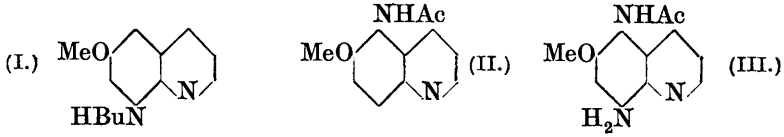
CCCXCIX.—*Attempts to find New Anti-malarials. Part III. Some Substituted Aminoalkylaminoquinolines.*

By Alfred William Baldwin.

Apart from any knowledge of the constitution of plasmoquine (see Introduction to Part I), the derivatives of 8-aminoquinoline have a special interest in connexion with the subject of this series on account of the fact that the aromatic amino-group can be alkylated by the usual methods without affecting the quinoline nitrogen; this is not the case with the isomeric 5-, 6-, and 7-aminoquinoline groups.

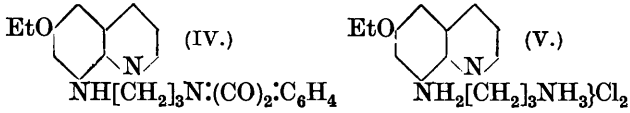
Thus, 8-amino-6-methoxyquinoline was found to yield an N-*butyl* derivative (I), when boiled under reflux with aqueous sodium carbonate and *n*-butyl iodide; there appeared to be very little

tendency towards further butylation either on the secondary or the tertiary nitrogen atom. Unfortunately, the salts of (I) were sparingly soluble in water, and were consequently unsuited for the projected biological investigation. It was, accordingly, sought to introduce further basic centres, and this was accomplished in two ways, leading to the formation of soluble salts. In the first method, 5-*acetamido*-6-*methoxyquinoline* (II) was nitrated and the product reduced to the 8-*amino*-derivative (III), which could be butylated and then deacetylated by hydrolysis. The second method produces



a wider range of salts of the desired type, and consists in the introduction of an amino-group into the side chain of the 8-alkylamino-substituent; this has been effected by the hydrolysis of the products of interaction of bromoalkylphthalimides and derivatives of 8-aminoquinoline. The aliphatic amino-group can then be alkylated by applying the method mentioned above.

To take a single case for purposes of illustration, 8-amino-6-ethoxyquinoline and γ-bromopropylphthalimide condensed, when heated together, with formation of the hydrobromide of (IV).



The successive action of hydrazine in boiling alcoholic solution and hydrochloric acid on this phthalimide resulted in smooth hydrolysis, and the dihydrochloride (V) was isolated (compare Ing and Manske, J., 1926, 2348). The butyl derivatives of the bases of the type (V) were prepared by the aqueous sodium carbonate–butyl iodide method, but, in general, these substances could not be fully purified. The specimens submitted for biological tests are indicated as in other parts of this series, *e.g.*, (V), a dihydrochloride, is R. 25 (see p. 2964).

Experimental.

8 - *Nitro*-5-*acetamido* - 6 - *methoxyquinoline*.—5-Nitro-6-methoxyquinoline (Decker and Engler, *Ber.*, 1909, **42**, 1740) was reduced to 5-amino-6-methoxyquinoline (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1920, **42**, 2285), of which 5·0 g. were acetylated by heating with acetic anhydride (4·0 c.c.) for 5 minutes. 5-*Acetamido*-

6-methoxyquinoline (II) crystallised from water in colourless needles, containing solvent of crystallisation which was lost at 100°. The anhydrous substance had m. p. 193° (Found: C, 66·7; H, 5·6; N, 12·6. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%).

A 60% yield of *8-nitro-5-acetamido-6-methoxyquinoline* was obtained under the following conditions. Acetamidomethoxyquinoline (5·0 g.) was cautiously added to concentrated sulphuric acid (15 c.c.), and, during this and the following operations, the temperature was not allowed to rise above 15°. When solution was complete, nitric acid (10 c.c.; *d* 1·42) was slowly introduced and the whole was allowed to remain for 1 hour, then mixed with ice and basified. The nitro-derivative crystallised from methyl alcohol in pale yellow needles, m. p. 265° (decomp.) (Found: C, 55·4; H, 4·3; N, 16·1. $C_{12}H_{11}O_4N_3$ requires C, 55·2; H, 4·2; N, 16·1%).

8-Amino-5-acetamido-6-methoxyquinoline (III).—The foregoing nitro-compound (5·5 g.) was reduced by means of iron and a little hydrochloric acid in alcoholic solution (compare West, J., 1925, **127**, 494), giving 4·0 g. of (III) in a pure condition. The *base* crystallised from water in pale, straw-coloured, flat needles, m. p. 207—208° (Found: C, 62·0; H, 5·7; N, 17·8. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

5-Acetamido-8-n-butylamino-6-methoxyquinoline (R. 23).—The foregoing amine was difficult to butylate by the normal procedure, but alkylation was finally effected by heating the base (1 mol.) with *n*-butyl iodide (3 mols.) in boiling xylene solution in the presence of an excess of sodium carbonate for 7 hours. The *product* crystallised from aqueous alcohol and then from benzene–light petroleum in pale yellow needles, m. p. 136° (Found: C, 67·1; H, 7·3; N, 13·9. $C_{16}H_{21}O_2N_3$ requires C, 66·9; H, 7·3; N, 14·6%). On heating with concentrated hydrochloric acid on the steam-bath, hydrolysis occurred, but the base subsequently isolated proved to be readily oxidisable and, for this reason, could not be fully purified. A solution of its hydrochloride (R. 24) (0·02 g. of base per c.c.) was prepared.

8-n-Butylamino-6-methoxyquinoline (I).—8-Amino-6-methoxyquinoline (1·0 g.) (Brit. Pat. 267,169) (hydrochloride, R. 29) was mixed with *n*-butyl iodide (1·6 g.), sodium carbonate (2·0 g.), and water (20 c.c.), and the whole refluxed for 6 hours. Hydrogen chloride was led into an ethereal extract of the product, and the precipitated salt crystallised, on addition of ether to its methyl-alcoholic solution, in orange-yellow needles, m. p. 159—160°, containing $1H_2O$ (Found: N, 9·9; Cl, 12·6. $C_{14}H_{19}ON_2Cl,H_2O$ requires N, 9·8; Cl, 12·5%). This *hydrochloride* (R. 31) was very sparingly soluble in water; the free *base* crystallised from aqueous methyl alcohol in colourless, flat

needles, m. p. 45° (Found : C, 72·8; H, 7·7; N, 11·7. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·8; N, 12·2%).

8-n-*Butylamino-6-ethoxyquinoline.*—8-Amino-6-ethoxyquinoline was obtained by the method of Brit. Pat. No. 267,169, and crystallised from alcohol in colourless needles, m. p. 67° (literature, 60°). The butylation and preparation of the *hydrochloride* (R. 30) were carried out as with the 8-amino-6-methoxyquinoline; the very sparingly soluble salt crystallised from ethyl alcohol–ether in orange-yellow plates, m. p. 171—172° (Found : N, 9·9; Cl, 12·7. $C_{15}H_{21}ON_2Cl$ requires N, 10·0; Cl, 12·7%). The corresponding *base* crystallised from aqueous methyl alcohol in very pale brown needles, m. p. 38—39° (Found : C, 73·7; H, 7·8; N, 11·8. $C_{15}H_{20}ON_2$ requires C, 73·8; H, 8·2; N, 11·5%).

αγ-Di-(6-*methoxy*-8-*quinolylamino*)*propane*,

$$(MeO{\cdot}C_9H_5N{\cdot}NH{\cdot}CH_2)_2CH_2.$$

—A mixture of 8-amino-6-methoxyquinoline (1·74 g.), trimethylene bromide (1·5 g.), sodium carbonate (2·5 g.), and water (20 c.c.) was refluxed for 3 hours. The hydrochloride, precipitated from an ethereal solution of the product, crystallised from alcohol in red needles, m. p. 222°, very sparingly soluble in water. The free *base* crystallised from alcohol in colourless needles, m. p. 131—132° (Found : C, 70·6; H, 6·2; N, 13·9. $C_{23}H_{24}O_2N_4$ requires C, 71·1; H, 6·2; N, 14·4%).

8-β-*Aminoethylamino*-6-*methoxyquinoline Dihydrochloride*, $MeO{\cdot}C_9H_5N{\cdot}NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_3\}Cl_2$.—8-Amino-6-methoxyquinoline (1 mol.) was mixed with β-bromoethylphthalimide (1·1 mols.) (Gabriel, *Ber.*, 1889, **22**, 1137; Ing and Manske's method, *loc. cit.*, was used for the preparation) and heated at 120—130° for 6 hours. The resulting solid was repeatedly washed with hot alcohol, and the remaining bright yellow *hydrobromide* of 8-β-*phthalimidoethylamino*-6-*methoxyquinoline* had m. p. 246—247° (yield, 80%) (Found : C, 56·1; H, 4·2; N, 9·5; Br, 18·9. $C_{20}H_{18}O_3N_3Br$ required C, 56·1; H, 4·2; N, 9·8; Br, 18·7%). In this case, difficulty was experienced in the isolation of the free phthalimide, but the hydrolysis with hydrazine hydrate, following the method given below for an analogue (but using 2·5 mols. of the hydrate), gave a 90% yield of the *dihydrochloride* (R. 34), which crystallised from alcohol in bright yellow needles, m. p. 263—264° (Found : C, 49·7; H, 5·9; N, 14·1; Cl, 24·2. $C_{12}H_{17}ON_3Cl_2$ requires C, 49·7; H, 5·9; N, 14·5; Cl, 24·5%). The base (1 mol.) was butylated by refluxing with *n*-butyl iodide (1·5—2 mols.) and aqueous sodium carbonate (>3 mols.) for 4 hours. The hydrochloride was precipitated from ethereal solution, isolated, and dissolved in water (R. 35; 0·0283 g. of base per c.c.).

8-γ-*Aminopropylamino*-6-*methoxyquinoline Dihydrochloride*,

$MeO{\cdot}C_9H_5N{\cdot}NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_3\}Cl_2$.—The condensation of γ-bromopropylphthalimide and 8-amino-6-methoxyquinoline was carried out like that just described, and the product crystallised from alcohol in bright yellow needles, m. p. 221°. This hydrobromide was triturated with dilute, aqueous sodium carbonate at 30—40°, and the 8-*γ-phthalimidopropylamino-6-methoxyquinoline* collected and crystallised from alcohol in very pale yellow, flat needles, m. p. 101—102° (yield, 55%) (Found: C, 69·3; H, 5·0; N, 11·3. $C_{21}H_{19}O_3N_3$ requires C, 69·8; H, 5·3; N, 11·6%). In all experiments on the hydrolysis of this and other phthalimides described in this communication, it was found essential to employ the pure substances and to avoid the use of too great an excess of hydrazine hydrate. A mixture of phthalimidopropylamino-methoxyquinoline (20 g., 1 mol.), hydrazine hydrate (3·2 c.c.; 1·1 mols.), and alcohol (100 c.c.) was refluxed for 1½ hours, at the end of which the intermediate product (compare Ing and Manske, *loc. cit.*) had separated completely. Alcohol was removed by distillation, and the white, spongy residue was heated for 15 minutes on the steam-bath with an excess of dilute hydrochloric acid. Phthalylhydrazide was removed by filtration, and the base rendered to chloroform and isolated as the *dihydrochloride* by leading hydrogen chloride into the solution. This salt (R. 36) crystallised from alcohol in bright orange needles, m. p. 251—252° (yield, 80%) (Found: N, 13·0; Cl, 23·1. $C_{13}H_{19}ON_3Cl_2$ requires N, 13·8; Cl, 23·4%). A solution (R. 37) of the *N*-butyl derivative (0·0223 g. of base per c.c.) was prepared in the usual manner. R. 27 was a solution (0·062 g. of base per c.c.) of the *N-iso*amyl derivative.

ε-Bromo-n-amylphthalimide, $Br[CH_2]_5{\cdot}N{:}(CO)_2{:}C_6H_4$, *and αε-Diphthalimidopentane*, $C_6H_4{:}(CO)_2{:}N{\cdot}[CH_2]_5{\cdot}N{:}(CO)_2{:}C_6H_4$.—αε-Dibromopentane (124 g.), prepared by von Braun's method (compare Dox and Yoder, *J. Amer. Chem. Soc.*, 1921, **43**, 1368), was mixed with phthalimide (31 g.), potassium carbonate (16 g.), and xylene (150 c.c.) and refluxed for 6 hours. The residue, after steam-distillation, was crystallised from alcohol and then extracted with light petroleum in a Soxhlet apparatus. Colourless needles (20 g.) m. p. 61°, consisting of ε-bromo-*n*-amylphthalimide (Found: C, 52·9; H, 4·8; N, 4·0; Br, 26·1. Calc. for $C_{13}H_{14}O_2NBr$: C, 52·7; H, 4·7; N, 4·7; Br, 27·0%) separated from the petroleum extract, and the residue, *αε-diphthalimidopentane*, crystallised from acetic acid in colourless needles, m. p. 188° (Found: C, 69·5; H, 5·0; N, 7·7. $C_{21}H_{18}O_4N_2$ requires C, 69·6; H, 5·0; N, 7·7%). The bromo-*n*-amylphthalimide has previously been described by Gabriel (*Ber.*, 1902, **35**, 1368), who obtained it by the action of hydrobromic acid on ε-phenoxyamylphthalimide and gave m. p. 61°.

8-(ε-*Amino*-n-*amylamino*)-6-*methoxyquinoline Dihydrochloride*, $MeO{\cdot}C_9H_5N{\cdot}NH_2{\cdot}[CH_2]_5{\cdot}NH_3\}Cl_2$.—The addition of ε-bromo-*n*-amylphthalimide to 8-amino-6-methoxyquinoline was carried out in the usual manner, and the *hydrobromide* crystallised from alcohol in yellow needles, m. p. 101—103°. The free 8-(ε-*phthalimido*-n-*amylamino*)-6-*methoxyquinoline*,

$$MeO{\cdot}C_9H_5N{\cdot}NH{\cdot}[CH_2]_5{\cdot}N{:}(CO)_2{:}C_6H_4,$$

crystallised from alcohol in colourless needles, m. p. 117—118° (yield, 50%) (Found: C, 70·8; H, 5·8; N, 10·6. $C_{23}H_{23}O_3N_3$ requires C, 71·0; H, 5·9; N, 10·8%). The hydrolysis was effected by hydrazine, quantitatively, and the resulting *dihydrochloride* (R. 38) crystallised from alcohol in orange-yellow needles, m. p. 83°, containing $3H_2O$ (Found: C, 46·6; H, 7·7; N, 10·3; Cl, 18·8. $C_{15}H_{23}ON_3Cl_2,3H_2O$ requires C, 46·6; H, 7·5; N, 10·9; Cl, 18·4%). The butylated salt was prepared in the usual manner, but this hydrochloride proved to be sparingly soluble in water and the free base was dissolved in a mixture of lactic acid (3 parts) and water (7 parts) (R. 39; 0·0284 g. of base per c.c.).

8-γ-*Aminopropylamino*-6-*ethoxyquinoline Dihydrochloride* (V).—The initial condensation was much more facile than in other examples and was complete in 20—30 minutes. The 8-γ-phthalimidopropylamino-6-ethoxyquinoline hydrobromide was well washed with alcohol and boiled with aqueous sodium carbonate in order to isolate the free *base* (IV), a treatment which appeared to be necessary in this case. The substance crystallised from alcohol in pale yellow needles, m. p. 127° (yield, 66%) (Found: C, 70·2; H, 5·8; N, 10·9. $C_{22}H_{21}O_3N_3$ requires C, 70·4; H, 5·6; N, 11·2%). Hydrolysis in the usual manner gave the *dihydrochloride* (R. 25) in theoretical yield; this salt crystallised from alcohol in orange-red needles, m. p. 242°, containing $1H_2O$ (Found: N, 12·1; Cl, 20·9. $C_{14}H_{21}ON_3Cl_2,H_2O$ requires N, 12·5; Cl, 21·1%). The butylated salt (R. 26; 0·0369 g. of base per c.c.) was prepared in the usual manner.

8-γ-*Aminopropylamino*-6-*methylquinoline Dihydrochloride*, $C_9H_5MeN{\cdot}NH_2{\cdot}[CH_2]_3{\cdot}NH_3\}Cl_2$.—In applying the Skraup reaction to 3-nitro-*p*-toluidine (20 g.), arsenic acid was used as the oxidising agent instead of picric acid as recommended by Noelting and Trautmann (*Ber.*, 1890, **23**, 3669), and 18 g., m. p. 121—122°, of the base were obtained. Reduction by West's method then gave 10 g. of 8-amino-6-methylquinoline, m. p. 58—60°.

The base condensed with γ-bromopropylphthalimide in the usual way, and 8-*γ-phthalimidopropyl*-6-*methylquinoline* crystallised from alcohol in pale, straw-coloured needles, m. p. 123° (yield, 45%) (Found: C, 73·2; H, 5·7; N, 12·3. $C_{21}H_{19}O_2N_3$ requires C, 73·1;

H, 5·5; N, 12·2%). The *dihydrochloride* (R. 21) obtained on hydrolysis in theoretical amount crystallised from alcohol in orange needles, m. p. 262° (Found : C, 53·7; H, 6·4; N, 14·2. $C_{13}H_{19}N_3Cl_2$ requires C, 54·2; H, 6·6; N, 14·6%). R. 22 was a solution of the *N*-butyl derivative (0·0258 g. of base per c.c.).

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THE UNIVERSITY OF MANCHESTER.
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