourless prisms, m. p. 276—277°, when reprecipitated from dilute solution in aqueous sodium hydroxide with acetic acid (Found: C, 51·05; H, 5·4; N, 42·5. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·95%).

5-*Dimethylamino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-2-dimethylamino-4 : 6-dimethylpyrimidine (15 g.) was converted into the tetra-azaindene in the same way, but more sodium dithionite (10 g.) was used and the *product* precipitated initially as the *hydrogen sulphite* which crystallised from water in needles, m. p. 174—176° (Found: C, 36·25; H, 5·15; N, 26·8. $C_8H_{11}N_5,H_2SO_3$ requires C, 37·05; H, 5·0; N, 27·0%). The *base* (6·4 g.) was obtained by decomposition of this salt in boiling dilute hydrochloric acid, and neutralisation with aqueous ammonia. It crystallised from toluene in colourless needles, m. p. 166° (Found: C, 54·35; H, 6·1; N, 41·15. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%).

5-*Ethylamino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—Prepared similarly from 5-amino-2-ethylamino-4 : 6-dimethylpyrimidine sulphate (20 g.), this *product* (7 g.) was also initially isolated as the hydrogen sulphite. It formed colourless needles (from methanol), m. p. 224° (Found: C, 54·3; H, 5·85; N, 40·0. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%).

The following homologues were obtained by the same general method, except that by avoiding the use of excessive amounts of sodium dithionite as decolorant intermediate isolation of the hydrogen sulphite was avoided.

7-*Methyl*-5-n-*propylamino*-1 : 2 : 4 : 6-*tetra-azaindene*, pale cream prisms (from 2-ethoxyethanol), m. p. 221° (Found: C, 57·2; H, 7·05; N, 36·65. $C_9H_{13}N_5$ requires C, 56·55; H, 6·8; N, 36·65%).

7-*Methyl*-5-iso*propylamino*-1 : 2 : 4 : 6-*tetra-azaindene*, colourless leaflets (from toluene), m. p. 213—215° (Found: C, 56·45; H, 6·35; N, 36·8%).

5-n-*Butylamino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*, cream-coloured needles (from toluene), m. p. 162° (Found: C, 58·7; H, 7·1; N, 35·25. $C_{10}H_{15}N_5$ requires C, 58·55; H, 7·3; N, 34·15%).

5-iso*Butylamino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*, cream-coloured plates (from chlorobenzene), m. p. 200° (Found: C, 57·8; H, 7·2; N, 34·2%).

5-n-*Amylamino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*, cream-coloured prisms (from toluene), m. p. 154° (Found: C, 60·4; H, 7·7; N, 32·2. $C_{11}H_{17}N_5$ requires C, 60·3; H, 7·75; N, 31·95%).

7-*Methyl*-5-*piperidino*-1 : 2 : 4 : 6-*tetra-azaindene*, colourless needles [from light petroleum (b. p. 100—120°)], m. p. 160—161° (Found: C, 60·4; H, 6·8; N, 31·75. $C_{11}H_{15}N_5$ requires C, 60·8; H, 6·9; N, 32·25%).

5-*Amino*-7-*ethyl*-3-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene* (from 2 : 5-diamino-4 : 6-diethylpyrimidine), pale yellow prismatic needles (from butanol), m. p. 219° (Found: C, 55·35; H, 6·45; N, 39·7. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%).

5-*Guanidino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-2-guanidino-4 : 6-dimethylpyrimidine (24 g., 0·14 mol.) in 3N-hydrochloric acid (140 c.c.) was diazotised and added to 3N-sodium hydroxide (270 c.c.) below 5°. The solution was neutralised with hydrochloric acid (charcoal) and filtered at the boil. The *product* (14 g.) crystallised on cooling. It crystallised from water in colourless needles, m. p. 227° (decomp.) (Found: C, 38·45; H, 4·85; N, 43·85. $C_7H_9N_7,1\frac{1}{2}H_2O$ requires C, 38·5; H, 5·5; N, 44·9%). The *sulphate* crystallised from water in pale cream-coloured needles, not molten at 330° (Found: C, 35·2; H, 4·3; N, 41·2. $C_7H_9N_7,\frac{1}{2}H_2SO_4$ requires C, 35·0; H, 4·2; N, 40·8%).

2-p-*Chloroanilino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-2-*p*-chloroanilino-4 : 6-dimethylpyrimidine (12·5 g., 0·05 mol.) was made into a paste in N-hydrochloric acid (125 c.c.) and diazotised with sodium nitrite at 15—20°. The solution which resulted after stirring the diazo-suspension for 16 hours in 2N-sodium hydroxide (185 c.c.) was nearly neutralised with hydrochloric acid (charcoal) and treated with excess of ammonium chloride. The *product* (6·9 g.) separated. It crystallised from butanol in pale yellow prisms, m. p. 242° (Found: C, 56·25; H, 4·0; N, 26·0. $C_{12}H_{10}N_5Cl$ requires C, 55·6; H, 3·9; N, 26·95%).

7-*Methyl*-5-p-*anisidino*-1 : 2 : 4 : 6-*tetra-azaindene*.—Prepared similarly from 5-amino-4 : 6-dimethyl-2-*p*-anisidinopyrimidine (5·8 g.), the crude *product* (4·3 g.) crystallised from butanol in yellow prisms, m. p. 215° (Found: C, 61·1; H, 5·0; N, 27·7. $C_{13}H_{13}ON_5$ requires C, 61·15; H, 5·1; N, 27·45%).

5-Amino-7-phenyl-1 : 2 : 4 : 6-tetra-azaindene.—Similarly prepared from 2 : 5-diamino-4-methyl-6-phenylpyrimidine (2·3 g.), the crude *product* (1·6 g.) crystallised from water in lemon-yellow prismatic needles, m. p. 90—95° (effervesce at 120—140°) (Found: C, 58·2; H, 4·85; N, 31·05. $C_{11}H_9N_5,H_2O$ requires C, 57·65; H, 4·8; N, 30·55%).

Ring-closure of Diazotised 2 : 5-Diamino-4-ethyl-6-methylpyrimidine.—The diazo-solution from the diaminopyrimidine (31·5 g.) was added in the usual manner to sodium hydroxide solution (5N; 250 c.c.) below 5° and, after hydrochloric acid had been added to reduce alkalinity somewhat, it was treated with charcoal and filtered. Excess of concentrated hydrochloric acid was added to the filtrate to give a strong acid reaction. *5-Amino-3 : 7-dimethyl-1 : 2 : 4 : 6-tetra-azaindene hydrochloride* (7·5 g.) separated. It crystallised from water in straw-coloured needles, m. p. 342° (Found: C, 42·75; H, 4·95; N, 35·9. $C_7H_9N_5$,HCl requires C, 42·1; H, 5·0; N, 35·1%). Addition of ammonium chloride to a hot solution of the hydrochloride in dilute aqueous sodium hydroxide gave the *base* as colourless needles, m. p. 327° (decomp.) (inserted at 315°) (Found: C, 51·5; H, 5·55; N, 43·15. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·95%).

The filtrate from the separation of the above hydrochloride was neutralised and evaporated to dryness. Water (400 c.c.) was added to redissolve salts, and the suspension was filtered. The crude *5-amino-7-ethyl-1 : 2 : 4 : 6-tetra-azaindene* (11 g.) crystallised from 2-ethoxyethanol in flat yellow needles (7 g.), m. p. 278—280° (inserted at 273°) (Found: C, 51·4; H, 5·5; N, 43·9. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·95%).

7-Dimethylamino-5-methylthio-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-4-dimethylamino-6-methyl-2-methylthiopyrimidine (19·8 g.) in water (50 c.c.) and concentrated hydrochloric acid (22 c.c.) was diazotised at 20° with sodium nitrite (7 g.) in water (20 c.c.). The diazo-solution was heated to 95—100° for 10 minutes. The hydrochloride of the tetra-azaindene (23 g.) crystallised on cooling. The *base* was obtained by adding acetic acid to a solution of the hydrochloride in dilute aqueous sodium hydroxide. It formed rectangular prisms (from dimethylformamide), not molten at 300° (Found: C, 45·65; H, 5·15; N, 32·95. $C_8H_{11}N_5S$ requires C, 45·95; H, 5·25; N, 33·5%). In a separate experiment ring-closure occurred giving a similar yield, when the diazo-solution was kept for 2 days at 20—25°.

7-Dimethylamino-1 : 2 : 4 : 6-tetra-azaindene.—The above 5-methylthio-1 : 2 : 4 : 6-tetra-azaindene (50 g.) was stirred and heated at 100—105° for 16 hours with Raney nickel (210 g.) in dimethylformamide (330 c.c.) and water (80 c.c.). The suspension was filtered while hot, and the filtrate treated with charcoal and then evaporated to dryness under reduced pressure. Treatment of the solid with cold water (300 c.c.) and addition of concentrated hydrochloric acid precipitated the sparingly soluble hydrochloride of unchanged starting material. The solution obtained by filtration was evaporated to dryness, giving the *hydrochloride* (28 g.; m. p. 277—278°) of 7-dimethylamino-1 : 2 : 4 : 6-tetra-azaindene. Recrystallised from aqueous acetone it had m. p. 288° (Found: C, 42·05; H, 4·4; N, 33·6. $C_7H_9N_5$,HCl requires C, 42·1; H, 4·5; N, 35·1%). The *base*, obtained by careful neutralisation of a concentrated solution in water of the hydrochloride, formed colourless prisms (from 2-ethoxyethanol), m.p. 261—264° (Found: C, 52·0; H, 5·3; N, 42·4. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·9%).

In an attempt to replace the dimethylamino-group by hydroxyl, the above hydrochloride (4·5 g.) was heated under reflux for 6 hours in 5N-hydrochloric acid. The solution was neutralised with aqueous ammonia and then made just acid with acetic acid. A crystalline solid (1·1 g.) was slowly precipitated. It was insoluble in organic solvents but was purified by neutralising with acetic acid a solution (charcoal) in dilute aqueous ammonia. The product, believed to be *4-aminopyrazole-6-carboxylic acid*, decomposed at 211° (Found: C, 37·55; H, 3·9; N, 32·85. $C_4H_5O_2N_3$ requires C, 37·8; H, 3·95; N, 33·1%). It dissolved in dilute hydrochloric acid, aqueous sodium hydroxide, or ammonia, and formed a diazonium compound (coupling with β-naphthol) with nitrous acid.

Diazouracil-6-aldoxime.—A solution of 5-amino-6-methyluracil (28 g., 0·2 mol.) in N-sodium hydroxide (200 c.c.) containing sodium nitrite (28 g.) was added to 2·5N-hydrochloric acid (400 c.c.) stirred at 15—20°. The white crystalline precipitate (40 g.) was filtered off. It crystallised from water in colourless needles, m. p. 245°, which were dried at 100° (Found: C, 30·3; H, 2·55; N, 34·9. Found, in material dried at 130°/0·5 mm.: C, 30·5; H, 2·5; N, 36·5; in material dried at 160°/0·5 mm.: C, 30·5; H, 2·55; N, 35·5%. $C_5H_3O_3N_5,H_2O$ requires C, 30·15; H, 2·5; N, 35·15%). After being dried azeotropically in boiling dichlorobenzene it had m. p. 239° (decomp.) (Found: C, 33·45; H, 2·15; N, 38·5. $C_5H_3O_3N_5$ requires C, 33·15; H, 1·65; N, 38·7%). Recrystallisation from water re-formed the *hydrate* (Found: C, 30·05; H, 2·5; N, 35·2%).

Miscellaneous Compounds related to the Foregoing Tetra-azaindenes.

2 : 6-*Diamino-5-formamido-4-methylpyrimidine.*—2 : 5 : 6-Triamino-4-methylpyrimidine (5 g.) and formic acid (98%; 15 c.c.) were refluxed for 7 hours, and the crystalline solid which formed on addition of ether was dissolved in hot water and made alkaline with aqueous ammonia. The precipitate of the *base* (3·2 g.) crystallised from water in colourless needles which melted below 300° only when heated rapidly (Found: C, 42·5; H, 5·45; N, 42·05. Calc. for $C_6H_9ON_5$: C, 43·1; H, 5·4; N, 41·9%).

2-*Amino-6-methylpurine.*—The above formamidopyrimidine (3 g.) was powdered and added to paraffin (80 c.c.) previously heated to 280°. After evolution of gas had ceased (5 minutes), the suspension was diluted with benzene and filtered off. Addition of saturated aqueous ammonium chloride to a solution of the solid (2·3 g.) in 0·5N-sodium hydroxide (20 c.c.) (charcoal) gave the product as colourless needles (1·8 g.). It crystallised from water, and when heated sintered and decomposed at 300—320° (Found: C, 48·1; H, 4·65; N, 48·5. Calc. for $C_6H_7N_5$: C, 48·3; H, 4·7; N, 47·0%).

2-*Amino*-4 : 6 : 7-*trimethylpteridine.*—Addition of diacetyl (4 g.) to a solution at 80° of 2 : 5 : 6-triamino-4-methylpyrimidine (6 g.) in water (50 c.c.) gave immediate precipitation of the *product* (4·5 g.) which crystallised from 2-ethoxyethanol in yellow plates, m. p. 312—313° (Found: C, 56·6; H, 5·9; N, 36·2. $C_9H_{11}N_5$ requires C, 57·15; H, 5·8; N, 37·05%).

2-*Amino-6-methyl-1′* : 2′ : 3′-*triazolo*(5′ : 4′-4 : 5)*pyrimidine.*—The crystalline precipitate which formed when sodium nitrite (3·5 g.) in water (30 c.c.) was added to a cooled solution of 2 : 5 : 6-triamino-4-methylpyrimidine (7 g.) in 2N-hydrochloric acid (75 c.c.) was redissolved in dilute aqueous sodium hydroxide. Addition of acetic acid reprecipitated the *product* (7·4 g.) which crystallised from much water in colourless plates, m. p. 284—285° (Found: C, 35·7; H, 5·2; N, 49·8. $C_5H_6N_6,H_2O$ requires C, 35·7; H, 4·8; N, 50·0%).

2-*Amino-6-methyl-1′* : 2′ : 3′-*oxadiazolo*(5′ : 4′-4 : 5)*pyrimidine.*—2 : 5-Diamino-4-hydroxy-6-methylpyrimidine (7·9 g.), prepared by catalytic reduction under pressure with Raney nickel and hydrogen of the azo-compound obtained by the action of diazotised *p*-chloroaniline on 2-amino-4-hydroxy-6-methylpyrimidine (Jaeger, *Annalen*, 1891, **262**, 365), was dissolved in 2N-hydrochloric acid (100 c.c.) and treated at 10° with sodium nitrite (3·5 g.) in water (20 c.c.). The solution was made alkaline with ammonia, whereupon the *oxadiazole* (5·7 g.) crystallised in cream-coloured needles which decomposed explosively at about 150° (Found: C, 40·7; H, 3·55; N, 46·5. $C_5H_5ON_5$ requires C, 39·8; H, 3·3; N, 46·4%).

2-*Amino-6-methyl-1′* : 2′ : 3′-*thiadiazolo*(5′ : 4′-4 : 5)*pyrimidine.*—The suspension which formed when sodium nitrite (17 g.) in water (50 c.c.) was added to a cooled solution of 2 : 5-diamino-4-methyl-6-mercaptopyrimidine (39 g.) in 2N-hydrochloric acid (375 c.c.) was kept overnight and filtered. The solid crystallised from dimethylformamide, to give the *product* in colourless needles (23·2 g.), m. p. 216° (Found: C, 36·0; H, 3·0; N, 41·9. $C_5H_5N_5S$ requires C, 35·9; H, 3·0; N, 41·9%).

2-*Amino-6-methyl-1′* : 3′-*thiazolo*(5′ : 4′-4 : 5)*pyrimidine.*—The solution which formed when 2 : 5-diamino-4-methyl-6-mercaptopyrimidine (5 g.) and formic acid (98%; 20 c.c.) were refluxed for 7 hours, was diluted with water (100 c.c.), treated with charcoal, and made strongly alkaline with aqueous sodium hydroxide. The *product* was collected (3·5 g.) and crystallised from butanol; it had m. p. 214° (Found: C, 43·25; H, 3·7; N, 34·75. $C_6H_6N_4S$ requires C, 43·35; H, 3·6; N, 33·75%).

2 : 2′-*Diamino-6-methyl-1′* : 3′-*thiazolo*(5′ : 4′-4 : 5)*pyrimidine.*—2 : 5-Diamino-4-chloro-6-methylpyrimidine (24 g.), potassium thiocyanate (15·6 g.), and 2N-hydrochloric acid (150 c.c.) were heated at 95° for 30 minutes, and the crystalline precipitate which formed on cooling was collected. This was recrystallised from water (charcoal), just sufficient ammonia being added to remove the acid reaction. The *hydrochloride* so obtained formed flat yellow needles (9 g.), m. p. 315° (decomp.) (Found: C, 33·9; H, 4·3; N, 34·35. $C_6H_7N_5S,HCl$ requires C, 33·1; H, 3·5; N, 32·2%). The *base* was precipitated by addition of sodium hydroxide to a solution of the hydrochloride in hot water. It crystallised from butanol in colourless plates, m. p. 276—278° (Found: C, 40·6; H, 3·85; N, 37·85; S, 17·7. $C_6H_7N_5S$ requires C, 39·8; H, 3·85; N, 38·7; S, 17·7%).

2′-*Amino*-5 : 6-*dihydro*-5-*keto*-6′-*methylpyrimidino*(4′ : 5′-2 : 3)-1 : 4-*thiazine* (XXVI).—2 : 5-Diamino-4-methyl-6-pyrimidylthioacetic acid (9·5 g.) and 2N-hydrochloric acid (120 c.c.) were refluxed for 30 minutes. Long prismatic needles (6·05 g.) of the hydrated *hydrochloride*, insoluble in dilute alkalis, separated on cooling (Found: C, 33·9; H, 4·3; N, 23·0. $C_7H_8ON_4S,HCl,H_2O$ requires C, 33·55; H, 4·4; N, 22·35%).

Preparation of 5-aminopyrimidine intermediates.

2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine*.—The method of Hull, Lovell, Openshaw, and Todd (*loc. cit.*) was modified to facilitate large-scale working.

(a) 2-*Amino*-4 : 6-*dimethyl*-5-*phenylazopyrimidine*. Aniline (186 g.) in water (400 c.c.), crushed ice (1200 g.), and 10N-hydrochloric acid (500 c.c.) was diazotised by the rapid addition of sodium nitrite (144 g.) in water (500 c.c.), and the diazo-solution was added to a stirred suspension of acetylacetone (300 g.) in water (2 l.) and anhydrous sodium carbonate (440 g.). Phenylazoacetylacetone formed rapidly and after 30 minutes it was collected and added without further treatment to guanidine nitrate (410 g.), 10N-sodium hydroxide (720 c.c.), and methanol (1600 c.c.). The mixture was stirred for 20 hours at 50°, and the azopyrimidine was collected and washed successively with methanol (500 c.c.), water (1 l. at 60°), and more methanol (200 c.c.). It was obtained as orange plates (410 g.), m. p. 227—229°. Hull, Lovell, Openshaw, and Todd (*loc. cit.*) gave m. p. 228—230°.

(b) 2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine*. The above azopyrimidine (300 g.) was suspended in methanol (500 c.c.) and reduced with hydrogen under pressure in the presence of Raney nickel (10—20 g.). After addition of water (200 c.c.) and heating to 60°, the solution of the diamine was filtered from catalyst and evaporated under reduced pressure. The residual solid was washed on to a filter with ether. It formed large colourless prisms (180 g.), m. p. 184·5—186·5°. Hull *et al.* give m. p. 183·5—184·5° for sublimed material.

Other 2 : 5-*Diaminopyrimidines*.—Many of these, used as intermediates in this work, were prepared by processes similar to that described above. The relevant 5-phenylazopyrimidines are listed in Table 2, and the syntheses are exemplified more completely by the following details for the preparation of 4 : 6-*dimethyl*-2-*methylamino*-5-*phenylazopyrimidine* :

Methylguanidine sulphate (36 g., 0·3 mol.), methanol (200 c.c.), and 11N-sodium hydroxide (66 c.c.) were stirred until complete solution was obtained. Phenylazoacetylacetone (41 g., 0·2 mol.) was added, and, after being warmed to 50° to effect solution, the mixture was kept at 20—25° for 5 days. The *product* was then filtered off, washed successively with 50% methanol, warm water, and more 50% methanol, and crystallised from toluene. It formed golden needles, m. p. 161° (Found : C, 63·8; H, 5·85; N, 29·15. $C_{13}H_{15}N_5$ requires C, 64·75; H, 6·2; N, 29·05%).

The following additional phenylazopyrimidines were made similarly but are not conveniently tabulated.

2-*Amino*-4-*methyl*-6-*phenyl*-5-*phenylazopyrimidine*. Prepared from guanidine nitrate (20 g.), phenylazobenzoylacetone (13·5 g.), methanol (60 c.c.) and 11N-sodium hydroxide (30 c.c.) kept for 2 days at 37°, the *compound* crystallised from ethanol in red-brown prisms, m. p. 158° (Found : C, 71·5; H, 5·0; N, 24·0. $C_{17}H_{15}N_5$ requires C, 70·55; H, 5·2; N, 24·2%).

2-*Amino*-6-*ethyl*-4-*methyl*-5-*phenylazopyrimidine*. Prepared similarly from 3-*phenylazohexane*-2 : 4-*dione* [m. p. 83—84°, from methanol (Found : C, 66·0; H, 6·0; N, 13·0. $C_{12}H_{14}O_2N_2$ requires C, 66·05; H, 6·4; N, 12·85%)], the *compound* crystallised from butanol in yellow-red needles m. p. 171° (Found : C, 64·75; H 5·1; N, 29·15. $C_{13}H_{15}N_5$ requires C, 64·75; H, 6·2; N, 29·05%).

2-*Amino*-4 : 6-*diethyl*-5-*phenylazopyrimidine*. Prepared similarly from 4-*phenylazoheptane*-3 : 5-*dione* [m. p. 76°, from methanol (Found : C, 66·75; H, 6·7; N, 12·55. $C_{13}H_{16}O_2N_2$ requires C, 67·25; H, 6·9; N, 12·1%)], the *compound* crystallised from methanol in red plates, m. p. 156° (Found : C, 66·5; H, 6·5; N, 27·2. $C_{14}H_{17}N_5$ requires C, 65·9; H, 6·6; N, 27·45%).

2-*Amino*-6-*methyl*-5-*phenylazo*-4-n-*propylpyrimidine*. Prepared similarly from 4-*phenylazooctane*-3 : 5-*dione* [m. p. 65°, from methanol–water (Found : C, 67·55; H, 6·65; N, 13·15. $C_{14}H_{18}O_2N_2$ requires C, 68·2; H, 7·3; N, 11·4%)], the *compound* crystallised from methanol in orange needles, m. p. 108° (Found : C, 66·0; H, 6·6; N, 27·85. $C_{14}H_{17}N_5$ requires C, 65·9; H, 6·6; N, 27·5%).

Reduction of Phenylazopyrimidines.—This was effected in all cases catalytically with hydrogen at or above atmospheric pressure over Raney nickel, and with methanol as solvent. After filtration from catalyst, the solvent was removed and the residue crystallised either as the base or as a salt such as the sulphate after (*a*) treatment with a solvent such as benzene or ether, or (*b*) with steam, to remove the aniline formed. Some of the bases were very soluble in water and when isolated as such required the addition of a large excess of sodium hydroxide. The methods used to prepare the diamines listed in Table 3 are exemplified by the following preparations. In the table, reduction was under pressure unless otherwise noted.

5-*Amino*-2-*guanidino*-4 : 6-*dimethylpyrimidine*. 2-Guanidino-4 : 6-dimethyl-5-phenylazopyrimidine (26·2 g.) in methanol (150 c.c.) was reduced at N.T.P. After filtration from

catalyst and removal of solvent, the pasty product was extracted twice with boiling benzene. The residue was dissolved at 80° in sufficient N-sulphuric acid, and on cooling the *sulphate* crystallised in colourless needles (14 g.), m. p. 229° (Found: C, 29·1; H, 5·3; N, 30·4. $C_7H_{12}N_6,H_2SO_4$ requires C, 30·2; H, 5·0; N, 30·2%).

5-Amino-4: 6-dimethyl-2-methylaminopyrimidine. 4: 6-Dimethyl-2-methylamino-5-phenylazopyrimidine (35 g.) was reduced in methanol, initially at 35° and under pressure. The filtrate from separation of the catalyst was steam-distilled to remove both solvent and aniline. 5N-Sulphuric acid was added to the aqueous solution to give a strong acid reaction and the *sulphate* was precipitated. It crystallised from water in colourless needles, m. p. 193° (Found: C, 32·2; H, 5·85; N, 22·05. $C_7H_{12}N_4,H_2SO_4$ requires C, 33·6; H, 5·6; N, 22·4%). The *base*, prepared by the action of aqueous sodium hydroxide on the sulphate, crystallised from xylene in colourless prisms, m. p. 113° (Found: C, 54·9; H, 7·2; N, 36·75. $C_7H_{12}N_4$ requires C, 55·25; H, 7·9; N, 36·85%).

2: 5-*Diamino*-4-*dimethylamino*-6-*methylpyrimidine*.—Dimethylamine (25% aqueous solution, 40 c.c.) was added to 2-amino-4-chloro-6-methyl-5-nitropyrimidine (19 g.) in dioxan (50 c.c.) initially at 40°. Crystals of 2-*amino*-4-*dimethylamino*-6-*methyl*-5-*nitropyrimidine* separated on cooling, and recrystallised from ethanol in golden needles, m. p. 192—193° (Found: C, 42·45; H, 5·55; N, 35·95. $C_7H_{11}O_2N_5$ requires C, 42·65; H, 5·55; N, 35·55%). This nitro-compound (15 g.) was reduced in methanol by hydrogen under pressure in the presence of Raney nickel, and 2: 5-*diamino*-4-*dimethylamino*-6-*methylpyrimidine* (11 g.) crystallised from benzene in colourless prisms, m. p. 117—119° (Found: C, 50·55; H, 7·6; N, 41·6. $C_7H_{13}N_5$ requires C, 50·3; H, 7·8; N, 41·9%).

2: 5-*Diamino*-4-*mercapto*-6-*methylpyrimidine*.—2-Amino-4-chloro-6-methyl-5-nitropyrimidine (19 g.) was added portionwise to a stirred melt of sodium sulphide nonahydrate (70 g.) at 95°. After a further 1 hour at this temperature, the mixture was cooled and the crystalline sodium salt of the mercaptopyrimidine collected. Almost pure *product* was precipitated when acetic acid was added to a solution of the salt in hot water. Crystallised from 2-ethoxyethanol–water, it had m. p. 310° (decomp.) (Found: C, 38·85; H, 5·25; N, 36·15. $C_5H_8N_4S$ requires C, 38·45; H, 5·15; N, 35·9%).

2: 5-*Diamino*-4-*methyl*-6-*methylthiopyrimidine*.—10N-Sodium hydroxide (14 c.c.) was added to a suspension, kept at 50°, of 2-amino-4-chloro-6-methyl-5-nitropyrimidine (4 g.) and *S*-methylthiuronium sulphate (6 g.) in dioxan (20 c.c.) and water (20 c.c.). After 15 minutes, the crude 2-*amino*-4-*methyl*-6-*methylthio*-5-*nitropyrimidine* (3 g.) was filtered off. It crystallised from butanol in yellow needles, m. p. 219° (Found: C, 36·25; H, 3·95; N, 27·05. $C_6H_8O_2N_4S$ requires C, 36·0; H, 4·0; N, 28·0%), and was reduced in methanolic solution with hydrogen under pressure over palladium on carbon. The 2: 5-*diamino*-4-*methyl*-6-*methylthiopyrimidine* so obtained crystallised from water in colourless prisms, m. p. 141—142° (Found: C, 41·85; H, 5·9; N, 34·0. $C_6H_{10}N_4S$ requires C, 42·35; H, 5·9; N, 33·0%).

2: 5-*Diamino*-4-*benzylthio*-6-*methylpyrimidine*.—2-*Amino*-4-*benzylthio*-6-*methyl*-5-*nitropyrimidine* [yellow prismatic needles from benzene, m. p. 155° (Found: C, 53·2; H, 4·4; N, 20·25. $C_{12}H_{12}O_2N_4S$ requires C, 52·2; H, 4·35; N, 20·3%)] was obtained similarly from *S*-benzylthiuronium chloride, and, reduced catalytically in butanol, gave the *diamine*, m. p. 160° (Found: C, 59·15; H, 6·0; N, 23·0. $C_{12}H_{14}N_4S$ requires C, 58·6; H, 5·7; N, 22·8%).

2: 5-*Diamino*-4-*methyl*-6-*pyrimidylthioacetic Acid*.—2: 5-Diamino-6-mercapto-4-methylpyrimidine (37 g.), chloroacetic acid (24 g.), and 2N-sodium hydroxide (300 c.c.) were heated together at 95° for 30 minutes. Addition of excess of acetic acid precipitated the *product* (48·5 g.) which was further purified by reprecipitation from alkaline solution. It formed cream-coloured needles, decomp. about 230° (Found: C, 35·85; H, 5·35; N, 25·2. $C_7H_{10}O_2N_4S,H_2O$ requires C, 36·2; H, 5·15; N, 24·1%).

5-Amino-4-*dimethylamino*-6-*methyl*-2-*methylthiopyrimidine*.—(a) 2-*Chloro*-4-*dimethylamino*-6-*methyl*-5-*nitropyrimidine*. Dimethylamine (162 c.c.; 25% aqueous solution), neutralised to litmus by the addition of glacial acetic acid, was added to 2: 4-dichloro-6-methyl-5-nitropyrimidine (62 g.) suspended in dioxan (240 c.c.) at 20°, and stirred at that temperature overnight. The crude *product* obtained by the addition of water gave golden needles (33·5 g.), m. p. 97—98°, from methanol (Found: C, 38·9; H, 4·05; N, 25·6. $C_7H_9O_2N_4Cl$ requires C, 38·8; H, 4·15; N, 25·85%).

(b) 4-*Dimethylamino*-2-*mercapto*-6-*methyl*-5-*nitropyrimidine*. Glacial acetic acid (30 g.) in methanol (100 c.c.) was added slowly to sodium sulphide nonahydrate (120 g.) in methanol (250 c.c.) kept below 20°, and the solution was added to the above chloronitropyrimidine (54 g.) dissolved in methanol (300 c.c.) at 40°. The mixture was warmed to 65° for several

minutes, the *thiol* beginning to separate. Precipitation was completed by addition of water and acidification with acetic acid. The product (45 g.; m. p. 225°), collected and recrystallised from acetic acid, formed lemon-yellow needles, m. p. 224° (Found: C, 39·15; H, 4·9; N, 25·65. $C_7H_{10}O_2N_4S$ requires C, 39·25; H, 4·65; N, 26·15%).

(c) 4-*Dimethylamino*-6-*methyl*-2-*methylthio*-5-*nitropyrimidine*. Methyl sulphate (30 c.c.) was added portionwise to the above thiol (43 g.) dissolved and stirred in 2N-sodium hydroxide (500 c.c.) at 20°. After 30 minutes, the crystalline *methylthiopyrimidine* was collected and recrystallised from light petroleum (b. p. 60—80°). It formed yellow prisms, m. p. 78° (Found: C, 42·25; H, 5·5; N, 24·5. $C_8H_{12}O_2N_4S$ requires C, 42·1; H, 5·25; N, 24·55%). Reduction of this product (18 g.) in methanol with hydrogen over Raney nickel at N.T.P. gave the required 5-*amino*-4-*dimethylamino*-6-*methyl*-2-*methylthiopyrimidine* (16 g.) which formed colourless needles, m. p. 70°, from light petroleum (b. p. 80—100°) (Found: C, 48·9; H, 7·4; N, 28·25. $C_8H_{14}N_4S$ requires C, 48·5; H, 7·05; N, 28·3%).

2 : 5-*Diamino*-4-*methoxy*-6-*methylpyrimidine*.—(a) 2-*Amino*-4-*methoxy*-6-*methyl*-5-*nitropyrimidine*. The solution obtained by adding 2-amino-4-chloro-6-methyl-5-nitropyrimidine (19 g.) to sodium (4·6 g.) dissolved in methanol (150 c.c.) was refluxed for 15 mintues and cooled to 0°. The crystalline precipitate of *methoxy*-compound was filtered off, washed with water (yield 17 g.), and recrystallised from 2-ethoxyethanol in yellow needles, m. p. 199° (Found: C, 39·2; H, 4·5; N, 30·85. $C_6H_8O_3N_4$ requires C, 39·15; H, 4·35; N, 30·45%).

(b) 2 : 5-Diamino-4-methoxy-6-methylpyrimidine resulted from the reduction of the nitro-compound (9·2 g.) in methanol with hydrogen over Raney nickel at N.T.P. The diamine was precipitated as the *sulphate* (10·4 g.) by adding 10N-sulphuric acid to the solution after filtration from catalyst. It formed colourless needles (from aqueous ethanol), m. p. 167—169° (Found: C, 25·4; H, 5·5; N, 20·05. $C_6H_{10}ON_4,H_2SO_4$ requires C, 25·8; H, 4·7; N, 20·05%).

2 : 5-*Diamino*-4-*chloro*-6-*methylpyrimidine*.—2-Amino-4-chloro-6-methyl-5-nitropyrimidine (38 g.) was reduced in methanol (150 c.c.) with hydrogen over Raney nickel at N.T.P., requiring 20 hours. Concentrated hydrochloric acid (20 c.c.) was added to the suspension, followed by sodium acetate crystals (40 g.) dissolved in water (20 c.c.). After filtration, evaporation left a residue which when digested with a little water at 0—5° gave the crude *base* (20 g.). It formed colourless needles (from water), m. p. 198° (decomp.) (Found: C, 37·55; H, 4·7; N, 34·7. $C_5H_7N_4Cl$ requires C, 37·85; H, 4·4; N, 35·3%).

2 : 5-*Diamino*-4-*methylpyrimidine*.—The above 2 : 5-diamino-4-chloro-6-methylpyrimidine (31 g.) was added to a suspension of zinc dust (100 g.) in 4N-sodium hydroxide (300 c.c.) and refluxed (10 minutes) until completely dissolved, and the whole filtered. Addition of 10N-sodium hydroxide (400 c.c.) to the chilled filtrate gave the crude solid *base*, which formed colourless prisms, m. p. 182—183°, from a hot dioxan solution dried over solid potassium hydroxide (Found: C, 48·45; H, 6·35; N, 45·45. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%). The base was very soluble in water giving strongly fluorescing solutions.

5-*Acetamido*-2-*amino*-4 : 6-*dimethylpyrimidine*.—Prepared from the diamine (13·8 g.) and acetic anhydride (12 c.c.) at 50°, and crystallised from butanol in colourless prisms, this *derivative* had m. p. 246—247° (Found: C, 53·1; H, 6·3; N, 31·9. $C_8H_{12}ON_4$ requires C, 53·3; H, 6·65; N, 31·1%).

2-*Amino*-5-*benzamido*-4 : 6-*dimethylpyrimidine*.—Prepared from the diamine shaken with benzoyl chloride in 2N-sodium hydroxide, the *benzoyl* derivative gave colourless prisms, m. p. 289·5—290·5°, from butanol (Found: N, 22·7. $C_{13}H_{14}ON_4$ requires N, 23·15%).

NN′-*Di*-(2-*amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)*urea*.—Carbonyl chloride was passed into a solution of the diamine (4·6 g.) in water (75 c.c.) and sodium acetate crystals (4·6 g.) at 20—25° until no diazotisable amine remained. Addition of sodium hydroxide precipitated the urea (insoluble in common solvents, and infusible) which gave the *dihydrochloride* as colourless leaflets when a solution in 5N-hydrochloric acid was treated with excess of acetone (Found: C, 39·3; H, 5·8; N, 28·5; Cl, 17·75. $C_{13}H_{18}ON_8,2HCl,H_2O$ requires C, 39·65; H, 5·6; N, 28·4; Cl, 18·05%).

2-*Amino*-4 : 6-*dimethyl*-5-*thioureidopyrimidine*.—The diamine (3·5 g.), potassium thiocyanate (2·6 g.), and 3N-hydrochloric acid (17 c.c.) were heated under reflux for 30 minutes. Addition of ammonia precipitated the *thiourea*, which crystallised from 2-ethoxyethanol in colourless prismatic needles, m. p. 235° (decomp.) (Found: C, 43·05; H, 6·3; N, 34·1. $C_7H_{11}N_5S$ requires C, 42·65; H, 5·6; N, 35·5%).

Ethyl N-2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyloxamate*.—The diamine (10 g.) and ethyl oxalate (30 c.c.) were refluxed for 5 hours. The solid precipitated by addition of light petroleum (50 c.c.; b. p. 100—120°) was extracted with boiling ethanol (100 c.c.), and the extract evaporated to dryness. Treatment of the residue with water (50 c.c.) at 50° left the *oxamate* (3·3 g.) which

crystallised from water in colourless plates, m. p. 189—190° (Found: C, 50·65; H, 5·95; N, 24·2. $C_{10}H_{14}O_3N_4$ requires C, 50·4; H, 5·9; N, 23·5%).

NN′-*Di*-(2-*amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)*malondiamide*.—The diamine (5·5 g.) and ethyl malonate (3·2 g.) were heated at 200—210° for 5 hours. The precipitate of crude *amide* obtained after cooling and addition of water was collected, dissolved in dilute hydrochloric acid, and reprecipitated with aqueous sodium hydroxide. It crystallised from glacial acetic acid in colourless needles (2·2 g.), m. p. 334·5° (Found: C, 51·7; H, 6·0; N, 32·35. $C_{15}H_{20}O_2N_8$ requires C, 52·3; H, 5·8; N, 32·55%).

2-*Amino*-4 : 6-*dimethyl*-5-p-*nitrobenzenesulphonamidopyrimidine*.—The diamine (4·4 g.), *p*-nitrobenzenesulphonyl chloride (4·4 g.), crystalline sodium acetate (4·1 g.), and water (12 c.c.) were refluxed for 2 hours, and cooled. The precipitate, collected, redissolved in dilute sodium hydroxide, and reprecipitated by acetic acid, afforded the *product* (2 g.) as pale yellow prisms (from ethanol), m. p. 230—232° (Found: C, 45·55; H, 5·05; N, 18·95. $C_{12}H_{13}O_4N_5S,C_2H_5{\cdot}OH$ requires C, 45·5; H, 5·15; N, 18·95%).

2-*Amino*-4 : 6-*dimethyl*-5-*sulphanilamidopyrimidine*.—The above nitro-compound was reduced by hydrogen in the presence of Raney nickel at N.T.P. The *amine* so formed crystallised from water–ethanol in rosettes of colourless needles, m. p. 280° (Found: N, 23·7. $C_{12}H_{15}O_2N_5S$ requires N, 23·9%).

2-*Amino*-5-*dimethylamino*-4 : 6-*dimethylpyrimidine*.—The diamine (4·6 g.), methyl iodide (4 c.c.), methanol (4 c.c.), and water (4 c.c.) were heated in a sealed tube at 100° for 4 hours. The resultant solution was evaporated to dryness. The crude *product* (3·5 g.; m. p. 132—144°) was obtained when ammonia was added to a solution of the residue in water (50 c.c.). It crystallised from toluene in colourless prisms (2 g.), m. p. 151—152° (Found: C, 57·8; H, 8·0; N, 33·1. $C_8H_{14}N_4$ requires C, 57·85; H, 8·4; N, 33·7%). The compound was unchanged after treatment in dilute hydrochloric acid solution with sodium nitrite.

2-*Amino*-5-p-*dimethylamino*-4 : 6-*dimethylphenylazopyrimidine*.—The diamine (13·8 g.) in 2N-hydrochloric acid (150 c.c.) was diazotised at 10° with sodium nitrite (7 g.) in water (25 c.c.). Dimethylaniline (24·2 g.) in 2N-hydrochloric acid (100 c.c.) was added, followed by sufficient sodium acetate to remove the acid reaction to Congo-red. More sodium acetate was added as required, and the mixture was stirred at 10° for 2 days until no diazo-reaction (alkaline R-salt) remained. The *azo*-compound was collected and crystallised from butanol (charcoal) in orange-brown prisms, m. p. 215—218° (Found: C, 62·05; H, 6·5; N, 31·6. $C_{14}H_{18}N_6$ requires C, 62·2; H, 6·65; N, 31·1%).

2-*Amino*-5-*iodo*-4 : 6-*dimethylpyrimidine*.—Potassium iodide (100 g.) was added to a diazo-solution from the diamine (70 g.) prepared as described immediately above. The crystalline suspension which formed was stirred at 85—95° until nitrogen evolution ceased. Boiling water was added, to effect complete solution, followed by excess of 10N-sodium hydroxide. The precipitate of the *iodo*-compound was collected and crystallised from toluene (charcoal) in yellow prisms (58·5 g.), m. p. 185° (Found: C, 29·65; H, 3·15; N, 17·35. $C_6H_8N_3I$ requires C, 28·9; H, 3·2; N, 16·85%).

Guanidine and Diguanide Derivatives of 2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine*.—N^1-(2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)-N^3-*cyanoguanidine*. The diamine (28 g.), sodium dicyanimide (20 g.), and water (50 c.c.) were warmed together to dissolve. 11N-Hydrochloric acid (19 c.c.) was added and the mixture was heated at 95° for 1½ hours. The crystals of the *dicyandiamide* which deposited were collected [27·5 g.; m. p. 278—279° (decomp.)] and gave colourless prisms, m. p. 297°, from wet 2-ethoxyethanol (Found: N, 46·5. $C_8H_{11}N_7$ requires N, 47·8%). The product was only sparingly soluble in water but dissolved in dilute hydrochloric acid or sodium hydroxide.

2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyldiguanide*. The diamine (9·2 g.), dicyandiamide (6 g.), and 4N-hydrochloric acid (16 c.c.) were heated under reflux for 2 hours, and then added to potassium iodide (20 g.) dissolved in water (25 c.c.). The *diguanide hydriodide* which separated on cooling recrystallised from water (charcoal) in colourless needles (8·6 g.), m. p. 276·5—277·5° (decomp.) (Found: C, 27·55; H, 4·0; N, 31·3. $C_8H_{14}N_8,HI$ requires C, 27·4; H, 4·3; N, 32·0%).

The following N^1-*alkyl*-N^5-2-*amino*-4 : 6-*dimethyl*-5-*pyrimidyldiguanide hydriodides* were prepared in a similar manner, from the appropriate alkylcyanoguanidines (Curd, Hendry, Kenny, Murray, and Rose, *loc. cit.*): N^1-*methyl*-, prismatic needles (from water), m. p. 244° (decomp.) (Found: C, 29·05; H, 4·75; N, 28·7. $C_9H_{16}N_8,HI$ requires C, 29·65; H, 4·65; N, 30·8%); N^1N^1-*dimethyl*-, colourless needles (from methanol), m. p. 254—260° (decomp.) (Found: C, 32·1; H, 5·25; N, 28·1. $C_{10}H_{18}N_8,HI$ requires C, 31·75; H, 5·05; N, 29·65%); N^1-iso-

propyl-, colourless prisms (from methanol), m. p. 257—259° (decomp.) (Found : 33·6; H, 5·4; N, 27·7. $C_{11}H_{20}N_8$,HI requires C, 33·65; H, 5·35; N, 28·55%); N^1N^1-cyclo*pentamethylene-*, colourless prisms (from water), m. p. 258° (decomp.) (Found : C, 37·6; H, 5·55; N, 25·6. $C_{13}H_{22}N_8$,HI requires C, 37·3; H, 5·5; N, 26·8%); and N^1-methyl-N^1-*iso*propyl-, isolated as *hydrochloride*, colourless prisms (from water), m. p. 263° (decomp.) (Found : C, 46·15; H, 7·35; N, 34·0. $C_{12}H_{22}N_8$,HCl requires C, 45·8; H, 7·3; N, 35·6%).

N^1-2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyl*-N^5-*ethyldiguanide*. N^1-(2-Amino-4 : 6-dimethyl-5-pyrimidyl)-N^3-cyanoguanidine (2 g.; prepared as described above), ethylamine (33% solution in water; 2·7 c.c.), acetic acid (1·8 c.c.) and 2-ethoxyethanol (3 c.c.) were heated under reflux for 7 hours. The *dihydriodide* was precipitated by dilution with water (20 c.c.) containing potassium iodide (10 g.). It gave colourless plates (from water), m. p. 304° (decomp.) (Found : C, 24·2; H, 4·5; N, 23·25. $C_{10}H_{18}N_8$,2HI requires C, 23·7; H, 3·95; N, 22·15%).

N^1N^5-*Di*-(2-*amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)*diguanide*. N^1-(2-Amino-4 : 6-dimethyl-5-pyrimidyl)-N^3-cyanoguanidine (4·1 g.), 2 : 5-diamino-4 : 6-dimethylpyrimidine (2·9 g.), concentrated hydrochloric acid (1·8 c.c.), water (3 c.c.), and 2-ethoxyethanol (5 c.c.) were heated under reflux for 16 hours. The crystalline *dihydrochloride* was collected and after crystallisation twice from water gave colourless plates, m. p. 286—288° (decomp.) (Found : C, 40·65; H, 6·25; N, 35·5. $C_{14}H_{21}N_{11}$,2HCl requires C, 40·4; H, 5·55; N, 37·0%).

N^1-(2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)-N^5-p-*chlorophenyldiguanide*. N^1-(2-Amino-4 : 6-dimethyl-5-pyrimidyl)-N^3-cyanoguanidine (2 g.), *p*-chloroaniline (1·4 g.), and concentrated hydrochloric acid (1 c.c.) were cautiously heated under reflux in an oil-bath for 2 hours. Water (25 c.c.) was added, and the crystals which formed were collected. The *hydrochloride* crystallised from water (2·3 g.) in rosettes of colourless needles, m. p. 259° (decomp.) (Found : C, 43·7; H, 5·4; N, 28·2. $C_{14}H_{17}N_8Cl$,HCl,H_2O requires C, 43·4; H, 5·15; N, 28·95%).

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