274. *Attempts to find New Antimalarials. Part VIII. Derivatives of 8-Aminoalkylaminoquinoline.*

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The methods developed in Part III of this series (J., 1929, 2959) have been extended to fresh examples, because several of the salts were found to possess powerful antimalarial properties in bird malaria (cf. Tate and Vincent, *Parasitology*, 1933, XXV, 411, whose work in collaboration with Prof. D. Keilin has covered many of the specimens submitted; especially, R.25 * and R.26, having therapeutic indices of 1 : 16, are nearly equal to plasmoquine in potency and resemble it in action, see also Part IX. We take this opportunity of thanking Professor Keilin and his colleagues for their valued co-operation).

Even small variations of no chemical interest were deemed worth making in the biological connexion. For instance, the 6-methoxyquinolines were usually more potent than the similarly substituted 6-ethoxyquinolines, and the length of the alkylaminoalkyl chain in position 8 has a considerable bearing on the activity.

* The numbers R.25, etc., identify specimens submitted for biological tests.

Moreover, the value of a drug is always a function of its therapeutic efficiency and its toxicity, and in the case of plasmoquine and its analogues a comparatively small diminution of toxicity with an equal or improved therapeutic efficiency might well transform the aspect of malaria therapy. The reader is referred to Part III (*loc. cit.*) and to the experimental section which follows. It has been found that ββ′-dichlorodiethyl ether reacts with potassium phthalimide with formation of *phthalo-β-(β′-chloroethoxy)-ethylimide*, $Cl{\cdot}C_2H_4{\cdot}O{\cdot}C_2H_4{\cdot}N(CO)_2C_6H_4$ (I) in practicable yield; the substance may be found of service in other connexions.

Experimental.

8-β-*Aminoethylamino*-6-*ethoxyquinoline Dihydrochloride*.—8-Amino-6-ethoxyquinoline (B.P. 267,169) was condensed in the usual way (J., 1929, 2962) with β-bromoethylphthalimide to 8-β-*phthalimidoethylamino*-6-*ethoxyquinoline*, which crystallised from benzene in greenish-yellow needles, m. p. 178—179° (yield, 75%) (Found: C, 69·9; H, 5·3; N, 11·3. $C_{21}H_{19}O_3N_3$ requires C, 69·8; H, 5·3; N, 11·6%). The removal of the phthalyl residue was effected by means of hydrazine, and the dihydrochloride of the resulting base crystallised from ethyl alcohol in orange needles (R.46), m. p. 247° (Found: C, 51·3; H, 6·4; N, 12·7; Cl, 22·8. $C_{13}H_{19}ON_3Cl_2$ requires C, 51·3; H, 6·3; N, 13·8; Cl, 23·3%). A solution (R.47) of the *N*-butyl derivative was prepared in the usual manner (*ibid.*).

8-γ-*Aminopropylaminoquinoline Dihydrochloride*.—8-Nitroquinoline (Knuppel, *Ber.*, 1896, **29**, 705) was reduced to 8-aminoquinoline by Dikshoorn's method (*Rec. trav. chim.*, 1929, **48**, 153). This aminoquinoline was condensed with γ-bromopropylphthalimide as in previous cases, the reaction being complete in 90 mins. The product, the hydrobromide of 8-γ-*phthalimidopropylaminoquinoline*, was basified with pyridine, and crystallised from alcohol in bright, yellow, flat needles, m. p. 111° (Found: C, 72·5; H, 5·0; N, 12·4. $C_{20}H_{17}O_2N_3$ requires C, 72·5; H, 5·1; N, 12·7%). The phthalyl residue was removed by means of hydrazine and 8-γ-*aminopropylaminoquinoline dihydrochloride* was obtained, on crystallisation from alcohol, in orange needles containing $1H_2O$ (R.40) (Found: C, 49·0; H, 6·5; N, 14·2; Cl, 24·3; H_2O, 6·2. $C_{12}H_{15}N_3,2HCl,H_2O$ requires C, 49·3; H, 6·5; N, 14·4; Cl, 24·3; H_2O, 6·2%). A solution (R.41) of the *N*-butyl derivative was prepared in the usual manner.

8-*Amino*-6-n-*butoxyquinoline*.—*p*-Aminophenol (50 g.) was *N*-acetylated in quantitative yield by refluxing with acetic acid (50 c.c.) for 6 hours (Hewitt and Ratcliffe, J., 1912, **101**, 1766). *p*-Acetamidophenol (30 g.) was butylated by refluxing with aqueous sodium hydroxide (80 c.c. of 10%) and *n*-butyl *p*-toluenesulphonate (50 g.) (Finzi, *Ann. Chim. Appl.*, 1925, **15**, 41) for 3 hours. The product was obtained in 70% yield after recrystallisation from benzene as colourless needles, m. p. 112°. *p*-*n*-Butoxyacetanilide (11 g.) was mixed with acetic acid (25 c.c.) and water (12·5 c.c.), cooled with ice and shaken, and nitrated by means of a mixture of nitric acid (25 c.c., *d* 1·42) and acetic acid (20 c.c.), which was added very slowly at below 5°. After stirring for 1 hour the product was isolated (a sample of this 2-nitro-*p*-*n*-butoxyacetanilide crystallised from aqueous ethyl alcohol in long, yellow needles, m. p. 85°). The whole product was then treated with boiling concentrated hydrochloric acid (150 c.c.) for 2 hours, and, on dilution to 6 volumes with water, the free base was precipitated. It crystallised from light petroleum containing a little benzene in bright red needles, m. p. 66° (yield, 9·5 g.) (Found: C, 57·3; H, 6·6; N, 13·1. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7; N, 13·3%). This 2-*nitro*-4-n-*butoxyaniline* (75 g.) mixed with arsenic acid (55 g.), glycerol (85 c.c.), and concentrated sulphuric acid (60 c.c.) was refluxed for 6 hours (oil-bath), and the whole then poured on ice, filtered, and the residue washed thoroughly with hot dilute hydrochloric acid. The product was collected from the basified filtrate and washings and, on crystallisation from the minimum of ethyl alcohol, 8-*nitro*-6-n-*butoxyquinoline* was obtained in colourless needles, m. p. 92° (yield, 25 g.) (Found: C, 63·4; H, 5·6; N, 11·3. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·7; N, 11·4%). This was reduced by West's method (J., 1925, **127**, 494), and the product had b. p. 200°/4 mm.; the distillate solidified, and was recrystallised from light petroleum, forming white needles of 8-*amino*-6-n-*butoxyquinoline*, m. p. 59° (Found: C, 72·5; H, 7·6; N, 12·9. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 13·0%).

8-γ-*Aminopropylamino*-6-n-*butoxyquinoline Dihydrochloride*.—The interaction of γ-bromopropylphthalimide with the above aminoquinoline was effected in the usual way and was complete in 2 hours. After removal of hydrogen bromide, 8-γ-*phthalimidopropylamino*-6-n-*butoxyquinoline* was obtained in almost colourless needles, m. p. 99°, by crystallisation from ethyl alcohol (yield, 75%) (Found: C, 71·2; H, 6·4; N, 10·3. $C_{24}H_{25}O_3N_3$ requires C, 71·5;

H, 6·2; N, 10·4%). The *dihydrochloride* of the product obtained by removal of the phthalyl residue crystallised from ethyl alcohol in bright yellow needles, m. p. 75—80° (R.44) (Found : C, 52·7; H, 7·3; N, 11·0; Cl, 19·2. $C_{16}H_{25}ON_3Cl_2,H_2O$ requires C, 52·7; H, 7·4; N, 11·5; Cl, 19·5%). A solution (R.45) of the *n*-butyl derivative was prepared in the usual manner.

Phthalo-β-(β′-*iodoethoxy*)*ethylimide*.—ββ′-Dichlorodiethyl ether (80 g.), along with phthalimide (31 g.) and potassium carbonate (16 g.), was refluxed for 3 hours. The excess of the chloro-ether was then removed by steam distillation, and the oily residue, which soon solidified, was dried and extracted with light petroleum (b. p. 40—60°), yielding colourless needles of *phthalo*-β-(β′-*chloroethoxy*)*ethylimide* (I) (31 g.), m. p. 72° (Found : C, 56·8; H, 4·8; N, 5·1; Cl, 13·5. $C_{12}H_{12}O_3NCl$ requires C, 56·8; H, 4·7; N, 5·5; Cl, 14·0%). The residue from the extraction, consisting of ββ′-*diphthalimidodiethyl ether*, crystallised from 50% acetic acid in long, colourless needles, m. p. 157° (Found : C, 65·9; H, 4·1; N, 7·6. $C_{20}H_{16}O_5N_2$ requires C, 65·9; H, 4·4; N, 7·7%). The chloro-compound (25 g.) was refluxed for 48 hours with potassium iodide (100 g.) and water (60 g.). The product was ground under water, dried, and crystallised from light petroleum, forming colourless tablets, m. p. 83—84° (yield, 23 g.) (Found : C, 42·2; H, 3·6; N, 4·4; I, 36·1. $C_{12}H_{12}O_3NI$ requires C, 41·7; H, 3·5; N, 4·1; I, 36·8%). This reaction may also be accomplished in acetone solution by using sodium iodide.

8-β-(β′-*Aminoethoxy*)*ethylamino*-6-*methoxyquinoline Dihydrochloride*.—The condensation with 8-amino-6-methoxyquinoline (B.P. 267,169), when carried out in the usual way, gave an inferior yield of an impure product, but the following modification led to much better results. 8-Amino-6-methoxyquinoline (10 g.) was refluxed with phthalo-β-(β′-iodoethoxy)ethylimide (22 g.) and *N*-sodium carbonate solution (100 c.c.) for 6 hours. The product, 8-β-(β′-*phthalimido-ethoxy*)*ethylamino*-6-*methoxyquinoline*, crystallised from benzene–light petroleum in bright yellow needles, m. p. 145° (yield, 10 g.) (Found : C, 67·6; H, 5·2; N, 10·8. $C_{22}H_{21}O_4N_3$ requires C, 67·5; H, 5·4; N, 10·8%). The phthalyl residue was removed as usual, and the *dihydrochloride* of the resulting base crystallised from alcohol in golden-orange plates, m. p. 224° (R.48) (Found : C, 50·1; H, 6·3; N, 12·1; Cl, 20·7. $C_{14}H_{21}O_2N_3Cl_2$ requires C, 50·3; H, 6·3; N, 12·6; Cl, 21·3%). A solution (R.49) of the *n*-butyl derivative was prepared for biological tests.

5-*Nitro*-2-*methoxy*-m-*xylene*.—*m*-2-Xylenol (50 g.) was methylated by means of methyl sulphate (100 g.) and aqueous sodium hydroxide (500 c.c. of 20%) below 60° (yield, 50 g., b. p. 181—182°) (cf. *Ber.*, 1908, **41**, 2339). The ether (20 g.) was then nitrated in glacial acetic acid (60 c.c.) after cooling to 10°, by adding nitric acid (20 c.c., *d* 1·42) in one portion. If reaction did not immediately occur, it was induced by addition of a few drops of fuming nitric acid. The product crystallised from ethyl alcohol in long, colourless needles, m. p. 91° (yield, 16 g.) (Found : C, 59·7; H, 6·0; N, 7·7. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1; N, 7·7%).

2-*Methoxy*-m-5-*xylidine*.—The reduction was effected by West's method (*loc. cit.*), and the reaction mixture was made alkaline and steam distilled. The distillate was acidified, concentrated to a small bulk, and the base then set free and isolated. A pure white product was obtained (yield, 50%); a specimen crystallised from water in long white needles, m. p. 61° (Found : C, 71·4; H, 8·4; N, 9·1. $C_9H_{13}ON$ requires C, 71·5; H, 8·6; N, 9·3%).

6-*Methoxy*-5 : 7-*dimethylquinoline*.—Methoxy-xylidine (52 g.), arsenic acid (56 g.), glycerol (84 c.c.), and sulphuric acid (60 c.c.) were together refluxed for 7 hours. The mass was then basified and steam-distilled, the distillate being acidified and concentrated to a small bulk. After cooling, a saturated solution of potassium dichromate (60 g.) was added and the whole was kept for several hours, the quinoline chromate then crystallising in orange needles. This salt was decomposed with formation of 6-*methoxy*-5 : 7-*dimethylquinoline*, which crystallised as long, colourless needles, m. p. 58° (yield, 18 g.) (Found : C, 77·2; H, 6·9; N, 7·4. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%).

8-*Nitro*-6-*methoxy*-5 : 7-*dimethylquinoline*.—The above quinoline (15 g.) was charged slowly into fuming nitric acid (45 c.c., *d* 1·52), surrounded by ice, the temperature never being allowed to exceed 20°. After 3 hours, the mixture was added to ice, and the solution rendered alkaline with sodium carbonate. The precipitated product was ground under water and washed; it crystallised from 60% ethyl alcohol in well-formed, white needles, m. p. 100·5° (yield, 95%) (Found : C, 61·8; H, 4·7; N, 11·7. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%). The *substance* was prepared in order that it might be converted into 8-amino-6-methoxy-5 : 7-dimethylquinoline and its aminoalkyl derivatives; the interesting point is that the 8-amino-group is introduced by nitration and subsequent reduction of a quinoline. In other cases reliance must be placed on a Skraup reaction of a substituted *o*-nitroaniline.

Preparation of Homogeneous Secondary Bases of Plasmoquine Type.—Numerous devices for the preparation of pure 8-γ-monoalkylaminopropylaminoquinolines have been tested, but none has given fully satisfactory results. Treatment of γ-phenoxypropyl bromide with a large excess of a primary aliphatic amine in the presence of aqueous sodium carbonate led to bases which were hydrolysed with hydrobromic acid and then condensed with 8-amino-6-methoxyquinoline. The biological properties of the resulting salts were not different from those previously obtained by alkylation of 8-γ-aminopropylamino-6-methoxyquinoline. But analysis of the γ-phenoxypropylalkylamine hydrochlorides showed that they were mixed with tertiary bases to a greater or less extent. This does not affect the final result, as the tertiary bases will afford dibromo-derivatives and then complex condensation products with aminomethoxyquinoline which would be separated on distillation.

γ-Phenoxypropyl bromide (18 g.) ("Organic Syntheses," Vol. IX, 72) was refluxed gently for 15 hours with *n*-propylamine (20 g.) and 2*N*-sodium carbonate (60 c.c.). Crude γ-phenoxy-di-*n*-propylamine hydrochloride separated from the cooled solution acidified with hydrochloric acid. The mixed salts crystallised from benzene in white needles, m. p. 131° (yield, 20 g.) (Found: C, 63·2; H, 8·0; N, 4·3; Cl, 15·2. $C_{12}H_{20}ONCl$ requires C, 62·8; H, 8·7; N, 6·1; Cl, 15·5%). In this particular case the contamination with tertiary base was not serious. This *hydrochloride* (20 g.) was gently refluxed for 15 hours with hydrobromic acid (80 c.c., *d* 1·7), diluted to 5 volumes, phenol extracted with ether, and the solution, containing the hydrobromide of γ-bromodi-*n*-propylamine, evaporated to dryness, the last traces of acid being removed by heating on the steam-bath under diminished pressure for 2 hours. This substance was mixed with 0·9 equiv. of 8-amino-6-methoxyquinoline and amyl acetate (80 c.c.) and refluxed for 24 hours. The solvent was then decanted from the dark red sticky mass, which was dissolved in water, and traces of amyl acetate removed by ether. The 8-γ-n-*propylaminopropylamino*-6-*methoxyquinoline* was precipitated, by addition of a large excess of sodium hydroxide, as a dark viscous oil, b. p. 225—230°/< 0·1 mm., forming a pale orange oil which exhibited a marked green fluorescence (Found: C, 70·1; H, 8·7; N, 15·3. $C_{16}H_{23}ON_3$ requires C, 70·3; H, 8·4; N, 15·4%).

8-γ-n-*Butylaminopropylamino*-6-*methoxyquinoline* was obtained in an entirely analogous manner. The crude γ-phenoxypropyl-*n*-butylamine hydrochloride crystallised from acetone containing a little ethyl alcohol in lustrous white plates, m. p. 176°, and the hydrobromide of γ-bromopropyl-*n*-butylamine was then prepared as above and condensed with 8-amino-6-methoxyquinoline in the same way, resulting in a similar orange-coloured oil, which showed a marked green fluorescence; b. p. 216°/< 0·1 mm. (Found: C, 71·3; H, 8·8; N, 14·6. $C_{17}H_{25}ON_3$ requires C, 71·1; H, 8·7; N, 14·6%).

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