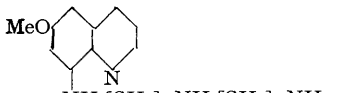
148. *Attempts to find New Antimalarials. Part XIX.*

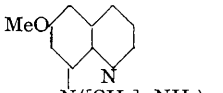
By W. L. Glen and Sir Robert Robinson.

New preparations of R. 63 (see preceding paper) have been made, and the high antimalarial activity confirmed by our biological colleagues. Fractionation of the meconates has afforded no specimen of higher activity and indeed a disconcerting result in some cases has been the reduction of activity in all fractions without traceable loss of material. No light has been shed on the nature of R. 63 by the synthesis of various substances that might have been produced in the formation reaction. A number of new antimalarials of the plasmoquin series have been prepared, including moderately long chains and, in some cases, amidine groups. One of these compounds is a potent antimalarial worthy of more extended biological examination.

R. 63 is obtained by a process which should be the γ-aminopropylation of 8-γ-aminopropylamino-6-methoxyquinoline. We have prepared a *meconate* which gave moderately satisfactory analytical figures for the dimeconate of 8-γ-aminopropyl-γ-aminopropyl-6-methoxyquinoline (I), but independent syntheses of this base (see the preceding and the following paper) have been effected and its salts are devoid of antimalarial properties.



(I)



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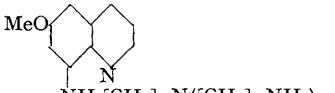


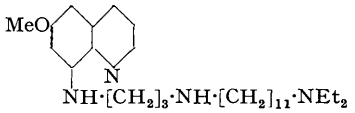
(III.)

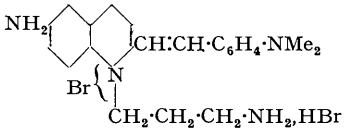
Whereas the indices of the hydrochloride and meconate of the analysed specimen were returned as 1 : 32, we describe a process of fractionation which has twice given a meconate with an index 1 : 64. This was also reported for the original specimen of R. 63 and for a specimen later prepared in the same way by Dr. D. C. Quin. It is certain that the active substance is not (II) or (III) and indeed the use of more than one equivalent of phthalo-γ-bromopropylimide leads to a product with greatly diminished activity.

In view of the consistent nitrogen content of active specimens it appeared improbable that a great departure from the structures (I) and (II) could be contemplated and this led us to study the demethylation of these bases. The results were of a negative character and further work in this direction is planned.

A problem somewhat similar to that of R. 63 is presented by R. 97 which, from its method of preparation, should be the meconate of (IV). The index was reported to be 1 : 62, but unfortunately the salts of the base could not be crystallised. With three methylene groups instead of eleven, the index of a similar crude preparation was 1 : 32. It is hoped that these substances may be prepared in a state of purity by the methods described in the following paper.

(IV.)





(V.)

The introduction of an amidine group into the side chain is described in the experimental section, but the products were weak antimalarials. The *bromide hydrobromide* (V) has been prepared by a series of reactions; it has no antimalarial properties, but is antiseptic and trypanocidal.

Experimental.

8-γ-*Phthalimidopropylamino*-6-*methoxyquinoline*.—The prescription of Baldwin (J., 1929, 2962) has been modified as follows: 8-Amino-6-methoxyquinoline (87 g.) and phthalo-γ-bromopropylimide (134 g.) were slowly heated to 100°, and when a homogeneous melt was obtained the temperature was cautiously raised to 110° and maintained for 20 minutes. Heat was generated and the temperature had to be carefully controlled. When the initial reaction had subsided, the mixture was heated (bath at 120°) for 10 hours. On cooling, an orange-yellow mass of mixed hydrobromides was obtained; this was powdered and extracted with a little alcohol to remove unchanged phthalo-γ-bromopropylimide. The salts were extracted with hot water and finally with dilute hydrochloric acid: 20—30% of aminomethoxyquinoline was recovered from the solutions. The insoluble residue was suspended in boiling alcohol, and pyridine slowly added until complete solution occurred (cf. the preceding paper). After 12 hours the product was collected, washed with a little alcohol, dried, and crystallised from alcohol containing a little pyridine; m. p. 100—101° (yield, 80 g.).

The alcohol–pyridine mother-liquor was diluted with a little water and kept for several days. The solid deposit was crystallised from a large volume of alcohol (yield, 10 g.) and obtained in small colourless needles, m. p. 166—167°, and proved to be diphthalimidopropyl-8-amino-6-methoxyquinoline (Found: C, 70·1; H, 5·1; N, 10·3. Calc. for $C_{32}H_{28}O_5N_4$: C, 70·0; H, 5·1; N, 10·3%).

An alcoholic solution of 8-γ-aminopropylamino-6-methoxyquinoline (Baldwin, *loc. cit.*) was treated with an excess of alcoholic meconic acid, and the precipitated *meconate* collected and extracted with boiling alcohol. The salt separated from aqueous alcohol (1 : 1) as an amorphous yellow powder, m. p. 165—166° (decomp.), soluble in hot alcohol, but readily soluble in hot water (Found: C, 50·2; H, 4·3; N, 6·7. $C_{13}H_{17}ON_3,2C_7H_4O_7,H_2O$ requires C, 50·0; H, 4·2; N, 6·5%).

R. 63.—8-γ-Aminopropylamino-6-methoxyquinoline (3 g.) and phthalo-γ-bromopropylimide (3·5 g.) were heated together at 115° for 7 hours. On cooling, a glassy mass was obtained, which was pulverised and obtained as a yellow powder (5·3 g.). The product was insoluble in ether, partly soluble in chloroform and in water, and completely soluble in boiling alcohol; the solutions deposited a sticky, intractable mass on cooling. A portion was basified, and the buff-coloured, sticky base converted into meconate, tartrate, and picrate, but these derivatives could not be crystallised.

A mixture of the crude hydrobromide (10 g.), alcohol (100 c.c.), and hydrazine hydrate (2 g.) was refluxed for 2 hours.

The solvent was removed, and the residue heated with excess of dilute hydrochloric acid for ½ hour on the steam-bath. Phthalhydrazide separated, and an orange-yellow solution was obtained, which was cooled in ice and filtered, and potassium carbonate added to form a pasty mass. This was extracted with chloroform, the extract dried, and hydrogen chloride passed into the filtered solution. The red hydrochloride which separated was washed with chloroform and dried over phosphoric oxide. It was a dark red, extremely deliquescent, amorphous substance which possessed a high antimalarial activity (Keilin) comparable with that of the product of Robinson and Tomlinson.

Exactly similar conditions were used for the condensation of 8-γ-aminopropyl-6-methoxyquinoline (1 mol.) with phthalobromopropylimide (*a*, 0·5; *b*, 1·0; *c*, 1·5 mols.). The crude hydrochlorides were dissolved in hot alcohol with exclusion of moisture. On cooling, a flocculent red precipitate separated, which was collected and washed with alcohol out of contact with the atmosphere. In each case a dark red powder was obtained, and the products were increasingly deliquescent as the proportion of phthalobromopropylimide was increased. The combined washings and mother-liquor from each experiment were evaporated to dryness in case they contained active material. The results of biological tests were as follows : Therapeutic indices, (*a*) 1 : 32, (*b*) 1 : 32, (*c*) 1 : 8 and indices of material recovered from mother-liquors (*a*) 1 : 16, (*b*) 1 : 16, (*c*) 1 : 4. In each case the activity of the material recovered from the mother-liquor was lower than that of the main product, indicating that active material had not been lost in the course of purification. As nothing was gained by variation of the proportions of the reagents, equivalent quantities were employed in all subsequent experiments.

The meconate was prepared from " R. 63 " base by treatment with an excess of hot alcoholic meconic acid. The precipitate was collected and washed with hot alcohol. It was an orange-yellow powder which darkened at 140—150°, and swelled and decomposed *ca.* 150—160°. Analysis showed that two molecules of meconic acid had combined with one of the base (Found : C, 49·5; H, 5·2; N, 7·9. $C_{16}H_{24}ON_4,2C_7H_4O_7,2H_2O$ requires C, 49·8; H, 5·0; N, 7·8%). This calculation is based on the assumption that the main product is an aminopropyl derivative of aminopropylaminomethoxyquinoline. On drying over phosphoric oxide in a high vacuum, 0·8322 g. lost 0·0384 g.; $2H_2O$ requires loss, 0·0414 g. (Found in anhydrous material : C, 52·9; H, 4·8; N, 8·5. $C_{16}H_{24}ON_4,2C_7H_4O_7$ requires C, 52·3; H, 4·7; N, 8·1%). The *meconate* was readily soluble in water, but non-deliquescent. The therapeutic index was 1 : 32 and therefore equal to that of the hydrochloride.

The *tartrate* was prepared in hot alcoholic solution, at once collected, washed with alcohol, and dried in a desiccator. It was obtained as a brownish-red amorphous powder, slightly deliquescent, and readily soluble in water (Found : C, 49·0; H, 6·4; N, 9·5. $C_{16}H_{24}ON_4,2C_4H_6O_6$ requires C, 49·0; H, 6·1; N, 9·5%). The index was reported as 1 : 8. The citrate also was prepared, but neither of these salts offered any advantage over the meconate.

8-γ-Aminopropylamino-6-methoxyquinoline (4·6 g.) and phthalo-γ-bromopropylimide (5·5 g.) were condensed as usual, and the R. 63 base solution saturated with potassium carbonate. The solution was extracted with chloroform (100 c.c.), and the base converted into meconate (i) (3·2 g.). Two more extractions (300 c.c.) and conversion into meconate gave (ii) (0·3 g.). (iii) (3·7 g.) was obtained similarly after addition of much solid potassium carbonate and exhaustive extraction. Fractions (i) and (ii) were orange-yellow powders and (iii) was somewhat darker in colour. This experiment was repeated (*b*) and Professor Keilin reports the following indices : (i *a*) and (i *b*), 1 : 64; (ii *a*) and (ii *b*), 1 : 32; (iii *a*), 1 : 4; (iii *b*), 1 : 8. Many similar fractionations have been carried out and always with the result that the highest activity (1 : 64) occurs in the base first extracted. Attempts to separate (i) into its constituents by treatment with solvents gave fractions which were all reported of lower activity than the original. In view of the possibility of the presence of hydrazine meconate in these specimens, the salt was prepared but, as expected, was found to be entirely devoid of antimalarial activity.

Further di-γ-phthalimidopropyl-8-amino-6-methoxyquinoline was hydrolysed by the hydrazine method, and the base converted into a meconate (Found : C, 55·5; H, 4·6; N, 7·4%). It was also bisaminopropylated and converted into meconate. Neither of these salts was a potent antimalarial (indices of both, 1 : 2).

Phthalo-ω-bromodecylimide.—A mixture of decamethylene dibromide (145 g.), powdered potassium carbonate (19 g.), and phthalimide (36 g.) was heated for 6 hours at 160—170°. The mass was cooled and extracted with hot water; on keeping, the oil solidified. Unchanged decamethylene dibromide was removed by extraction with successive quantities of alcohol at 30—40°. The product was extracted with light petroleum (Soxhlet), and *phthalobromodecylimide* (32 g., 35%) separated from the solution and crystallised from alcohol, forming small colourless prisms, m. p. 57—58° (Found : C, 59·8; H, 6·6; N, 3·9. $C_{18}H_{24}O_2NBr$ requires C, 59·0; H, 6·6; N, 3·8%). The residue in the thimble was crystallised from alcohol; m. p. 135—136° (6·5 g.) (Braun, *Ber.*, 1909, **42**, 4541, gives m. p. 136° for diphthalimidodecane); 30 g. of dibromodecane were recovered.

8-*ω-Phthalimidodecylamino*-6-*methoxyquinoline.*—A mixture of phthalo-ω-bromodecylimide (23 g.) and 8-amino-6-methoxyquinoline (13·5 g.) was heated at 100—110° for 24 hours. The orange-yellow crystalline mass was repeatedly extracted with hot water, and the residue triturated with aqueous sodium carbonate solution, washed with water, and extracted with ether. The ethereal extract was shaken with a little concentrated hydrochloric acid, and the resulting yellow precipitate of 8-*ω-phthalimidodecylamino*-6-*methoxyquinoline hydrochloride* collected and washed with ether. After crystallisation from alcohol, it had m. p. 151—153° (decomp.) (Found : C, 68·2; H, 7·0. $C_{28}H_{33}O_3N_3,HCl$ requires C, 67·8; H, 6·9%).

The crude hydrochloride was triturated with warm 10% sodium carbonate solution, and the free *base* obtained as a viscous oil which ultimately solidified on scratching and keeping. The substance was repeatedly crystallised from alcohol, and formed greenish-yellow prisms (9 g.), m. p. 83—84° (Found : C, 73·0; H, 7·1; N, 9·2. $C_{28}H_{33}O_3N_3$ requires C, 73·0; H, 7·2; N, 9·2%).

8-*ω-Aminodecylamino*-6-*methoxyquinoline Dihydrochloride* (R. 95; index, 1 : 7).—A solution of 8-ω-phthalimidodecylamino-6-methoxyquinoline (5·5 g.) and hydrazine hydrate (6·6 c.c.) in alcohol (80 c.c.) was refluxed for 2 hours; a colourless product then separated from the hot solution. The alcohol was evaporated, and the residue heated with an excess of 10% hydrochloric acid for ½ hour on the steam-bath. After standing for 12 hours, the filtrate from phthalhydrazide was basified and extracted with ether. The ethereal solution of the free base was dried, and the *dihydrochloride* precipitated in the usual manner (4 g., 83%). The salt was readily soluble in water, giving a clear orange-yellow solution which became turbid when much diluted, indicating hydrolysis. It crystallised from alcohol in orange-red prisms, m. p. 172° (Found : C, 59·5; H, 8·0; N, 10·1; Cl, 17·2. $C_{20}H_{31}ON_3,2HCl$ requires C, 59·6; H, 8·2; N, 10·4; Cl, 17·6%).

8-*ω-Aminodecyl-ω-aminodecylamino*-6-*methoxyquinoline.*—8-ω-Aminodecylamino-6-methoxyquinoline (1·8 g.) was heated with excess of phthalo-ω-bromodecylimide for 24 hours at 100—110°. The product was extracted several times with hot water and once with dilute hydrochloric acid, and the insoluble residue dried. The pulverised product was triturated with ether, then basified, and extracted with chloroform. After evaporation the residue (2·4 g.) was refluxed for 2 hours with hydrazine hydrate (0·3 c.c.) and alcohol (20 c.c.), then evaporated to dryness and heated on the steam-bath for ½ hour with an excess of dilute hydrochloric acid. The orange-red filtrate from phthalylhydrazide was treated with sodium carbonate and extracted with ether. The solvent was removed, and alcoholic meconic acid added. The orange-coloured *meconate* was collected and washed with warm alcohol, followed by ether, and finally dried in a desiccator. The product was readily soluble in water to an orange solution (Found : C, 60·7; H, 6·5; N, 6·8. $C_{30}H_{52}ON_4,2C_7H_4O_7$ requires C, 59·8; H, 6·8; N, 6·4%). The substance is a weak antimalarial.

8-*ω*-*Aminodecyl*-*γ*-*aminopropylamino*-6-*methoxyquinoline*.—A mixture of 8-*γ*-aminopropylamino-6-methoxyquinoline (1·5 g.) and phthalo-*ω*-bromodecylimide (3·1 g.) was heated for 24 hours at 100—101°. The product was repeatedly extracted with hot water until the extracts were almost colourless, and the process repeated with hot dilute hydrochloric acid. The residue was dried, washed with ether, basified, and extracted with ether. Dry hydrogen chloride was passed into the dried ethereal solution and the oily red hydrochloride obtained was collected, freed from ether, and basified with aqueous sodium carbonate. All attempts to obtain the base in solid form failed, so it was rendered to chloroform and dried, and the solution evaporated. The residual 8-*ω*-phthalimidodecyl-*γ*-aminopropylamino-6-methoxyquinoline (1·7 g.) was dissolved in alcohol (10 c.c.) and refluxed with an excess of hydrazine hydrate for 1½ hours; a solid then separated. The alcohol was distilled, and the residue heated with an excess of dilute hydrochloric acid for ½ hour on the steam-bath. The orange solution was filtered, made alkaline, and extracted with ether. The ethereal extract was dried, filtered, and excess of a cold, saturated solution of meconic acid in alcohol added. The *meconate* which separated was collected and washed with alcohol and ether. 0·5 G. of a yellow powder, m. p. 160—164°, was obtained (Found : C, 57·5; H, 6·4; N, 7·9. $C_{23}H_{38}ON_4,2C_7H_4O_7$ requires C, 56·4; H, 5·9; N, 7·1%). We have frequently found that meconates of known bases have anomalous compositions and an analysis such as this indicates the presence of less than the equivalent of meconic acid in the salt.

Condensation of 8-*γ*-*Aminopropylamino*-6-*methoxyquinoline and* 11-*Chloro*-1-*diethylaminoundecane Hydrochloride*.—Equivalent quantities of the two reactants were dissolved in a little alcohol and heated for 40 hours at 115—120° in a flask fitted with a short air-condenser. The product was dissolved in a small volume of chloroform, and cold alcoholic meconic acid added until precipitation of the meconate was complete. The product was collected and washed with alcohol, and the filtrate and washings set aside. The meconate was dissolved in a mixture of water (30 c.c.) and alcohol (20 c.c.), and the solution filtered. A yellow powder separated, which was collected, washed with alcohol, and dried. It melted at *ca.* 155°. This material was submitted to biological test (Fraction I) and proved to be a potent antimalarial (R. 97; index, 1 : 62).

The filtrate and washings were evaporated to dryness under reduced pressure, and the residue dissolved in water, basified, and extracted with ether. The ethereal extract was dried, and dry hydrogen chioride passed. The very hygroscopic, red hydrochloride which separated was washed with ether and dried (Fraction II). This material had only moderate antimalarial activity (R. 99; index. 1 : 8). Satisfactory analyses of these salts were not obtained.

Condensaiton of 8-*γ*-*Aminopropylamino*-6-*methoxyquinoline and* 3-*Chloro*-1-*diethylaminopropane Hydrochloride*.—8-*γ*-Aminopropylamino-6-methoxyquinoline (10·5 g.) and 3-chloro-1-diethylaminopropane hydrochloride (8·5 g.) (Magidson and Strukov, *Arch. Pharm.*, 1933, **271**, 572) were heated together at 110—120° for 48 hours. On cooling, an orange-red semi-solid mass was obtained, which was triturated with ether. basified, and extracted with chloroform. The extract was dried. filtered, and evaporated to dryness under reduced pressure. The residue was dissolved in hot alcohol and treated with an excess of meconic acid in the usual manner. The meconate was collected, washed with hot alcohol, and dried in a vacuum desiccator (R. 113). An amorphous yellow powder was obtained which decomposed between 160° and 165°. Attempts to fractionate a chloroform solution of the free base by adsorption on alumina were unsuccessful. R. 113 is a potent, non-toxic, antimalarial (index, 1 : 32).

Condensation of 8-*γ*-*Aminopropylamino*-6-*methoxyquinoline and* 2-*Bromo*-5-*diethylaminopentane Hydrobromide*.—Equivalent quantities (7·7 g. and 10 g. respectively) were heated together at 120° for 15 hours. The mixture was cooled, digested with warm dilute hydrochloric acid, basified, and extracted with chloroform. The solvent was removed from the dried extract, and the residue dissolved in alcohol, filtered, and treated with excess of alcoholic meconic acid solution. The meconate was collected, washed with alcohol, and dried; it was a yellow powder, m. p. 150—155° (decomp.) [R. 103; two fractions separated (*a*) from alcohol, (*b*) from water, indices of both, 1 : 32].

8-*γ*-p-*Acetamidobenzenesulphonamidopropylamino*-6-*methoxyquinoline*.—Equivalent quantities of 8-*γ*-aminopropylamino-6-methoxyquinoline and *p*-acetamidobenzenesulphonyl chloride were heated for 1 hour at 40—50° in dry chloroform solution. After 12 hours, the mixture was diluted with ether, the precipitated material collected and extracted with warm dilute hydrochloric acid, and the solution filtered and cooled. The filtrate was neutralised with dilute aqueous ammonia, and the precipitated base collected, thoroughly washed with water, and dried. Difficulty was experienced in crystallising the product; it was purified by solution in alcohol and reprecipitation with ether, the process being repeated several times. A dark brown *product*, m. p. 189°, was obtained (Found : C, 58·2; H, 6·1; N, 13·0. $C_{21}H_{24}O_4N_4S$ requires C, 58·8; H, 5·6; N, 13·1%).

The meconate, prepared in the usual manner, was readily soluble in water, and formed a yellow powder which darkened at 158° and decomposed between 158° and 168°.

11-*Diethylaminoundecanol*.—The method of Magidson and his collaborators (*Arch. Pharm.*, 1935, **273**, 320) was modified. A solution of ethyl 11-diethylaminoundecoate (20 c.c.) in ethyl alcohol (200 c.c.) was added very quickly to molten sodium (20 g.) in a flask (bath at 150°) fitted with a very efficient, wide condenser. After 20 minutes alcohol (100 c.c.) was added, followed, after another 20 minutes, by another 100 c.c. The mixture was refluxed for 1 hour.

The products of several such reductions were combined, and the mass cautiously diluted with water and steam-distilled. The residue was cooled, and the oily layer separated, washed thrice with hot water, and rendered to ether. The washings were cooled and extracted with ether, and the combined ethereal solutions dried. The solvent was removed, and the residue fractionated. The yield was 13 g., b. p. 180—184°/20 mm., from 20 c.c. of ester. Conversion into the chloride hydrochloride followed the description of Magidson (*loc. cit.*), but the reaction with thionyl chloride was advantageously effected at — 5°.

5-*Chloro*-8-*ω*-*diethylaminoundecylamino*-6-*methoxyquinoline Hydrochloride* (R. 98).—A mixture of 5-chloro-8-amino-6-methoxyquinoline (10·5 g.), 11-diethylaminoundecyl chloride hydrochloride (15·0 g.), and alcohol (10 c.c.) was heated for 24 hours at 100—110° and then for 24 hours at 110—120°. A short air condenser was used, so that the alcohol gradually evaporated. The red, crystalline mass was triturated with ether, and the solid matter collected and thoroughly washed with ether. It was then extracted with alcohol, leaving a residue of 5-chloro-8-amino-6-methoxyquinoline hydrochloride (the free base, after crystallisation from methyl alcohol, melted at 149—150° and caused no depression of m. p. when mixed with an authentic specimen of 5-chloro-8-amino-6-methoxyquinoline).

The alcoholic solution was concentrated, cooled, and diluted with a large volume of ether; 5-*chloro*-8-*ω*-*diethylamino*-*undecylamino*-6-*methoxyquinoline hydrochloride* was then precipitated. After crystallising from alcohol and from alcohol–ether. it formed small, colourless prisms, m. p. 126—128°, readily soluble in water to a golden-yellow solution (Found : C, 63·5; H, 8·6; N, 8·9; Cl, 14·6. $C_{25}H_{40}ON_3Cl,HCl$ requires C, 63·8; H, 8·7; N, 8·9; Cl, 15·1%). Antimalarial activity was observed only with the maximum tolerated dose.

The free base was a pale yellow, uncrystallisable oil. The meconate, prepared in the usual way, was an orange-red solid which was not investigated, as it was almost insoluble in water. A crude specimen had m. p. 141—142°. The dihydrochloride, precipitated from a solution of the base in ether in the usual manner, was a viscous red oil.

8-*ω*-*Carboxydecylamino*-6-*methoxyquinoline and Derivatives*.—*Ethyl ester*. Ethyl 11-bromoundecoate (62 g.) and 8-amino-6-methoxyquinoline (55 g.) were heated together at 120—130° for 12 hours. The mass was thoroughly triturated and washed with ether; the solid material was aminomethoxyquinoline hydrobromide (18 g. of the base

recovered). The ethereal solution was shaken with dilute hydrochloric acid; the yellow hydrochloride that separated was collected, washed with ether and with hot water, and triturated with aqueous sodium carbonate. The free *base*, isolated by means of ether (yield, 34 g.), after several crystallisations from alcohol, had m. p. 43—47°, not raised by recrystallisation (Found: C, 71·2; H, 8·9; N, 7·3. $C_{23}H_{34}O_2N_2$ requires C, 71·5; H, 8·8; N, 7·3%). This ester was recovered unchanged (m. p. and mixed m. p.) after being heated with saturated ethyl-alcoholic ammonia for 7 hours at 95—100° in a sealed tube (Found: N, 7·5%).

The acid. The above ester (20 g.) was refluxed for 2 hours on the steam-bath with alcoholic potassium hydroxide (1200 c.c. of 5%). Most of the alcohol was distilled, and concentrated hydrochloric acid added in slight excess, followed by aqueous sodium carbonate just to neutralise mineral acid (Congo-red). The buff-coloured precipitate was collected, washed with water, dried, and crystallised from alcohol (yield, 14 g., 75%), forming pale yellow, prismatic needles, m. p. 110—111°, soluble in aqueous acids and alkalis (Found: C, 70·7; H, 8·2; N, 7·8. $C_{21}H_{30}O_3N_2$ requires C, 70·4; H, 8·4; N, 7·8%).

The amide. Thionyl chloride (7 c.c.), dissolved in benzene (10 c.c.), was gradually added to a suspension of the acid (3·6 g.) in benzene (110 c.c.) cooled in ice-salt and efficiently agitated. The temperature was then raised to 40° and maintained until evolution of sulphur dioxide ceased. The mixture was cooled to 0° and slowly added with vigorous stirring to a large excess of aqueous ammonia (*d* 0·88) cooled to — 10°. The *amide* was precipitated as a pale yellow solid which tended to become green on standing; it was collected, thoroughly washed with water, dried, and crystallised from alcohol, forming buff-coloured prisms, m. p. 113—114° (yield, 30%) (Found: C, 70·9; H, 8·8; N, 12·0. $C_{21}H_{31}O_2N_3$ requires C, 70·6; H, 8·7; N, 11·8%).

An attempt to prepare the related nitrile by dehydration with phosphoric oxide in benzene solution was unsuccessful.

8-ω-*Cyanodecylamino*-6-*methoxyquinoline*.—A mixture of 8-amino-6-methoxyquinoline (17·4 g.) and 11-bromoundeconitrile (24·6 g.) (Trunel, *Compt. rend.*, 1933, **197**, 435) was heated at 110—120° for 17 hours under nitrogen. The melt gradually solidified to an orange-yellow crystalline mass. After cooling, it was triturated with ether, and the solid material (8-amino-6-methoxyquinoline hydrobromide) collected and washed with ether. When the ethereal extract and washings were concentrated, the condensation product separated; it was collected and washed with ether (yield, 7 g., 38%, allowing for 8 g. of recovered aminomethoxyquinoline). 8-ω-*Cyanodecylamino*-6-*methoxyquinoline* crystallised from alcohol in colourless prisms, m. p. 84—85° (Found: C, 74·5; H, 8·8; N, 12·3. $C_{21}H_{29}ON_3$ requires C, 74·4; H, 8·6; N, 12·4%).

8-ω-*Guanyldecylamino*-6-*methoxyquinoline* (R. 101).—A mixture of powdered cyanodecylaminomethoxyquinoline (3·4 g.), alcohol (1·4 c.c.), and light petroleum (50 c.c.) was saturated with hydrogen chloride at — 5°, and the solid occasionally broken up until all the orange-red material had disappeared. The vessel was then stoppered securely and kept in a refrigerator for 4 weeks. The solvent was decanted, and the residue freed from hydrogen chloride and light petroleum under diminished pressure. The imino-ether hydrochloride was pulverised, mixed with an excess of saturated ethyl-alcoholic ammonia, and heated in a sealed vessel at 40—50° for 6 hours. When cold, the alcoholic solution of the amidine was separated from ammonium chloride, and the ammonia and alcohol removed under reduced pressure. The residue was rubbed with ether, collected, dried,and triturated with a little chilled alcohol. The readily soluble amidine hydrochloride was precipitated by the addition of a large volume of dry ether to the filtered solution. This procedure was repeated twice, and the *product* finally crystallised from a little water, from which it separated in small, buff-coloured, prismatic needles (3 g.), m. p. 76—77° (Found: N, 13·4. $C_{21}H_{32}ON_4,HCl,H_2O$ requires N, 13·5%). The salt was dehydrated at 30—40° (Found: C, 64·5; H, 8·7; N, 14·3. $C_{21}H_{32}ON_4,HCl$ requires C, 64·2; H, 8·4; N, 14·3%).

R. 101 showed no antimalarial action at the M.T.D. of 6 × 10·24 mg. It was weakly active against trypanosomes in mice (Warrington Yorke).

8-ω-*Cyanodecylaminoquinoline*.—A mixture of 8-aminoquinoline (9 g.) and 11-bromoundeconitrile (12 g.) was heated for 24 hours at 110—120° under nitrogen. The orange-red condensate was thoroughly triturated and washed with ether, and then repeatedly extracted with hot water until the extracts were almost colourless. The dark red, viscous residue solidified on cooling, and was pulverised and triturated with cold aqueous sodium carbonate. The greyish-yellow, thick gum eventually solidified (5 g.). It crystallised from alcohol in small, greyish-yellow prisms, m. p. 60—61° (Found: C, 77·8; H, 8·6; N, 13·8. $C_{20}H_{27}N_3$ requires C, 77·6; H, 8·7; N, 13·6%).

8-ω-*Guanyldecylaminoquinoline*.—The preparation was like that of guanyldecylaminomethoxyquinoline, and the resulting base resembled its 6-methoxy-derivative in physical and chemical properties. The *hydrochloride* separated from alcohol in small, almost colourless, prismatic needles, m. p. 92—93° (Found: C, 66·5; H, 8·8; N, 15·5. $C_{20}H_{30}N_4,HCl$ requires C, 66·2; H, 8·5; N, 15·5%).

8-γ-*Cyanopropylaminoquinoline*.—Equivalent quantities of 8-aminoquinoline and γ-bromobutyronitrile were heated together at 90° under nitrogen for 12 hours, and the temperature then raised to 100—110° for a further 12 hours. The orange-red product was washed with ether and crystallised from alcohol. The *base* was liberated and repeatedly crystallised from alcohol; it formed small, grey prisms, m. p. 52—53° (Found: C, 74·2; H, 6·4; N, 19·9. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·2; N, 19·9%).

8-γ-*Guanylpropylaminoquinoline*.—The preparation from the cyanopropylaminoquinoline was like that described above. The *hydrochloride* crystallised from alcohol in small, colourless prisms which darkened at 148°, m. p. 152—154° (Found: C, 58·8; H, 6·4; N, 21·1. $C_{13}H_{16}N_4,HCl$ requires C, 59·0; H, 6·4; N, 21·2%).

ψ-6-*Amino*-2-p-*dimethylaminostyryl*-1-γ-*aminopropylquinolinium Bromide Hydrobromide* (V).—A mixture of 6-aminoquinaldine (16 g., m. p. 185—186°, by reduction of 6-nitroquinaldine with stannous chloride and hydrochloric acid) and acetic anhydride (20 g.) was heated for 20 minutes on the steam-bath. 6-Acetamidoquinaldine (18 g.) was crystallised from much boiling water. The product was a hydrate, m. p. 90—100°; after drying at 70° the m. p. was 168—169°.

A solution of 6-acetamidoquinaldine (12 g.) and phthalo-γ-bromopropylimide (20 g.) in nitrobenzene (20 c.c.) was heated for 7 hours at 120—130°. The product was cooled, washed with ether, refluxed with alcohol, and collected from the hot mixture (13 g.). This quaternary salt, crystallised from a mixture of alcohol (75 c.c.) and water (25 c.c.), formed pale yellow prisms which darkened at 235—240°, m. p. 240—245° (decomp.) (Found: C, 58·9; H, 4·9; N, 8·7; Br, 16·8. $C_{23}H_{22}O_3N_3Br$ requires C, 58·9; H, 4·7; N, 9·0; Br, 17·1%). A mixture of ψ-6-*acetamido*-2-*methyl*-1-γ-*phthalimidopropylquinolinium bromide* (4·7 g.), *p*-dimethylaminobenzaldehyde (2 g.), alcohol (200 c.c.), water (10 c.c.), and a few drops of piperidine was refluxed for 9 hours. The solution became deep purple, and a dark red crystalline solid separated. The product was collected from the hot solution, thoroughly washed with hot alcohol, and dried (3 g.) (Found: C, 64·1; H, 5·2; N, 9·3; Br, 12·8. $C_{32}H_{31}O_3N_4Br$ requires C, 64·1; H, 5·2; N, 9·4; Br, 13·3%).

A mixture of this ψ-6-*acetamido*-2-p-*dimethylaminostyryl*-1-γ-*phthalimidopropylquinolinium bromide* (4·0 g.), water (50 c.c.), and hydrobromic acid (55 c.c. of 48%) was gently refluxed for 8 hours, and the solution cooled, filtered, and evaporated to dryness on the steam-bath. The residue was extracted with boiling chloroform, dried, extracted with a little hot alcohol, and collected. The *bromide hydrobromide*, crystallised twice from aqueous alcohol, formed dark purple prisms, which were freely soluble in water (Found: C, 51·9; H, 5·6; N, 11·3; Br, 30·6. $C_{22}H_{27}N_4Br,HBr$ requires C, 51·9; H, 5·5; N, 11·0; Br, 31·5%). This salt (R. 100) showed no antimalarial activity at the M.T.D. of 6 × 10 mg.

The following is reported by Professor C. H. Browning, F.R.S. Antiseptic properties: *Staphylococcus*; 1 : 20,000

inhibits in peptone water; 1 : 40,000 inhibits in serum. *B. coli*; 1 : 40,000 inhibits in peptone water; 1 : 100,000 inhibits in serum. Trypanocidal action in mice infected with *T. brucei* : 1 : 1000 may cure; the blood is slowly cleared of trypanosomes after treatment; 1 : 20,000 has only slight action.

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