303. *Derivatives of 6-Methoxyquinaldine with Basic Substituents in the 4-Position.*

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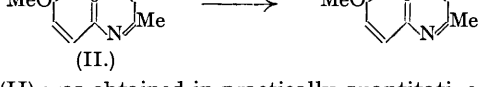
Attention is directed to the smooth replacement of the sulphonic acid group in quinoline-4-sulphonic acids by reaction with amines as a means of preparing quinolines substituted in the 4-position by basic groups.

IN contrast with the activity shown by certain 4-dialkylaminoalkylamino-6-methoxyquinolines in bird malaria (Magidson and Rubtsov, *J. Gen. Chem. Russia*, 1937, **7**, 1896), no activity was observed in analogous quinaldines (*e.g.*, Kermack and Smith, *J.*, 1931, 3096; Krichevskii *et al.*, *J. Microbiol. Epidemiol. Immunobiol. Russia*, 1935, **14**, 642). In view of the greater accessibility of the quinaldines as compared with the quinolines of this type, the present author, towards the end of 1941, began a further investigation of other 6-methoxyquinaldines, but, while the work was still in progress, essentially the same project was independently covered by Holcomb and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**, 1309), who actually record the observation of antimalarial activity in 4-γ-diethylaminopropylamino-6-methoxyquinaldine (I), and the writer's interest was then withdrawn from this topic although the work, as now described below, differed in technical detail from that of Holcomb and Hamilton. In the interval, however, much attention has been devoted to the subject of quinolines substituted in the 4-position by basic side-chains in view of the marked antimalarial properties of resochin (7-chloro-4-δ-diethylamino-α-methylbutylaminoquinoline), which can be regarded as being derived from mepacrine by ablation of the methoxylated benzene ring, and the corresponding 3-methyl compound, sontochin (D.R.-P. 683,692; U.S.P. 2,233,970). Much has recently been published in the United States in this connection (*e.g.*, Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1208, 1214; Tarbell *et al.*, *ibid.*, p. 1217; Carmack *et al.*, *ibid.*, p. 1220; Pearson, Jones, and Cope, *ibid.*, p. 1225; Riegel *et al.*, *ibid.*, p. 1229; Breslow *et al.*, *ibid.*, p. 1232; Elderfield *et al.*, *ibid.*, p. 1250). The method regularly used for the introduction of the aliphatic basic side-chains into the 4-position of quinolines has been to condense the appropriate 4-chloro-compounds with the appropriate amines at a high temperature, and fair yields have been reported as a rule. Occasionally, phenol has been added as a catalyst but it does not appear to have the same marked influence in the quinoline series as it has with 5-chloroacridines (cf. Magidson and Grigorowsky, *Ber.*, 1936, **69**, 400). Potassium iodide has also been applied as a catalyst but there is little evidence of its efficaciousness, and glacial acetic acid has been used as a solvent in such condensations with aliphatic amines (Meyer and Drutel, *Compt. rend.*, 1936, **205**, 148) although its use is more familiar with anilines (*e.g.*, Fischer, Diepolder, and Wölfel, *J. pr. Chem.*, 1925, **109**, 59).

The present paper records the use of 6-*methoxyquinaldine*-4-*sulphonic acid* (II) for this purpose in an application of a method outlined in the patent literature (D.R.-P. 615,184). In the original patent, quinoline-2- or -4-sulphonic acids were condensed with amines with or without the addition of a catalyst, such as zinc chloride, but the latter was used in the experiments described below, in which (II) has been condensed with ammonia to give 4-amino-6-methoxyquinaldine (III), with α-aminopyridine to give 4-α-*pyridylamino*-6-*methoxyquinaldine* (IV) in poor yield, with γ-diethylaminopropylamine to give (I) (characterised as the dihydrochloride), and with δ-diethylamino-α-methylbutylamine to give 4-δ-*diethylamino*-α-*methylbutylamino*-6-*methoxyquinaldine* (V) (characterised as the *dihydrobromide*). The sulphonic



(II.)

(I) R = $CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$
(III) R = H
(IV) R = C_5H_4N
(V) R = $CHMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$

acid (II) was obtained in practically quantitative yield from 4-chloro-6-methoxyquinaldine and sodium sulphite in aqueous solution (cf. Besthorn and Geisselbrecht, *Ber.*, 1920, **53**, 1017), and subsequent condensation with amines proceeded as a smooth homogeneous reaction affording products which readily crystallised in the crude state (cf. Bachman and Cooper, *J. Org. Chem.*, 1944, **9**, 307). Holcomb and Hamilton (*loc. cit.*) failed to isolate a satisfactory condensation product from 4-chloro-6-methoxyquinaldine and α-aminopyridine, but a small yield of the expected product was readily isolated using the sulphonic acid. Furthermore, condensation with ammonia proceeded particularly readily with the sulphonic acid in marked contrast with

the behaviour of 4-chloroquinolines (cf. Elderfield *et al.*, *loc. cit.*; Backeberg and Marais, *J.*, 1942, 381).

Tests for therapeutic activity in *P. relictum* infections in canaries were kindly carried out by Dr. Ann Bishop at the Molteno Institute, Cambridge, on sodium 6-methoxyquinaldine-4-sulphonate, 4-α-pyridylamino-6-methoxyquinaldine (IV), and 4-δ-diethylamino-α-methylbutylamino-6-methoxyquinaldine (V) dihydrobromide, but no activity was detected. It is now obvious that a methyl group in the 2-position in quinolines, though not in the 3-position (cf. sontochin), has a marked dystherapeutic effect probably by presenting to the host a point of metabolic attack.

Experimental.

6-Methoxyquinaldine-4-sulphonic Acid (II).—Ethyl β-*p*-anisidinocrotonate (Coffey, Thomson, and Wilson, *J.*, 1936, 856) was cyclised by Limpach's technique (*Ber.*, 1931, **64**, 969) and the resulting 4-hydroxy-6-methoxyquinaldine was converted into the chloro-compound in 90% yield following the method of Fischer *et al.* (*loc. cit.*). 4-Chloro-6-methoxyquinaldine (5 g.) was refluxed with an aqueous solution (40 c.c., adjusted to pH 8 with N-hydrochloric acid) of sodium sulphite heptahydrate (12 g.) until a homogeneous solution was obtained (3½ hours) and then for a further ½ hour. The solution, treated with norite, was filtered and cooled, affording a copious separation of colourless prisms of the sodium salt The free *acid*, precipitated by acidifying an aqueous solution of the sodium salt to Congo-red with 16% hydrochloric acid, separated from water in pale cream-coloured hydrated prisms which lost part of the water of crystallisation in a vacuum desiccator, darkened at about 296°, and had m. p. 302—303° (decomp.) (Found : C, 48·6; H, 5·0; N, 5·2. $C_{11}H_{11}O_4NS,H_2O$ requires C, 48·7; H, 4·8; N, 5·2%). The yield was nearly quantitative.

4-Amino-6-methoxyquinaldine (III).—6-Methoxyquinaldine-4-sulphonic acid (6 g.), 25% aqueous ammonia solution (30 c.c.), and zinc chloride (1 g.) were heated in a sealed tube at 130° for 20 hours. On cooling, large yellow plates were deposited. The mixture was warmed to effect solution, cooled, and treated with excess of 2N-sodium hydroxide (25—30 c.c.). The precipitated oil rapidly crystallised in colourless needles (3·75 g.; 84%), m. p. 206°. Recrystallisation from dilute aqueous alcohol afforded thin plates, m. p. 208—209° (Found : C, 70·0; H, 6·5; N, 14·9. Calc. for $C_{11}H_{12}ON_2$: C, 70·2; H, 6·4; N, 14·9%). Koenigs and v. Loesch (*J. pr. Chem.*, 1935, **143**, 59) record m. p. 211—213°, and Backeberg and Marais (*loc. cit.*) record m. p. 209°.

4-α-Pyridylamino-6-methoxyquinaldine (IV).—6-Methoxyquinaldine-4-sulphonic acid (5·06 g.), freshly distilled α-aminopyridine (3·8 g.), zinc chloride (1 g.), and water (25 c.c.) were heated in a sealed tube at 140° for 30 hours. The product was distributed between ether and excess of 2N-sodium hydroxide. The ether was well washed with water, dried, and evaporated, affording a cream-coloured *solid* (0·33 g.; 6·2%), which separated from benzene in rosettes of fine colourless prisms, m. p. 196—197° (Found : C, 72·6; H, 5·7; N, 15·5. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·8%).

4-γ-Diethylaminopropylamino-6-methoxyquinaldine (I) *Dihydrochloride*.—6-Methoxyquinaldine-4-sulphonic acid (5·06 g.), γ-diethylaminopropylamine (4·3 g.), zinc chloride (1·2 g.), and water (18 c.c.) were heated in a sealed tube at 140° for 24 hours. The product was distributed between ether and 3N-sodium hydroxide. The ethereal solution was well washed with water, dried, and evaporated, affording a stiff pale yellow syrup which crystallised completely in the form of transparent plates (4·26 g.; 71%); the solid did not remelt on the boiling water-bath. The base was dissolved in a small volume of warm alcohol and treated with the calculated volume of alcoholic hydrochloric acid. The dihydrochloride, obtained on evaporation, separated from ethyl alcohol–ethyl acetate (1 : <1) in minute clusters of colourless prisms, m. p. 134° (Found, in material dried over sulphuric acid in a vacuum : C, 53·7, 54·2; H, 7·9, 7·8; N, 10·5. $C_{18}H_{27}ON_3,2HCl,1\frac{1}{2}H_2O$ requires C, 53·9; H, 8·0; N, 10·5. Calc. for $C_{18}H_{27}ON_3,2HCl,2H_2O$: C, 52·7; H, 8·0; N, 10·2%). Holcomb and Hamilton (*loc. cit.*) obtained a dihydrate, and record m. p. 126—127°; Van Arendonk and Shonle (*J. Amer. Chem. Soc.*, 1944, **66**, 1284) record m. p. 125—126°.

4-δ-Diethylamino-α-methylbutylamino-6-methoxyquinaldine (V) *Dihydrobromide*.—6-Methoxyquinaldine-4-sulphonic acid (7·6 g.), δ-diethylamino-α-methylbutylamine (9·6 g.), zinc chloride (1 g.), and water (20 c.c.) were heated in a sealed tube at 150° for 20 hours. The product was isolated as in the preceding case and the *base*, obtained initially as an amber syrup (6·6 g.; 67%), rapidly crystallised, affording a cream-coloured solid, m. p. 120—122°, clearing at 123° (Found : OMe, 9·5. $C_{20}H_{31}ON_3$ requires OMe, 9·4%). The *dihydrobromide*, obtained by neutralisation with the calculated volume of N-hydrobromic acid and evaporation to dryness, separated from ethyl alcohol–ethyl acetate (approx. 1 : 2) in clusters of colourless radiating prisms, m. p. 197—198° (Found : C, 48·7; H, 6·7; N, 8·4; Br, 32·3. $C_{20}H_{31}ON_3,2HBr$ requires C, 48·9; H, 6·7; N, 8·6; Br, 32·6%). The dihydrochloride of this base has been described by Holcomb and Hamilton (*loc. cit.*).

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