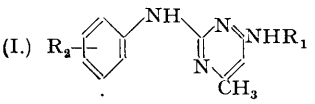
273. *Synthetic Antimalarials. Part XXXVIII.* 2-(6′-*Quinolylguanidino*)-4-β-*diethylaminoethylamino-* and 4-(6′-*quinolylguanidino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidines.*

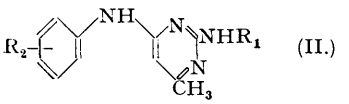
By (the late) J. M. Gulland and P. E. Macey.

Two quinolyl analogues of the phenylguanidinopyrimidines of Parts IV and XXV are prepared by similar methods.

Among the pyrimidine derivatives described in previous parts having significant antimalarial activity are compounds of types (I), (II), (III), and (IV); R_1 = basic alkyl, R_2 = one of many varied substituents and must usually be in the *p*-position.



(I.)



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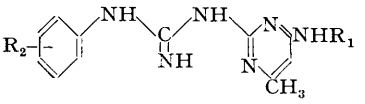

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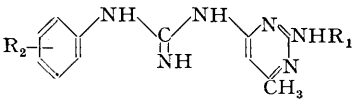
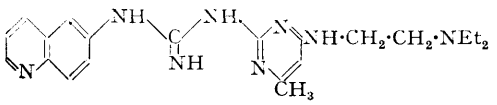


(IV.)

It might be expected that the *p*-substituted phenyl nucleus would be replaceable by a 6′-quinolyl group, to give compounds also of interest from the point of view of providing a link between the older quinoline antimalarials and those of the pyrimidine series. Curd, Graham, Richardson, and Rose (Part XXII, *J.*, 1947, 1613) have shown that this leads to retention of activity in the case of compounds of type (I) but not of type (II), a result which has not so far been explained, although, as the authors point out, it is in line with the case of the 6′-bromo-2-naphthylamino-compounds (Parts V and VI, *J.*, 1946, 366). In general it can be seen that, in active compounds of type (II), R_2 is always a strongly negative substituent such as chloro-, nitro- or cyano-, whereas in type (I) some activity results when R_2 is a group having a positive inductive effect or negative inductive and positive tautomeric effects. If this is significant it may be connected with the presence of a virtual guanidino-group in type (I), in which case the wider range of substituents might be permissible in both classes (III) and (IV).



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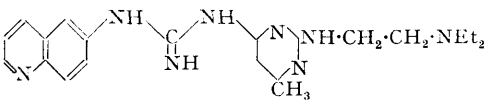
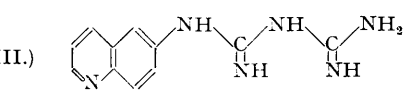


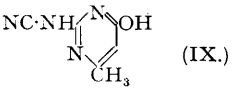
(VI.)

(V) and (VI) were therefore prepared by methods analogous to those used by Curd and Rose (Part IV, *J.*, 1946, 362) and Crowther, Curd, and Rose (Part XXV, *J.*, 1948, 586).

In the former case 6-aminoquinoline (VII) (Knueppel, *Annalen*, 1900, **310**, 84) reacted readily with dicyandiamide in hydrochloric acid to yield 6-diguanidoquinoline (VIII) which condensed with ethyl acetoacetate in sodium hydroxide solution giving 2-(6′-quinolylguanidino)-



(VIII.)



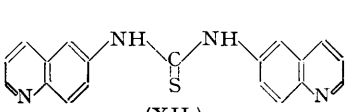
(IX.)

4-hydroxy-6-methylpyrimidine, an identical specimen of which was prepared by interaction of (VII) and 2-cyanamino-4-hydroxy-6-methylpyrimidine (IX) (Pohl, *J. pr. Chem.*, 1908, **77**, 533). This reacted successively with phosphoryl chloride and β-diethylaminoethylamine to yield (V).

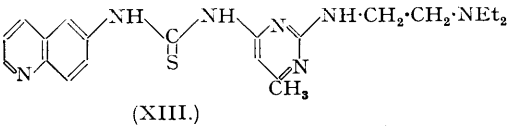
In the latter case 6-guanidinoquinoline was prepared from (VII) and cyanamide *via* the nitrate, but the yield was low and the product was difficult to obtain free from an unidentified red impurity. Reaction of (VII) with *S*-methyl*iso*thiouronium sulphate (Arndt, *Ber.*, 1921, **54**, 2236) gave a 50—60% yield of 6-guanidinoquinoline sulphate which was converted quantitatively into the free base. Attempts to condense this with 2-hydroxy-4-methylthio-6-methylpyrimidine (X) (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431) or 2-β-diethyl-

aminoethylamino-4-ethylthio-6-methylpyrimidine, prepared from sodium ethyl sulphide and 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (Part VI, *J.*, 1946, 370), were unsuccessful under various conditions. This work was done before the publication of Part XXV, in which Crowther, Curd, and Rose report that the condensation of *p*-chlorophenylguanidine with (X) required 48 hours in boiling *o*-dichlorobenzene, conditions more vigorous than were used here.

A much more satisfactory route to (VI) proved to be *via* 6-*iso*thiocyanatoquinoline (XI), which was prepared from (VII) and thiocarbonyl chloride after unsuccessful attempts from carbon disulphide. Under certain conditions (VII) and thiocarbonyl chloride yielded mainly the diquinolyl thiourea (XII), as found by Schönhöfer and Henecka (G.P. 583,207); this also resulted from the interaction of (VII) and (XI). (XI) reacted readily with 4-amino-2-β-diethylaminoethylamino-6-methylpyrimidine (Hull, Lovell, Openshaw, and Todd, Part XI, *J.*, 1947, 41), and the resultant thiourea (XIII) was converted into the guanidine (VI) by means of ammonia and mercuric oxide.



(XII.)



(XIII.)

Compounds (V), (VI), and (VII) were tested by Dr. D. G. Davey, of Imperial Chemical Industries Ltd. against *P. gallinaceum*.

Experimental.

6-Diguanidoquinoline Hydrochloride.—6-Aminoquinoline (8·0 g.), dicyandiamide (5·5 g.), concentrated hydrochloric acid (12·0 g.), and water (44 c.c.) were heated at 100° under reflux for 10½ hours, neutralised with concentrated ammonia solution and cooled. The *product* which separated recrystallised from water in colourless prisms, m. p. 258° (4·5 g.) (Found: C, 50·0; H, 5·2; N, 31·5. $C_{11}H_{12}N_6$,HCl requires C, 49·9; H, 4·95; N, 31·8%). It formed an alkaline solution in water. The *base* was precipitated by adding 5N-sodium hydroxide, and formed colourless plates from water, m. p. 165° (Found: C, 58·0; H, 5·4; N, 36·0. $C_{11}H_{12}N_6$ requires C, 57·9; H, 5·3; N, 36·8%).

2-(6′-Quinolylguanidino)-4-hydroxy-6-methylpyrimidine Dihydrochloride.—6-Aminoquinoline (15 g.), 2-cyanamino-4-hydroxy-6-methylpyrimidine (16 g.), concentrated hydrochloric acid (22·5 g.), and water (55 c.c.) were heated at 100° for 10½ hours. The yellow solution was cooled to 0° and treated with concentrated hydrochloric acid (36 c.c.) to complete precipitation of the *hydrochloride*. This dissolved in water at 40°, and, when the solution was made 10% with respect to hydrochloric acid, separated as fine colourless needles, m. p. 242° (Found: N, 22·0; Cl′, 18·7. $C_{15}H_{14}ON_6$,2HCl,H_2O requires N, 21·8; Cl′, 18·4%).

2-(6′-Quinolylguanidino)-4-hydroxy-6-methylpyrimidine.—(*a*) The crude hydrochloride above was dissolved in water at 40° and the *base* precipitated with excess of concentrated ammonia solution, dried, and digested with methanol; it then had m. p. 275° (yield 37% from 6-aminoquinoline). It formed colourless plates from nitrobenzene, m. p. 275° (Found: C, 61·0; H, 5·0; N, 28·6. $C_{15}H_{14}ON_6$ requires C, 61·2; H, 4·8; N, 28·6%).

(*b*) 6-Diguanidoquinoline hydrochloride (2·5 g.) and sodium hydroxide (0·7 g.) were dissolved in warm 92% ethanol (16 c.c.). Ethyl acetoacetate (3·0 c.c.) was added, and the solution left for 24 hours; it had then solidified to a white mass. After being washed with ethanol and water and digested with methanol it had m. p. 278°, not depressed by mixture with (*a*).

4-Chloro-2-(6′-quinolylguanidino)-6-methylpyrimidine.—2-(6′-Quinolylguanidino)-4-hydroxy-6-methylpyrimidine (11 g.) and phosphoryl chloride (22 c.c.) were heated under reflux in an oil-bath at 120—130° for 45 minutes to give a golden oil. This was poured on crushed ice (300 g.) containing sodium hydroxide (44 g.), the pale salmon-coloured precipitate was dissolved in warm 10% hydrochloric acid, and the solution was stirred with charcoal, filtered, and poured into excess of sodium hydroxide solution. The cream precipitate, roughly dried, was used for the next stage. It could be purified by passing down an alumina column in chloroform, and formed colourless needles from aqueous ethanol, m. p. 208° (Found: C, 58·0; H, 4·1. $C_{15}H_{13}N_6Cl$ requires C, 57·6; H, 4·2%). When the reaction mixture was poured on ice with no sodium hydroxide, the *hydrochloride* was obtained. This formed fine colourless needles from water on addition of hydrochloric acid (Found: C, 46·8; H, 4·3; Cl′, 18·0. $C_{15}H_{13}N_6Cl$,2HCl requires C, 46·7; H, 3·9; Cl′, 18·4%).

2-(6′-Quinolylguanidino)-4-β-diethylaminoethylamino-6-methylpyrimidine.—4-Chloro-2-(6′-quinolylguanidino)-6-methylpyrimidine (above yield), β-diethylaminoethylamine (6·0 g.), chlorobenzene (40 c.c.), sodium hydroxide (6·0 g.), and water (40 c.c.) were stirred and boiled under reflux for 45 minutes. The chlorobenzene and the excess of amine were removed in steam, and the brownish solid was collected and dissolved in N-acetic acid, and the solution was warmed with decolourising charcoal, filtered, and poured into iced sodium hydroxide solution. The precipitated cream solid became brown and sticky when collected. It was dried and extracted in a Soxhlet apparatus with ethyl acetate from which it formed colourless prisms, m. p. 196—197° (3·8 g.). The *product* recrystallised from acetone in colourless prisms, m. p. 197° (Found: C, 64·3; H, 7·0; N, 28·5. $C_{21}H_{28}N_8$ requires C, 64·2; H, 7·2; N, 28·6%).

2-β-Diethylaminoethylamino-4-ethylthio-6-methylpyrimidine.—Sodium (0·8 g.) was dissolved in

absolute ethanol (45 c.c.) and ethylthiol (2·5 c.c.) added, followed by 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (7·5 g.). The solution was refluxed for 1 hour, the solvent evaporated, water (80 c.c.) added, and the oil extracted with benzene, which was distilled off to leave a golden oil (8·1 g.). When cooled in solid carbon dioxide this crystallised but melted again at 16°. With excess of picric acid in ethanol, it formed a *picrate* which gave yellow prisms from ethanol, m. p. 158° (Found: S, 4·1. $C_{13}H_{24}N_4S,2C_6H_3O_7N_3$ requires S, 4·4%). Distillation in a vacuum yielded the pure *base* as a colourless oil which crystallised on standing; b. p. 105—115°/0·04 mm., m. p. 24° (Found: N, 20·9; S, 11·7. $C_{13}H_{24}N_4S$ requires N, 20·9; S, 11·9%).

6-*Guanidinoquinoline Sulphate*.—*S*-Methyl*iso*thiouronium sulphate (5·2 g.) and 6-aminoquincline (2·6 g.) were heated in an oil-bath at 160—180° for 2 hours. The cooled mass was digested with ethanol, and the light-brown solid collected, washed with ethanol and ether, and crystallised from water (500 c.c.) with a little decolourising charcoal. The *product* formed colourless, alum-shaped crystals from water, m. p. 302° (5·3 g.) (Found: SO_4'', 20·3. $C_{10}H_{10}N_4,\frac{1}{2}H_2SO_4$ requires SO_4'', 20·4%). The excess of amine could be recovered by precipitating the hydrochloride from the ethanol with concentrated hydrochloric acid.

6-*Guanidinoquinoline*.—(*a*) 6-Guanidinoquinolinium sulphate (5·9 g.) was triturated with 8% sodium hydroxide solution (80 c.c.) and the mixture of oil and water extracted continuously and exhaustively with ether. Evaporation of the solvent yielded the theoretical amount of the *base* which crystallised from acetone as colourless prisms, m. p. 175—176° (Found: C, 63·8; H, 5·0; N, 30·1. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%). (*b*) 6-Aminoquinoline (7·5 g.) and cyanamide (7·4 g.) were melted on a water-bath and then cooled. Concentrated hydrochloric acid (24 c.c.) was added down a funnel dipping below the surface and caused a violent reaction. When this had subsided 2N-nitric acid (50 c.c.) was added, and the solution, cooled in an ice-box, slowly deposited an orange-coloured solid (9·5 g.). This was dissolved in warm water, cooled somewhat, filtered free from the red solid which separated initially, cooled further, and scratched; light orange-coloured crystals then separated. These were recrystallised from water with decolourising charcoal and a little nitric acid as almost colourless long prisms, m. p. 185° (decomp.). Treated with 8% sodium hydroxide solution and extracted continuously with ether this yielded 6-guanidinoquinoline, m. p. 173° not depressed by mixture with specimen from (*a*). Heated with 1 molecular proportion of 2-β-diethylaminoethylamino-4-ethylthio-6-methylpyrimidine or 2-hydroxy-4-methylthio-6-methylpyrimidine for various times up to 12 hours and at temperatures up to 180°, 6-guanidinoquinoline caused the evolution of alkylthiol, but in all cases sulphur-containing mixtures were obtained and crystalline products could not be isolated.

6-iso*Thiocyanatoquinoline*.—Thiocarbonyl chloride (2·1 c.c.) was added in one portion to a vigorously stirred solution of 6-aminoquinoline (3·0 g.) in concentrated hydrochloric acid (1·8 c.c.) and water (35 c.c.). After 1¼ hours, by which time the smell of thiocarbonyl chloride had ceased, the yellow precipitate was filtered off and washed with water, in which it partly dissolved, and the filtrate and washings were poured into excess of iced sodium hydroxide solution. The white precipitate was collected, washed with sodium hydroxide solution and water, dried, and extracted exhaustively with light petroleum (b. p. 40—60°) in a Soxhlet apparatus. 6-iso*Thiocyanatoquinoline*, m. p. 94° (2·8 g.), separated from the extract. It formed colourless needles, m. p. 94°, when a solution in pyridine was diluted and cooled (Found: N, 14·8; S, 17·6. $C_{10}H_6N_2S$ requires N, 15·0; S, 17·2%).

NN′-*Di*-6′-*quinolylthiourea*.—6-*iso*Thiocyanatoquinoline was melted with 6-aminoquinoline (1 mol.) in a water-bath. The melt hardened to a white solid, m. p. 197°, which formed colourless prisms from methanol, m. p. 198° (Schönhöfer and Henecka, G.P. 583,207, give m. p. 199°; Haskelberg, *J. Org. Chem.*, 1947, **12**, 434, gives m. p. 217°) (Found: N, 16·7; S, 9·9. Calc. for $C_{19}H_8N_4S$: N, 17·0; S, 9·7%).

4-(6′-*Quinolylthioureido*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—4-Amino-2-β-diethylaminoethylamino-6-methylpyrimidine (3 g.) and 6-*iso*thiocyanatoquinoline (3 g.) were melted and heated on a water-bath for ½ hour. The resulting pale yellow solid was ground with benzene and heated again for ¼ hour after all the solvent had evaporated, then ground with more benzene, and collected; it then had m. p. 171° (4·7 g.). The *product* formed a mass of colourless needles from ethanol, m. p. 179—180° (Found: N, 23·6; S, 7·9. $C_{21}H_{27}N_7S$ requires N, 24·0; S, 7·8%).

4-(6′-*Quinolylguanidino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—4-(6′-Quinolylthioureido)-2-β-diethylaminoethylamino-6-methylpyrimidine (2·0 g.), dissolved in 12% (w/v) methanolic ammonia (60 c.c.), was stirred with yellow mercuric oxide (2·0 g.) for 4 hours at 35—40° under reflux. The black suspension was cooled and stirred with excess of dilute hydrochloric acid, and the rest of the mercury precipitated with sodium sulphide. The mercuric sulphide was filtered off, the cloudy filtrate centrifuged, and the centrifugate poured into excess of 2N-sodium hydroxide. The white solid precipitated (1·8 g., m. p. 193—194°) crystallised from 95% acetone as long colourless prisms, m. p. 200° (1·2 g.). Recrystallisation from benzene or 97% acetone then gave long colourless prisms, m. p. 198° (Found: C, 64·2; H, 6·9; N, 28·5. $C_{21}H_{28}N_8$ requires C, 64·2; H, 7·2; N, 28·6%).

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