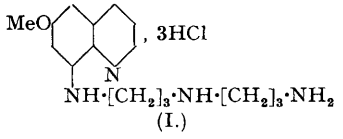
147. *Attempts to find New Antimalarials. Part XVIII.*

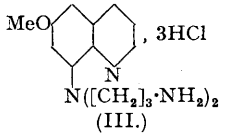
By D. C. Quin and Sir Robert Robinson.

Robinson and Tomlinson (J., 1934, 1524) condensed 8-γ-aminopropylamino-6-methoxyquinoline with phthalo-γ-bromopropylimide and after hydrolysis of the product obtained a hydrochloride (R.63) which proved to be the most potent antimalarial of the plasmoquin series yet encountered. Tested by Professor D. Keilin and his colleagues against *Plasmodium relictum* in canaries, its index was found to be 1/64, which is about twice as good as that of plasmoquin (1/32). These figures are not precise but indicate the order of the activities. The constitution of R.63 is unknown and in the present communication it is shown that two of the more probable structures can be excluded (cf. Part XX).

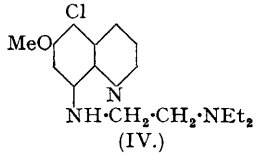
The most probable structure for R.63 was thought to be (I) and to avoid ambiguity in the synthesis we desired to introduce the side chain *en bloc*. It was found that the phenoxyl group of phthalo-γ-(γ-phenoxypropylamino)propylimide, $PhO\cdot[CH_2]_3\cdot NH\cdot[CH_2]_3\cdot N(CO)_2C_6H_4$ (II), could be replaced by bromine and the product was used to attach the complex side-chain to the amino-group of 8-amino-6-methoxyquinoline. On hydrolysis (I) was obtained, but it proved to be almost devoid of antimalarial activity. Similarly, the *hydrochloride* (III), prepared from aminomethoxyquinoline by introducing two γ-phthalimidopropyl groups and subsequent hydrolysis, was found to be a feeble antimalarial. A chlorine atom in position 5 has been found to reduce



(I.)



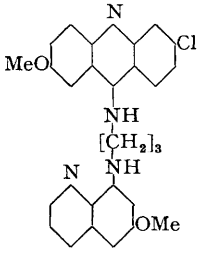
(III.)

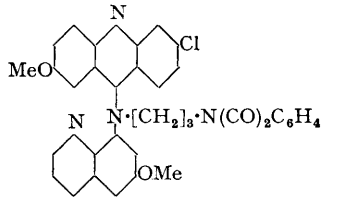


(IV.)

toxicity in the plasmoquin series. The *base* (IV) has been synthesised and is found to have weak antimalarial properties.

The present work was completed in 1937 and included the commencement of an attempt to combine the atebrin and the plasmoquin type. Unfortunately this aspect was not pursued. Condensation of 2 : 5-dichloro-7-methoxyacridine and 8-γ-aminopropylamino-6-methoxyquinoline afforded 2-*chloro*-5-(6′-*methoxyquinolyl*-8′-γ-*aminopropylamino*)-7-*methoxyacridine* (V), and dichloromethoxyacridine and 8-γ-phthalimidopropylamino-6-methoxyquinoline gave 2-*chloro*-5-γ-*phthalimidopropylamino*-(N-6′-*methoxy*-8′-*quinolyl*)-7-*methoxyacridine* (VI). It is hoped that an opportunity will be found to repeat these preparations and extend the series.

(V.)




(VI.)

Biological results will be reported in detail by Professor D. Keilin, F.R.S., and his collaborators in another place and this applies also to the following communications. The therapeutic indices mentioned are the ratio of minimum effective dose to maximum tolerated dose for canaries infected with *Plasmodium relictum*.

Experimental.

8-β-*Phthalimidoethyl*-6-*methoxyquinoline*.—The condensate from 8-amino-6-methoxyquinoline (30 g., prepared by reducing the nitro-compound with stannous chloride and hydrochloric acid) and phthalo-β-bromoethylimide (48 g.) (Baldwin, J., 1929, 2962) was washed with boiling alcohol (250 c.c.), refluxed with alcohol (100 c.c.), and pyridine added until a homogeneous solution resulted. On cooling, the *base* separated in light yellow prisms (25—30 g.), m. p. 153—155°, and 152° after recrystallisation from acetone (Found : C, 69·6; H, 5·1; N, 12·3. $C_{20}H_{17}O_3N_3$ requires C, 69·1; H, 5·0; N, 12·1%). The hydrochloride has m. p. 248°. After hydrolysis by the hydrazine method, aminoethylamino-methoxyquinoline, b. p. 195—197°/2 mm., is better isolated by means of ether than by means of chloroform, as the latter solvent extracts more impurities.

8-γ-Aminopropylamino-6-methoxyquinoline, prepared according to Baldwin (*loc. cit.*), has b. p. 205°/3 mm., 193°/0·5 mm. Its dihydrochloride has m. p. 252°. 8-γ-Aminopropylamino-6-methoxyquinoline (10·3 g.) was condensed with phthalo-β-bromoethylimide (23·5 g.). After hydrolysis the base was distilled and the fraction, b. p. 223°/0·5 mm., which should contain 8-bis-(β-aminoethyl)-γ-aminopropylamino-6-methoxyquinoline, was tested as hydrochloride (R.81, index 1 : 4—1 : 8). R.80 (index, 1 : 4) and R.89 were hydrochlorides of 8-bis-(γ-aminopropyl)-γ-aminopropylamino-6-methoxyquinoline, b. p. 217°/1 mm., prepared similarly from phthalo-γ-bromopropylimide.

Phthalo-γ-(γ-phenoxypropylamino)propylimide Hydrobromide (as II).—γ-Phenoxypropylamine (Lohmann, *Ber.*, 1891, **24**, 2632) was obtained by hydrazine hydrolysis of the related phthalimide (70% yield, using phenoxypropyl bromide, phthalimide, and potassium carbonate) in about 90% yield. A mixture of the amine (20 g.), phthalo-γ-bromopropylimide (34·5 g.), and dioxan (60 c.c.) was refluxed for 8 hours. The cold solution was filtered from phenoxypropylamine hydrobromide, m. p. 176°, and a second crystallisation could be induced by scratching. This *salt*, twice crystallised from methanol, had m. p. 184° and a mixture with that of m. p. 176° had m. p. 153°. It did not depress the m. p. of

a specimen, previously obtained from a condensation in xylene solution, which had been analysed (Found : C, 57·0; H, 5·6; N, 6·1. $C_{20}H_{22}O_3N_2$,HBr requires C, 57·2; H, 5·5; N, 6·7%).

Phthalo-γ-(γ-bromopropylamino)propylimide Hydrobromide.—A mixture of the above salt (5 g.) and hydrobromic acid (15 c.c., saturated at 0°) was heated in a sealed tube at 100° for 2·5 hours. After addition of water (40 c.c.), phenol was removed by extraction with ether and during this process the *product* crystallised. It separated from methanol in colourless prismatic needles (0·75 g.), m. p. 195° (Found : C, 41·8; H, 4·7; N, 6·4; Br, 38·3. $C_{14}H_{16}O_2N_2$,HBr requires C, 41·4; H, 4·4; N, 6·9; Br, 39·4%).

8-*γ-Phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline Dihydrobromide.*—A mixture of the last-mentioned salt (2 g.), 8-amino-6-methoxyquinoline (0·8 g.), and dioxan (10 c.c.) was refluxed for 8 hours. After cooling, the residue was collected and crystallised from methanol; m. p. 222—223° (Found : N, 9·9; Br, 27·1; MeO, 4·8. $C_{24}H_{26}O_3N_4$,2HBr requires N, 9·7; Br, 27·6; 1MeO, 5·3%). Hydrolysis by means of hydrazine, followed by conversion into a hydrochloride, afforded crude 8-*γ-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride* (I, R.92) (inactive at the maximum tolerated dose) as an exceedingly deliquescent, yellow powder (Found : N, 14·4; Cl, 24·8; MeO, 7·8. $C_{16}H_{24}ON_4$,3HCl requires N, 14·1; Cl, 26·8; 1MeO, 7·8%). The analysis indicates replacement of a part of the hydrogen chloride by water.

2 : 4-*Dinitro-β-aminoethylaniline.*—Condensation of 1-chloro-2 : 4-dinitrobenzene (10 g.) and ethylenediamine (9 g.) in boiling alcohol (75 c.c.) gave a mixture of the required product and bisdinitrophenylethylenediamine. The latter was separated by taking advantage of its sparing solubility in hot 10% hydrochloric acid. The filtrate deposited the *hydrochloride* (8·5 g.), m.p. 250° (decomp.) (Found : C, 36·9; H, 4·3; N, 21·7. $C_8H_{10}O_4N_4$,HCl requires C, 36·5; H, 4·2; N, 21·4%). The free *base* crystallised from aqueous alcohol in yellow plates, m. p. 54°, identical with a specimen later prepared from 2 : 4-dinitroanisole and ethylenediamine (Found : C, 42·6; H, 4·5; N, 24·7. $C_8H_{10}O_4N_4$ requires C, 42·5; H, 4·4; N, 24·8%).

2 : 4-*Dinitro*-N-*γ-phenoxypropyl-β-aminoethylaniline Hydrochloride.*—A mixture of dinitrophenylethylenediamine (8·5 g.), potassium carbonate (8·5 g.), γ-phenoxypropyl bromide (8 g.), and ethyl acetate (100 c.c.) was refluxed for 5 hours. The solvent was evaporated, and the residue extracted with warm ether. The *hydrochloride* was precipitated from the combined extracts by passage of hydrogen chloride and crystallised from alcohol; yield, 11 g., m. p. 114° (Found : C, 51·7; H, 5·5; N, 14·2; Cl, 8·8. $C_{17}H_{20}O_5N_4$,HCl requires C, 51·5; H, 5·3; N, 14·2; Cl, 9·0%). The next stage was to have been the replacement of the phenoxyl group by bromine, but this was abandoned when it was found possible to use phthalimido instead of dinitrophenyl as a protecting group.

8-*Di-γ-phthalimidopropylamino-6-methoxyquinoline.*—(*a*) A mixture of 8-γ-phthalimidopropylamino-6-methoxyquinoline (5·5 g.) and phthalo-γ-bromopropylimide (4·1 g.) was heated at 120° for 6 hours. The product was treated with boiling alcohol, leaving a residue of phthalimidopropylaminomethoxyquinoline hydrobromide; the solution afforded more of the unchanged materials, which were removed. The filtrates were evaporated; the straw-coloured residue contained a substance which was very sparingly soluble in boiling alcohol, although it had not previously separated (0·07 g. required 1 l. for solution). The fawn-coloured needles (Found : C, 61·8; H, 5·2; N, 8·4; Br, 11·7. $C_{32}H_{28}O_5N_4$,HBr requires C, 61·0; H, 4·6; N, 8·9; Br, 12·8%) were treated with hot aqueous sodium carbonate; the *base* crystallised from alcohol, in which it was very sparingly soluble, in colourless feathery needles (0·5 g.), m. p. 166° (Found : C, 70·2; H, 5·3; N, 10·6; MeO, 4·8. $C_{32}H_{28}O_5N_4$ requires C, 70·0; H, 5·1; N, 10·2; 1MeO, 5·7%). The condensation was also effected in boiling dioxan with the same results.

(*b*) The same substance, identified as the base, was also obtained as a by-product of the condensation of 8-amino-6-methoxyquinoline and phthalo-γ-bromopropylimide at 120—130° under the conditions prescribed by Baldwin (*loc. cit.*). A mixture of the bis-phthalimide (1·5 g.), hydrazine hydrate (0·275 c.c.), and alcohol (50 c.c.) was refluxed for 3 hours, the solvent removed, and the residue heated on the steam-bath for ½ hour, cooled, and filtered through kieselguhr. The basified filtrate was extracted with ether, and the hydrochloride precipitated from the dried solution by passage of hydrogen chloride as a very deliquescent yellow solid. It was dissolved in alcohol and reprecipitated with ether (R.93, index 1 : 2). Five years later the preparation was repeated, and the salt obtained in yellow needles by keeping an alcoholic solution in ether vapour under diminished pressure (Found in material dried in a high vacuum at 110° : C, 48·2; H, 7·0; N, 14·0; Cl, 26·7. $C_{16}H_{23}ON_4$,3HCl requires C, 48·4; H, 6·8; N, 14·1; Cl, 26·8%). It is therefore 8-*bis-γ-aminopropylamino-6-methoxyquinoline trihydrochloride* (III).

5-*Chloro-8-β-diethylaminoethylamino-6-methoxyquinoline.*—5-Chloro-8-amino-6-methoxyquinoline has m. p. 154° (Robinson and Tomlinson, *loc. cit.*, give m. p. 150—152°). It was condensed in alcoholic solution with β-chlorotriethylamine hydrochloride following the general method of Magidson and Strukov (*Arch. Pharm.*, 1933, **271**, 359), according to which the mixture is heated on the steam-bath and alcohol allowed slowly to evaporate by way of an inefficient condenser. The basic *product* (2 g. from 3 g.) crystallised from alcohol in light yellow plates, m. p. 76° (Found : C, 62·9; H, 7·5; N, 13·4; Cl, 12·0. $C_{16}H_{22}ON_3Cl$ requires C, 62·5; H, 7·2; N, 13·7; Cl, 11·5%). The dihydrochloride (R.86) crystallised from alcohol in reddish-orange, stellate clusters of needles, m. p. 179—181°.

2-*Chloro-5-(6′-methoxyquinolyl-8′-γ-aminopropylamino-7-methoxyacridine* (V).—A mixture of 2 : 5-dichloro-7-methoxyacridine (2·8 g.), 8-γ-aminopropylamino-6-methoxyquinoline (2·3 g.), and phenol (7·5 g.) was heated on the steam-bath for 10 hours. After washing with ether, the residue was triturated with dilute hydrochloric acid and then with alcohol. The bright yellow hydrochloride was heated at 80° with aqueous sodium acetate, the base collected and dissolved in acetic acid, and the solution poured in a thin stream with stirring into dilute aqueous ammonia. The *substance* (V), crystallised from ether and from benzene, had m. p. 114° (Found : C, 62·7; H, 5·9; N, 10·2; Cl, 6·7; MeO, 12·2. $C_{27}H_{25}O_2N_4Cl$,$3H_2O$ requires C, 62·2; H, 6·0; N, 10·4; Cl, 6·8; 2MeO, 12·2%). The *dihydrochloride* formed yellow needles from alcohol, m. p. 223° (decomp.) (Found : C, 58·9; H, 4·9; N, 10·7; MeO, 11·1. $C_{27}H_{25}O_2N_4Cl$,2HCl requires C, 59·1; H, 5·0; N, 10·1; 2MeO, 11·4%).

The *compound* (VI) was obtained by heating a mixture of 2 : 5-dichloro-7-methoxyacridine (3·8 g.), 8-γ-phthalimidopropylamino-6-methoxyquinoline (5·0 g.), and phenol (12 g.) for 8 hours at 100°. The mass was extracted with ether and then with boiling alcohol (3 × 100 c.c.). The residual red hydrochloride became yellow on treatment with aqueous ammonia. The base was collected and extracted with more hot alcohol (300 c.c.); it crystallised from much boiling alcohol, in which it was very sparingly soluble, in needles which collapsed at *ca.* 140° and then had m. p. 253° (decomp.) (Found : N, 8·6. $C_{35}H_{27}O_4N_4Cl$,$3H_2O$ requires N, 8·5%).

The work was interrupted at this stage, but a hydrolysed hydrochloride was prepared by the usual hydrazine process. It formed bright scarlet crystals which became purplish at 100°. The dark carmine aqueous solution became yellow on dilution, probably as the result of hydrolysis.

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