[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of 1-Substituted Aminobenzo(f)quinolines*

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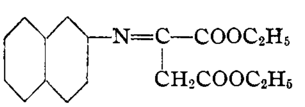
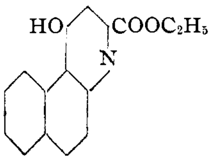
The importance of synthetic antimalarials has made it desirable to study several series of benzoquinolines.[1] In this particular investigation the preparation of a number of 1-substituted aminobenzo(f)quinolines was effected by the condensation of 1-chlorobenzo(f)quinoline[2] with various amines.

The synthesis of 1-chlorobenzo(f)quinoline involved, first, the condensation of 2-naphthylamine with oxalacetic ester to give 2-naphthyliminosuccinic ester (I).



I



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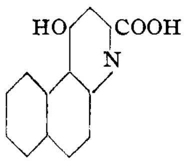

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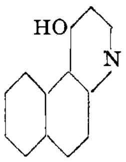

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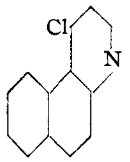

V

When (I) was cyclized in mineral oil, preheated to 230°, 1-hydroxy-3-carbethoxybenzo(f)quinoline (II) resulted, and (II) upon hydrolysis in alkaline solution gave 1-hydroxy-3-carboxybenzo(f)quinoline (III). By heating (III) near its melting point, carbon dioxide was evolved yielding 1-hydroxybenzo(f)quinoline (IV).

Our attempts to prepare (III) by the oxidation of 1-hydroxy-3-methylbenzo(f)quinoline[3] were unsuccessful. Alkyl groups on the nitrogen containing ring appear to be inert toward oxidation by the usual methods when hydroxyl is also present on the ring.[4]

The final step in the synthesis of 1-chlorobenzo(f)quinoline (V) was accomplished by refluxing (IV) with an excess of phosphorus oxychloride.

The amines: morpholine, piperidine, γ-N-morpholinopropylamine, and γ-N-diethylaminopropylamine, were condensed with (V) giving very good yields of the corresponding 1-substituted aminobenzo(f)quinolines. The γ-N-morpholinopropylamine derivative was crystallized as a dihydrate from ethanol–water solution.

Hydrogenation of (I) at 80° and 500 pounds pressure in the presence of Raney nickel resulted in the formation of diethyl 2-naphthylaminosuccinate, a low-melting crystalline solid, which gave the corresponding acid upon saponification with alcoholic potassium hydroxide. These two compounds have been reported by Hell and Poliakoff,[5] who condensed bromosuccinic ester with 2-naphthylamine and then hydrolyzed the resulting ester. However, they reported the ester as an unstable oil, with characteristics differing markedly from those observed in this Laboratory. The acid prepared in this investigation was identical in physical properties with the 2-naphthylaminosuccinic acid reported by Hell and Poliakoff.

Experimental

Diethyl 2-Naphthyliminosuccinate (I).—A mixture of 20 g. (0.14 mole) of 2-naphthylamine and 31.5 ml. (0.19 mole) of oxalacetic ester was allowed to stand for forty-eight hours over concentrated sulfuric acid in a vacuum desiccator. The crude product was recrystallized twice from ethanol, yielding 18 g. (41%) of a bright yellow crystalline solid, m. p. 66–67°. It was very soluble in the common organic solvents, and was readily cleaved by warming in mineral acids.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.95; H, 6.11. Found: C, 68.82, 69.10; H, 6.21, 6.11.

1-Hydroxy-3-carbethoxybenzo(f)quinoline (II).—Thirty-seven grams (0.12 mole) of (I) was added slowly to mineral oil, preheated to 230°. The cooled product was collected by filtration, washed with benzene, and crystallized from glacial acetic acid, m. p. 215–217°. The yield was 20 g. (65%).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 61.91; H, 4.90. Found: C, 71.86, 71.64; H, 4.90, 4.95.

1-Hydroxy-3-carboxybenzo(f)quinoline (III).—This acid was obtained in quantitative yield by refluxing (II) for two hours in 5% sodium hydroxide, followed by acidification with dilute hydrochloric acid. The product was extremely insoluble in common organic solvents. It melted at 302° with loss of carbon dioxide.

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.28; H, 3.79. Found: C, 70.32, 70.07; H, 3.97, 3.76.

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(1) Clem and Hamilton, THIS JOURNAL, **62**, 2349 (1940); Utermohlen and Hamilton, *ibid.*, **63**, 156 (1941).

(2) The preparation of 1-chlorobenzo(f)quinoline has been reported in the patent literature, but the intermediates in its synthesis have not been described. Carpmael, English Patent 481,874 (*Chem. Zentr.*, **109**, II, 117 (1938).

(3) Conrad and Limpach, *Ber.*, **21**, 532 (1888).

(4) Jacobs and Gould, THIS JOURNAL, **61**, 2890 (1939).

(5) Hell and Poliakoff, *Ber.*, **25**, 969 (1892).

1-Hydroxybenzo(f)quinoline (IV).—Fifteen grams (0.06 mole) of (III) was heated at its melting point until the evolution of carbon dioxide had ceased. The cooled product was decolorized with charcoal and crystallized from ethanol. The yield was 9.5 g. (76%) of a white crystalline solid, m. p. 286–288°.

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65. Found: C, 79.85, 79.71; H, 4.61, 4.51.

1-Chlorobenzo(f)quinoline (V).—Twelve grams (0.06 mole) of (IV) was refluxed for four hours in 70 ml. of phosphorus oxychloride. The excess oxychloride was removed under reduced pressure and the residue was poured into water, forming the soluble hydrochloride. The crude product was precipitated upon the addition of alkali, and purified by treatment with decolorizing charcoal, followed by recrystallization from ethanol; m. p. 62–63°; lit. 67°.[2] It was quite soluble in the common organic solvents. The yield was 12.3 g. (92%).

Anal. Calcd. for $C_{13}H_8NCl$: C, 73.07; H, 3.77. Found: C, 72.83, 72.85; H, 3.90, 3.82.

1-Substituted Aminobenzo(f)quinolines.—These derivatives were prepared by refluxing 1-chlorobenzo(f)quinoline with the appropriate amine, which was used in excess to remove the hydrogen chloride formed in the reaction. They were soluble in the common organic solvents, and formed soluble hydrochlorides.

(a) **1-N-Morpholinobenzo(f)quinoline.**—Two grams (0.009 mole) of (V) and 5 ml. of morpholine were refluxed for eight hours at 150°. The mixture, which solidified when cooled, was washed with water to remove the excess amine, and the product was decolorized with charcoal and crystallized from ethanol, yielding 2.2 g. (86%) of white needles; m. p. 146–148°.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.03, 77.24; H, 6.05, 6.06.

(b) **1-N-Piperidinobenzo(f)quinoline.**—Refluxing 2 g. (0.009 mole) of (V) and 5 ml. of piperidine for 8 hours, and working up the mixture as described above, yielded 2.1 g. (85%) of white needles; m. p., 138–140°.

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.42; H, 6.91. Found: C, 82.53, 82.34; H, 7.00, 7.16.

(c) **1-γ-N-Morpholinopropylaminobenzo(f)quinoline Dihydrate.**—Two grams (0.009 mole) of (V) and 5 ml. of γ-N-morpholinopropylamine were heated for eight hours at 150–170°. The solid product which formed upon pouring the mixture into water, was washed free of the excess amine, then dissolved in dilute hydrochloric acid. When the solution was made neutral to litmus, some unchanged (V) separated. The product was obtained upon the addition of more base. It was decolorized and crystallized from ethanol–water solution as a dihydrate; m. p. 75–76°. The yield was 2.4 g. (70%).

Anal. Calcd. for $C_{20}H_{23}N_3O \cdot 2H_2O$: C, 67.20; H, 7.61; H_2O, 10.08. Found: C, 67.07; H, 7.45; H_2O, 9.56.

(d) **1-γ-N-Diethylaminopropylaminobenzo(f)quinoline.**—Refluxing 2 g. (0.009 mole) of (V) with 5 ml. of diethylaminopropylamine, and working up the mixture as described in the preceding procedure, yielded 2.1 g. (70%) of a crystalline solid; m. p. 59–60°.

Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20. Found: C, 77.90, 78.02; H, 8.16, 8.16.

Diethyl 2-Naphthylaminosuccinate.—The properties of this compound were found to differ markedly from those reported by earlier workers.[5]

Hydrogenation of 21 g. of (I) was carried out in 600 ml. of absolute ethanol in the presence of Raney nickel catalyst at 80° and 500 lb. pressure. The product crystallized from ethanol in long white needles, m. p. 63–65°. It was quite soluble in the common organic solvents, and formed a difficultly soluble hydrochloride; m. p. 140°.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71. Found: C, 68.39, 68.34; H, 6.74, 6.88.

2-Naphthylaminosuccinic Acid.—Careful saponification of the above ester with alcoholic potassium hydroxide yielded the corresponding acid; m. p. 186°. This compound proved to be the same as that reported by Hell and Poliakoff.[5]

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 64.58; H, 5.10.

Summary

1. The intermediates in the synthesis of 1-chlorobenzo(f)quinoline have been described.

2. Several 1-substituted aminobenzo(f)quinolines have been prepared.

3. Diethyl 2-naphthylaminosuccinate has been shown to be a stable crystalline solid, rather than an unstable oil, as reported by earlier workers.

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