329. *Attempts to find New Antimalarials. Part XI. Some Aminoalkylarylquinoline Derivatives.*

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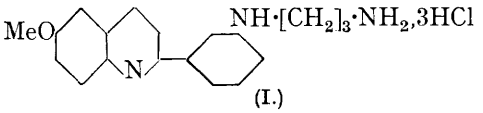
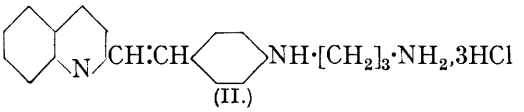
The plan in this section of the work was to prepare aminoalkylaminophenyl and aminoalkylaminostyryl derivatives of quinoline in order that their antimalarial properties might be studied.

A few such salts have been obtained by applications of known methods. 2-*m*-Aminophenyl-6-methoxyquinoline has been condensed with phthalo-γ-bromopropylimide, and the product hydrolysed, yielding the salt (I). In order to remove the aryl group farther from the quinoline nucleus we next treated 2-*p*-aminostyrylquinoline in a similar fashion



(I.)



(II.)

and obtained (II). The 6-methoxy-derivative of this salt was also obtained and the work was extended to some analogous examples in the cinnamylidenequinaldine group.

Experimental.

2-m-*Nitrophenyl*-6-*methoxyquinoline*-4-*carboxylic Acid.*—A mixture of *p*-anisidine (36 g.), *m*-nitrobenzaldehyde (31 g.), pyruvic acid (22 g.), and absolute ethyl alcohol (150 c.c.) was refluxed for ½ hour and cooled, and the white crystalline acid collected (yield, 95%). The substance was purified by solution in alcoholic potassium hydroxide and reprecipitation and by recrystallisation from acetic acid; it formed cream-coloured micro-needles, m. p. 268—269° (Found : C, 62·5; H, 3·5. $C_{17}H_{12}O_5N_2$ requires C, 63·0; H, 3·3%). This very sparingly soluble *acid* could not be decarboxylated by heating alone, or with glycerol, or dimethylaniline.

2-(m-γ-*Phthalimidopropylaminophenyl*)-6-*methoxyquinoline.*—Equivalent quantities of 2-(*m*-aminophenyl)-6-methoxyquinoline [Kinkelin and Miller, *Ber.*, 1887, **20**, 1919. The yield obtained by these authors was 15—18% and this can be approximately doubled by working up a mixture of nitrocinnamaldehyde (75 g.), anisidine (50 g.), and concentrated hydrochloric acid (80 g.) that has been heated at 180° for 6 hours] and phthalo-γ-bromopropylimide were heated together at 120—130° for 2 hours. The red solid obtained was powdered, washed with benzene, and crystallised from alcohol, forming dark red needles (yield 60%), m. p. 202—203° (Found : C, 62·5; H, 4·4; N, 8·0. $C_{27}H_{23}O_3N_3$,HBr requires C, 62·5; H, 4·6; N, 8·1%). This *hydro-*

bromide was triturated with aqueous ammonia; the *base* crystallised from alcohol in long white needles, m. p. 149—150° (Found: C, 74·1; H, 5·4; N, 9·3. $C_{27}H_{23}O_3N_3$ requires C, 74·1; H, 5·3; N, 9·6%).

2-(m-γ-*Aminopropylaminophenyl*)-6-*methoxyquinoline Hydrochloride* (I).—The foregoing substituted phthalimide (2 g.) was powdered, suspended in boiling alcohol (40 c.c.), and hydrazine hydrate (0·25 g. of 95%) added. After refluxing for 2 hours the alcohol was removed and the residue heated on the steam-bath for 15 minutes with an excess of dilute hydrochloric acid. The filtered liquid was basified and extracted with chloroform, and the *hydrochloride* precipitated from the dried extract by means of hydrogen chloride. The salt crystallised from alcohol–ether in light brown plates, m. p. 240—241° (yield, 80%) (Found: C, 51·8; H, 6·5; N, 9·6; Cl, 23·8. $C_{19}H_{21}ON_3,3HCl,1·5H_2O$ requires C, 51·5; H, 6·8; N, 9·5; Cl, 24·0%). The substance is hygroscopic and sparingly soluble in ethyl alcohol. A specimen was dried in a vacuum over phosphoric oxide at 110° (Found: C, 54·4; H, 6·0; N, 9·9. $C_{19}H_{21}ON_3,3HCl$ requires C, 54·7; H, 5·7; N, 10·1%) (R50 in the series for biological tests).

2-(o-*Nitrophenyl*)-6-*methoxyquinoline*.—A mixture of *o*-nitrocinnamaldehyde (15 g.), *p*-anisidine (19 g.), and concentrated hydrochloric acid (30 g.) was heated (oil-bath at 160°) for 5 hours. The resulting black mass was extracted with a mixture of ethyl alcohol (100 c.c.) and concentrated hydrochloric acid (100 c.c.), and the solution basified. The solid was collected, powdered, mixed with sand, and extracted with benzene, from which the *base* crystallised in long, light yellow needles, m. p. 133—134° (yield, 38%) (Found: C, 68·6; H, 4·6; N, 9·9. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0%).

2-(o-*Aminophenyl*)-6-*methoxyquinoline*.—A solution of crystallised stannous chloride (8 g.) in concentrated hydrochloric acid (10 c.c.) was added to the nitro-compound (2 g.), dissolved in glacial acetic acid (25 c.c.), and the whole was boiled for 10 minutes, cooled, made alkaline, and extracted with chloroform. The *base* so isolated crystallised from ethyl acetate and then from benzene as cream-coloured needles, m. p. 158—159° (Found: C, 76·6; H, 5·5; N, 11·5. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

2-p-*Nitrobenzylidene*-6-*methoxyquinaldine*.—A mixture of 6-methoxyquinaldine (compare Browning, Cohen, Ellingworth, and Gulbransen, *Brit. Med. J.*, 1923, II, 326) (25 g.), *p*-nitrobenzaldehyde (22 g.), and acetic anhydride (10 c.c.) was heated (oil-bath at 120—130°) for 3 hours. After cooling, the yellow solid was collected, washed, and crystallised from alcohol, forming long yellow needles, m. p. 165—166° (yield, 75%) (Found: C, 70·6; H, 4·6; N, 9·1. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·2%). The *base* is sparingly soluble in the common organic solvents when cold, readily soluble in the hot media.

2-p-*Aminobenzylidene*-6-*methoxyquinaldine*.—(A) A solution of the nitro-derivative (10 g.) in glacial acetic acid (300 c.c.) was mixed with crystallised stannous chloride (18 g.) in concentrated hydrochloric acid (25 c.c.) and boiled for ½ hour. The stannichloride, which separated in long yellow needles on cooling, was collected and treated with aqueous alkali, and the base extracted with chloroform. On passage of dry hydrogen chloride into the dried solution the hydrochloride was obtained as a light yellow solid. The free *base* crystallised from aqueous alcohol in clusters of yellow needles, m. p. *ca.* 162—165° (decomp.) with gradual softening from 130° [Found: C, 73·7, 73·7; H, (5·3), 6·1; N, 9·6. $C_{18}H_{16}ON_2,H_2O$ requires C, 73·5; H, 6·1; N, 9·5%]. (B) As the yield in (A) was not satisfactory, the nitro-derivative (10 g.) was also reduced by means of iron and a little concentrated hydrochloric acid in hot alcoholic solution (West, J., 1925, **127**, 494); the yield of pure base was 60%.

2-p-γ-*Phthalimidopropylaminostyryl*-6-*methoxyquinoline*.—2-*p*-Aminobenzylidene-6-methoxyquinaldine (7 g.) and phthalo-γ-bromopropylimide (9 g.) were heated together at 110—120° for 3 hours and the resulting solid was powdered and washed with benzene. On repeated crystallisation from alcohol it was obtained as dark reddish-brown needles, m. p. 241° (Found: N, 7·6. $C_{29}H_{25}O_3N_3,HBr$ requires N, 7·7%). This *hydrobromide* is sparingly soluble in cold alcohol, methyl alcohol or acetone and insoluble in benzene.

The hydrobromide was made into a thin paste with aqueous sodium hydroxide and after ½ hour the base was collected and washed; as it still contained bromine, it was suspended in chloroform and vigorously shaken with excess of aqueous ammonia. The chloroform solution was washed, dried over potassium carbonate, and concentrated; the *base* then crystallised on addition of light petroleum. Recrystallisation from alcohol furnished bright golden-yellow plates, m. p. 191—192° (Found: C, 75·2; H, 5·4; N, 9·0. $C_{29}H_{25}O_3N_3$ requires C, 75·2; H, 5·4; N, 9·1%).

2-(p-γ-*Aminopropylaminostyryl*)-6-*methoxyquinoline*.—A suspension of the phthalimido-base (4 g.) in absolute alcohol (100 c.c.) was boiled for 2 hours after the addition of hydrazine hydrate

(5 c.c. of 95%). After removal of the alcohol and digestion with dilute hydrochloric acid the free *base* was isolated; it crystallised from 50% alcohol in golden-yellow plates, m. p. 156° (Found : C, 71·5; H, 7·1; N, 11·6. $C_{21}H_{23}ON_3,H_2O$ requires C, 71·8; H, 7·1; N, 11·9%. Found in material dried over phosphoric oxide at 110° in a high vacuum : N, 12·5. $C_{21}H_{23}ON_3$ requires N, 12·6%). It is freely soluble in alcohol and becomes red on exposure to air. Its dilute acid solutions are brilliant red, but it gives yellow solutions in concentrated acids.

The base (1 g.) was dissolved in absolute methyl alcohol (20 c.c.) and dry hydrogen chloride was passed until the colour, which at first was dark red, became bright yellow. On cooling, the *hydrochloride* crystallised in yellow needles, m. p. 222—223°, which were hygroscopic and freely soluble in water (Found : C, 49·8; H, 6·6; N, 7·7; Cl, 21·8. $C_{21}H_{23}ON_3,3HCl,3·5H_2O$ requires C, 49·8; H, 6·5; N, 8·4; Cl, 21·7%. Found in a specimen dried at 110° in a high vacuum : C, 56·7; H, 6·1; N, 9·3; Cl, 23·9. $C_{21}H_{23}ON_3,3HCl$ requires C, 56·9; H, 5·9; N, 9·5; Cl, 24·1%) (R59).

2-(p-*γ-Phthalimidopropylaminostyryl*)*quinoline*.—The method of Bulach (*Ber.*, 1889, **22**, 285) for the reduction of *p*-nitrobenzylidenequinaldine was not found convenient and an 80% yield was obtained by applying West's method (*loc. cit.*). 2-*p*-Aminostyrylquinoline (5 g.) and phthalo-*γ*-bromopropylimide (4·5 g.) were heated at 110—120° for 3 hours. After cooling, the *hydrobromide* was finely powdered and washed with hot benzene. The dark reddish-brown residue (yield, about 70%) was very sparingly soluble in most solvents and crystallised from acetic acid in dark red, microscopic needles, m. p. 248—249° (Found : N, 8·1. $C_{28}H_{23}O_2N_3,HBr$ requires N, 8·2%). This salt was suspended in cold aqueous ammonia for 2 hours, and the *base* collected, washed, and dried; it crystallised from alcohol in golden needles, m. p. 175—176° (Found : C, 77·3; H, 5·3; N, 9·8. $C_{28}H_{23}O_2N_3$ requires C, 77·5; H, 5·3; N, 9·7%).

2-(p-*γ-Aminopropylaminostyryl*)*quinoline*.—2-*p*-*γ*-Phthalimidopropylaminostyrylquinoline (5·3 g.) was hydrolysed with hydrazine hydrate (2·5 g. of 95%), and by following the usual procedure an 85% yield of the hydrochloride was obtained. It was crystallised by saturating a solution in absolute methyl alcohol with dry hydrogen chloride. Repeated crystallisations furnished long, dark red needles which blackened at 150°, m. p. 269—276° (decomp.), easily soluble in water and sparingly soluble in alcohol (Found : C, 54·9; H, 6·4; N, 9·9; Cl, 23·6. $C_{20}H_{21}N_3,3HCl,1·5H_2O$ requires C, 54·6; H, 6·1; N, 9·6; Cl, 24·2%. Found in dried material: C, 57·9; H, 6·0; N, 10·1. $C_{20}H_{21}N_3,3HCl$ requires C, 58·2; H, 5·8; N, 10·2%) (R57).

The *hydrochloride* was treated with aqueous sodium hydroxide and when the original dark red colour had changed to pure yellow (*ca.* 30 minutes) the *base* was isolated; it crystallised from 50% alcohol in long golden-yellow needles, m. p. 141—142°, becoming red when exposed to air, and soluble in the usual organic solvents (Found : N, 13·7. $C_{20}H_{21}N_3$ requires N, 13·9%).

2-m-*Nitrocinnamylidenequinaldine*.—Quinaldine (10 g.), *m*-nitrocinnamaldehyde (12 g.), and acetic anhydride (5 c.c.) were heated together at 110—120° for 3 hours. After cooling, the yellow crystalline solid was washed with alcohol and crystallised from benzene and then from methyl alcohol, forming long lemon-yellow needles, m. p. 158—159° (yield, 90%) (Found : C, 75·7; H, 4·7; N, 9·3. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·6; N, 9·3%). The *base* is almost insoluble in cold organic solvents and dissolves sparingly on heating. When bromine is added to a cold chloroformic solution, a solid bromo-derivative is precipitated. The *methiodide*, prepared in boiling absolute methyl-alcoholic solution, crystallised from that solvent in yellowish-green needles, m. p. 229—230° (decomp.), soluble in the usual organic solvents (Found : N, 6·2; I, 29·2. $C_{20}H_{17}O_2N_2I$ requires N, 6·5; I, 29·5%).

2-m-*Aminocinnamylidenequinaldine*.—A solution of crystallised stannous chloride (30 g.) in concentrated hydrochloric acid (30 c.c.) was slowly added to a boiling one of nitrocinnamylidenequinaldine (10 g.) in acetic acid (175 c.c.). A red colour was developed and a yellow crystalline stannichloride separated; after cooling, the solid was collected and vigorously shaken with aqueous sodium hydroxide (50%). Ice was then added, and the *base* extracted by chloroform. On crystallising from benzene and then from methyl alcohol, it was obtained as clusters of yellow needles, m. p. 147°, sparingly soluble in most organic solvents (Found : C, 83·5; H, 6·2; N, 10·3. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·8; N, 10·2%). It is not easily soluble in cold dilute acids, but after diazotisation it may be coupled with β-naphthol to a dark red azo-compound. The hydrogen sulphate separated from boiling 2*N*-sulphuric acid in yellowish-brown needles, which darkened at 220° and melted at 237° (decomp.).

2-m-*Nitrocinnamylidene*-6-*methoxyquinaldine*.—6-Methoxyquinaldine (10 g.), *m*-nitrocinnamaldehyde (10 g.), and acetic anhydride (4 c.c.) were heated together at 110—120° for 3 hours. The product crystallised from alcohol in long yellow needles, m. p. 197—198°, soluble in acetone and benzene, easily soluble in chloroform, and sparingly soluble in ether, ethyl alcohol,

methyl alcohol, and light petroleum (Found : C, 71·9; H, 5·0; N, 8·4. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·8; N, 8·4%).

2-m-*Aminocinnamylidene*-6-*methoxyquinaldine*.—Crystallised stannous chloride (5 g.) in concentrated hydrochloric acid (5 c.c.) was added to a boiling solution of 2-*m*-nitrocinnamylidene-6-methoxyquinaldine (2 g.) in acetic acid (50 c.c.). After the stannichloride had been isolated and treated with aqueous sodium hydroxide (50%), and the solution extracted with chloroform, 2-m-*aminocinnamylidene*-6-*methoxyquinaldine hydrochloride* was precipitated by passing dry hydrogen chloride into the extract. This salt crystallised from absolute methyl-alcoholic hydrogen chloride in brownish-yellow needles, m. p. 250—251° (yield, 65%), easily soluble in water and hygroscopic (Found : C, 60·1; H, 5·8; N, 7·1; Cl, 17·4. $C_{20}H_{18}ON_2,2HCl,1{\cdot}5H_2O$ requires C, 59·9; H, 5·7; N, 7·0; Cl, 17·5%. Found in a dried specimen : N, 7·6. $C_{20}H_{18}ON_2,2HCl$ requires N, 7·5%). Ammonia was added to the hydrochloride dissolved in water; the *aminocinnamylidene*-6-*methoxyquinaldine* which separated crystallised from 50% alcohol in light yellow needles, m. p. 139—140°, becoming red when exposed to air (Found : C, 75·1; H, 6·0; N, 8·9. $C_{20}H_{18}ON_2,H_2O$ requires C, 75·0; H, 6·3; N, 8·8%. Found in a specimen dried at 110° over phosphoric oxide : N, 9·4. $C_{20}H_{18}ON_2$ requires N, 9·3%). It dissolves in dilute and concentrated acids to red and yellow solutions respectively.

8-*Nitro*-6-*methoxyquinaldine*.—A mixture of 3-nitro-*p*-anisidine (25 g.), paraldehyde (40 g.), and concentrated hydrochloric acid (50 g.) was gently heated on a steam-bath under reflux until a vigorous reaction commenced; it was then removed for a time from the source of heat, well shaken, and finally heated on the bath for 4 hours. The dark solid obtained on pouring into excess of aqueous sodium hydroxide was collected, washed, dried, powdered with sand, and exhausted with ether. The residue on evaporation of the solvent crystallised from alcohol in long yellowish-brown needles, m. p. 186—187° (yield, *ca.* 50%) (Found : C, 60·6; H, 4·5; N, 12·6. $C_{11}H_{10}O_3N_2$ requires C, 60·6; H, 4·6; N, 12·8%). The *base* closely resembles the well-known lower homologue.

8-*Amino*-6-*methoxyquinaldine*.—(A) A solution of crystallised stannous chloride (17 g.) in concentrated hydrochloric acid (25 c.c.) was slowly added to one of 8-nitro-6-methoxyquinaldine (4·8 g.) in boiling glacial acetic acid (40 c.c.). The resulting red solution was boiled for 5 minutes, cooled, poured on ice, basified with sodium hydroxide solution, and extracted with chloroform. On passage of dry hydrogen chloride into the chloroform extract the hydrochloride was obtained as a dark red, sticky mass. Repeated interconversion from the base into the hydrochloride and vice versa afforded the pure *base*, which crystallised from 50% methyl alcohol in long white needles, m. p. 102° (Found : C, 68·6; H, 6·3; N, 14·4. $C_{11}H_{12}ON_2,0{\cdot}25H_2O$ requires C, 68·6; H, 6·2; N, 14·5%).

(B) As the yield of the base in (A) was unsatisfactory, the nitromethoxyquinaldine was also reduced with iron and hydrochloric acid in alcoholic solution (West's method); the isolated product was distilled, b. p. 175—185°/5 mm. The process was an improvement on (A). The best method tested was, however, the following.

8-Nitro-6-methoxyquinaldine (1 g.) was dissolved in alcohol (250 c.c.) and concentrated hydrochloric acid (5 c.c.) and after addition of platinum oxide (0·05 g.) the mixture was agitated in an atmosphere of pure dry hydrogen until the theoretical volume of the gas was absorbed. The base was isolated as a pale green, spongy mass, which crystallised from 50% methyl alcohol in long white needles identical with the analysed material (yield, 40%).

2-p-*Nitrobenzylidene*-8-*nitro*-6-*methoxyquinaldine*.—The condensation of 8-nitro-6-methoxyquinaldine with benzaldehyde could not be effected. A mixture of 8-nitro-6-methoxyquinaldine (1 g.), *p*-nitrobenzaldehyde (0·7 g.), and acetic anhydride (1 c.c.) was heated at 120° for 3 hours. The resulting solid crystallised from alcohol in long yellow needles, m. p. 182—183° (yield, 95%), easily soluble in benzene and sparingly soluble in alcohol (Found : C, 59·9; H, 3·9; N, 11·5. $C_{18}H_{13}O_5N_3,1{\cdot}5H_2O$ requires C, 60·0; H, 3·6; N, 11·7%). Similarly, 2-p-*dimethylaminobenzylidene*-8-*nitro*-6-*methoxyquinaldine* crystallised from alcohol in dark red, clustered needles, m. p. 204—205° (Found : N, 12·3. $C_{20}H_{19}O_3N_3$ requires N, 12·0%), and 2-m-*nitrocinnamylidene*-8-*nitro*-6-*methoxyquinaldine* crystallised from benzene in long yellow needles, m. p. 223—224°, sparingly soluble in alcohol or benzene, and readily soluble in acetone, chloroform, or acetic acid (Found : N, 11·5. $C_{20}H_{15}O_5N_3$ requires N, 11·1%).

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