Antimalarial Agents. V. 5-Methylquinolines and 5-Quinolinecarboxylic Acids (1)

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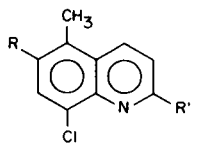
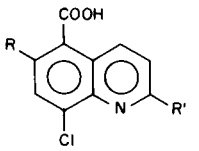
Several routes are available for the preparation of 5-quinolinecarboxylic acids (II). The most direct methods for the 2-substituted derivatives of II seem to be the oxidation of the corresponding 2-substituted 5-methylquinolines (I) or the Doebner-Miller synthesis, *i.e.*, the condensation of *m*-aminobenzoic acids with acetaldehyde and a second aldehyde (OCH-R'). Instead of a mixture of the latter two aldehydes, their aldol condensation product (OCH-CH=CH-R', *e.g.* cinnamaldehyde) can be used.

Our attempts to synthesize 6,8-dichloro-2-phenyl-5-quinolinecarboxylic acid (IIc) from 5-amino-2,4-dichlorobenzoic acid (III) and cinnamaldehyde were not successful under a variety of conditions; thus, 5-cinnamylideneamino-2,4-dichlorobenzoic acid (m.p. 198-200°, from ethyl acetate, acceptable analysis) was the only product isolated when the Doebner-Miller reaction of III with cinnamaldehyde was carried out in concentrated hydrochloric acid/zinc chloride at 25° or 120°, in concentrated hydrochloric acid/zinc chloride/arsenic pentoxide at 25°, and acetic acid at 80°; polyphosphoric acid at 25°, and concentrated sulfuric acid/arsenic pentoxide at 50-60° (15 minutes) or at 140-150° (3 hours) resulted in tars from which no quinolinecarboxylic acid (IIc) could be obtained; glacial acetic acid/arsenic pentoxide at 115° yielded only 5-acetamido-2,4-dichlorobenzoic acid (m.p. 243-246°, from acetic acid, acceptable analysis). Traces of 6,8-dichloro-2-methyl-5-quinolinecarboxylic acid (IId) and starting material (III) only were isolated from the tars obtained in the reactions of III with a mixture of acetaldehyde and *p*-chlorobenzaldehyde, or acetaldehyde and 3,4-dichlorobenzaldehyde in concentrated hydrochloric acid at 25°. The Doebner-Miller reaction of 3-amino-4-chlorobenzoic acid (IV) with cinnamaldehyde did not produce any 8-chloro-2-phenyl-5-quinolinecarboxylic acid (IIa) when carried out in polyphosphoric acid at 25°, acetic acid/zinc chloride at 115° and acetic acid/arsenic pentoxide at 115°; when acetic acid was used at 115° the only product isolated was 3-cinnamylideneamino-4-chlorobenzoic acid (m.p. 205-208°, from acetone, acceptable analysis); in a single case (concentrated sulfuric acid/arsenic pentoxide, 4 hours at 140-150°) a trace of IIa was obtained. Thus it appears that the reactivity of the amino acids III and IV in the Doebner-Miller quinoline syntheses is considerably reduced by the carboxyl group and by the chlorine atom.



I

Ia, R = H, R' = Ph
Ib, R = Cl, R' = H
Ic, R = Cl, R' = Ph



II

IIa, R = H, R' = Ph
IIb, R = Cl, R' = H.H_2O
IIc, R = Cl, R' = Ph
IId, R = Cl, R' = Me
IIe, R = R' = H
IIf, R = Cl, R' = *p*-ClC_6H_4

The amino acids reacted readily, however, with glycerol in a Skraup synthesis to give 6,8-dichloro-5-quinolinecarboxylic acid monohydrate (IIb) and 8-chloro-5-quinolinecarboxylic acid (IIe, m.p. 323-325°, acceptable analysis) in 24% and 38% yield, respectively. Since the latter product has been reported (2) to melt seven degrees lower than our sample, it was analyzed.

A replacement of the carboxyl group in III and IV by a methyl group increased the reactivity of the corresponding toluidines, *i.e.*, 5-amino-2,4-dichlorotoluene (V) and 3-amino-4-chlorotoluene (VI), in both the Doebner-Miller and Skraup quinoline syntheses. The 5-methyl-2-phenylquinolines Ia and Ic were obtained from VI and V, respectively, in *ca.*, 14% yield by the Doebner-Miller method; the Skraup synthesis of Ib gave a 57% yield based on V. The oxidation of Ia seems to be a more reliable method for the preparation of IIa than its direct synthesis from IV and cinnamaldehyde by the Doebner-Miller method.

None of the products tested (Ib, Ic, IIa, IIb, and III-V) had any antimalarial activity (3) at 40, 160 and 640 mg/kg; Ib exhibited 100% toxicity in 4 days at 640 mg/kg but did not cause any photosensitization (4) at 500 mg/kg; Ia and IIb were not phototoxic at 500 and 400 mg/kg, respectively. 8-Chloro-2-phenyl-5-quinolinecarboxylic acid (IIa) was quite phototoxic since it caused photosensitization at 100 mg/kg.

EXPERIMENTAL

Materials.

The pure *m*-aminobenzoic acids III (6) and IV (5), and the di-

chlorotoluidine V (7) were prepared and used. The remaining starting materials, including VI, are commercially available and were freshly pruified.

Methods.

The Doebner-Miller syntheses with the *m*-aminobenzoic acids III and IV were carried out by stirring the mixture or solution of reactants and solvent at a desired temperature. The solid was filtered off and treated with hot water and/or solvents, acids and/or bases. The extract and the aqueous filtrate of the original solid were worked up separately to isolate the products formed or the unreacted amino acids. In the cases where acetic acid or ethanol was the reaction solvent, the filtrate of the reaction mixture was evaporated and the residue was worked up. The preparation of 6,8-dichloro-2-methyl-5-quinolinecarboxylic acid (IId) is given as an example, although the experiment was designed for the synthesis of 2-(*p*-chlorophenyl)-6,8-dichloro-5-quinolinecarboxylic acid (IIf).

The Skraup syntheses with III, IV and V, the Doebner-Miller syntheses with the *m*-toluidines V and VI, as well as the oxidation of Ia to IIa are described in detail below.

8-Chloro-5-methyl-2-phenylquinoline (Ia).

The product (m.p. 126-129°) was prepared and purified by the method described for Ic below; VI was used instead of V. The yield was 14%.

Anal. Calcd. for $C_{16}H_{12}ClN$ (IIIa). C, 75.74; H, 4.73; N, 5.52. Found: C, 75.73; H, 5.03; N, 5.66.

6,8-Dichloro-5-methylquinoline (Ib).

A mixture of 52.8 g. (0.30 mole) of 5-amino-2,4-dichlorotoluene (V), 54.2 g. (0.56 mole) of glycerol, 36.2 g. (0.25 mole) of arsenic acid and 167 g. of concentrated sulfuric acid was heated at 150-160° for 5 hours. The dark reaction mixture was heated with 300 ml. of water and filtered hot through Celite. The filtrate was made alkaline with 20% aqueous sodium hydroxide to give a solid. It was recrystallized from ethanol to obtain 36.1 g. (57%) of the product, m.p. 117-119.

Anal. Calcd. for $C_{10}H_7Cl_2N$ (Ib): C, 56.60; H, 3.30; N, 6.60. Found: C, 56.85; H, 3.59; N, 6.50.

6,8-Dichloro-5-methyl-2-phenylquinoline (Ic).

A mixture of 8.8 g. (50 mmoles) of 5-amino-2,4-dichlorotoluene (V), 6.6 g. (50 mmoles) of cinnamaldehyde, and 7.1 g. (50 mmoles) of arsenic acid in 150 ml. of glacial acetic acid was refluxed for 30 minutes. The ice-cold reaction mixture was filtered and the filtrate was stripped of acetic acid *in vacuo* at room temperature. The syrupy residue was filtered and the solid was washed several times with cold ethanol yielding 2.1 g. (14%) of yellow solid, m.p. 142-146°. It was recrystallized from ethyl acetate to obtain 1.5 g. of product, m.p. 147-149.

Anal. Calcd. for $C_{16}H_{11}Cl_2N$ (Ic): C, 66.68; H, 3.85; Cl, 24.61; N, 4.86. Found: C, 66.49; H, 4.03; Cl, 24.96; N, 5.03.

8-Chloro-2-phenyl-5-quinolinecarboxylic Acid (IIa).

A mixture of 10.1 g. (40 mmoles) of 8-chloro-5-methyl-2-phenylquinoline (Ia) and 5.3 g. (41 mmoles) of chromic oxide in 82 ml. of dilute sulfuric acid (1:1 by volume) was refluxed for 4 hours. A second portion of 5.3 g. of chromic oxide was added and the mixture was refluxed for 15 hours. After an addition of another 5.3 g. of chromic oxide the reaction mixture was refluxed an additional 24 hours, cooled and filtered. The solid was washed with 6*N* sulfuric acid, treated with 2*N* sodium hydroxide, and filtered to recover 4.5 g. of Ia. The filtrate was decolorized with Nuchar and acidified with acetic acid to obtain 1.9 g. (33% yield considering recovered Ia) of the product, m.p. 248-251°. The melting point of the product was raised to 251-253° by recrystallization from chloroform.

Anal. Calcd. for $C_{16}H_{10}ClNO_2$ (IIa): C, 67.73; H, 3.53; N, 4.94. Found: C, 67.88; H, 3.97; N, 5.30.

This product was identical with a sample obtained in a very low yield from 3-amino-4-chlorobenzoic acid (IV) and cinnamaldehyde (in concentrated sulfuric acid/arsenic pentoxide 4 hours at 140-150°) by the Doebner-Miller method.

6,8-Dichloro-5-quinolinecarboxylic Acid Monohydrate (IIb).

A mixture of 41.2 g. (20 mmoles) of 3-amino-4,6-dichlorobenzoic acid (III), 36.8 g. (45 mmoles) of glycerol, 30.0 g. (0.21 mole) of arsenic acid and 44.4 g. of concentrated sulfuric acid was heated at 150-160° for 5 hours, diluted with 600 ml. of water, boiled and filtered hot using Celite. The filtrate was allowed to stand at room temperature for 6 hours and filtered to obtain 14.1 g. of solid which was recrystallized from ethanol-water; 12.5 g. (24%) of the product m.p. 260-262° was recovered.

Anal. Calcd. for $C_{10}H_5Cl_2NO_2 \cdot H_2O$ (IIb): C, 46.15; H, 2.69; N, 5.38. H_2O, 6.93; Found: C, 46.10; H, 3.24; N, 5.31; H_2O, 6.90.

6,8-Dichloro-2-methyl-5-quinolinecarboxylic Acid (IId).

To a stirred mixture of 5.0 g. (25 mmoles) of 3-amino-4,6-dichlorobenzoic acid (III), 3.5 g. (25 mmoles) of *p*-chlorobenzaldehyde and 3.5 g. (23 mmoles) of zinc chloride in 100 ml. of concentrated hydrochloric acid was added dropwise 5.0 g. (114 mmoles) of acetaldehyde at 30°. The reaction mixture was refluxed for 3 hours and filtered. The filtrate was diluted with 500 ml. of water and extracted with ether. The ether solution was worked up to obtain 3.9 g. of a solid which was extracted with hot benzene. The benzene solution contained unreacted III. The benzene insoluble solid was recrystallized from ethanol to recover 640 mg. of product, m.p. 244-245°, which was established to be IId rather than the expected 2-(*p*-chlorophenyl)-6,8-dichloro-5-quinolinecarboxylic acid (IIf).

Anal. Calcd. for $C_{11}H_7Cl_2NO_2$ (IId): C, 51.55; H, 2.73; N, 5.47. Found: C, 51.64; H, 2.90; N, 5.66.

The same product (IId) was obtained when 3,4-dichlorobenzaldehyde was used instead of *p*-chlorobenzaldehyde.

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