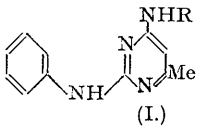
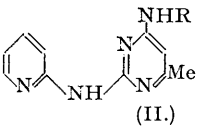
122. *Synthetic Antimalarials. Part XXVI. Pyridyl- and Pyrimidyl-aminopyrimidines.*

By F. H. S. Curd, W. Graham, and F. L. Rose.

Several pyrimidylamino- and pyridylamino-pyrimidines analogous to the anilinopyrimidines of earlier parts in this series of papers have been prepared for testing as antimalarial agents.

Some of the earlier contributions to this series of papers have been concerned with the chemical modification of substances of type (I), initially described in Part I (Curd and Rose, *J.*, 1946, 343),


(I.)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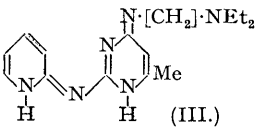
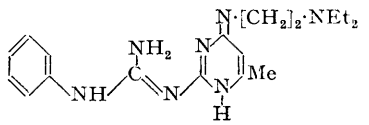
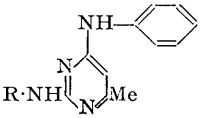

(III.)

in which the benzene ring was variously substituted and the R group was of the alkylaminoalkyl class. In all the modifications of this particular type, the benzene ring has been retained intact, although in two it has been incorporated into other cyclic systems, namely, naphthalene (Part V, Curd, Raison, and Rose, *J.*, 1946, 366) and quinoline (Part XXII, Curd, Graham, Richardson, and Rose, *J.*, to appear). Although the introduction of quinoline into the molecule provided analogues of (I) carrying a heterocyclic system attached to position 2 of the pyrimidine ring, yet the linkage to the quinoline nucleus was through amino-groups in positions 5, 6, and 8 of the latter; that is, the resulting substances were still substituted anilinopyrimidines. It appeared to be of interest therefore to investigate the preparation of analogues of (I) in which the heterocyclic grouping was directly substituted into the 2-amino-group of the pyrimidine. The most closely related compounds would be those in which the benzene ring was replaced either by pyridine or by a second pyrimidine nucleus. It was appreciated that antimalarial activity was most likely to be associated with those variants in which the new ring system carried substituents of the same class and in the same relative position as those which induce activity in the anilinopyrimidines, for example, *para* chlorine, but, because of the difficulties involved in the preparation of many such derivatives, use was made in the initial experiments of less favourable, but more readily available structures. Thus, 4-hydroxy-2-methylthio-6-methylpyrimidine (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) and 2-aminopyridine were condensed to form 2-(2′-*pyridylamino*)-4-*hydroxy*-6-*methylpyrimidine* which was converted into 4-*chloro*-2-(2′-*pyridylamino*)-6-*methylpyrimidine* with phosphoryl chloride. This chloropyrimidine was condensed with β-diethylaminoethylamine at 130° to give 2-(2′-*pyridylamino*)-4-β-*diethylamino-ethylamino*-6-*methylpyrimidine* (as II). The possible significance of prototropy in relation to the antimalarial activity of type (I) has been discussed in previous communications in this series (see Part XII, *J.*, 1947, 154). Structure (II, R = C_2H_4·NEt_2) possesses additional possibilities of this kind; for example, the form (III) which is analogous in some respects to one of the hypothetical tautomers (IV) of the 2-arylguanidino-4-aminoalkylamino-6-methylpyrimidine type described in Part IV (*J.*, 1946, 362), of which several members were notable for their marked antimalarial activity. Against that, it was appreciated that (IV) was not the particular tautomer considered to be biologically significant in this type since the conjugation within the molecule was only partial (see Part XII).

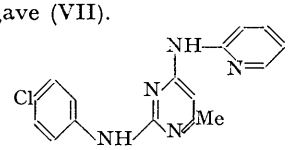
(IV.) 

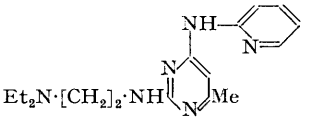

(V.)

In addition to the tautomeric features associated with 2-aminopyridine, it was considered that this basic structure might effectively replace the basic alkyl side chain of (I) and of its active isomer (V). For the preparation of substances (II, R = substituted Ph) corresponding to the latter type, the 4-chloro-2-(2′-pyridylamino)-6-methylpyrimidine described above was brought into reaction with *p*-nitroaniline and *p*-chloroaniline in boiling dilute hydrochloric acid solution to give (II, R = *p*-C_6H_4·NO_2) and (II, R = *p*-C_6H_4Cl) respectively.

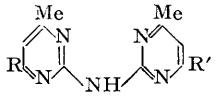
2-*p-Chloroanilino*-4-(2′-*pyridylamino*)-6-*methylpyrimidine* (VI), bearing the same relation to (I), was prepared by interaction of 2-aminopyridine and 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (Curd and Rose, *J.*, 1946, 349). 2-Aminopyridine and 4-chloro-2-β-diethyl-

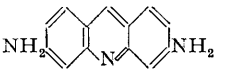
aminoethylamino-6-methylpyrimidine (Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 373) similarly gave (VII).

(VI.) 

 (VII.)

Unsuccessful attempts were made to condense 2-amino-4 : 6-dimethylpyrimidine in the same way with 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine and 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine, to give the dipyrimidylamines analogous to (VI) and (VII), but the preparation of isomeric (VIII, R = Me, R′ = NH·$[CH_2]_2$·NEt_2) was achieved by an indirect method involving total synthesis of the added pyrimidine ring. For this purpose 4-hydroxy-2-guanidino-6-methylpyrimidine (Crowther, Curd, and Rose, Part XXV, previous paper) prepared by the original method from 2-cyanoamino-4-hydroxy-6-methylpyrimidine and

(VIII.) 

 (IX.)

ammonia, and also by a new synthesis from diguanide and ethyl acetoacetate, was condensed in boiling acetic acid solution with acetylacetone to give 6′-*hydroxy*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine*. This with phosphoryl chloride gave the corresponding 6′-chloro-derivative which was then heated with β-diethylaminoethylamine to form (VIII, R = Me, R′ = NH·$[CH_2]_2$·NEt_2). The same chloropyrimidine served for the preparation of the simpler substance 6′-*dimethylamino*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine* by interaction with dimethylamine.

Condensation of 4-hydroxy-2-guanidino-6-methylpyrimidine with a further molecule of ethyl acetoacetate gave 6 : 6′-*dihydroxy*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine*. This, converted into the corresponding 6 : 6′-dichloropyrimidine by treatment with phosphoryl chloride, followed by reaction with dimethylamine and *iso*propylamine, gave (VIII, R = R′ = NMe_2) and (VIII, R = R′ = $NHPr^{\beta}$); these could be regarded as structurally related to 2 : 8-diaminoacridine (IX, "proflavine"), and for this reason they were examined by our colleague Dr. A. R. Martin for antibacterial activity. They were inactive, however, against the several organisms used in the test.

The final amino-derivatives were examined for antimalarial activity by our colleague, Dr. D. G. Davey, using chicks infected with *P. gallinaceum*. They were all inactive.

Experimental.

2-(2′-*Pyridylamino*)-4-*hydroxy*-6-*methylpyrimidine*.—The solid obtained by heating at 150—160° for 100 hours a mixture of 2-aminopyridine (14 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (Wheeler and Merriam, *loc. cit.*) (12 g.) was ground, heated at 100° under diminished pressure to remove unchanged 2-aminopyridine, and extracted with a little boiling benzene. The undissolved *hydroxypyrimidine* gave colourless fine needles, m. p. 172—173°, from methanol–benzene (Found: C, 59·6; H, 5·2; N, 27·9. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 4·95; N, 27·7%). After crystallisation twice from water the compound had m. p. 205—207° (Found: C, 59·3; H, 4·8; N, 27·5%), but it reverted to the lower-melting form after several recrystallisations from benzene.

4-*Chloro*-2-(2′-*pyridylamino*)-6-*methylpyrimidine*.—The above hydroxypyrimidine (11 g.) and phosphoryl chloride (45 c.c.) were heated for 4 hours in an oil-bath kept at 115—120°. Excess of phosphoryl chloride was removed under diminished pressure at 100°, the residue cooled, added to ice, and the precipitated solid dissolved in hydrochloric acid. Addition of ammonia gave the *chloropyrimidine* which after being washed and dried in a vacuum formed colourless prismatic rhombs (8·9 g.), m. p. 199—201°, from benzene (Found: C, 54·8; H, 4·2. $C_{10}H_9N_4Cl$ requires C, 54·5; H, 4·1%).

2-(2′-*Pyridylamino*)-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (II, R = C_2H_4·NEt_2) (6371).—The chloropyrimidine (3 g.) and β-diethylaminoethylamine (2·8 c.c.) were stirred for 10 hours at 130°. The melt was cooled, dissolved in dilute hydrochloric acid, made alkaline with sodium hydroxide, and the oil extracted into chloroform. The chloroform layer was washed with water, extracted with several lots of 5% acetic acid, and the acid extract basified with sodium hydroxide. The precipitated oil was re-extracted into chloroform, washed with water, dried (Na_2SO_4), and the solvent distilled off. The residual oil was converted into the *dihydrochloride* by evaporating to dryness a solution in dilutehydrochloric acid, and after repeated crystallisation from ether–ethanol formed hygroscopic colourless micro-needles (3 g.), m. p. 150°, resolidifying and melting at 239—241° (Found: C, 45·6; H, 7·2; N, 19·6; Cl, 17·2. $C_{16}H_{24}N_6,2HCl,2·5H_2O$ requires C, 45·9; H, 7·4; N, 20·1; Cl, 17·0%).

4-p-*Nitroanilino*-2-(2′-*pyridylamino*)-6-*methylpyrimidine* (II, R = *p*-C_6H_4·NO_2) (6373).—The solution obtained by boiling the above chloropyrimidine (2·85 g.), *p*-nitroaniline (1·78 g.), concentrated hydrochloric acid (1·5 c.c.), and water (15 c.c.), rapidly deposited a yellow solid. After 1 hour more

water (10 c.c.) and hydrochloric acid (1·5 c.c.) were added, and refluxing was continued for a further 1 hour. The precipitated *dihydrochloride* crystallised from 2-ethoxyethanol in fine yellow needles (4 g.), decomposing above 320° (Found: C, 47·3; H, 4·8; N, 20·5; Cl, 18·6. $C_{16}H_{14}O_2N_6$,2HCl,0·5H_2O requires C, 47·5; H, 4·3; N, 20·8; Cl, 17·6%).

4-p-*Chloroanilino*-2-(2′-*pyridylamino*)-6-*methylpyrimidine* (II, R = *p*-C_6H_4Cl) (6372).—Similarly prepared from the chloropyrimidine (2·9 g.), *p*-chloroaniline (1·7 g.), concentrated hydrochloric acid (1·45 c.c.), and water (15 c.c.), this formed a *dihydrochloride* which crystallised from dilute hydrochloric acid in colourless needles (4 g.), m. p. 268—270° (Found: C, 50·5; H, 4·15; N, 18·1; Cl, 27·4. $C_{16}H_{14}N_5Cl$,2HCl requires C, 49·9; H, 4·2; N, 18·2; Cl, 27·7%).

2-p-*Chloroanilino*-4-(2′-*pyridylamino*)-6-*methylpyrimidine* (VI) (6047).—The melt obtained by stirring for 10 hours at 125—135° a mixture of 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (Curd and Rose, *loc. cit.*) (16 g.) and 2-aminopyridine (7·9 g.) was cooled, dissolved in concentrated hydrochloric acid, treated with water, and left overnight. Extraction with hot ethanol of the crystalline precipitate left the *dihydrochloride* which recrystallised from dilute hydrochloric acid in colourless needles (4·5 g.), m. p. 284—287° (Found: C, 49·9; H, 4·2; N, 18·3; Cl, 27·5. $C_{16}H_{14}N_5Cl$,2HCl requires C, 49·9; H, 4·2; N, 18·2; Cl, 27·7%). The dihydrochloride with sodium hydroxide gave the free *base* which formed a colourless micro-crystalline powder from benzene, m. p. 143° (Found: C, 61·1; H, 4·6; N, 22·1. $C_{16}H_{14}N_5Cl$ requires C, 61·6; H, 4·5; N, 22·45%).

4-(2′-*Pyridylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (VII) (6046).—The solution from refluxing for 4 hours a mixture of 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (5·5 g.) (Curd, Davis, Owen, Rose, and Tuey, *loc. cit.*), 2-aminopyridine, 10N-hydrochloric acid (2·5 c.c.), and water (25 c.c.), gave an oil on addition of sodium hydroxide. This was worked up as described above for (II, R = C_2H_4·NEt_2) and converted into the *dihydrobromide* from which excess of water and hydrobromic acid were removed by repeated evaporation to dryness with ethanol–benzene. Repeated crystallisation from ethanol–ether gave hygroscopic colourless needles (2·5 g.) m. p. 150° (efferv.) (Found: C, 36·6; H, 6·2; N, 15·7; Br, 29·7. $C_{16}H_{24}N_6$,2HBr,3·5H_2O requires C, 36·6; H, 6·3; N, 16·0; Br, 30·45%).

4-*Hydroxy*-2-*guanidino*-6-*methylpyrimidine*.—Diguanide sulphate (43·4 g.) was dissolved with stirring in ethanol (50 c.c.) and 11N-sodium hydroxide (40 c.c.), ethyl acetoacetate (28·6 g.) added, and the mixture kept for 48 hours at laboratory temperature. Extraction of the precipitated solid with hot ethanol, then cold water, gave 4-hydroxy-2-guanidino-6-methylpyrimidine (26 g.), m. p. 302—304° (Found: C, 42·6; H, 5·5. Calc. for $C_6H_9ON_5$; C, 43·1; H, 5·4%), identical with that prepared by the method of Crowther, Curd, and Rose (Part XXV, *loc. cit.*).

6′-*Hydroxy*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine*.—4-Hydroxy-2-guanidino-6-methylpyrimidine (11·6 g.), acetylacetone (15 c.c.), and acetic acid (60 c.c.), refluxed for 8 hours, gave on dilution with water and addition of ammonia the *product* (13·8 g.) which formed colourless prisms from butanol, m. p. 266—267° (Found: C, 56·8; H, 6·05; N, 29·9. $C_{11}H_{13}ON_5$ requires C, 57·1; H, 5·7; N, 30·3%).

6′-*Chloro*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine*.—The above hydroxypyrimidine (8 g.) and phosphoryl chloride (16 c.c.), after being heated at 100° for ½ hour and added to ice and dilute ammonia, gave the solid *product* which, after being dried in a vacuum over sodium hydroxide (yield 7 g.), formed colourless prisms from acetone, m. p. 172—173° (Found: C, 52·9; H, 4·95; N, 27·45. $C_{11}H_{12}N_5Cl$ requires C, 52·8; H, 4·8; N, 28·0%).

6′-β-*Diethylaminoethylamino*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = Me, R′ = NH·C_2H_4·NEt_2) (3952).—The above chloropyrimidine (4·5 g.) and β-diethylaminoethylamine (10 c.c.) were heated for 1½ hours in an oil-bath kept at 130—140°. After removal of the excess of amine under diminished pressure at 100°, the residue was taken up in dilute acetic acid, and the oil obtained by adding sodium hydroxide was extracted into ether. The solvent was distilled off and the gummy residue dissolved in sufficient N-hydrochloric acid to give a faintly acid solution. Addition of sodium iodide (15 g.) precipitated the *dihydriodide* which, after recrystallisation from water (yield 4·3 g.), had m. p. 246—252°, and after further recrystallisation from ethanol formed pale yellow prisms, m. p. 247—250° (Found: C, 33·9; H, 5·7; N, 15·8. $C_{17}H_{27}N_7$,2HI,H_2O requires C, 33·8; H, 5·15; N, 16·2%).

6′-*Dimethylamino*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine* (6541).—The above chloropyrimidine (9·6 g.), dimethylamine (27 c.c. of 25% solution in water), and 2-ethoxyethanol (30 c.c.) were heated in a pressure bottle for 18 hours at 100°. The mixture was diluted with water (250 c.c.), made acid with acetic acid, filtered, and the filtrate evaporated to dryness. The residue was dissolved in water (50 c.c.), charcoaled, and potassium bromide (5 g.) added as a saturated solution. The precipitated *hydrobromide* was collected; after being twice recrystallised from ethanol, it formed colourless needles (7·7 g.), m. p. 288—290° (Found: C, 43·0; H, 6·05; N, 23·4; Br, 22·2. $C_{13}H_{18}N_6$,HBr,1·5H_2O requires C, 42·6; H, 6·0; N, 22·95; Br, 21·85%).

6 : 6′-*Dihydroxy*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = OH).—4-Hydroxy-2-guanidino-6-methylpyrimidine (8·4 g.), ethyl acetoacetate (9·6 g.), and sodium (4·6 g.) dissolved in methanol (150 c.c.) were mixed and refluxed for 16 hours. The precipitate which had formed dissolved on adding water (250 c.c.). The solution was treated with charcoal and made acid with acetic acid. The crude *product* (10·3 g.), which was precipitated, was taken up in dilute ammonia, filtered from a little insoluble solid, and reprecipitated with acetic acid. It was very sparingly soluble in the common organic solvents, melted with decomposition above 330°, and was used in the next stage of the reaction series without further treatment (Found: C, 48·05; H, 4·95; N, 27·45. $C_{10}H_{11}O_2N_5$,H_2O requires C, 47·8; H, 5·2; N, 27·9%).

6 : 6′-*Dichloro*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = Cl).—This *compound* was prepared from the dihydroxypyrimidine (12 g.) and phosphoryl chloride (20 c.c.) by heating for 2 hours at 100° and adding to ice and dilute sodium hydroxide. It formed pale yellow prisms (9·4 g.) from toluene, m. p. 178—179° (Found: C, 44·85; H, 3·55; N, 25·8. $C_{10}H_9N_5Cl_2$ requires C, 44·45; H, 3·3; N, 25·9%).

6 : 6′-*Bisdimethylamino*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = NMe_2) (6558).—Prepared by the method used for the 6′-dimethylamino-derivative described above, using the 6 : 6′-

dichloropyrimidine (10·5 g.), dimethylamine (40 c.c. of a 25% solution in water), and 2-ethoxyethanol (30 c.c.), precipitating the crude product from a clarified solution in dilute hydrochloric acid with sodium hydroxide, and crystallising from toluene, this *compound* formed colourless needles, m. p. 155—156°, which retained toluene after ½ hour in a vacuum at 100° (Found : C, 60·75; H, 7·2; N, 31·3. $C_{14}H_{21}N_7,\frac{1}{4}C_7H_8$ requires C, 61·0; H, 7·4; N, 31·6%).

6 : 6′-*Di*iso*propylamino*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = $NHPr^{\beta}$) (5141).—Similarly prepared from the dichloropyrimidine (2·7 g.) and *iso*propylamine (2·5 c.c.), this *compound* formed colourless prisms from toluene, m. p. 226—227° (Found : C, 60·4; H, 7·95; N, 30·8. $C_{16}H_{25}N_7$ requires C, 60·9; H, 7·95; N, 31·1%).

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