337. *The Synthesis of β-6-Methoxyquinolyl(4)ethylamine, β-6-Methoxyquinolyl(4)propionamidine, and β-6-Methoxyquinolyl(4)ethylguanidine.*

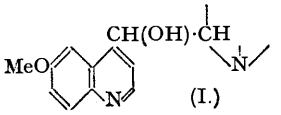
By James Walker.

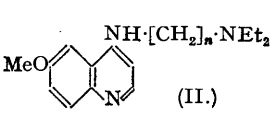
β-6-Methoxyquinolyl(4)-ethylamine, -propionamidine, and -ethylguanidine have been synthesized. In common with quinine, each possesses a strongly basic group separated by a chain of two carbon atoms from the 4-position of 6-methoxyquinoline. The substances were devoid of antimalarial activity.

In quinine, the significance of which in the chemotherapy of malaria requires no emphasis, one finds that a strongly basic group is separated from the 4-position of 6-methoxyquinoline by a chain of two carbon atoms as shown in the partial formula (I), where details of the quinuclidine ring system are omitted for the sake of clarity.

Although Giemsa and Oesterlin (*Arch. Schiffs- u. Tropen-Hygiene*, 1933, **37**, Beiheft 4), in studying numerous modifications of the quinine molecule, have attached considerable significance to the alcoholic hydroxyl group, and its replacement in the cinchona alkaloids by chlorine results in loss of antimalarial activity (Cohen and King, *Proc. Roy. Soc.*, 1938, *B*, **125**, 49), the prime necessity for the carbinol group appears to be discounted by the activity of 4-ω-dialkylaminoalkylamino-6-methoxyquinolines (II) (Magidson and Rubtsov, *J. Gen. Chem. Russia*, 1937, **7**, 1896) in

avian malaria. King and his colleagues (*Proc. Roy. Soc.*, 1938, *B*, **125**, 60; *J.*, 1940, 1307) have shown that some latitude is possible with the quinuclidine half of the quinine molecule by demon-


(I.)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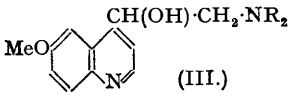
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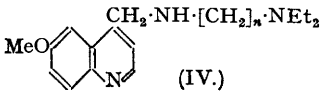
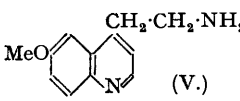

(IV.)

strating antimalarial activity in certain carbinolamines of type (III; R = alkyl), thus inviting comparison of types (II) and (III). Interposing a methylene group between the quinoline ring in (II) and the proximate nitrogen atom of the aliphatic diamine group, giving substances of type (IV), has been shown to have a dystherapeutic effect (Schönhöfer, " Medicine in its Chemical Aspects," 1938, **3**, 66; Work, *J.*, 1942, 426). Assuming, in line with current thought regarding the mode of action of drugs, that the antimalarial activity of quinine is due to its interference with the function of an essential structure in the parasite, it is likely that the two basic groups play a large part in the reaction and, if it is due to multipoint fit on a protein, the distance separating the basic centres should be significant. The three bases, β-6-methoxyquinolyl(4)-ethylamine (V), -propionamidine (VI), and -ethylguanidine (VII) were therefore synthesized since, in common with quinine, each possesses a strongly basic group separated by a chain of two carbon atoms from the 4-position of 6-methoxyquinoline.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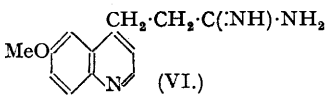
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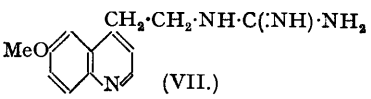
(VII.)

Condensation of 6-methoxylepidine with chloral was most advantageously carried out by heating them together at 120° in the presence of a little xylene as a flux. The use of pyridine as solvent at water-bath temperature (Alberts and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 1284; Clemo and Hoggarth, *J.*, 1939, 1242) was much less satisfactory, the methoxyl group in the 6-position appearing to reduce significantly the reactivity of the methyl group in the other nucleus. Hydrolysis of the resulting *ααα-trichloro-β-hydroxy-γ-6-methoxyquinolyl*(4)*propane* (VIII) afforded β-6-*methoxyquinolyl*(4)*acrylic acid* (IX), which was also obtained in less satisfactory over-all yield from 6-methoxyquinoline-4-aldehyde and malonic acid. Notwithstanding the use of freshly prepared selenium dioxide (Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654) for the preparation of 6-methoxyquinoline-4-aldehyde, *αβ-bis*-6-*methoxyquinolyl*(4)*ethylene* (X), together with quininic acid, was formed in considerable amount during the oxidation of 6-methoxylepidine, indicating the formation of this type of compound not to be attributable solely to ageing of the selenium dioxide used in the oxidation. Hydrogenation of the unsaturated acid (IX) afforded β-6-*methoxyquinolyl*(4)*propionic acid* (XI), which was converted through the *methyl* ester into the *hydrazide*, from which the amine (V), characterised as the *dihydrochloride*, was obtained in good yield by Naegeli's modification (*Helv. Chim. Acta*, 1929, **12**, 227) of the Curtius degradation. The acid (XI) was also converted through the *amide* into the *nitrile* from which the amidine (VI), characterised as the *nitrate* and as the *benzoate*, was prepared by the orthodox Pinner method. When 6-methoxyquinolylethylamine (V) was liberated from the dihydrochloride in concentrated aqueous solution with the calculated volume of standard alkali and refluxed with *S*-methyl*iso*thiourea sulphate in the usual way, an indifferent yield of the required guanidine (VII) was obtained and the product was difficult to purify. An excellent method, however, was found to be the interaction of the amine (V) dihydrochloride with *S*-methyl*iso*thiourea sulphate in concentrated aqueous ammonia at room temperature, the crude guanidine (VII) sulphate readily separating. This seemingly unorthodox technique has previously been used for the conversion of amino-acids into guanidino-acids (D.R.-P. 535,070; Schütte, *Z. physiol. Chem.*, 1943, **279**, 52) and is presumably applicable generally to primary and secondary amines which are stronger bases than ammonia, so that the ammonia, present in large excess, competes at a disadvantage with a more powerful nucleophilic reagent for the *S*-methyl*iso*thiourea. The guanidine (VII) was characterised as the *nitrate*.

Tests for therapeutic activity in *P. relictum* infections in canaries were kindly carried out by Dr. Ann Bishop at the Molteno Institute, Cambridge, on (V) (dihydrochloride) and (VI) (nitrate). Miss I. M. Tonkin kindly tested (V) (dihydrochloride), (VI) (nitrate and benzoate), and (VII)

(nitrate) for therapeutic activity in *P. gallinaceum* infections in chicks. No antimalarial action was observed.

Experimental.

6-Methoxylepidine.—The following reduction of 2-chloro-6-methoxylepidine is an improvement on previously described procedures. The chloro-compound (100 g.) (Ainley and King, *Proc. Roy. Soc.*, 1938, *B*, **125**, 60) in alcohol (750 c.c.) containing aqueous sodium hydroxide [23 g. (20% excess) in 75 c.c.] was vigorously stirred (mercury seal) in an atmosphere of hydrogen in the presence of palladised strontium carbonate (9 g.), the vessel being kept in a bath at 50—55° throughout. The anticipated volume of hydrogen was absorbed in a few hours, and the alcohol was removed by distillation from the filtered solution. The crude product was taken up in excess of 2N-sulphuric acid, filtered from any unreduced material, and the reduction product was liberated by careful addition, with stirring, of 40% aqueous sodium hydroxide. The precipitated oil quickly crystallised, affording 6-methoxylepidine monohydrate (88·2 g.; 96%), m. p. 52°.

αα-Trichloro-β-hydroxy-γ-6-methoxyquinolyl(4)propane (VIII).—6-Methoxylepidine monohydrate (108·7 g.) was dehydrated by exhaustive azeotropic distillation with benzene and then mixed with anhydrous chloral (125 g.; 1½ mols.) and xylene (15 c.c.) which served as a flux. The mixture was heated at 118—120° for 15 hours, becoming solid during the process. The *product* crystallised from alcohol in colourless rectangular plates (165 g.; 91%), m. p. 196—197° (Found: C, 48·5; H, 4·1; Cl, 33·4. $C_{13}H_{12}O_2NCl_3$ requires C, 48·7; H, 3·7; Cl, 33·2%).

The final mother-liquors were treated in the manner described below with potassium hydroxide to convert any remaining chloral–methoxylepidine into the acrylic acid, but only a small amount (7·5 g.) of unchanged 6-methoxylepidine was recovered.

β-6-Methoxyquinolyl(4)acrylic Acid (IX).—(A) The above chloral–methoxylepidine (146·5 g.) was added in portions to a solution of potassium hydroxide (146 g.) in absolute alcohol (600 c.c.) which was heated and stirred on the water-bath. A vigorous reaction took place after each addition, and finally the mixture was left for one hour on the water-bath. The precipitated potassium chloride was removed and washed with spirit. The alcoholic solution and washings, diluted with an equal volume of water, were concentrated under reduced pressure on the water-bath to remove alcohol. The aqueous solution, treated with norite, afforded, on acidification with glacial acetic acid, a yellow precipitate of the acrylic acid monohydrate (89 g.; 79%). The *acid* separated from 90% acetic acid in pale yellow fine needles which showed an intense yellow fluorescence in ultra-violet light, m. p. 277—278° (Found: C, 62·9; H, 5·2; loss at 110° in a vacuum, 7·8. Found, for anhydrous material: C, 67·5; H, 4·8. $C_{13}H_{11}O_3N,H_2O$ requires C, 63·2; H, 5·2; H_2O, 7·3. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%).

(B) 6-Methoxyquinoline-4-aldehyde (29·3 g.) (Kwartler and Lindwall, *J. Amer. Chem. Soc.*, 1937, **59**, 524) and malonic acid (37·5 g.) were condensed in pyridine (72 c.c.) containing piperidine (2 c.c.) on the water-bath for 3 hours and finally under reflux for ¼ hour. The product was isolated in the usual way and purified by reprecipitation from solution in excess of aqueous sodium hydroxide and recrystallisation from 90% acetic acid (yield, 25·3 g.; 65%), m. p. 277°.

αβ-Bis-6-methoxyquinolyl(4)ethylene (X).—The selenium-containing residues from the oxidation of 6-methoxylepidine in dioxan (Kaplan's conditions, *loc. cit.*) were extracted with hot pyridine. The hot solution was treated with norite and cooled, whereupon a solid separated. The solid was extracted with chloroform, and quininic acid remained undissolved, m. p. after recrystallisation from nitrobenzene, 279—280° (Found: C, 65·0; H, 4·2. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·4%). The reddish-orange chloroform extract was filtered through alumina, affording a clear orange solution with a strong greenish-blue fluorescence. Evaporation to dryness and recrystallisation of the residue from ethyl acetate afforded fine yellow prisms of the *ethylene*, m. p. 195—196° [Found: C, 76·6; H, 5·4; N, 8·4; *M* (Rast), 368. $C_{22}H_{18}O_2N_2$ requires C, 77·2; H, 5·3; N, 8·2%; *M*, 342].

β-6-Methoxyquinolyl(4)propionic Acid (XI).—The above acrylic acid (IX) (25·3 g.) was dissolved in a slight excess of 2N-aqueous sodium hydroxide and shaken in an atmosphere of hydrogen in the presence of palladised strontium carbonate (7 g.). The theoretical volume of hydrogen was readily absorbed (in 3 hours) and no further absorption took place on continued shaking (for 1 hour). The product (24·3 g.) was isolated in the usual way. The *acid* separated from 30% aqueous acetic acid in fine colourless prisms, m. p. 225—226° (Found: C, 67·2; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%). The solid and its solution in aqueous acetic acid both showed an intense bluish-white fluorescence in ultra-violet light.

The *methyl* ester (24·9 g.) was obtained by refluxing the acid (25 g.) with methanol (150 c.c.) and concentrated sulphuric acid (9 c.c.) for 8 hours. It was isolated in the normal way, and separated from ligroin containing a little benzene in colourless rectangular prisms, m. p. 90° (Found: C, 68·3; H, 5·9. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%).

The *amide*, obtained by treating the methyl ester (24·9 g.) in methyl alcohol (50 c.c.) with excess of concentrated aqueous ammonia (300 c.c.) at 37° for 5 days, separated from water in colourless needles (19·6 g.), m. p. 187—188° (Found: C, 67·5; H, 6·0; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%).

The *hydrazide*, obtained by refluxing the methyl ester (29·2 g.) with a slight excess of 50% hydrazine hydrate in methyl alcohol (70 c.c.) for 5 hours, separated from spirit in minute colourless prisms (28 g.), m. p. 161—162° (Found: C, 63·2; H, 6·0; N, 16·8. $C_{13}H_{15}O_2N_3$ requires C, 63·7; H, 6·1; N, 17·1%).

β-6-Methoxyquinolyl(4)propionitrile.—The above amide (5·5 g.) was refluxed with phosphorus oxychloride (6 c.c.) in dry chloroform (20 c.c.) for 25 minutes, the solid rapidly dissolving. Solvent and excess of phosphorus oxychloride were removed in a vacuum on the water-bath and the residue was distributed between ether and ice-cold aqueous alkali. The ethereal solution was dried over sodium sulphate and evaporated, the desiccant being washed with acetone to recover some of the product which crystallised out, and the thick colourless syrup (4·9 g.) promptly crystallised on removal of the solvent.

The *nitrile* separated from benzene–ligroin (*ca.* 1 : 1) in clusters of transparent, colourless, rectangular prisms, m. p. 96—97° (Found : N, 13·3. $C_{13}H_{12}ON_2$ requires N, 13·2%).

β-6-Methoxyquinolyl(4)propionamidine (VI) *Nitrate.*—A solution of the above nitrile (6·66 g.) in a mixture of absolute alcohol (15 c.c.) and dioxan (15 c.c.) was saturated with hydrogen chloride at 0° and kept in the ice-chest for several days. The solvent and excess of hydrogen chloride were removed at room temperature in a vacuum and the residue was warmed at 37° with 10% alcoholic ammonia (90 c.c.) for a week. The small amount of ammonium chloride was rejected and the filtered solution, on evaporation to dryness, afforded a crude hydrochloride (7·7 g.) which could not be satisfactorily crystallised. The main bulk of the product was dissolved in a small volume of water and treated with a similar solution of an equal weight of ammonium nitrate, and the mixture was evaporated to dryness. The *nitrate* crystallised from about 1½ times its own weight of water in clusters of fine colourless needles, m. p. 190—191° (decomp.) (Found : C, 53·3; H, 5·5; N, 18·6. $C_{13}H_{15}ON_3,HNO_3$ requires C, 53·4; H, 5·5; N, 19·2%).

β-6-Methoxyquinolyl(4)propionamidine Benzoate.—The crude amidine hydrochloride, prepared from the nitrile (7·2 g.) as described above, was dissolved in a small volume of water and treated with a slight excess of sodium benzoate in concentrated aqueous solution. The precipitated *benzoate* (11·3 g.) separated from about 8 times its own weight of water in colourless prisms, m. p. 192° (Found : C, 68·0; H, 6·0; N, 11·9. $C_{13}H_{15}ON_3,C_7H_6O_2$ requires C, 68·4; H, 6·0; N, 11·9%). The benzoate was much more soluble in spirit than in water.

β-6-Methoxyquinolyl(4)ethylamine (V) *Dihydrochloride.*—The above hydrazide (31·9 g.) was dissolved in 40% aqueous acetic acid (325 c.c.) and cooled below 0° while an aqueous solution (100 c.c.) of sodium nitrite (36 g.) was added dropwise with thorough stirring. The azide quickly separated and the solid was collected after 1½ hours. The filtrate was neutralised to pH 8·5 with solid sodium carbonate and the azide was re-suspended in the slightly alkaline liquor and again collected, washed with water, and dried overnight in a vacuum over phosphoric oxide. The crude *dry* azide was then cautiously warmed in dry benzene (100 c.c.) until reaction set in. After the spontaneous reaction subsided the mixture was refluxed for 20 minutes and cooled. The brown solution was treated with concentrated hydrochloric acid (50 c.c.) and the benzene was removed on the water-bath after the reaction had ceased. Water was added to keep the hydrochloride in solution, and the *dihydrochloride*, obtained after decolourisation with charcoal and evaporation to dryness, separated from 90% alcohol in fine colourless needles (29·7 g.; 83%), m. p. 253° (Found : C, 52·7; H, 6·0; N, 10·4. $C_{12}H_{14}ON_2,2HCl$ requires C, 52·4; H, 5·8; N, 10·2%).

β-6-Methoxyquinolyl(4)ethylguanidine (VII) *Nitrate.*—The preceding dihydrochloride (3 g.) and *S*-methyl*iso*thiourea sulphate (3 g.; 2 equivs.) were dissolved in concentrated aqueous ammonia (35 c.c.) at room temperature and set aside for 42 hours, crystallisation of solid commencing within 2 hours. The crude methoxyquinolylethylguanidine sulphate was collected, washed with a little water, and dried in a vacuum (yield, 2·8 g.); recrystallisation at this stage afforded a somewhat gelatinous product. The reaction mother-liquors were evaporated to dryness and worked up for nitrate (0·11 g.). The crude sulphate (1 g.) was dissolved in hot water (*ca.* 10 c.c.) and treated with a warm aqueous solution (2 c.c.) of ammonium nitrate (2 g.), whereupon the *nitrate* crystallised out. Recrystallisation from a small volume of water afforded colourless clusters of extremely fine felted needles, m. p. 239° (decomp.), giving a positive Sakaguchi reaction (Found : C, 50·6; H, 5·7; N, 22·5. $C_{13}H_{16}ON_4,HNO_3$ requires C, 50·8; H, 5·6; N, 22·8%). The over-all yield of the nitrate was 70%.

When the foregoing reaction was carried out in hot aqueous solution, using (in the order of mixing) 1 mol. of amine dihydrochloride, 2 mols. of sodium hydroxide, and 1 equiv. of *S*-methyl*iso*thiourea sulphate, the yield and quality of the product were markedly inferior.

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