*The Synthesis of Trypanocides. Part III.** 4-*Amino*-6-(4-*amino*-1 : 6-*dimethylpyrimidinium*-2-*amino*)-1 : 2-*dimethylquinolinium Salts and Related Compounds.*

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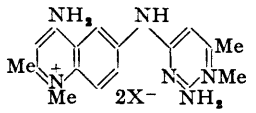
The preparation of analogues of " Antrycide " wherein a quaternised pyrimidine nucleus is linked through the 2-position to a quinolinium salt is described. The structure of the intermediate 4-amino-1 : 6-dimethylpyrimidinium iodides with a reactive group in the 2-position was established by hydrolysis to 1 : 6-dimethyluracil and that of 4-amino-2-chloro-1-methylpyrimidinium iodide by removal of the 2-chlorine atom to give 4-amino-1-methylpyrimidinium iodide.

In the investigation of compounds related to " Antrycide " salts [4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium salts] (I), it was desirable to study the compounds wherein a quaternised pyrimidine nucleus was linked through the 2-position to the 6-position of a 4 : 6-diamino-1 : 2-dimethylquinolinium salt, *e.g.* (II; R = R″ = Me, R = NH_2, X = I; and R = Me, R′ = NH_2, R″ = H, X = I). The unquaternised compound, 4-amino-6-(4-amino-6-methyl-2-pyrimidylamino)-2-methylquinoline (III), has been described (*J.*, 1953, 50) and the present communication describes the preparation of its quaternary derivatives and of related compounds.

Attempts were made to introduce two quaternary methyl groups directly into the base (III) by the action of methyl iodide and of methyl sulphate, but pure products were hard to obtain. So quaternary pyrimidine derivatives of type (IV; R = SMe or Cl, R′ = Me) were prepared, having a reactive group in the 2-position.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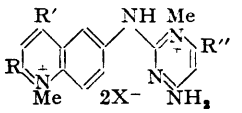
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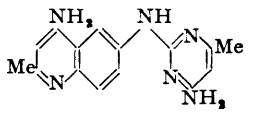
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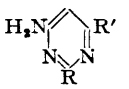
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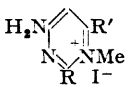
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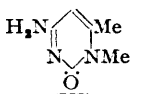
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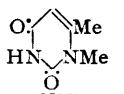
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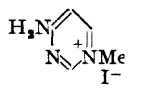

(VIII)

With methyl iodide in 2-ethoxyethanol under reflux, 4-amino-2-chloro-6-methylpyrimidine (IV; R = Cl, R′ = Me) (Gabriel and Colman, *Ber.*, 1899, **32**, 2921) gave 4-amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (V; R = Cl, R′ = Me). Careful crystallisation failed to show the presence of the 3 : 6-dimethyl isomer. The crude salt and the crystallised material were separately condensed with aniline, to give 4-amino-2-anilino-1 : 6-dimethylpyrimidinium iodide (V; R = NHPh, R′ = Me) in yields comparable in both quality and quantity. With methyl iodide in boiling methanol, 4-amino-2-anilino-6-

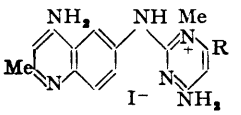
* Part II, *J.*, 1953, 59.

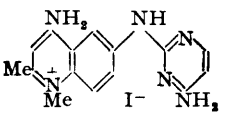
methylpyrimidine (IV; R = NHPh, R′ = Me) (Gabriel and Colman, *loc. cit.*) gave the same iodide (V; R = NHPh, R′ = Me). The structure of the chloro-compound (V; R = Cl, R′ = Me) was proved by a two-stage alkaline hydrolysis, first, to 4-amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI), and then to 1 : 6-dimethyluracil (VII), the constitution of which is well established (Behrend and Thurm, *Annalen*, 1902, **323**, 160; Behrend and Hesse, *ibid.*, 1903, **329**, 341).

The pyrimidinium salt (V; R = Cl, R′ = Me), with 4 : 6-diamino-1 : 2-dimethylquinolinium chloride in hot aqueous solution, gave, after conversion of the product into the iodide, 4-amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1 : 2-dimethylquinolinium di-iodide (II; R = R″ = Me, R′ = NH_2, X = I). With 4 : 6-diamino-2-methylquinoline and 6-amino-1-methylquinolinium iodide, it gave 4-amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-2-methylquinoline iodide (IX; R = Me) and 6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1-methylquinolinium di-iodide (II; R = R′ = H, R″ = Me, X = I) respectively.

An alternative intermediate was the pyrimidine with a labile 2-methylthio-group. With methyl iodide in methanol under reflux, 4-amino-6-methyl-2-methylthiopyrimidine (IV; R = SMe, R′ = Me) (Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41) gave 4-amino-1 : 6-dimethyl-2-methylthiopyrimidinium iodide (V; R = SMe, R′ = Me), this structure being established by hydrolysis by acid or alkali to 4-amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI). Attempts to replace the methylthio-group of the product (V; R = SMe, R′ = Me) by an anilino-residue were unsuccessful. Replacement by a quinoline residue was therefore not attempted.

The diquaternary salt (II; R = Me, R′ = NH_2, R″ = H, X = I) was prepared by heating 4-amino-2-chloro-1-methylpyrimidinium iodide (V; R = Cl, R′ = H) with 4 : 6-diamino-1 : 2-dimethylquinolinium iodide in aqueous acid. The pyrimidine derivative (V; R = Cl, R′ = H) was prepared by heating 4-amino-2-chloropyrimidine (IV; R = Cl, R′ = H) (Gabriel, *Ber.*, 1905, **38**, 1691) under reflux with methyl iodide in 2-ethoxyethanol and its structure proved by removal of the 2-chlorine atom to give 4-amino-1-methylpyrimidinium iodide (VIII) of proved constitution (see the following paper). The use of

(IX) 

 (X)

4 : 6-diamino-2-methylquinoline instead of 4 : 6-diamino-1 : 2-dimethylquinolinium iodide gave the monoquaternary salt (IX; R = H). An isomer of it, namely, (X), was similarly prepared from 4-amino-2-chloropyrimidine (IV; R = Cl, R′ = H) and 4 : 6-diamino-1 : 2-dimethylquinolinium iodide.

The quaternary pyrimidylaminoquinoline derivatives described above had a trypanocidal activity much lower than that of " Antrycide."

Experimental

4-Amino-2-chloro-1 : 6-dimethylpyrimidinium Iodide (V; R = Cl).—4-Amino-2-chloro-6-methylpyrimidine (Gabriel and Colman, *loc. cit.*) (28·5 g.), 2-ethoxyethanol (100 c.c.), and methyl iodide (27·2 c.c.) were heated under reflux for 6 hr. After cooling, the product was filtered off and washed with a small volume of 2-ethoxyethanol and with hot ethyl acetate. Thus prepared it had m. p. 198—200° (decomp.) and was pure enough for further work (yield, 32 g.). The *quaternary salt* was crystallised from hot water from which it separated as colourless prisms, m. p. 198—200° (decomp.) (Found : C, 25·05; H, 3·2; N, 14·4%; 1 mg. equiv. to 1·315 mg. of Ag halide. $C_6H_9N_3ClI$ requires C, 25·2; H, 3·2; N, 14·7%; 1 mg. equiv. to 1·28 mg. of Ag halide).

4-Amino-1 : 6-dimethyl-2-methylthiopyrimidinium Iodide (V; R = SMe).—4-Amino-6-methyl-2-methylthiopyrimidine (Hull *et al.*, *loc. cit.*) (7·75 g.), methyl iodide (6·2 c.c.), and methanol (100 c.c.) were heated under reflux for 15 hr. After cooling, the solid which had crystallised was filtered off and dried. Crystallisation from water gave the *quaternary salt* as needles, m. p. 258°

(decomp.) (Found : C, 28·3; H, 4·0; N, 14·65; I, 42·4. $C_7H_{12}N_3SI$ requires C, 28·3; H, 4·0; N, 14·1; I, 42·8%).

4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI).—4-Amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (1·0 g.) and N-sodium hydroxide (20 c.c.) were heated under reflux for 15 min. The *oxopyrimidine*, which separated on cooling, crystallised from water in colourless prisms, m. p. 340—342° (decomp.) (Found : C, 51·65; H, 6·2; N, 30·25. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%). The same compound was obtained by the action of boiling concentrated hydrochloric acid or of cold dilute alkali on 4-amino-1 : 6-dimethyl-2-methylthiopyrimidinium iodide.

Hydrolysis of 4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (VI).—4-Amino-1 : 2-dihydro-1 : 6-dimethyl-2-oxopyrimidine (1·0 g.) and N-sodium hydroxide (20 c.c.) were heated under reflux for 5 hr. The solution was filtered and the filtrate acidified with 2N-hydrochloric acid. The acid solution was evaporated to dryness in a vacuum, and the residue extracted with boiling, dry alcohol. The residue, after evaporation of the alcohol, was sublimed in a high vacuum (bath-temp. 140—150°). The sublimate crystallised from alcohol had m. p. 220°, undepressed on admixture with 1 : 6-dimethyluracil.

4-Amino-2-anilino-1 : 6-dimethylpyrimidinium Iodide (V; R = NHPh).—(*a*) 4-Amino-2-anilino-6-methylpyrimidine (3·0 g.), ethanol (10 c.c.), and methyl iodide (4·5 c.c.) were heated under reflux for 4 hr. The white *salt* which separated on cooling crystallised from water as rhombs, m. p. 266° (decomp.) (Found : C, 41·55; H, 4·4; N, 16·0; I, 36·55. $C_{12}H_{15}N_4I$ requires C, 42·1; H, 4·4; N, 16·4; I, 37·1%).

Addition of sodium hydroxide solution to an aqueous solution precipitated the anhydro-base (*2-anilino-1 : 4-dihydro-4-imino-6-methylpyrimidine*) which crystallised from chlorobenzene as colourless cubes, m. p. 230° (Found, in material dried in a vacuum at 100° : C, 67·15; H, 6·5. $C_{12}H_{14}N_4$ requires C, 67·2; H, 6·5%).

(*b*) 4-Amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (2·85 g.), aniline (0·95 g.), water (20 c.c.), and concentrated hydrochloric acid (3 drops) were heated under reflux for 1 hr. The solid, which separated on cooling, was filtered off and dissolved in water, and the solution made alkaline with aqueous sodium hydroxide. The precipitated solid was filtered off and, after drying, crystallised from chlorobenzene : it had m. p. and mixed m. p. 230—232°. The crude starting material as described above gave similar results.

4-Amino-2-chloro-1-methylpyrimidinium Iodide (V; R = Cl, R′ = H).—4-Amino-2-chloropyrimidine (Gabriel, *loc. cit.*) (2·85 g.), 2-ethoxyethanol (10 c.c.), and methyl iodide (1·5 c.c.) were heated under reflux for 5 hr. After cooling, the *quaternary salt* which separated was collected, washed with ethyl acetate, and purified by crystallisation from water, then having m. p. 202—204° (decomp.) (Found : C, 22·2; H, 2·6; N, 15·0. $C_5H_7N_3ClI$ requires C, 22·1; H, 2·6; N, 15·4%).

4-Amino-1-methylpyrimidinium Iodide (VIII).—4-Amino-2-chloro-1-methylpyrimidinium iodide (1·0 g.), hydriodic acid (55%; 10 c.c.), and red phosphorus (2·0 g.) were heated on the steam-bath for 45 min. After dilution with water (20 c.c.) and filtration, the filtrate was evaporated to dryness in a vacuum. The residue had m. p. 202—204° after crystallisation from alcohol–ethyl acetate, undepressed in admixture with 4-amino-1-methylpyrimidinium iodide.

4-Amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1 : 2-dimethylquinolinium Di-iodide (II; R = R″ = Me, R′ = NH_2, X = I).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride (2·6 g.), 4-amino-2-chloro-1 : 6-dimethylpyrimidinium iodide (2·8 g.), water (10 c.c.), and concentrated hydrochloric acid (1·0 c.c.) were heated under reflux for 1 hr. The solid which crystallised on cooling was dissolved in water and salted out with sodium iodide. The *quinolinium di-iodide* crystallised from water as flat prisms, m. p. 298—300° (decomp.) (Found : C, 33·9; H, 4·4; N, 14·35; I, 41·75. $C_{17}H_{22}N_6I_2,2H_2O$ requires C, 34·0; H, 4·3; N, 14·0; I, 42·3%).

Similarly, from 4 : 6-diamino-2-methylquinoline, *4-amino-6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-2-methylquinoline iodide* (IX), m. p. 254°, was obtained (Found : C, 41·35; H, 5·3; N, 18·05; I, 26·95. $C_{16}H_{19}N_6I,2·5H_2O$ requires C, 41·1; H, 5·1; N, 18·0; I, 27·2%). The use of 6-amino-1-methylquinolinium chloride gave *6-(4-amino-1 : 6-dimethylpyrimidinium-2-amino)-1-methylquinolinium di-iodide* (II; R = R′ = H, R″ = Me), m. p. 282° (decomp.) (Found : C, 34·0; H, 3·45; N, 12·05; I, 45·05. $C_{16}H_{19}N_5I_2,1·5H_2O$ requires C, 34·2; H, 3·9; N, 12·5; I, 45·2%).

Similar reactions of 4-amino-2-chloro-1-methylpyrimidinium iodide with 4 : 6-diamino-1 : 2-dimethylquinolinium iodide and 4 : 6-diamino-2-methylquinoline gave *4-amino-6-(4-amino-1-methylpyrimidinium-2-amino)-1 : 2-dimethylquinolinium di-iodide* (II; R = Me, R′ = NH_2, R″ =

H, X = I), m. p. 316—318° (decomp.) (Found: C, 33·0; H, 4·35; N, 14·9. $C_{16}H_{20}N_6I_2,H_2O$ requires C, 33·8; H, 3·9; N, 14·8%), and *4-amino-6-(4-amino-1-methylpyrimidinium-2-amino)-2-methylquinoline iodide hydriodide* (IX; R = H), m. p. >300° after crystallisation from water (Found: C, 31·3; H, 4·0; N, 14·4. $C_{15}H_{17}N_6I,HI$ requires C, 31·4; H, 3·8; N, 14·7%) respectively.

4-Amino-6-(4-amino-2-pyrimidylamino)-1 : 2-dimethylquinolinium Iodide Hydriodide (X).—4-Amino-2-chloropyrimidine (2·0 g.), 4 : 6-diamino-1 : 2-dimethylquinolinium iodide (4·85 g.), water (15 c.c.), and concentrated hydrochloric acid (1·0 c.c.) were heated under reflux for 1 hr. The *product* was filtered off and crystallised from water; it then had m. p. 340—342° (decomp.) (Found: C, 33·75; H, 3·2. $C_{15}H_{17}N_6I,HI$ requires C, 33·6; H, 3·4%).

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