1 : 2 : 4 : 6-*Tetra-azaindenes and* 1 : 4 : 6-*Triazaindan-2-ones from* 5-*Aminopyrimidines.*

By F. L. Rose.

[Reprint Order No. 5533.]

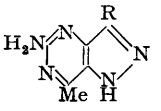
Earlier work leading to the formation of 1 : 2 : 4 : 6-tetra-azaindenes through the diazotisation of 5-amino-4-methylpyrimidines has been extended, with only partial success, in endeavours to prepare members of the series most nearly isosteric with the important natural purines, and, in particular, adenine. 6-Methyl groups have been introduced into several 5-nitropyrimidines through substitution of a diethyl malonate radical for chlorine, followed by degradative hydrolysis, thus providing essential intermediates not available by direct nitration. The primary nitropyrimidinylmalonic esters were themselves reduced to the 5-aminopyrimidines, which by internal condensation gave triazaindan-2-ones, and immediately, by diazotisation, the corresponding 1 : 2 : 4 : 6-tetra-azaindene-3 : 3-dicarboxylic esters. These substances were used in various subsidiary syntheses. Studies have also been made on the stepwise replacement of the chlorine atoms of 2 : 4-dichloropyrimidines by thiol and dialkylamino-groups.

A previous communication (Rose, *J.*, 1952, 3448) described the preparation of a number of 5-amino-4-methylpyrimidines (III), and showed how the action of caustic alkalis on their diazonium salts led to the formation of 1 : 2 : 4 : 6-tetra-azaindenes (II), in a manner analogous to the production of indazoles from *o*-toluidines. Since the tetra-azaindene ring system was isomeric with that of purine, it was made the subject of a detailed investigation in the hope that substances might result which would interfere with cell purine metabolism and might therefore form the basis for new chemotherapeutic agents. It was indeed noted that the compound (I; R = H) showed some therapeutic action against a tubercular infection in mice. The preparation of the isomers of several biologically important purines was also described, but attempts to produce the analogue (II; $R^1 = H$, $R^2 = NH_2$) of adenine failed. The dimethylamino-homologue (II; $R^1 = H$, $R^2 = NMe_2$) was synthesised successfully, but attempted replacement of the dimethylamino-group by hydroxyl, for conversion into the chloro-derivative and amination, led to fission of the pyrimidine ring. Direct synthesis of either the hypoxanthine (II; $R^1 = H$, $R^2 = OH$) or the adenine isomer from the appropriate 5-aminopyrimidine (III; $R^1 = H$, $R^2 = OH$ or NH_2) was not

possible because it was known that the latter, on diazotisation, would immediately form oxadiazole or triazole ring systems analogous to those in (IV) and (V), respectively. An indirect approach was therefore necessary, and the experimental work to that end, although it did not lead to full realisation of the objective, is here recorded, together with an account of a number of related syntheses.

It had already (*loc. cit.*) been shown that interaction of the 5-diazonium group with the adjacent 4-methyl group was facilitated by the presence in the pyrimidine ring of a 6-methylthio- and a 6-dimethylamino-substituent, so that ring-closure sometimes occurred even in acid solution, usually on heating. It was suggested that this process proceeded through the initial formation of diazosulphonium and triazolinium ionic structures, and one example of the former was isolated and characterised. A quaternary triazolinium salt (VI; X = I) has now been isolated.

As a result of these earlier experiences with the action of nitrous acid on 5-amino-pyrimidines, several apparently feasible routes to (II; R^1 = H, R^2 = NH_2 or OH) were examined, based on the notion that the penultimate intermediates should carry substituents in position 7 of the 1 : 2 : 4 : 6-tetra-azaindene system, capable of conversion into amino(or hydroxy)-groups under comparatively mild experimental conditions. Of the possible routes, the amination of (II; R^1 = H, R^2 = SMe) seemed the most likely to succeed. Attempts to prepare the necessary 5-aminopyrimidine (III; R^1 = H, R^2 = SMe) by reduction of the corresponding 2-chloro-derivative (III; R^1 = Cl, R^2 = SMe) failed, the chlorine atom resisting the action of zinc dust under a variety of conditions, and also catalytic hydrogenation. Another method, requiring the initial preparation of (VII; R^1 = H, R^2 = OH), was successful as far as this point but was later abandoned for the time being because of the objectionable and persistent odour associated with the corresponding chloropyrimidine No readily characterisable products resulted from attempts to remove preferentially one of the methylthio-groups from (II; R^1 = R^2 = SMe) by heating it with excess of Raney nickel containing much occluded hydrogen (Mozingo's method), nor was it possible to remove the methylthio- and the benzyl group from (II; R^1 = SMe, R^2 = NMe·CH_2Ph) to give the near homologue (II; R^1 = H, R^2 = NHMe) of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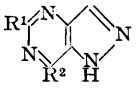
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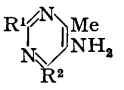
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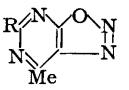
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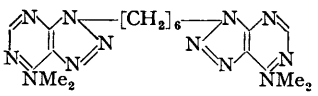
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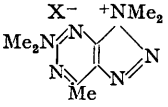
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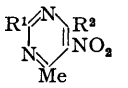
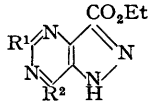

(VII)

one of the required final products. Ultimately, compound (VIII; R^1 = Me, R^2 = NH_2) was synthesised by a quite different approach. Of the several analogues prepared, this substance most nearly resembled the desired isomer of adenine, and was made in quantity for biological examination. Its synthesis resulted indirectly from the production of the nitropyrimidine intermediates required for some of the unsuccessful investigations listed above, and in particular of (VII; R^1 = H or Me, R^2 = OH). It is now well established that in the pyrimidine series a nitro-group can be introduced directly into position 5 only when two or three groups such as amino or hydroxyl are already present in position 2, 4, or 6, so that the derivatives of (VII) referred to would not be available by nitration of the corresponding hydroxy-methyl(or dimethyl)pyrimidines. A method similar to that used by Königs and Fulde (*Ber.*, 1927, **60**, 2108) for the synthesis of 4-methyl-3-nitropyridine, namely, the interaction of 4-chloro-3-nitropyridine with ethyl malonate followed by degradation of the malonyl residue to methyl, was therefore adapted to the pyrimidine series. Thus, the dichloronitropyrimidine (IX; R = Me) was found to react efficiently with diethyl malonate in light petroleum in the presence of strong aqueous sodium

hydroxide. Anhydrous conditions, such as those used by Königs and Fulde (*loc. cit.*), were shown to be unnecessary. The red sodium salt of (X; $R^1 = Me$, $R^2 = Cl$, $R^3 = H$) separated from the reaction mixture and was converted into the oily *aci*-form by treatment with cold mineral acid. The dichloropyrimidine (IX; R = H) reacted similarly with diethyl malonate, the organic solvent here being omitted, and gave (X; $R^1 = H$, $R^2 = Cl$, $R^3 = H$) as a crystalline solid on acidification of the more soluble sodium derivative. Decomposition of the products by a short treatment with hot dilute hydrochloric acid gave the required intermediates (VII; $R^1 = Me$, $R^2 = OH$; and $R^1 = H$, $R^2 = OH$) in good yields. Both compounds were soluble in water, the former being much less soluble as its sodium salt. The product (VII; $R^1 = Me$, $R^2 = OH$) was reduced catalytically to the amine (III; $R^1 = Me$, $R^2 = OH$) and this with nitrous acid gave the oxadiazole (IV; R = Me). In this case only 1 mol. of nitrous acid was absorbed: the corresponding 2-hydroxypyrimidine (III; $R^1 = R^2 = OH$) reacted rapidly with 2 mols. of nitrous acid (Rose, *loc. cit.*) to give the oxadiazole (IV; R = OH) with nitrosation of the methyl group.

Although in the above condensations with diethyl malonate only one chlorine atom in the dichloropyrimidines was replaced, despite the use of a large excess of ester, the second chlorine atom evidently retained a marked degree of lability, since the monochloro-compound (X; $R^1 = Me$, $R^2 = Cl$, $R^3 = H$) reacted with cold dimethylamine, to give the amine (X; $R^1 = Me$, $R^2 = NMe_2$, $R^3 = H$).

The behaviour of other chloropyrimidines was then investigated. The dichloro-compound (VII; $R^1 = R^2 = Cl$) reacted similarly with diethyl malonate in light petroleum in the presence of strong sodium hydroxide solution, and the precipitated red sodium salt gave the solid ester (X; $R^1 = Cl$, $R^2 = Me$, $R^3 = H$). The melting point of the crude product was not raised by recrystallisation, and there was no evidence of a second isomer's having been formed by alternative replacement of the 2-chlorine atom. The orientation given followed from the subsequent behaviour of the compound. The condensation of the monochloropyrimidine (VII; $R^1 = NH_2$, $R^2 = Cl$) also proceeded smoothly with diethyl malonate in aqueous acetone, and the product (X; $R^1 = NH_2$, $R^2 = Me$, $R^3 = H$) was obtained solid on acidification of the solution of the resultant sodium salt. Hydrolysis with hot dilute hydrochloric acid gave (XI), a nitropyrimidine which like (VII; $R^1 = H$ and Me, $R^2 = OH$) could not be obtained by direct nitration. Hydrolysis with hot dilute sodium hydroxide solution for a few minutes gave a different product (XII), isolated as its disodium salt.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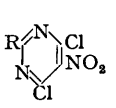
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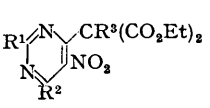
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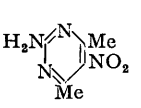
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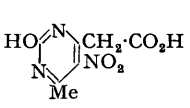
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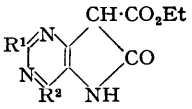
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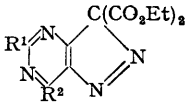
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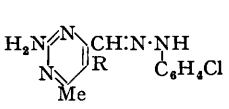
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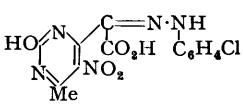
(XVI)

Three of the above nitropyrimidylmalonic esters (X; $R^1 = Cl$ and NH_2, $R^2 = Me$, $R^2 = H$; and $R^1 = Me$, $R^2 = Cl$, $R^3 = H$) were reduced catalytically over Raney nickel in cold methanol to form the corresponding 5-aminopyrimidines, all obtained solid. The amines were stable in the cold but, when they were heated in hot organic solvents, or more readily in hot aqueous solutions made alkaline with sodium carbonate or acid with hydrochloric acid, intramolecular condensation occurred with the production of the corresponding triazaindan-2-ones (XIII; $R^1 = Cl$ and NH_2, $R^2 = Me$; and $R^1 = Me$, $R^2 = Cl$), substances which like the tetra-azaindenes were isosteric with the purines and therefore of potential pharmacological interest in their own right. An attempt to cause the last-mentioned triazaindanone to react with ammonia to give the near analogue of adenine failed,

but aqueous dimethylamine at 140° gave (XIII; $R^1 = Me$, $R^2 = NMe_2$) in good yield, the ester group remaining intact. Diazotisation of the 5-amino-group was effected in all three instances of (X), but because of the sensitivity of the amines to acid it was most satisfactory to add dilute hydrochloric acid to a solution of the amines in aqueous dioxan containing sodium nitrite. In no case when alkaline R-salt was used could even the transient existence of a diazonium group be demonstrated, but self-coupling occurred instantaneously, even in the acid solution, to yield the tetra-azaindenes (XIV; $R^1 = Cl$ and NH_2, $R^2 = Me$; and $R^1 = Me$, $R^2 = Cl$). The chlorine atom of the third compound was very reactive, being replaced by methoxyl to give (XIV; $R^1 = Me$, $R^2 = OMe$) during attempted recrystallisation from methanol. The products were colourless low-melting crystalline solids, soluble in hydrocarbon solvents. When stirred with dilute aqueous sodium hydroxide they slowly dissolved. Acidification of the resultant solutions with acetic acid precipitated, with effervescence, the monoesters (VIII; $R^1 = Cl$ and NH_2, $R^2 = Me$; and $R^1 = Me$, $R^2 = Cl$). The second of these showed the intense fluorescence typical of the parent tetra-azaindene (I; R = H). On treatment in phenol with gaseous ammonia at 140°, the first product gave material identical with the second, while the third ester gave the adenine analogue (VIII; $R^1 = Me$, $R^2 = NH_2$) referred to earlier. In neither case was there any indication of carboxyamide formation. Several attempts were made to hydrolyse and decarboxylate the last compound, but all were unsuccessful.

It seemed likely that the diesters (X) could be used to prepare a series of pyrimidylglycines, substances again of potential chemotherapeutic interest. To that end, diazotised *p*-chloroaniline was first coupled with (X; $R^1 = NH_2$, $R^2 = Me$, $R^3 = H$) in dilute sodium hydroxide solution. The insolubility of the product in alkali supported the expected structure (X; $R^1 = NH_2$, $R^2 = Me$, $R^3 = \cdot N{:}N\cdot C_6H_4Cl$-*p*). Treatment for a few minutes with hot aqueous-ethanolic sodium hydroxide removed both ethoxycarbonyl groups forming the hydrazone (XV; $R = NO_2$). This formulation was suggested by its behaviour on catalytic hydrogenation, when only 3 mols. of hydrogen were absorbed, yielding the corresponding 5-aminopyrimidine (XV; $R = NH_2$), a substance exhibiting intense fluorescence in ultra-violet light. The diester (X; $R^1 = Cl$, $R^2 = Me$, $R^3 = H$) coupled likewise with diazotised chloroaniline, giving (X; $R^1 = Cl$, $R^2 = Me$, $R^3 = \cdot N{:}C_6H_4Cl$-*p*), and this with aqueous-ethanolic sodium hydroxide gave again a substance (XVI) having hydrazone properties. Sodium hypochlorite and the ester (X; $R^1 = NH_2$, $R^2 = Me$, $R^3 = H$) at 20° in dilute aqueous sodium hydroxide gave a good yield of the monochloroester ($R^3 = Cl$), and amongst the other related preparations was that of (I; $R = NH_2$) obtained by reduction with sodium dithionite of the coupling product (I; $R = \cdot N{:}N\cdot C_6H_4\cdot SO_3H$-*p*). The new diamine reacted with nitrous acid to give a diazonium salt which produced a purple colour with alkaline R-salt.

There remain several pyrimidine derivatives required as intermediates in the foregoing investigations. The bismethylthiopyrimidine (III; $R^1 = R^2 = SMe$) needed for ring-closure to the corresponding tetra-azaindene was obtained in good over-all yield by the addition of methyl sulphate to the solution of the aminodimercaptopyrimidine resulting from the treatment of (VII; $R^1 = R^2 = Cl$) at 100° with excess of aqueous sodium sulphide. A similar sequence of reactions was used to prepare the homologue (III; $R^1 = R^2 = SEt$). The same dichloromethylnitropyrimidine with 1 mol. of sodium sulphide in aqueous dioxan at 20° gave the nitromonothiol of the presumed orientation (VII; $R^1 = Cl$, $R^2 = SH$) which was converted into the corresponding methylthio-compound (VII; $R^1 = Cl$, $R^2 = SMe$) with methyl sulphate in aqueous sodium carbonate. Catalytic reduction then resulted in the required (III; $R^1 = Cl$, $R^2 = SMe$). The replacement of one or both chlorine substituents in the compound (VII; $R^1 = R^2 = Cl$) by amine residues could also be controlled by choice of experimental conditions. Thus excess of dimethylamine in aqueous dioxan gave the nitrodiamine (VII; $R^1 = R^2 = NMe_2$), subsequently reduced to the triamine (III; $R^1 = R^2 = NMe_2$), while prior neutralisation of the dimethylamine with acetic acid permitted only monosubstitution resulting in the chloronitroamine (VII; $R^1 = Cl$, $R^2 = NMe_2$). The orientation suggested for this compound followed previous experience with 2 : 4-dichloropyrimidines, and was also in accord with the observed behaviour upon diazotisation of the corresponding 5-aminopyrimidine, formed by catalytic

reduction, which cyclised smoothly to the tetra-azaindene (II; $R^1 = Cl$, $R^2 = NMe_2$). The benzylmethylaminopyrimidine (VII; $R^1 = Cl$, $R^2 = NBzMe$) was prepared similarly and was converted into the corresponding 2-methylthio-compound (VII; $R^1 = SMe$, $R^2 = NMe{\cdot}CH_2Ph$) by successive treatment with sodium sulphide and methyl sulphate. Both of these 5-nitropyrimidines were reduced to the 5-aminopyrimidines but, upon diazotisation and heating to form the tetra-azaindenes, the chlorine atom of the former was replaced by hydroxyl, to give the compound (II; $R^1 = OH$, $R^2 = NMe{\cdot}CH_2Ph$). The methylthiopyrimidine behaved normally.

Finally, the dipyrimidyl compound (V) was prepared, primarily for test as a trypanocide, from intermediates available in this research, namely, from (IX; R = H) by successive treatment with dimethylammonium acetate and hexamethylenediamine, followed by reduction and tetrazotisation of the resultant diamine.

Experimental

Tetra-azaindenes.

5 : 7-*Dimethylthio*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-6-methyl-2 : 4-dimethylthiopyrimidine (18 g.) in water (200 c.c.) and concentrated hydrochloric acid (20 c.c.) was diazotised at 5—10° by the slow addition of sufficient sodium nitrite (6·2 g.) in water (10 c.c.) to give a reaction on starch–iodide paper. The solution of the diazonium salt (which gave a red colour with alkaline R-salt solution and did not evolve nitrogen at room-temperature) was added during 8 min. to vigorously stirred 4N-sodium hydroxide (150 c.c.) kept below 10°. After a further 10 minutes' stirring without cooling, part of the excess of sodium hydroxide was neutralised by acetic acid, and the *product* (4·5 g.) was finally precipitated by adjustment to pH 7 after treatment with charcoal and filtration. Crystallised from 2-ethoxyethanol, it had m. p. 270—272° (Found: C, 39·9; H, 4·0; N, 25·2. $C_7H_8N_4S_2$ requires C, 39·65; H, 3·75; N, 26·4%).

5 : 7-*Diethylthio*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-2 : 4-diethylthio-6-methylpyrimidine (11·45 g.) was diazotised and treated with sodium hydroxide as described above. The *product* crystallised from benzene in prisms, m. p. 135—136° (Found: C, 45·3; H, 5·0; N, 24·9. $C_9H_{12}N_4S_2$ requires C, 45·0; H, 5·0; N, 23·35%).

5-*Chloro*-7-*dimethylamino*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-2-chloro-4-dimethylamino-6-methylpyrimidine (4·7 g.) in water (50 c.c.) and concentrated hydrochloric acid (9 c.c.) was diazotised and converted into the azaindene in 2N-sodium hydroxide (120 c.c.) as described above. The crude *product* (1·4 g.), crystallised from dimethylformamide, had m. p. 240—250° (decomp.) (Found: C, 42·75; H, 4·15; N, 34·75. $C_7H_8N_5Cl$ requires C, 42·6; H, 4·6; N, 35·5%). The chloro-compound was recovered unchanged after attempted reduction with hydrogen in water at 50 atm./100—110° over palladium–charcoal. Attempted reduction with stannous chloride in boiling concentrated hydrochloric acid for 15 hr. gave, after dilution, removal of the tin as sulphide, and adjustment to pH 5, only 7-*dimethylamino*-5-*hydroxy*-1 : 2 : 4 : 6-*tetra-azaindene*, m. p. 360° (Found, after drying at 100°: C, 44·55; H, 5·0; N, 38·2. $C_7H_9ON_5,\frac{1}{2}H_2O$ requires C, 44·7; H, 5·3; N, 37·2%).

7-*Benzylmethylamino*-5-*hydroxy*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-4-benzylmethylamino-2-chloro-6-methylpyrimidine (14 g.) in 2N-hydrochloric acid (120 c.c.) was diazotised at 20°. The solution was heated to, and kept at, the boil until it no longer gave a red colour with alkaline R-salt solution. There was no evolution of gas (nitrogen). The *product* (9·2 g.) precipitated on neutralisation with ammonia was purified by a second precipitation from hot acid; it decomposed above 300° and was free from chlorine (Lassaigne's test) (Found: C, 61·3; H, 5·3; N, 27·0. $C_{13}H_{13}ON_5$ requires C, 61·15; H, 5·1; N, 27·45%).

7-*Benzylmethylamino*-5-*methylthio*-1 : 2 : 4 : 6-*tetra-azaindene*.—The solution obtained by diazotising 5-amino-4-benzylmethylamino-6-methyl-2-methylthiopyrimidine (6·85 g.) in 4N-hydrochloric acid (18 c.c.) at 10—15° was kept at 70° until a coupling reaction with alkaline R-salt was no longer obtained. Ring-closure was rapid and the oily precipitate solidified (5·5 g.) when excess of sodium acetate was added. The *product* crystallised from butanol in straw-coloured needles, m. p. 225° (decomp.) (Found: C, 59·3; H, 5·4; N, 24·5. $C_{14}H_{15}N_5S$ requires C, 58·95; H, 5·25; N, 24·55%).

5-*Amino*-3 : 3-*diethoxycarbonyl*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—2-Amino-4-diethoxycarbonylmethyl-6-methyl-5-nitropyrimidine (20 g.) was reduced in methanol (420 c.c.) with

hydrogen under pressure in the presence of Raney nickel. The solution of the diamine, which was not isolated, was filtered from catalyst, and the bulk of the solvent evaporated under reduced pressure at <30°. Dioxan (70 c.c.) was added and the contaminant crystalline residue (2·5 g., later shown to be the triazaindanone, see below) filtered off. Sodium nitrite (5 g.) in water (15 c.c.) was added, followed dropwise during 7 min. by 5N-hydrochloric acid (17 c.c.) (acid to Congo-red) with stirring below 20°. Water (150 c.c.) was added and the *product* (7·6 g.) collected after it had solidified. It crystallised from xylene in colourless needles, m. p. 136—140° (Found: C, 48·9; H, 5·4; N, 24·2. $C_{12}H_{15}O_4N_5$ requires C, 49·15; H, 5·1; N, 23·9%), soluble in benzene and methanol. The solutions did not fluoresce in ultra-violet light. Partial hydrolysis occurred when the product (2·2 g.) was dissolved in N-sodium hydroxide (30 c.c.) and reprecipitated with acetic acid (effervescence), to give 5-*amino*-3-*ethoxycarbonyl*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene* (1·6 g.) which crystallised from water (charcoal) in colourless needles, m. p. 263—265° (decomp.) when inserted at 230° (Found: C, 49·0; H, 4·9; N, 30·5. $C_9H_{11}O_2N_5$ requires C, 48·9; H, 5·0; N, 31·7%). Solutions of this substance exhibited strong blue fluorescence in ultra-violet light. The same amine (crystalline form, fluorescence, mixed m. p.) was obtained when gaseous ammonia was passed into 5-chloro-3-ethoxycarbonyl-7-methyl-1 : 2 : 4 : 6-tetra-azaindene (5 g., see below) in phenol (10 g.) at 140° until a sample gave complete solution in dilute hydrochloric acid. Addition of water and a little methanol gave the crude product (3 g.) which crystallised from water (charcoal) (1·65 g.).

The dioxan-insoluble substance obtained during the reduction described above was formed in relatively greater quantity if the methanolic filtrates were set aside or warmed to 50°. The product decomposed without melting when heated, and was almost insoluble in organic solvents, including dimethylformamide, but dissolved in dilute aqueous sodium carbonate and sodium hydroxide, the solutions giving the colourless crystalline hydrochloride of 5-*amino*-3-*ethoxycarbonyl*-7-*methyl*-4 : 6-*di-azaoxindole* when added to excess of hot dilute hydrochloric acid (Found: C, 44·1; H, 5·0; N, 21·4; Cl, 12·55. $C_{10}H_{12}O_3N_4$,HCl requires C, 44·05; H, 4·75; N, 20·55; Cl, 13·0%).

5-*Chloro*-3 : 3-*diethoxycarbonyl*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-2-chloro-4-diethoxycarbonyl-6-methylpyrimidine (30 g.) in dioxan (60 c.c.) was diazotised by the method described immediately above, with sodium nitrite (7·5 g.) in water (20 c.c.) and 4N-hydrochloric acid (30 c.c.). After 10 min., water (700 c.c.) was added and the precipitate (26·7 g.) was collected. The *product* crystallised from benzene–light petroleum in rectangular prisms, m. p. 89° (Found: C, 46·0; H, 3·3; N, 17·1. $C_{12}H_{13}O_4N_4Cl$ requires C, 46·1; H, 4·15; N, 17·9%). Partial hydrolysis to 5-*chloro*-3-*ethoxycarbonyl*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene* was effected by suspending the diester (27 g.) in water (50 c.c.) and adding 11N-sodium hydroxide (28 c.c.) below 50°. Acidification (charcoal) of the solution precipitated a yellow solid (13·9 g.; m. p. 204°), which gave colourless fibrous needles, m. p. 208° (decomp.), when a portion (1 g.), redissolved in 0·5N-sodium carbonate (40 c.c.), was treated with acetic acid (Found: C, 45·4; H, 4·2; N, 22·8. $C_9H_9O_2N_4Cl$ requires C, 44·9; H, 3·75; N, 23·3%). The product crystallised from acetic acid, but with some production of ionic chlorine.

7-*Chloro*-3 : 3-*diethoxycarbonyl*-5-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—5-Amino-4-chloro-4-diethoxycarbonylmethyl-2-methylpyrimidine (20 g.) in dioxan (50 c.c.) was diazotised as above, with sodium nitrite (5 g.) in water (15 c.c.) and 4N-hydrochloric acid (22 c.c.) below 30°. After 10 min., water (150 c.c.) was added and the oily *product* stirred until solid (15·75 g.; m. p. 64°). It was freely soluble in organic solvents but was obtained as colourless prisms, m. p. 67·5°, when a solution in benzene was concentrated under reduced pressure (Found: C, 46·0; H, 4·2; N, 17·8. $C_{12}H_{13}O_4N_4Cl$ requires C, 46·1; H, 4·15; N, 17·9%). Earlier attempts to crystallise the chloro-compound from hot methanol gave colourless rectangular prisms, m. p. 124°, of 3 : 3-*diethoxycarbonyl*-7-*methoxy*-5-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene* (Found: C, 50·4; H, 5·4; N, 18·8. $C_{13}H_{16}O_5N_4$ requires C, 50·65; H, 5·2; N, 18·2%).

Dissolution of the chlorodiethoxycarbonylmethyl compound (1 g.) in cold N-sodium hydroxide (17 c.c.) followed by acidification with dilute acetic acid (effervescence) gave 7-*chloro*-3-*ethoxycarbonyl*-5-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene* (0·5 g.) which formed cream-coloured crystals (from aqueous acetone), m. p. 211° (decomp.) inserted at 200° (Found: C, 45·2; H, 4·0; N, 21·9. $C_9H_9O_2N_4Cl$ requires C, 44·9; H, 3·75; N, 23·3%).

This chloro-compound was converted into 7-*amino*-3-*ethoxycarbonyl*-5-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene* as described above for the 5-amino-7-methyl isomer by passing ammonia into the 7-chloro-tetra-azaindene (5 g.) in phenol (10 g.) at 140—150°. After cooling, the phenol was extracted with benzene (3 × 100 c.c.), and the residual solid (3·95 g.; m. p. 246—250°) collected with water. A solution in dilute aqueous sodium hydroxide (charcoal) gave colourless crystals,

m. p. 256° (decomp.), when acidified with dilute acetic acid (Found, after drying at 60°: C, 45·1; H, 5·1; N, 31·1. $C_9H_{11}O_2N_5,H_2O$ requires C, 45·2; H, 5·4; N, 29·3%).

3 : 5-*Diamino*-7-*methyl*-1 : 2 : 4 : 6-*tetra-azaindene*.—Sulphanilic acid (25 g.) in water (250 c.c.) and 11N-sodium hydroxide (15 c.c.) was reprecipitated with concentrated hydrochloric acid (52 c.c.) and diazotised at 10—20° with sodium nitrite (10 g.) in water (50 c.c.). 11N-Sodium hydroxide was added to make the whole alkaline to Brilliant Yellow, followed immediately by a solution of 5-amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene (23·5 g.) in water (250 c.c.) and 11N-sodium hydroxide (15 c.c.). The intermediate azo-derivative was precipitated as an orange crystalline solid when the resultant solution was made acid at 40—50° to Congo-red with concentrated hydrochloric acid. It was collected, washed with water and methanol, then dried (36 g.). The diamine was obtained initially as the crystalline (presumed) hydrogen sulphite (22 g.) by adding sodium dithionite (hydrosulphite) (30 g.) during 5 min. to a supension of the azo-compound (36 g.) in water (100 c.c.) at 80—100°, and then cooling. The *hydrochloride* (17 g.) crystallised when a solution of this sulphite (31 g.) in N-hydrochloric acid (220 c.c.) was boiled gently for 10 min., nearly neutralised with 11N-sodium hydroxide, and cooled. It crystallised from water in golden needles, not melted at 300° (Found, after drying at 100°: C, 34·9; H, 4·7; N, 39·9; Cl, 16·35. $C_6H_8N_6,HCl,\frac{1}{2}H_2O$ requires C, 34·35; H, 4·75; N, 40·1; Cl, 16·95%). The diamine hydrochloride was soluble in dilute aqueous sodium hydroxide or excess of hydrochloric acid. It gave a diazonium salt with nitrous acid (purple colour with alkaline R-salt).

Reaction of chloropyrimidines with diethyl malonate, and products derived thereby.

2-*Amino*-4-*diethoxycarbonylmethyl*-6-*methyl*-5-*nitropyrimidine*.—11N-Sodium hydroxide (37·5 c.c.) was added during 10 min. to a vigorously stirred solution of 2-amino-4-chloro-6-methyl-5-nitropyrimidine (23·8 g.) in diethyl malonate (30 g.) and acetone (100 c.c.) cooled in a water-bath. The internal temperature rose to 38°. After a further 10 min., water (100 c.c.) was added to dissolve the sodium derivative which had separated (charcoal), and the *product* was precipitated by acetic acid (yield, 33 g.; m. p. 127—128°). It crystallised from toluene in yellow prisms, m. p. 129·5° (Found: C, 46·2; H, 4·9; N, 18·0. $C_{12}H_{16}O_6N_4$ requires C, 46·15; H, 5·15; N, 17·95%).

2-*Amino*-4 : 6-*dimethyl*-5-*nitropyrimidine*.—The above ester (46·8 g.) in 2N-hydrochloric (300 c.c.) was refluxed with stirring for $2\frac{3}{4}$ hr., the ethanol formed being allowed to distil off. The hot solution (charcoal) was made alkaline with ammonia and chilled; the precipitated *product* (20·2 g.; m. p. 221—223°) crystallised from water in yellow needles, m. p. 225° (Found: C, 43·0; H, 4·8; N, 32·7. $C_6H_8O_2N_4$ requires C, 43·0; H, 4·8; N, 33·3%).

4-*Carboxymethyl*-2-*hydroxy*-6-*methyl*-5-*nitropyrimidine*.—The above ester (3 g.) was refluxed in 1·5N-sodium hydroxide (23 c.c.) until test showed no precipitation with acid (10 min.). The resultant solution was taken to dryness under reduced pressure after adjustment of the pH to 6—7 by acetic acid. Sodium acetate was removed by digestion with ethanol (20 c.c.), and the yellow crystalline *disodium* salt of the product was precipitated from a solution of the residue in water (3 c.c.) (charcoal) by excess of ethanol (Found, after drying at 50°: C, 24·9; H, 3·2; N, 13·2; ash, 35. $C_7H_5O_5N_3Na_2,2H_2O$ requires C, 24·6; H, 3·1; N, 14·3; ash, 36·2%).

Diethyl α-(2-*Amino*-6-*methyl*-5-*nitro*-4-*pyrimidinyl*)-α-*chloromalonate*.—Sodium hypochlorite solution (20 c.c.; bleach liquor) was added during 15 min. to the above ester (5·2 g.) stirred in solution in 11N-sodium hydroxide (3 c.c.) and water (50 c.c.) at 20°. The precipitated *chloro*-derivative (4·65 g.) crystallised from benzene in pale yellow needles, m. p. 122° (Found: C, 41·6; H, 4·3; N, 17·1; Cl, 11·5. $C_{12}H_{15}O_6N_4Cl$ requires C, 41·6; H, 4·35; N, 16·15; Cl, 10·2%).

Diethyl α-(2-*Amino*-6-*methyl*-5-*nitro*-4-*pyrimidinyl*)-α-p-*chlorophenylazomalonate*.—*p*-Chloroaniline (16·5 g.) in water (250 c.c.), and concentrated hydrochloric acid (15 c.c.) was diazotised at 20° by the rapid addition of sodium nitrite (7·5 g.) in water (30 c.c.), and the diazonium solution was added to the above ester (31·2 g.) in water (500 c.c.) and 11N-sodium hydroxide (30 c.c.), kept at 5—10°. After 30 min. the *azo*-compound was collected (36·9 g.; m. p. 171°). It crystallised from ethanol in orange prisms, m. p. 173° (decomp.) (Found: C, 47·7; H, 4·5; N, 20·0; Cl, 7·8. $C_{18}H_{19}O_6N_6Cl$ requires C, 48·0; H, 4·2; N, 18·7; Cl, 7·9%).

2-*Amino*-6-p-*chlorophenylhydrazono*-4-*methyl*-5-*nitropyrimidine*.—A mixture of the above chlorophenylazo-derivative (6 g.), ethanol (70 c.c.), and 11N-sodium hydroxide (10 c.c.) was refluxed for 15 min., cooled, neutralised with acetic acid, and diluted with water (140 c.c.). The *hydrazone* [3·25 g.; m. p. 242° (decomp.)] was obtained as yellow crystals, m. p. 246° (decomp.),

by adding boiling water (15 c.c.) to a solution of the crude product in dimethylformamide (charcoal) (Found : C, 46·7; H, 3·6; N, 25·6. $C_{12}H_{11}O_2N_6Cl$ requires C, 47·0; H, 3·6; N, 27·4%).

2 : 5-*Diamino*-6-p-*chlorophenylhydrazono*-4-*methyl*-6-*pyrimidine*.—The above nitropyrimidine (2 g.) in dimethylformamide (25 c.c.) was reduced at room temperature and pressure in the presence of Raney nickel (H_2 uptake, 465 c.c.; theory for NO_2, 590 c.c.). After filtration from catalyst, boiling water (125 c.c.) was added and the *product* (1·15 g.) crystallised on cooling. It recrystallised from butanol as dark iridescent platelets, m. p. 228° (Found : C, 51·4; H, 4·7; N, 29·1. $C_{12}H_{13}N_6Cl$ requires C, 52·1; H, 4·7; N, 30·4%). Solutions of the diamine in organic solvents exhibited intense fluorescence in ultra-violet light.

Diethyl 2-*Chloro*-6-*methyl*-5-*nitro*-4-*pyrimidinylmalonate*.—2 : 4-Dichloro-6-methyl-5-nitropyrimidine (125 g.) dissolved in diethyl malonate (183·5 g.) and light petroleum (b. p. 60—80°; 500 c.c.) was stirred vigorously (cooling with ice-water), and 11N-sodium hydroxide (126 c.c.) was added at such a rate that the temperature kept below 30° (5 min.). After 15 min., the red sodium salt that had separated as a viscous paste was collected, washed with more light petroleum, and redissolved in cold water (charcoal); 5N-sulphuric acid was added to make the whole just acid to Congo-red. The *product* was precipitated as a pale yellow solid (152 g.; m. p. 48—50°). It crystallised from light petroleum (b. p. 60—80°) in colourless fibrous needles, m. p. 48—50° (Found : C, 44·0; H, 4·3; N, 12·2. $C_{12}H_{14}O_6N_3Cl$ requires C, 43·45; H, 4·2; N, 12·65%).

Diethyl 5-*Amino*-2-*chloro*-6-*methyl*-4-*pyrimidinylmalonate*.—The above nitropyrimidine (50 g.) in methanol (400 c.c.) was reduced with hydrogen under pressure in the presence of Raney nickel. The solution was filtered at 45°, then chilled in ice-salt, and the crystalline *amine* (23 g.; m. p. 141°) was collected. Recrystallised from methanol, it formed colourless needles, m. p. 141° (Found : C, 47·5; H, 5·2; N, 14·4. $C_{12}H_{16}O_4N_3Cl$ requires C, 47·75; H, 5·3; N, 13·95%).

5-*Chloro*-3-*ethoxycarbonyl*-7-*methyl*-1 : 4 : 6-*triazaindan*-2-*one*.—The precipitate formed when excess of hydrochloric acid was added to a solution of the above amine (1 g.) in boiling 2N-sodium carbonate (10 c.c.) was collected and heated in a little water. The initial solution gave place to a crystalline deposit of the *product* (0·4 g.) as colourless prisms, which decomposed between 200° and 300° without melting and was insoluble in organic solvents (Found : C, 47·4; H, 3·9; N, 15·6. $C_{10}H_{10}O_3N_3Cl$ requires C, 46·95; H, 3·9; N, 16·45%). The compound, dissolved in dilute sodium carbonate solution, gave a deep purple precipitate with ferric chloride in dilute acetic acid.

Diethyl α-(2-*Chloro*-6-*methyl*-5-*nitro*-4-*pyrimidinyl*)-α-p-*chlorophenylazomalonate*.—Prepared as described for the corresponding 2-aminopyrimidine, from the above 2-chloropyrimidine (13·2 g.) and diazotised *p*-chloroaniline (6·6 g.), this *compound* crystallised from ethanol in red prisms, m. p. 98° (Found : C, 46·2; H, 3·6; N, 14·0; Cl, 15·3. $C_{18}H_{17}O_6N_5Cl_2$ requires C, 45·95; H, 3·6; N, 14·85; Cl, 15·15%). 11N-Sodium hydroxide (10 c.c.) was added to the azo-derivative (6·8 g.) in boiling ethanol (50 c.c.), and after 5 min. the mixture was diluted with water (50 c.c.) and acidified with concentrated hydrochloric acid. The precipitate of *ethyl* α-p-*chlorophenylazo*-α-(2-*hydroxy*-6-*methyl*-5-*nitro*-4-*pyrimidinyl*)*acetate* was collected, and purified by reprecipitation (3 g.) from solution (charcoal) in dilute aqueous sodium carbonate. It was insoluble in organic solvents and had m. p. 234° (decomp.) (Found : C, 44·6; H, 2·8; N, 18·7; Cl, 10·6. $C_{13}H_{10}O_5N_5Cl$ requires C, 44·4; H, 2·85; N, 19·9; Cl, 10·1%).

Diethyl α-(4-*Chloro*-2-*methyl*-5-*nitro*-6-*pyrimidinyl*)*malonate*.—Prepared as described above for the 2-chloro-4-methyl isomer by using 4 : 6-dichloro-2-methyl-5-nitropyrimidine (104 g.) in diethyl malonate (160 g.), light petroleum (b. p. 40—60°, 500 c.c.), and 11N-sodium hydroxide (200 c.c.) added during 15 min. The red *sodium* salt was collected and washed with brine. A little was crystallised by adding acetone to a solution in ethyl acetate (charcoal); it formed orange-red prisms, m. p. 150—152° (Found : Cl, 10·85. $C_{12}H_{13}O_6N_3ClNa$ requires Cl, 10·75%), and was decomposed as above with 5N-sulphuric acid. The *product* was a yellow viscous oil (150 g.). Sufficient was obtained for analysis by distillation of 10 g. (b. p. 140—142°/0·01 mm.) before the remainder decomposed violently (Found : C, 43·85; H, 4·8. $C_{12}H_{14}O_6N_3Cl$ requires C, 43·45; H, 4·2%).

Diethyl 6-*Dimethylamino*-2-*methyl*-5-*nitro*-4-*pyrimidinylmalonate*.—The above chloronitropyrimidine (6·65 g.) in methanol (15 c.c.) was added to dimethylamine (14 c.c.; 32% aqueous solution) below 10°. Addition of acetic acid gave the *dimethylaminopyrimidine* as an oil which solidified (5·4 g.; m. p. 89°). It formed golden-yellow needles, m. p. 89°, from light petroleum (b. p. 60—80°) (Found : C, 49·3; H, 5·5; N, 15·4. $C_{14}H_{20}O_6N_4$ requires C, 49·4; H, 5·9; N, 16·45%).

Diethyl 5-Amino-4-chloro-2-methyl-6-pyrimidinylmalonate.—The above chloronitropyrimidine (6 g.) was reduced in methanol in the presence of Raney nickel at room temperature and pressure. After filtration from catalyst and distillation of the solvent under reduced pressure, the solid residue was crystallised from light petroleum (b. p. 100—120°). The *product* (3·5 g.) formed colourless needles, m. p. 90° (Found: C, 48·1; H, 5·3; N, 14·4. $C_{12}H_{16}O_4N_3Cl$ requires C, 47·75; H, 5·3; N, 13·95%).

7-Chloro-3-ethoxycarbonyl-5-methyl-1 : 4 : 6-triazaindan-2-one.—The above aminopyrimidine (2·6 g.) was refluxed for 5 min. in water (30 c.c.) containing sodium carbonate (3 g.; anhydrous). The *triazaindanone*, which decomposed without melting when heated, was precipitated by acetic acid, and purified by a further precipitation (1·25 g.) (Found: C, 46·7; H, 4·1; N, 16·5; Cl, 13·65. $C_{10}H_{10}O_3N_3Cl$ requires C, 46·95; H, 3·9; N, 16·45; Cl, 13·9%).

7-Dimethylamino-3-ethoxycarbonyl-5-methyl-1 : 4 : 6-triazaindan-2-one.—The above chlorotriazaindanone (10·8 g.) and dimethylamine (80 c.c.; 30% aqueous solution) were heated at 140° for 1 hr. Addition of concentrated hydrochloric acid until faintly alkaline and cooling precipitated the *base* (9·8 g.). It gave colourless prisms (not melted on heating) when a solution in dilute sodium hydroxide was neutralised with acetic acid (Found: C, 54·8; H, 5·9; N, 21·1. $C_{12}H_{16}O_3N_4$ requires C, 54·55; H, 6·05; N, 21·2%).

4-Hydroxy-2 : 6-dimethyl-5-nitropyrimidine.—The solution obtained when diethyl 4-chloro-2-methyl-5-nitro-6-pyrimidinylmalonate (50 g.) was refluxed for 1¼ hr. with vigorous stirring in 4N-hydrochloric acid (80 c.c.) was evaporated to dryness under reduced pressure, finally at 100°. The crude *product* crystallised from water in colourless needles (18 g.), m. p. 222° (Found: C, 42·8; H, 4·3; N, 25·5. $C_6H_7O_3N_3$ requires C, 42·6; H, 4·15; N, 24·9%). The product gave a sparingly soluble sodium salt when added to dilute aqueous sodium hydroxide.

5-Amino-4-hydroxy-2 : 6-dimethylpyrimidine.—The above nitropyrimidine (6 g.) in methanol (100 c.c.) was reduced in the presence of palladium–charcoal at room temperature and pressure. The methanol was distilled from the filtered suspension, and the *amine* (3 g.) crystallised from ethanol as colourless needles, m. p. 200° (Found: C, 51·9; H, 6·6; N, 31·3. $C_6H_9ON_3$ requires C, 51·8; H, 6·45; N, 30·2%). Addition of sodium nitrite to the amine in dilute hydrochloric acid gave initially a solution of a diazonium compound (purple colour with alkaline R-salt) which on standing, or more rapidly on warming, gave a crystalline precipitate of *2 : 6-dimethyl-1′ : 2′ : 3′-oxadiazolo(5′ : 4′-4 : 5)pyrimidine*, that crystallised from water in cream-coloured rectangular plates, m. p. 188° (Found: C, 42·3; H, 4·6; N, 32·7. $C_6H_6ON_4,H_2O$ requires C, 42·85; H, 4·7; N, 33·35%).

Diethyl 4-Chloro-5-nitro-6-pyrimidinylmalonate.—4 : 6-Dichloro-5-nitropyrimidine (29·1 g.) was dissolved in diethyl malonate (73 c.c.). Water (300 c.c.) was added, followed during 10 min. by 11N-sodium hydroxide (91 c.c.) with vigorous stirring, the temperature being kept at 25—30°. After a further 5 min. the filtered suspension was made acid with concentrated hydrochloric acid. The precipitated *product* (16·1 g.), which solidified, crystallised from methanol in pale yellow prisms, m. p. 104° (Found: C, 40·9; H, 4·1; N, 13·6. $C_{11}H_{12}O_6N_3Cl$ requires C, 41·55; H, 3·8; N, 13·2%).

4-Hydroxy-6-methyl-5-nitropyrimidine.—The above ester (2·5 g.), concentrated hydrochloric acid (7·5 c.c.), and water (5 c.c.) were refluxed for 1½ hr. The resultant solution (charcoal) was evaporated to dryness under reduced pressure. The crystalline residue of the *hydrochloride* (1·1 g.) of the product was collected under acetone. It was recrystallised when acetone was added to its very concentrated solution in water, and then had m. p. 254° (Found, after drying at 100°: C, 28·5; H, 3·9; N, 21·6. $C_5H_5O_3N_3,HCl,H_2O$ requires C, 28·65; H, 3·8; N, 20·05%). The sodium salt was very soluble in water.

5-Nitro- and 5-amino-pyrimidines prepared by other routes.

4-Chloro-6-dimethylamino-5-nitropyrimidine.—Dimethylamine (84 c.c.; 30% aqueous solution), made neutral to Brilliant-yellow with acetic acid, was added to a stirred solution of 4 : 6-dichloro-5-nitropyrimidine (27 g.) in dioxan (100 c.c.) at 15—20°. After 2 hr., water (300 c.c.) was added and the *product* (26·8 g.; m. p. 102°) collected. It crystallised from aqueous dioxan in bright yellow needles, m. p. 104° (Found: C, 36·0; H, 3·5; N, 25·7; Cl, 17·5. $C_6H_7O_2N_4Cl$ requires C, 35·6; H, 3·45; N, 27·7; Cl, 17·5%).

2-Chloro-4-dimethylamino-6-methyl-5-nitropyrimidine.—This was prepared as described immediately above but with dimethylamine (162 c.c.), 2 : 4-dichloro-6-methyl-5-nitropyrimidine (62 g.), and dioxan (240 c.c.). The reaction mixture was stirred 16 hr. and the precipitated *product* (33·4 g.; m. p. 97—98°) collected without addition of water. It crystallised from light

petroleum (b. p. 80—100°) in golden needles, m. p. 97° (Found : C, 38·9; H, 4·05; N, 24·9. $C_7H_9O_2N_4Cl$ requires C, 38·8; H, 4·15; N, 25·85%). Reduction of the nitro-compound (30 g.) in methanol in the presence of Raney nickel (pressure) gave *5-amino-2-chloro-4-dimethylamino-6-methylpyrimidine* (21·3 g.) which crystallised from light petroleum in colourless needles, m. p. 63° (Found : C, 44·9; H, 6·0; N, 29·95. $C_7H_{11}N_4Cl$ requires C, 45·05; H, 5·9; N, 30·05%).

2 : 4-*Bisdimethylamino-6-methyl-5-nitropyrimidine.*—Interaction of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (52 g.) in dioxan (200 c.c.) with dimethylamine (225 c.c.; 20% aqueous solution) not previously neutralised with acetic acid gave the *bisdimethylamino*-compound (48 g.; m. p. 108—110°) which crystallised from light petroleum (b. p. 100—120°) in golden needles, m. p. 122—123° (Found : C, 48·4; H, 6·85; N, 30·85. $C_9H_{15}O_2N_5$ requires C, 48·0; H, 6·65; N, 31·1%). Reduction of this substance in methanol in the presence of Raney nickel gave *5-amino-2 : 4-bisdimethylamino-6-methylpyrimidine* which crystallised from light petroleum (b. p. 60—80°) in pale yellow flat needles, m. p. 75° (Found : C, 55·1; H, 8·55; N, 36·15. $C_9H_{17}N_5$ requires C, 55·4; H, 8·7; N, 35·9%).

4-Benzylmethylamino-2-chloro-6-methyl-5-nitropyrimidine.—Prepared as described for the above corresponding 4-dimethylaminopyrimidine (reaction temp. 35—40°), but with 2 : 4-dichloro-6-methyl-5-nitropyrimidine (30 g.), in dioxan (120 c.c.), and benzylmethylamine (42 g.) in water (50 c.c.) and acetic acid (neutralise). The initial gummy *product* solidified under methanol and, crystallised from butanol, had m. p. 114° (Found : C, 53·3; H, 4·3; N, 19·0. $C_{13}H_{13}O_2N_4Cl$ requires C, 53·35; H, 4·45; N, 19·15%). Reduction in ethyl acetate in the presence of Raney nickel gave 5-amino-4-benzylmethylamino-2-chloro-6-methylpyrimidine purified as the *picrate* (m. p. 146°) for analysis (Found : C, 46·4; H, 3·8; N, 20·8. $C_{13}H_{15}N_4Cl,C_6H_3O_7N_3$ requires C, 46·35; H, 3·65; N, 19·9%).

1 : 6-*Di-(4-dimethylamino-5-nitro-6-pyrimidylamino)hexane.*—4-Chloro-6-dimethylamino-5-nitropyrimidine (12 g.) was added quickly to a well-stirred mixture of hexamethylenediamine (3·6 g.) and triethylamine (12 g.) in dioxan (20 c.c.), and the whole gradually warmed to 70°. The dioxan was distilled off underre duced pressure and water (100 c.c.) added, followed by concentrated acid to acidity to Congo-red. The crude *product* (11 g.) was collected and crystallised from butanol in golden prisms, m. p. 142—144° (Found, after drying at 100° : C, 49·4; H, 6·8; N, 30·2. $C_{18}H_{28}O_4N_{10},\frac{1}{4}BuOH$ requires C, 48·9; H, 6·5; N, 30·0%).

2-Chloro-4-methyl-6-methylthio-5-nitropyrimidine.—Sodium sulphide nonahydrate (12 g.) in water (20 c.c.) was added during 20 min. to 2 : 4-dichloro-6-methyl-5-nitropyrimidine (10·4 g.), stirred in dioxan (40 c.c.) and cooled to 10—15°. After 1 hr., water (100 c.c.) was added, followed by acetic acid just to remove the alkaline reaction to Brilliant-yellow. The filtered (charcoal) suspension was made acid to Congo-red with concentrated hydrochloric acid. The precipitated thiol was redissolved in water (150 c.c.) and sodium carbonate (5·3 g.; anhydrous), and methyl sulphate (4 c.c.) was stirred in. After 2 hr., the crude *product* (6·7 g.) was collected. Crystallised from light petroleum, it had m. p. 68—69° (Found : C, 34·05; H, 2·85; N, 19·85. $C_6H_6O_2N_3SCl$ requires C, 32·8; H, 2·75; N, 19·15%).

5-Amino-2-chloro-4-methyl-6-methylthiopyrimidine.—The above nitro-compound (11 g.) was reduced in methanol (200 c.c.) in the presence of Raney nickel at room temperature and pressure. After filtration and removal of the solvent under reduced pressure, the *product* crystallised from light petroleum (b. p. 100—120°) as colourless needles, m. p. 110° (Found : C, 38·8; H, 4·35; N, 21·7. $C_6H_8N_3SCl$ requires C, 38·0; H, 4·25; N, 22·16%). The chloro-compound was recovered unchanged after refluxing for periods up to several hours with zinc dust in aqueous methanol and dilute aqueous ammonium chloride; the chlorine atom was not removed by hydrogen in the presence of palladium–charcoal at temperatures up to 60°.

5-Amino-4-methyl-2 : 6-dimethylthiopyrimidine.—2 : 4-Dichloro-6-methyl-5-nitropyrimidine (97 g.) was added in portions during 10 min. to a stirred solution of sodium sulphide nonahydrate (500 g.) in water (500 c.c.) heated on the steam-bath. The temperature rose from 90° to 105°. After a further 15 min. the solution was adjusted to pH 7 with acetic acid, then cooled, and the crude 5-amino-4-methyl-2 : 6-dimercaptopyrimidine collected. This was purified somewhat by dissolution in cold dilute sodium hydroxide and re-precipitation with acetic acid. The product (56·9 g.) was re-dissolved in water (600 c.c.) and 11N-sodium hydroxide (150 c.c.), and methyl sulphate (108·5 g.) was added with stirring during 40 min. at 10—15°. After a further 10 min. the crude *dimethylthiopyrimidine* was collected, dissolved in N-hydrochloric acid (435 c.c.) (charcoal), and re-precipitated by excess of sodium hydroxide (yield, 64·5 g.; m. p. 64°). When crystallised from light petroleum (b. p. 80—100°) it had m. p. 75° (Found : C, 42·3; H, 6·0; N, 20·7. $C_7H_{11}N_3S_2$ requires C, 41·8; H, 5·5; N, 20·9%).

5-Amino-2 : 6-diethylthio-4-methylpyrimidine was prepared in the same way but with

ethyl sulphate. It was isolated as an oil which was used for the preparation of the corresponding tetra-azaindene (see above) without further purification.

4-*Benzylmethylamino*-2-*mercapto*-6-*methyl*-5-*nitropyrimidine*.—Sodium sulphide nonahydrate (2 g.) was dissolved in ethanol (25 c.c.), and acetic acid (3 g.) was added, at <15°. The solution was added rapidly to 4-benzylmethylamino-2-chloro-6-methyl-5-nitropyrimidine (7·4 g.) in ethanol (100 c.c.) at 60°. The mixture was heated to 70° for 5 min., water (100 c.c.) was then added followed by acetic acid until neutral to Brilliant-yellow. The precipitated *product* (7 g.; m. p. 180—182°) crystallised from acetic acid in yellow prismatic needles, m. p. 198° (Found: C, 53·6; H, 5·0; N, 20·9. $C_{13}H_{14}O_2N_4S$ requires C, 53·8; H, 4·85; N, 19·3%). Addition of methyl sulphate (2·9 c.c.) to a solution of the thiol (5·8 g.) in 2N-sodium hydroxide (60 c.c.) at 30° gave after 30 min. 4-*benzylmethylamino*-6-*methyl*-2-*methylthio*-5-*nitropyrimidine* (5 g.; m. p. 89°) which formed yellow prisms [from light petroleum (b. p. 80—100°)], m. p. 90° (Found: C, 55·2; H, 5·2; N, 19·9. $C_{14}H_{16}O_2N_4S$ requires C, 55·2; H, 5·25; N, 18·4%). Reduction of this nitro-compound (50 g.) in methanol (800 c.c.), under pressure and in the presence of Raney nickel, gave after filtration and distillation of the solvent, 5-amino-4-benzylmethylamino-6-methyl-2-methylthiopyrimidine (45 g.) which was used in its crude form for conversion into the corresponding tetra-azaindene. A little was heated with acetic anhydride to convert it into the corresponding 5-*acetamidopyrimidine* which crystallised from water in colourless plates, m. p. 102° (Found: C, 57·7; H, 6·7; N, 16·7. $C_{16}H_{20}ON_4S,H_2O$ requires C, 57·5; H, 6·6; N, 16·75%).

Miscellaneous compounds related to the foregoing tetra-azaindenes.

2-*Dimethylamino*-6-*methyl*-1′ : 2′ : 3′-*triazolo*(5′ : 4′-4 : 5)*pyrimidine* 1′-*Methiodide*.—Sodium nitrite (0·7 g.) in water was added to a solution of 5-amino-2 : 4-bisdimethylamino-6-methylpyrimidine (1·95 g.) in N-hydrochloric acid (25 c.c.), cooled in ice. The resultant solution gave no colour with alkaline R-salt. Sodium iodide (5 g.) in water (10 c.c.) was added and the precipitated *methiodide* was filtered off. It crystallised from water in golden-yellow needles, decomp. at 140° without melting (Found: C, 32·2; H, 4·6; N, 24·6. $C_9H_{15}N_6I$ requires C, 32·3; H, 4·5; N, 25·1%).

1 : 6-*Di*-[6-*dimethylamino*-1′ : 2′ : 3′-*triazolo*(5′ : 4′-4 : 5)*pyrimid*-1′-*yl*]*hexane*.—1 : 6-Di-(4-dimethylamino-5-nitro-6-pyrimidylamino)hexane (1·55 g.) was reduced in butanol (290 c.c.) in the presence of Raney nickel at room temperature and pressure. Water (100 c.c.) and sufficient acetic acid were added to dissolve the diamine at 40°, and the catalyst was separated by filtration. The crude diamine which remained after removal of the solvents under reduced pressure was diazotised in water (20 c.c.) and concentrated hydrochloric acid (3 c.c.) at 10° by a slight excess of sodium nitrite in water. The *triazolo*-compound (1 g.) was precipitated by dilute aqueous sodium hydroxide. It crystallised from butanol in colourless needles (0·6 g.), m. p. 183—184° (Found: C, 52·7; H, 6·7; N, 40·05. $C_{18}H_{26}N_{12}$ requires C, 52·7; H, 6·35; N, 41·0%).

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