9. *The Synthesis of Trypanocides. Part II.** 4-*Amino*-6-(2-*amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-1 : 2-*dimethylquinolinium* ("*Antrycide*" †) *Salts and Related Compounds.*

By A. D. Ainley, (the late) F. H. S. Curd, W. Hepworth, A. G. Murray, and C. H. Vasey.

Prolonged treatment of 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (I) with excess of methyl iodide gave a product of high trypanocidal activity, and careful fractionation of the methochloride showed it to be a mixture containing (II; X = I) and (III; X = Cl).

The diquaternary derivatives of (I) were synthesised by unambiguous routes, involving quaternisation of 2-amino-4-chloro-6-methylpyrimidine, separation and identification of the products, and their condensation with 4 : 6-diamino-1 : 2-dimethylquinolinium salts. Thus 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (XVII; R = Cl, X = I) gave the dichloride (III; X = Cl) ("Antrycide" chloride). Confirmation that linkage between pyrimidine and quinoline nuclei occurred through the 6-position of the latter was obtained by an alternative synthesis of (III; X = Cl) in which (XVII; R = Cl, X = I) was condensed with 6-amino-4-methoxy-1 : 2-dimethylquinolinium iodide, and the methoxy-group in the product was replaced by amino- by treatment with ammonia.

Conditions are described for the quaternisation of (I) with methyl sulphate to give either (II; X = SO_4Me) or (III; X = SO_4Me) as the main product.

Preparations of 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (II; X = I), made by the action of methyl iodide in boiling alcoholic solution on the non-quaternised compound (I), showed varying trypanocidal activity unless rigorously purified: further, material obtained from the mother-liquors of the purification exhibited high activity, suggesting the presence of varying proportions of a highly active contaminant (see Curd and Davey, *Brit. J. Pharm.*, 1950, **5**, 25). This paper describes the isolation of this impurity, its identification, and synthesis of its active constituent, together with that of related compounds by alternative routes.

The substance (substance B), m. p. 300—301°, first isolated from the mother-liquors from the first crystallisations of (II; X = I), was later found to be the main product when the reaction of methyl iodide was carried out in alcohol in a sealed tube at 100°. It appeared to be an entity, $C_{17}H_{22}N_6I_2$, with one or two molecules of water of crystallisation, formed from two molecules of methyl iodide and one of the base (I), to give a dimethiodide, probably (III; X = I) or (IV; X = I).

In the few recorded descriptions of the preparation of quaternary salts of pyrimidine derivatives carrying only amino- or substituted amino-groups as functional substituents, their orientation had not been established. The behaviour of the model compound 2-amino-4-anilino-6-methylpyrimidine (V) (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1131) was therefore studied. In boiling alcohol this gave smoothly a monoquaternary iodide; hydrolysis by concentrated hydrochloric acid at 170—180° then gave aniline and 1 : 6-dimethyluracil (VI), establishing the constitution 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII), since the constitution of (VI) was considered to be rigidly proved by Behrend and Hesse (*Annalen*, 1903, **329**, 349). Under milder acid conditions the main product was 4-anilino-1 : 6-dimethylpyrimid-2-one (VIII). Hydrolysis of (VII) with alkali also gave (VIII) accompanied by products of further hydrolysis, aniline and 1 : 6-dimethyluracil. 4-Anilino-6-methyl-2-methylthiopyrimidine (IX), prepared by the action of aniline on 4-chloro-6-methyl-2-methylthiopyrimidine (Wheeler and MacFarland, *Amer. Chem. J.*, 1909, **42**, 431), with methyl iodide in boiling ethanol similarly gave the iodide (X), identified by acid hydrolysis to the above compound (VIII).

* Part I, preceding paper.

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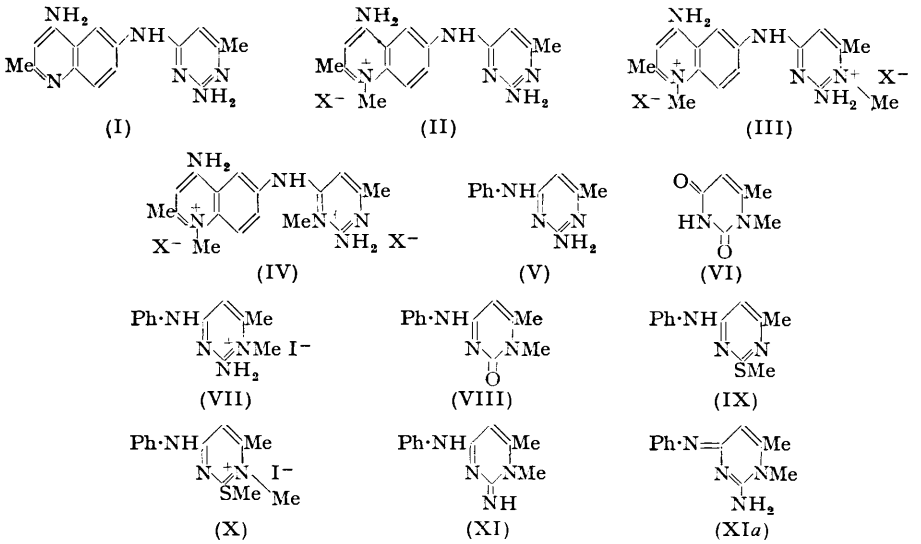
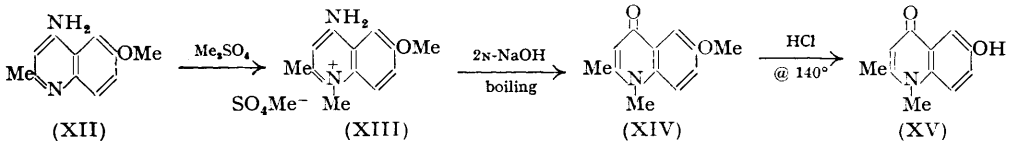
Certain transformations of 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII) illustrate the nature of such quaternary salts. With cold alkali, it gave the base (XI or XI*a*), and treatment with hydriodic acid reconstituted the original quaternary salt, thus



indicating that the latter could equally well be regarded as the hydriodide of a dihydro-imino-derivative (cf. 2-amino-1-methylquinolinium iodide, Chichibabin *et al.*, *Ber.*, 1921, **54**, 822).

By analogy with the quaternisation of (V) to (VII), the formula (III; X = I) seemed more likely than (IV; X = I) for substance B, and, following the success achieved with the model compound, attempts were made to determine its constitution by acid hydrolysis; despite much effort, no pyrimidine derivative could be isolated. The only product isolated, formed by concentrated hydrochloric acid at 200°, was 6-hydroxy-1 : 2-dimethylquinol-4-one (XV). The structure of this was confirmed by its synthesis from 4-amino-6-methoxy-2-methylquinoline (XII). This was accomplished *via* (XIII) and (XIV) as shown in the scheme. The formation of a 6-hydroxy- from a 6-amino-2-methylquinoline derivative by concentrated hydrochloric acid was further exemplified by the conversion, under similar conditions but at 200°, of 6-amino- into the same 6-hydroxy-1 : 2-dimethylquinol-4-one (XV).



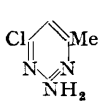
It thus appeared that determination of the constitution of substance B by degradative methods was likely to be difficult, and unambiguous synthetic routes were therefore investigated. This involved a study of the quaternisation of 2-amino-4-chloro-6-methylpyrimidine (XVI), the orientation of the quaternised derivatives, and their subsequent condensation with 4 : 6-diamino-1 : 2-dimethylquinolinium salts, so that linking through the 6-amino-group of the latter was effected.

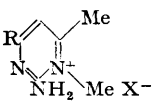
2-Amino-4-chloro-6-methylpyrimidine reacted with methyl iodide, either in a sealed tube at 115° or in solution in 2-ethoxyethanol at 85°. The crude quaternised pyrimidine obtained in both cases was a mixture of two or more compounds. The more soluble and major product, m. p. 261—262° (decomp.), was 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (XVII; R = Cl, X = I) because with concentrated hydrochloric acid at 160—170° for 12 hours or with boiling 8% sodium hydroxide for 8 hours it gave 1 : 6-

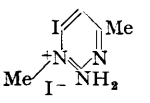
methyluracil (VI), and with aniline in aqueous solution in presence of a little hydrochloric acid it gave 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII). The less soluble component, m. p. 260° (decomp.), of the mixture had the empirical formula $C_6H_9N_3I_2$, and it appeared that replacement of chlorine by iodine had taken place with formation of a methiodide of 2-amino-4-iodo-6-methylpyrimidine. It was identified as the 3-methiodide (XVIII) because, on hydrolysis with boiling 2N-sodium hydroxide, 3 : 6-dimethyluracil (XIX) was formed. It condensed with aniline to give an isomer of (VII), which was therefore 2-amino-4-anilino-3 : 6-dimethylpyrimidinium iodide (XX).

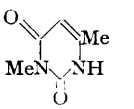
From quaternisation of (XVI) in 2-ethoxyethanol at 90—95° there was obtained in addition another apparent entity, m. p. 256° (decomp.), different from (XVIII) but having the same empirical formula. This was at first thought to be 2-amino-4-iodo-1 : 6-dimethylpyrimidinium iodide (XVII; R = X = I) but was later shown to be a mixture of this with (XVIII), since on condensation with aniline a mixture of (VII) and (XX) resulted. Since at a slightly lower temperature (85°) only 2-amino-4-chloro-1 : 6-dimethyl- and 2-amino-4-iodo-3 : 6-dimethyl-pyrimidinium iodide were formed, this would appear to indicate that quaternisation is the first reaction, followed by halogen exchange with methyl iodide, which presumably occurs more readily with 2-amino-4-chloro-3 : 6-dimethylpyrimidinium iodide than with the corresponding 1-methiodide. Such halogen exchanges are similar to that observed, *e.g.*, by Brydówna (*Rocz. Chem.*, 1932, **12**, 89; *Chem. Abs.*, 1933, **27**, 298) who obtained 4-iodo-1-methylquinolinium iodide from 4-chloroquinoline and methyl iodide.

Methyl sulphate similarly reacted with (XVI); in nitrobenzene at 80—90° it gave smoothly the methosulphate (XVII; R = Cl, X = SO_4Me), and addition of sodium iodide to its cold aqueous solution afforded 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide. If, however, the quaternisation was carried out at 100—110° another substance was also formed, which was shown to be anhydro-2-amino-3 : 6-dimethyl-4-sulphatopyrimidinium hydroxide (XXI) by analysis and by acid hydrolysis to the pyrimidone (XXII). This was identical with an authentic sample prepared by methylation of 2-amino-4-hydroxy-6-methylpyrimidine with excess of methyl iodide in alcoholic solution containing 1 equivalent of potassium hydroxide (Jaeger, *Annalen*, 1891, **262**, 369; Ganapathi *et al.*, *Proc. Indian Acad. Sci.*, 1942, **16**, *A*, 115), and proved to have this constitution by its hydrolysis to 3 : 6-dimethyluracil (Majima, *Ber.*, 1908, **41**, 180). Addition of sodium iodide to the aqueous layer after the separation of (XXI) precipitated the iodide (XVII; R = Cl, X = I).


(XVI)


(XVII)


(XVIII)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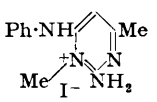
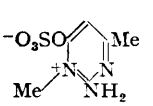
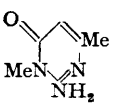
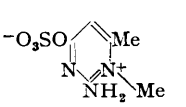

(XX)


(XXI)


(XXII)


(XXIII)

All attempts to isolate 2-amino-4-chloro-3 : 6-dimethylpyrimidinium methosulphate have failed but there is little doubt that it is a precursor of (XXI), and confirmation of its probable formation came from a quaternisation carried out at 80—90° which was worked up by extraction with water, and in which no formation of (XXI) was detected. After precipitation of the 1-methiodide with sodium iodide, the filtrates yielded 2-amino-3 : 6-dimethylpyrimid-4-one.

2-Amino-4-chloro-1 : 6-dimethylpyrimidinium methosulphate underwent an almost quantitative decomposition at 200° into methyl chloride and anhydro-2-amino-1 : 6-dimethyl-4-sulphatopyrimidinium hydroxide (XXIII).

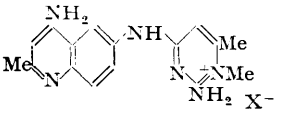
Whereas alkaline hydrolysis of 2-amino-4-chloro-1 : 6-dimethyl- and of 2-amino-4-iodo-3 : 6-dimethyl-pyrimidinium iodide afforded the corresponding dimethyluracils, partial hydrolysis was effected by boiling with water. With the former compound the

solution developed acidity, but if it was buffered at pH 4—6, 2-amino-1 : 6-dimethylpyrimid-4-one semihydriodide gradually separated. Under similar conditions, (XVIII) gave 2-amino-3 : 6-dimethylpyrimid-4-one, though hydrolysis was not so easy.

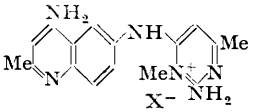
Although the products derived from 2-amino-4-chloro-6-methylpyrimidine and quaternising agents are referred to as quaternary salts, they, like the corresponding 4-anilino-derivatives, can also be regarded as the salts of the corresponding dihydroiminopyrimidines. Rapid hydrolysis has, however, in this case prevented the isolation of the corresponding bases.

When (XVII; R = Cl, X = I) was condensed with 4 : 6-diamino-1 : 2-dimethylquinolinium chloride hydrochloride in boiling water, (III; X = Cl) was obtained. This salt, and the corresponding di-iodide and dibromide, were sparingly soluble in water, whereas the dimethosulphate (III; X = SO_4Me) was very soluble. When the chloride (III; X = Cl) was heated with methyl sulphate in nitrobenzene at 95—100° methyl chloride was evolved and the dimethosulphate remained suspended in the nitrobenzene. 2-Amino-4-chloro-1 : 6-dimethylpyrimidinium iodide was also condensed with 4 : 6-diamino-2-methylquinoline in the presence of hydrochloric acid to give the chloride hydrochloride (XXIV; X = Cl). Proof that the pyrimidinium moiety was linked through the amino-group in the 6-position of the quinoline nucleus was obtained by condensing (XVII; R = Cl, X = I) with 6-amino-4-methoxy-1 : 2-dimethylquinolinium iodide to give 6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-4-methoxy-1 : 2-dimethylquinolinium di-iodide which, on treatment with alcoholic ammonia in presence of ammonium chloride at 140°, gave (III; X = I).

The formation of (XVIII) along with (XVII; R = Cl, X = I) in the quaternisation of (XVI) with methyl iodide allowed the preparation of analogous compounds quaternised in the 3-position of the pyrimidine ring. Thus by reaction of (XVIII) with 4 : 6-diamino-1 : 2-dimethylquinolinium chloride hydrochloride, and isolation of the product as the iodide there was obtained the di-iodide (IV; X = I). In contrast to its isomer (III), (IV) was converted into the corresponding base 4-amino-6-(2 : 3-dihydro-2-imino-3 : 6-dimethyl-4-pyrimidylamino)[or 4-amino-6-(2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-pyrimidylimino)]-1 : 2-dimethylquinolinium iodide by sodium carbonate. By condensation with 4 : 6-diamino-2-methylquinoline, (XVIII) gave the hydrochloride of (XXV; X = I).

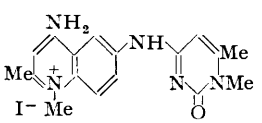


(XXIV)



(XXV)

Alkaline hydrolysis of (III) gave two different products according to experimental conditions. Refluxing for 20 minutes with 1 equiv. of sodium hydroxide gave a compound, m. p. 305°, which was considered to be 4-amino-6-(1 : 2-dihydro-2-keto-1 : 6-dimethyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (XXVI) on account of its non-identity with the isomeric 6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinol-4-one iodide (XXVII), m. p. 306°, which was prepared by condensing 6-amino-1 : 2-



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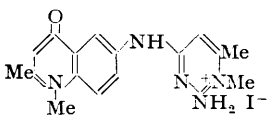
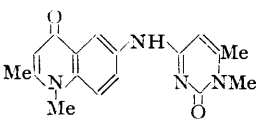


(XXVII)



(XXVIII)

dimethylquinol-4-one with 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide. By an excess of boiling aqueous sodium hydroxide, (III) was converted into (XXVIII), which was also produced by alkaline hydrolysis of (XXVII).

The synthesis by unambiguous routes, and the characterisation, of a number of the possible quaternary derivatives of (I) greatly facilitated the further study of the products of the direct quaternisation reaction. It became clear that substance B and (III; X = I)

were not identical, the former probably being a mixture. When it was converted into the corresponding chloride, and this was treated with sodium carbonate, the resulting mixture was more readily separated, and gave, from aqueous solution, 4-amino-6-(2-amino-1 : 6-dimethylpyridinium-4-amino)-1 : 2-dimethylquinolinium dichloride (III; X = Cl) as the least soluble component. A more soluble product was isolated as the iodide, and identified as (II; X = I).

The quaternisation of (I) with methyl sulphate gave, according to the conditions, either the monoquaternary salt (II; X = SO_4Me) or the diquaternary salt (III; X = SO_4Me).

Experimental

Quaternisation of 4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-2-*methylquinoline* (I) *with Methyl Iodide.*—(*a*) The base (I) (10 g.), methyl iodide (17·5 c.c.), and alcohol (125 c.c.) were boiled under reflux on the steam-bath for 6 hours. Complete solution was never obtained but the mixture became thick and pink. After cooling, the solid was filtered off, washed with acetone, and dried (13·2 g.); it had m. p. 296—298° (Found: I, 38·0%). This solid (11·2 g.) was crystallised from 50% alcohol, and the mother-liquors (A) retained. The crystalline product (5·4 g.) had m. p. 314—316° (Found: I, 28·5%) and after two further crystallisations from 50% alcohol gave 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (2·8 g.), m. p. 322—323°, as described in Part I (*loc. cit.*).

The mother-liquors (A) were evaporated to dryness to give an orange residue (5·7 g.) (Found: I, 40·1%). This was dissolved in hot water, and the solution made alkaline to Brilliant-yellow with ammonia and salted out with sodium iodide. The precipitated product was collected, washed with acetone, and dried (5·35 g.) (Found: I, 42·0%). This material (4 g.) was crystallised twice from 75% alcohol to give a new *dihydrate* (substance B) (0·45 g.), m. p. 300—301° unchanged on further crystallisation (Found: C, 33·7; H, 4·5; N, 14·2; I, 42·5. $C_{17}H_{22}N_6I_2,2H_2O$ requires C, 34·0; H, 4·5; N, 14·0; I, 42·5%).

(*b*) The base (I) (2·5 g.), methyl iodide (2·5 g.), and alcohol (15 c.c.) were heated together in a sealed tube at 100° for 16 hours. After cooling, the contents of the tube were filtered off and crystallised from 50% alcohol to give the *monohydrate* of substance B, m. p. 300—301° unaltered by further crystallisation and undepressed on admixture with the material described in (*a*) (Found: C, 35·3; 34·8; H, 4·7; 4·4; N, 14·5; 14·4; I, 43·6. $C_{17}H_{22}N_6I_2,H_2O$ requires C, 35·1; H, 4·2; N, 14·45; I, 43·6%).

Separation of the Constituents of Substance B.—Substance B (10 g.) was dissolved in hot water (700 c.c.), and concentrated hydrochloric acid (8·2 c.c.) added. The precipitate, which was filtered off after cooling, still contained iodine, and was therefore freed from iodine by redissolving it in water and salting it out with sodium chloride (yield, 5·9 g.). A sample of this product was reconverted into the di-iodide by treating the aqueous solution with sodium iodide. The above chloride (5·0 g.) was dissolved in water (150 c.c.), and sodium carbonate added until the mixture was alkaline (Brilliant-yellow). The precipitate was collected and extracted with hot water (35 c.c.). The aqueous extract was treated with sodium iodide and cooled, and the product separated. After further recrystallisation from water it had m. p. 326°, undepressed on admixture with 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide. The solid residue from the extraction with hot water was purified by repeated crystallisation from a larger volume of hot water to give 4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium dichloride (III; X = Cl), m. p. 316—317° (decomp.) alone or mixed with an authentic specimen (see p. 67).

2-*Amino*-4-*anilino*-1 : 6-*dimethylpyrimidinium Iodide* (VII).—2-Amino-4-anilino-6-methylpyrimidine (2 g.) (Banks, *loc. cit.*), alcohol (12 c.c.), and methyl iodide (3 c.c.) were refluxed together for 18 hours, the mixture cooled, and the product filtered off. Crystallisation from alcohol gave the *iodide* (VII) as colourless, flat, rectangular prisms (2·6 g.), m. p. 250° (Found: C, 42·5; H, 4·6; N, 16·6; I, 36·9. $C_{12}H_{15}N_4I$ requires C, 42·1; H, 4·4; N, 16·4; I, 37·1%).

When a solution of the above methiodide (2 g.) in warm water (300 c.c.) was cooled and made alkaline to Clayton-yellow with sodium hydroxide, the corresponding *base* (XI or XI*a*) was precipitated. Recrystallised from aqueous alcohol, it formed colourless needles, m. p. 229—230° (Found: C, 67·5; H, 6·5; N, 25·6. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·5; N, 26·2%). This base was dissolved in dilute hydriodic acid, and the solution made alkaline to Brilliant-yellow with sodium carbonate and treated with sodium iodide, giving the original quaternary salt, m. p. and mixed m. p. 250°.

Acid Hydrolysis of 2-*Amino*-4-*anilino*-1 : 6-*dimethylpyrimidinium Iodide* (VII).—(*a*) The

above methiodide (1 g.) and 9% aqueous hydrochloric acid were heated in a sealed tube at 118—120° for 12 hours. The mixture was filtered, and the filtrate made alkaline with sodium hydroxide. The precipitated product was washed with water and crystallised from aqueous alcohol to give 4-*anilino*-1 : 6-*dimethylpyrimid*-2-*one* (VIII) (0·4 g.) as colourless cubes, m. p. 298—299° (Found : C, 66·8; H, 6·0; N, 19·6. $C_{12}H_{13}ON_3$ requires C, 66·9; H, 6·0; N, 19·5%).

(*b*) The iodide (VII) (1 g.) and concentrated hydrochloric acid (10 c.c.) were heated at 170—180° for 14 hours, diluted with water, and made alkaline with sodium hydroxide. After filtration from a little precipitated material the filtrate was extracted with chloroform, the aqueous layer being retained (A). The chloroform extract was extracted with 3·5% aqueous hydrochloric acid, and the extract treated with sodium nitrite and coupled with alkaline β-naphthol to give benzeneazo-β-naphthol, m. p. and mixed m. p. 131° after crystallisation from alcohol. The aqueous layer (A, above) was acidified with hydrochloric acid and evaporated to dryness. The residue was extracted thoroughly with boiling methanol, the extracts were evaporated to dryness, and the residue was triturated with cold chloroform, dried, and sublimed in a high vacuum at 140—180°. The sublimate was extracted with boiling alcohol (2 c.c.), and the filtered extract allowed to cool. The product which separated crystallised in colourless needles, m. p. 221—222° undepressed on admixture with authentic 1 : 6-dimethyluracil (Found: C, 51·1; H, 5·3; N, 20·0. Calc. for $C_6H_8O_2N_2$: C, 51·4; H, 5·7; N, 20·0%).

Alkaline Hydrolysis of 2-*Amino*-4-*anilino*-1 : 6-*dimethylpyrimidinium Iodide*.—Sodium hydroxide solution (40% ; 30 c.c.) was added to a solution of this iodide (10 g.) in water (30 c.c.), and the resulting suspension was boiled under reflux for 16 hours. Ammonia was evolved, and the originally flocculent precipitate became granular. This crystallised from aqueous ethanol in cubes (2·1 g.), m. p. 298—299°, identical with the pyrimidone (VIII) described above. The alkaline filtrate was extracted with chloroform, and the aqueous solution acidified with hydrochloric acid and evaporated to dryness. The residue was heated to 140—180°/0·3 mm.; a colourless material sublimed, which crystallised from ethanol in needles, m. p. 221—222°, identical with the 1 : 6-dimethyluracil described above. The chloroform extract was extracted with acid, and the aniline obtained was identified as above (benzeneazo-β-naphthol, m. p. 131°).

4-*Anilino*-6-*methyl*-2-*methylthiopyrimidine* (IX).—Aniline (4 g.), 4-chloro-6-methyl-2-methylthiopyrimidine (7 g.) (Wheeler and MacFarland, *loc. cit.*), and glacial acetic acid (50 c.c.) were heated on the steam-bath with stirring for 45 minutes with concentrated hydrochloric acid (3 drops). The solution was cooled, diluted with water (150 c.c.) and neutralised to Brilliant-yellow with sodium hydroxide. The solid *pyrimidine* (IX) crystallised from a small volume of ethanol in colourless plates (8·5 g.), m. p. 129—131° (Found : C, 62·2; H, 5·55; N, 18·65. $C_{12}H_{13}N_3S$ requires C, 62·2; H, 5·6; N, 18·2%).

4-*Anilino*-1 : 6-*dimethyl*-2-*methylthiopyrimidinium Iodide* (X).—The preceding compound (IX) (5 g.), methyl iodide (7·5 c.c.), and alcohol (30 c.c.) were boiled together under reflux for 12 hours. The *iodide* (X) was filtered off, after cooling, and recrystallised from alcohol as colourless needles, m. p. 240° (decomp.) (Found : C, 42·0; H, 4·7; N, 11·3. $C_{13}H_{16}N_3IS$ requires C, 41·9; H, 4·3; N, 11·3%).

Hydrolysis. The iodide (X) (2 g.) and concentrated hydrochloric acid (30 c.c.) were refluxed together for 6 hours. Methanethiol was evolved. The resulting solution was cooled, filtered, and made alkaline with sodium hydroxide. The precipitated product was washed with water and crystallised from aqueous alcohol to give 4-anilino-1 : 6-dimethylpyrimid-2-one (0·9 g.), m. p. and mixed m. p. 298—299° (Found : C, 67·0; H, 5·9; N, 19·6. Calc. for $C_{12}H_{13}ON_3$: C, 66·9; H, 6·0; N, 19·5%).

Acid Hydrolysis of Substance B.—Substance B (3 g.) was heated with concentrated hydrochloric acid in a sealed tube at 200° for 12 hours. The solid product was separated and crystallised from water to give pale yellow needles of 6-*hydroxy*-1 : 2-*dimethylquinol*-4-*one*, m. p 333° (0·2 g.) (Found : C, 69·35; H, 5·6; N, 7·6. $C_{11}H_{11}O_2N$ requires C, 69·7; H, 5·8; N, 7·4%), identical with that described below.

4-*Amino*-6-*methoxy*-1 : 2-*dimethylquinolinium Methyl Sulphate* (XIII).—4-Amino-6-methoxy-2-methylquinoline (3·5 g.) was dissolved in dry nitrobenzene (40 c.c.) at 90—95°, and methyl sulphate (2·4 g.) added; the mixture was stirred for 1 hour at 90—95°, cooled, and filtered, and the precipitate was washed with benzene and crystallised from ethanol to give fine colourless needles of the *sulphate* (XIII), m. p. 262—263° (5·4 g.) (Found : C, 49·45; H, 5·7; N, 9·1. $C_{13}H_{18}O_5N_2S$ requires C, 49·6; H, 5·7; N, 8·9%).

6-*Methoxy*-1 : 2-*dimethylquinol*-4-*one*.—To a solution of the foregoing salt (XIII) (4·5 g.) in water (30 c.c.), 8% sodium hydroxide (20 c.c.) was added, and the solution was boiled for 2 hours, ammonia being evolved. After cooling, the precipitate was collected, washed with cold water,

and recrystallised from water to give colourless needles of a hydrated form of 6-*methoxy*-1 : 2-*dimethylquinol*-4-*one* (XIV), m. p. 84° (2·0 g.), which lost water at 100°, giving the anhydrous compound, m. p. 149—150° (Found, in substance dried *in vacuo* at 80° : C, 70·9; H, 7·1; N, 6·9. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%).

6-*Hydroxy*-1 : 2-*dimethylquinol*-4-*one*.—(*a*) The methoxyquinolone (XIV) (1·2 g.) was heated with concentrated hydrochloric acid in a sealed tube at 140—150° for 12 hours. The product was dissolved in water and made alkaline with ammonia, giving pale yellow needles of the hydroxyquinolone (0·7 g.), m. p. 333° (Found : C, 69·4; H, 6·15; N, 7·15. Calc. for $C_{11}H_{11}O_2N$: C, 69·7; H, 5·8; N, 7·4%).

(*b*) 6-Amino-1 : 2-dimethylquinol-4-one (0·7 g.) (see Part I) was heated with concentrated hydrochloric acid (10 c.c.) at 200° for 12 hours. The dark brown suspension was evaporated to dryness, and the resultant solid was recrystallised from water made alkaline by ammonia, to give pale yellow needles of 6-hydroxy-1 : 2-dimethylquinol-4-one, m. p. 333°, identical with the product described in (*a*).

Quaternisation of 2-*Amino*-4-*chloro*-6-*methylpyrimidine* (XVI) *with Methyl Iodide*.—(*a*) The pyrimidine (XVI) (19·2 g.) and methyl iodide (8·8 c.c.) were heated at 115° ± 3° for 6 hours. The resulting pale cream-coloured solid (34 g.) was finely powdered and extracted with boiling ethyl acetate (200 c.c.), and the insoluble material (26·9 g.) collected. Evaporation of the ethyl acetate extract and crystallisation of the residue gave unchanged (XVI) (6·4 g.), m. p. and mixed m. p. 178—179°. The material insoluble in ethyl acetate was separated by fractional crystallisation from water into two constituents. The more soluble, 2-*amino*-4-*chloro*-1 : 6-*dimethylpyrimidinium iodide* (XVII; R = Cl, X = I), separated from water as pale cream-coloured plates, m. p. 261—262° (decomp.) (Found : C, 25·2; H, 3·4; N, 14·4%; 1 mg. ≡ 1·332 mg. of Ag halides. $C_6H_9N_3ClI$ requires C, 25·2; H, 3·15; N, 14·7%; 1 mg. ≡ 1·326 mg. of Ag halides). The less soluble constituent, 2-*amino*-4-*iodo*-3 : 6-*dimethylpyrimidinium iodide* (XVIII), crystallised from water, in which it was sparingly soluble, as small colourless plates, m. p. 260° (decomp.) (Found : C, 19·4; H, 2·4; N, 10·7; I, 67·3. $C_6N_9N_3I_2$ requires C, 19·1; H, 2·4; N, 11·1; I, 67·3%). When the reaction was carried out at a slightly lower temperature (112° ± 3°) for 3 hours, very little quaternisation occurred and 86% of the pyrimidine was recovered unchanged.

(*b*) The pyrimidine (XVI) (50 g.), methyl iodide (24 c.c.), and 2-ethoxyethanol (130 c.c.) were heated in a water-bath at 85° ± 5° for 18 hours; (XVI) gradually dissolved, and pale cream-coloured crystals separated. After cooling, the product was collected and extracted with boiling ethyl acetate (200 c.c.) to remove unchanged material. The insoluble residue (44 g.) was extracted with boiling water (300 c.c.) and filtered hot. The residue crystallised from a large volume of water to give the iodide (XVIII) (4·25 g.), m. p. and mixed m. p. 260° (decomp.). The above hot aqueous extract, on cooling, deposited pale cream-coloured plates (25·4 g.) which crystallised from water to give pure 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (15·5 g.), m. p. and mixed m. p. 261—262° (decomp.).

Quaternisation of 2-*Amino*-4-*chloro*-6-*methylpyrimidine* (XVI) *with Methyl Sulphate*.—(*a*) A mixture of methyl sulphate (80 c.c.) and nitrobenzene (150 c.c.) was heated to 80—85° with agitation. 2-Amino-4-chloro-6-methylpyrimidine (100 g.) was gradually added (1 hour), the temperature being kept at 80—90°. After a further ½ hour's stirring at this temperature the mixture was cooled and the crystalline product which had separated washed well with acetone (yield, 58%). A small sample was rapidly crystallised from alcohol and dried in a vacuum, to give 2-*amino*-4-*chloro*-1 : 6-*dimethylpyrimidinium methyl sulphate* (XVII; R = Cl, X = SO_4Me) as pale cream-coloured needles, m. p. 155—157° (decomp.) (Found : C, 31·2; H, 4·5; N, 15·6. $C_7H_{12}O_4N_3ClS$ requires C, 31·15; H, 4·45; N, 15·6%). It is extremely soluble in water. Treatment of an aqueous solution with sodium iodide precipitated the corresponding quaternary iodide, m. p. and mixed m. p. 261—262° (decomp.).

(*b*) After reaction as above, the cooled mixture was treated with water (125 c.c.) and then benzene (125 c.c.), and the aqueous layer was separated and carefully neutralised with sodium hydroxide. Unchanged pyrimidine (9 g.) was precipitated, and filtered off. The filtrate was heated to 70°, and sodium iodide (75 g.) added. On cooling, 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide crystallised, and was washed with alcohol [yield, 53%; m. p. and mixed m. p. 261—262° (decomp.)]. The filtrate was evaporated somewhat under diminished pressure; the solid (24·5 g.) which separated was crystallised from water and identified as 2-amino-3 : 6-dimethylpyrimid-4-one, m. p. 318° undepressed on admixture with material made by the method of Ganapathi *et al.* (*loc. cit.*).

(*c*) After reaction as above, but at 100—110°, water (300 c.c.) and benzene (100 c.c.) were

added, and a white solid separated. This was collected (3 g.), dissolved in dilute sodium carbonate solution, and reprecipitated with hydrochloric acid. Crystallisation from a very large volume of water gave *anhydro-2-amino-3 : 6-dimethyl-4-sulphatopyrimidinium hydroxide* (XXI) as a white powder, m. p. 339—340° (Found: C, 33·0; H, 4·3; N, 19·3; S, 14·4. $C_6H_9O_4N_3S$ requires C, 32·8; H, 4·1; N, 19·15; S, 14·6%), insoluble in all the usual organic solvents. The original aqueous layer was separated from the benzene–nitrobenzene layer and neutralised to pH 7·5 with sodium hydroxide to precipitate unchanged material (13%). This was filtered off, and the filtrate treated with sodium iodide (73 g.) at 70° to give (XVII; R = Cl, X = I) (43%) which, crystallised from water, had m. p. and mixed m. p. 261—263°.

Hydrolysis of (XXI). The anhydro-hydroxide (XXI) (2 g.), water (10 c.c.), and sulphuric acid (7 c.c.) were heated together at 145° for 1½ hours, and the solution cooled and neutralised with sodium hydroxide. It was then evaporated to dryness, and the residue extracted several times with boiling alcohol. The combined extracts deposited a solid on cooling which, recrystallised from alcohol, gave 2-amino-3 : 6-dimethylpyrimid-4-one (XXII), m. p. and mixed m. p. 316—318°.

Anhydro-2-amino-1 : 6-dimethyl-4-sulphatopyrimidinium Hydroxide (XXIII).—The methosulphate (XVII; R = Cl, X = SO_4Me) (50 g.) in a 200-c.c. Kjeldahl flask was plunged into an oil-bath at 200°. The issuing gas was collected in a trap cooled to −79° (solid carbon dioxide–methanol). When gas evolution had ceased (*ca.* 15 min.), the product was cooled to below 100°, and water (150 c.c.) added. Complete solution was momentarily obtained, followed by rapid crystallisation. Recrystallisation of the product from water gave the *anhydro*-compound (XXIII) as colourless crystals (13 g.), m. p. 334—336° (decomp.) (Found: C, 30·6; H, 4·7; N, 17·8. $C_6H_9O_4N_3S,H_2O$ requires C, 30·3; H, 4·65; N, 17·7%), insoluble in the usual organic solvents. The gas evolved during the reaction was identified as methyl chloride (yield, 95%), b. p. −25°.

Hydrolysis of 2-Amino-4-chloro-1 : 6-dimethylpyrimidinium Iodide (XVII; R = Cl, X = I).—(a) *With acid.* The iodide (1 g.) and concentrated hydrochloric acid (10 c.c.) were heated together in a sealed tube at 160° ± 5° for 12 hours, then filtered, and the filtrate was neutralised with sodium hydroxide and evaporated to dryness. The powdered residue was extracted with boiling absolute alcohol (3 × 25 c.c.), and the alcoholic extracts were combined and evaporated to 3 c.c. The crystalline material which separated on cooling recrystallised from alcohol, giving colourless laminæ, m. p. 219—220° undepressed in admixture with authentic 1 : 6-dimethyluracil made by Behrend and Thurn's method (*Annalen*, 1902, **323**, 166).

(b) *With alkali.* The iodide (XVII; R = Cl, X = I) (2·86 g.) and 8% aqueous sodium hydroxide (20 c.c.) were boiled under reflux for 8 hours. Ammonia was evolved. After cooling, the solution was neutralised with hydrochloric acid and evaporated to dryness in a vacuum. The residual solid was finely ground and extracted with boiling absolute alcohol (2 × 25 c.c.), and the combined alcoholic extracts were treated with carbon and evaporated to small bulk. The crystalline 1 : 6-dimethyluracil which separated (0·5 g.), when crystallised from alcohol, had m. p. and mixed m. p. 220°.

(c) *With water.* The iodide (20 g.) and water (100 c.c.) were refluxed together for 5 hours with gradual addition of sodium hydrogen carbonate to keep the solution at pH 4—6. A yellow solid gradually separated. This was collected and purified, first by dissolution in water followed by salting out with sodium iodide, and then by crystallisation from water to give practically colourless crystals of 2-amino-1 : 6-dimethylpyrimid-4-one semihydriodide (see Part III, to be published), m. p. and mixed m. p. 284—285°.

Hydrolysis of 2-Amino-4-iodo-3 : 6-dimethylpyrimidinium Iodide (XVIII).—(a) *With alkali.* The iodide (3·77 g.) and 8% aqueous sodium hydroxide (30 c.c.) were boiled under reflux for 3 hours. Ammonia was slowly evolved. The resulting solution was neutralised with hydrochloric acid, filtered, and evaporated to dryness in a vacuum. Extraction of the residue with boiling alcohol (2 × 30 c.c.), evaporation of the combined extracts to dryness, and crystallisation of the residue from a little water gave long, thin prisms, m. p. 261—262°, undepressed by authentic 3 : 6-dimethyluracil made by Wheeler and McFarland's method (*loc. cit.*).

(b) *With water.* The iodide (1·2 g.) and water (25 c.c.) were boiled under reflux for 4·25 hours. The acidity to Congo-red which developed was neutralised by periodic addition of sodium hydrogen carbonate. After cooling, the mixture was filtered from unchanged material (0·3 g.), m. p. and mixed m. p. 258—259° (decomp.), and made alkaline to Clayton-yellow with sodium hydroxide. The precipitated product was collected and crystallised from water to give 2-amino-3 : 6-dimethylpyrimid-4-one (0·33 g.), m. p. 316—318° undepressed on admixture with authentic material.

Condensation of the Iodide (XVII; R = Cl, X = I) *with Aniline.*—This iodide (5·72 g.) was dissolved in boiling water (50 c.c.), aniline hydrochloride (2·6 g.) added, and the mixture refluxed for 1 hour. The product which separated on cooling was collected and dissolved in water (50 c.c.), and the solution filtered and salted with potassium iodide. The precipitated material crystallised from water to give 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII) (5·35 g.), m. p. 250° alone or on admixture with material described above.

4-*Amino*-6-(2-*amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-1 : 2-*dimethylquinolinium Salts* (III).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloride (13 g.) and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (14·3 g.) were boiled in water (350 c.c.) for ½ hour. The product, which soon began to separate, was collected after cooling, washed with N-hydrochloric acid (50 c.c.), and then with water (50 c.c.), and dissolved in hot water (800 c.c.); the solution (carbon) was filtered, and excess of sodium chloride added to the filtrate. The product so obtained was collected, but as it contained traces of iodide, it was redissolved in hot water (900 c.c.), and a mixture of hydrochloric acid (20 c.c.) and water (30 c.c.) added. The precipitated product was washed acid-free with water and crystallised from water to give the *dichloride* (III; X = Cl) as colourless needles (16·65 g.), m. p. 316—317° (decomp.) (Found: C, 49·2; H, 6·5; N, 19·6; Cl, 16·9. $C_{17}H_{22}N_6Cl_2,2H_2O$ requires C, 48·9; H, 6·2; N, 20·1; Cl, 17·0%). The corresponding "*di-iodide*," prepared by dissolving the above dichloride in hot water and salting it out with excess of sodium iodide, crystallised from water as colourless needles, m. p. 312—313° (decomp.) (Found: C, 33·8; H, 4·0; N, 13·8. $C_{17}H_{22}N_6I_2,2H_2O$ requires C, 34·0; H, 4·3; N, 14·0%). When this quaternary salt was first made it was the *monohydrate*, m. p. 301—302° (decomp.) (Found: C, 34·8; H, 4·3; N, 14·4; I, 43·2. $C_{17}H_{22}N_6I_2,H_2O$ requires C, 35·05; H, 4·1; N, 14·4; I, 43·6%), but subsequently this form could not be obtained either when the compound was made in the above manner or from the quinolinium iodide hydriodide and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide. The *dibromide* (III; X = Br), prepared from the above dichloride by dissolving it in hot water and adding sodium bromide, crystallised from water as colourless needles, m. p. 316° (decomp.) (Found: C, 41·7, 41·4; H, 5·2, 4·9; N, 17·1, 16·9; Br, 32·4. $C_{17}H_{22}N_6Br_2,H_2O$ requires C, 41·8; H, 4·9; N, 17·2; Br, 32·8%).

Conversion of (III; X = Cl) *into the Corresponding Dimethosulphate.*—The dihydrate of (III; X = Cl) (62 g.) was suspended in nitrobenzene (400 c.c.) and toluene (200 c.c.) and freed from water by azeotropic distillation. Toluene (100 c.c.) was then distilled off, and the mixture cooled to 50°. Methyl sulphate (previously neutralised over potassium carbonate) (41 g.) was added. and the mixture heated at 100° until gas evolution (methyl chloride) was complete (*ca.* 3 hours). After cooling, the product was collected and washed with methanol (100 c.c.). The crude product thus obtained was suspended in methanol (600 c.c.), and the mixture refluxed for 1½ hours, 2N-Sodium carbonate (*ca.* 4 c.c.) was then added gradually to the hot suspension until a sample dissolved in water to give a soluton at pH 6. The suspension was then cooled, and the product collected and dried to give the dimethosulphate (III; X = SO_4Me), m. p. 265—266°, undepressed on admixture with material described on p. 70.

4-*Amino*-6-(2-*amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-2-*methylquinoline Salts* (XXIV).—4 : 6-Diamino-2-methylquinoline (2·6 g.) was dissolved in a hot mixture of 2N-hydrochloric acid (22·5 c.c.) and water (7·5 c.c.), a solution of 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (4·3 g.) in hot water (30 c.c.) added, and the mixture boiled for 1 hour. After cooling, the product was collected and crystallised first from water and then from aqueous 2-ethoxyethanol to give the *hydrochloride* of the iodide (XXIV; X = I) as pale cream-coloured needles, m. p. 260—262° (Found: C, 37·9; H, 5·2; N, 16·4%; 1 mg. ≡ 0·726 mg. Ag halides. $C_{16}H_{19}N_6I,HCl,3H_2O$ requires C, 37·5; H, 5·1; N, 16·4%; 1 mg. ≡ 0·738 mg. Ag halides). The corresponding *hydriodide* was obtained by dissolving this hydrochloride in hot water, making the solution just alkaline with 2N-sodium carbonate, and adding excess of potassium iodide. It separated from water as aggregates of short, cream-coloured needles, m. p. 290—292° (decomp.) (Found, in material dried at 90°: C, 34·0; H, 4·1; N, 14·5. $C_{16}H_{19}N_6I,HI,H_2O$ requires C, 33·8; H, 3·9; N, 14·8%. Found, in material dried at room temperature: C, 32·1; H, 4·4; N, 13·9; I, 41·8. $C_{16}H_{19}N_6I,HI,3H_2O$ requires C, 31·8; H, 4·3; N, 13·9; I, 42·1%). The *hydrochloride* of the chloride (XXIV; X = Cl) was obtained by dissolving the methiodide hydriodide in 2N-hydrochloric acid, and adding 2N-sodium carbonate solution to alkalinity (Brilliant-yellow) and then excess of sodium chloride; cream-coloured needles, m. p. 333° (decomp.) (Found: C, 44·4; H, 5·9; N, 19·6. $C_{16}H_{19}N_6Cl,HCl,3·5H_2O$ requires C, 44·6; H, 6·3; N, 19·5%), were obtained from aqueous alcohol.

6-*Amino*-4-*methoxy*-1 : 2-*dimethylquinolinium Iodide.*—6-Acetamido-4-methoxy-2-methyl-

quinoline (Jacini, *Gazzetta*, 1941, **71**, 53) (47 g.), methyl iodide (28·5 g.), and 2-ethoxyethanol (30 c.c.) were heated under reflux on the steam-bath for 2 hours. After cooling, the thick pasty mass was diluted with ethyl acetate (100 c.c.) and filtered, and the solid well washed with ethyl acetate. Repeated crystallisation from water gave *6-acetamido-4-methoxy-1 : 2-dimethylquinolinium iodide monohydrate* as pale fawn crystals (54 g.), m. p. 313° (Found : N, 7·7. $C_{14}H_{17}O_2N_2I,H_2O$ requires N, 7·2%).

The above product (30 g.) was boiled under reflux with 4N-hydrochloric acid (300 c.c.) for 30 minutes. The solution was then cooled and neutralised to pH 4 by the addition of sodium hydroxide solution. The solid which separated was collected and crystallised from water (2·5 l.) to yield the *iodide* of the 6-amino-compound as yellow needles, m. p. 248° (18 g.) (Found : C, 44·1; H, 4·55; N, 8·4. $C_{12}H_{15}ON_2I$ requires C, 43·65; H, 4·6; N, 8·5%).

6-(2-Amino-1 : 6-dimethylpyrimidinium-4-amino)-4-methoxy-1 : 2-dimethylquinolinium Di-iodide.—The above 6-acetamido-iodide (18·5 g.), the iodide (XVII; R = Cl, X = I) (14·0 g.), concentrated hydriodic acid (15 c.c.), and water (160 c.c.) were boiled under reflux for 1 hour, cooled, and filtered. The solid obtained was crystallised several times from water to give the required di-iodide as a *hemihydrate*, pale yellow crystals, m. p. 305° (22 g.) (Found : C, 37·0; H, 4·35; N, 11·6. $C_{18}H_{23}ON_5I_2,0·5H_2O$ requires C, 36·8; H, 4·1; N, 11·9%), sparingly soluble in ethyl alcohol and cold water but readily soluble in boiling water.

Conversion of 4-Methoxy- into 4-Amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium Di-iodide.—The methoxy-di-iodide (4·0 g.), 7% ammoniacal ethyl alcohol (25 c.c.), and ammonium chloride (4·0 g.) were heated in a sealed tube at 140° for 6 hours. After cooling, the tube contents were washed out with ethyl alcohol, the excess of ammonia boiled off, and after dilution with water the suspension was neutralised with hydriodic acid. The solid was dissolved in boiling water (300 c.c.), and excess of potassium iodide added. The precipitate was filtered off and crystallised from water, 4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium di-iodide (3·0 g.) being obtained as pale cream needles, m. p. 310° (decomp.) undepressed on admixture with material prepared as above (Found : C, 34·8; H, 4·4; N, 13·6. Calc. for $C_{17}H_{22}N_6I_2,H_2O$: C, 35·05; H, 4·1; N, 14·4%).

2-Amino-4-anilino-3 : 6-dimethylpyrimidinium Iodide (XX).—Aniline (1·8 c.c.) was added to a suspension of 2-amino-4-iodo-3 : 6-dimethylpyrimidinium iodide (3·77 g.) in water (30 c.c.), and the mixture boiled under reflux for 1 hour. Complete dissolution had not occurred when the product began to separate after a few minutes' boiling. After cooling, the crystalline *iodide* (XX) was collected, washed with a little cold water, and crystallised from water as colourless prisms, m. p. 273° (decomp.) (Found : C, 42·5; H, 4·4; N, 16·1. $C_{12}H_{15}N_4I$ requires C, 42·1; H, 4·4; N, 16·4%). When the above iodide was dissolved in water and treated with excess of 10% sodium carbonate solution, the corresponding base (*2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-phenyliminopyrimidine* or *4-anilino-2 : 3-dihydro-2-imino-3 : 6-dimethylpyrimidine*) was obtained; it crystallised from benzene as colourless rectangular plates, m. p. 220—221° (Found : C, 67·3; H, 6·8; N, 25·8. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·6; N, 26·2%), or from alcohol as colourless leaflets of the *semi-alcoholate* having the same m. p. (Found : C, 65·4; H, 7·2; N, 23·5. $C_{12}H_{14}N_4,0·5C_2H_6O$ requires C, 65·8; H, 7·2; N, 23·6%).

When a suspension of the above base (1·07 g.) in 5N-sodium hydroxide (25 c.c.) was boiled for 1 hour, only a faint trace of ammonia could be detected and the filtrate obtained after cooling, dilution with water (40 c.c.), and collection of the solid, showed a very slight positive test for diazotisable material. The solid recovered (1 g.) was unchanged material, m. p. and mixed m. p. 220—221°.

4-Amino-6-(2-amino-3 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium Di-iodide (IV; X = I).—*4* : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloride (13 g.), 2-amino-4-iodo-3 : 6-dimethylpyrimidinium iodide (18·85 g.) and water (150 c.c.) were refluxed together for 1 hour. The hot mixture was treated with sodium iodide and cooled, and the product (15·8 g.) collected. It was dissolved in hot water (500 c.c.), and the solution made alkaline to Brilliant-yellow with 2N-sodium carbonate (19·5 c.c.) and treated with excess of sodium iodide. The precipitated product, which was very sparingly soluble in water, crystallised from 40% aqueous alcohol to give *4-amino-6-(2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-pyrimidylimino)-1 : 2-dimethylquinolinium iodide* [or the corresponding imino-form] as yellowish prisms, m. p. 328° (decomp.) (Found : C, 46·8; H, 4·8; N, 18·9; I, 29·1. $C_{17}H_{21}N_6I$ requires C, 46·8; H, 4·8; N, 19·3; I, 29·1%). When the above base (2·5 g.) was dissolved in hot 1·3% aqueous hydriodic acid (60 c.c.), and the solution cooled, it gave the *di-iodide* (IV; X = I) which crystallised from water as clusters of pale cream-coloured, long, flat, rectangular prisms, m. p. 295° (decomp.) (Found : C, 36·5; H, 4·4; N, 14·7; I, 44·5. $C_{17}H_{22}N_6I_2$ requires C, 36·2; H,

3·9; N, 14·9; I, 45·0%). The di-iodide (12 g.) was converted into the corresponding *dichloride* by dissolving it in water (500 c.c.) and shaking it with excess of freshly precipitated silver chloride (20 g.) until the solution was free from iodide, followed by evaporation of the filtered solution to dryness under reduced pressure and crystallisation of the residue from 80% propanol (with the addition of a little hydrochloric acid on the first crystallisation); it formed pale cream-coloured tablets, m. p. 247° (decomp.) (Found: C, 48·1; H, 6·3; Cl, 16·7. $C_{17}H_{22}N_6Cl_2,2{\cdot}5H_2O$ requires C, 47·9; H, 6·3; Cl, 16·7%).

4-*Amino*-6-(2-*amino*-3 : 6-*dimethylpyrimidinium*-4-*amino*)-2-*methylquinoline Iodide* (XXV; X = I).—4 : 6-Diamino-2-methylquinoline dihydrochloride (1·3 g.) was refluxed with 2-amino-4-iodo-3 : 6-dimethylpyrimidinium iodide (1·9 g.) in water (130 c.c.) for 1 hour. The clear solution was cooled, made faintly alkaline with sodium carbonate, and treated with potassium iodide. The sticky precipitate so obtained slowly hardened and was crystallised from water, to give the *hydrochloride* of the iodide (XXV; X = I) as pale cream-coloured prismatic needles, m. p. 245—246° (Found: C, 37·9; H, 4·6; N, 16·7%; 1 mg. ≡ 0·688 mg. of Ag halides. $C_{16}H_{19}N_6I,HCl,2{\cdot}5H_2O$ requires C, 38·1; H, 5·0; N, 16·7%; 1 mg. ≡ 0·752 mg. of Ag halides).

6-(2-*Amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-1 : 2-*dimethylquinol*-4-*one Iodide* (XXVII).—6-Amino-1 : 2-dimethylquinol-4-one (1·95 g.), 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (3 g.), water (50 c.c.), and concentrated hydrochloric acid (1 c.c.) were refluxed for 1 hour. The resulting solution was treated with excess of sodium iodide and cooled. The product which separated, when crystallised from water and then from 50% alcohol, gave the *iodide* (XXVII) as colourless needles, m. p. 306° (Found: C, 42·4; H, 5·2; N, 14·4; I, 26·0. $C_{17}H_{20}ON_5I,2{\cdot}5H_2O$ requires C, 42·3; H, 5·2; N, 14·5; I, 26·3%).

6-(1 : 2-*Dihydro*-2-*keto*-1 : 6-*dimethyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinol*-4-*one* (XXVIII).—(*a*) The di-iodide (III; X = I) (2 g.) and 10% aqueous sodium hydroxide (70 c.c.) were refluxed for 3 hours. The product which had separated was washed with water and crystallised from 50% alcohol to give the *quinolone* (XXVIII) as colourless needles, m. p. >380° (Found: C, 60·7; H, 6·2; N, 16·9. $C_{17}H_{18}O_2N_4,1{\cdot}5H_2O$ requires C, 60·7; H, 6·2; N, 16·6%).

(*b*) The quinolone iodide (XXVII) (1 g.) was dissolved in boiling water (140 c.c.), 4% sodium hydroxide solution (3 c.c.) added, and the mixture refluxed for 1 hour. The product was collected hot, washed with water, and crystallised from 50% alcohol to give the same compound as in (*a*), m. p. >380° (Found: C, 60·7; H, 5·9; N, 16·8%). Light absorption in 1% hydrochloric acid: Max. 2980 Å, ε 32,920; min. 2650 Å, ε 8764.

4-*Amino*-6-(1 : 2-*dihydro*-2-*keto*-1 : 6-*dimethyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Iodide* (XXVI).—The di-iodide (III; X = I) (2 g.) was boiled under reflux with water (50 c.c.) and 4% aqueous sodium hydroxide (4 c.c.) for 20 minutes. The resulting precipitate was collected hot, washed with water, and crystallised from 50% alcohol, giving the *iodide* (XXVI) as practically colourless, short, stumpy needles, m. p. 305° (decomp.) (sintering at 200°) (Found: C, 43·3; H, 5·3; N, 14·5; I, 26·4. $C_{17}H_{20}ON_5I,2H_2O$ requires C, 43·0; H, 5·1; N, 14·8; I, 26·9%). Light absorption in 1% hydrochloric acid: Max. 3020 Å, ε 31,220; min. 2680 Å, ε 8806.

4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Methyl Sulphate* (II; X= SO_4Me).—(*a*) Anhydrous 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (I) (11·2 g.) was stirred with 2-ethoxyethanol (160 c.c.) and neutral methyl sulphate (5·3 g.) at room temperature for 4 days. The solid product was filtered off, washed with cold methanol, extracted with hot methanol (100 c.c.), and recrystallised twice from aqueous methanol to give the *methosulphate* (II; X = SO_4Me) as cream-coloured crystals, m. p. 278—279° (4·5 g.) (Found: C, 49·9; H, 5·35; N, 20·4; S, 7·8. $C_{17}H_{22}O_4N_6S$ requires C, 50·2; H, 5·4; N, 20·7; S, 7·9%). This was converted into the corresponding iodide, m. p. 313° (see Part I), by treating an aqueous solution with sodium iodide.

(*b*) The quinoline (I) (11·2 g.) was suspended in nitrobenzene (120 c.c.) and benzene (40 c.c.), and the mixture was freed from traces of water by azeotropic distillation, the benzene being finally distilled off until the temperature of the mixture rose to 145°. It was then cooled to 70°, and methyl sulphate (5·3 g.) was added during ½ hour. The temperature was kept at 70—75° for 18 hours, and the product then filtered off, washed with cold methanol, and recrystallised from aqueous methanol to give the same methosulphate (8·7 g.) as that in (*a*), m. p. and mixed m. p. 278—279°.

Diquaternisation of 4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-2-*methylquinoline with Methyl Sulphate.*—The quinoline (11·2 g.), suspended in nitrobenzene (120 c.c.) and benzene (40 c.c.), was dried by azeotropic distillation as described above, and methyl sulphate (10·25 g.)

was added at 100—105°. The reaction was slightly exothermic, and the temperature was kept at 120° for 3 hours. The mixture was cooled to 50° and filtered ; the residue was washed with cold methanol (100 c.c.), suspended in boiling methyl alcohol (100 c.c.), isolated again by filtration, thoroughly washed with boiling methyl alcohol, and finally crystallised from aqueous methyl alcohol (85% by volume) to give white crystals of 4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium di(methyl sulphate), m. p. 265—266° (10 g.) (Found : C, 42·6; H, 5·2; N, 16·1; S, 12·3. Calc. for $C_{19}H_{28}O_8N_6S_2$: C, 42·9; H, 5·27; N, 15·8; S, 12·05%).

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