4,6-Disubstituted Quinolines and Decahydroquinolines

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This paper describes the synthesis of some 4,6-disubstituted quinolines and decahydroquinolines.

IN CONNECTION with a general study of the chemistry of Iboga alkaloids, it was of interest to synthesize some quinolines and decahydroquinolines. A modified Doebner-Miller synthesis (1) on *p*-aminobenzoic acid with methyl vinyl ketone gave the expected 4-methylquinoline-6-carboxylic acid (I). Oxidation of the 4-methyl group using a variety of oxidizing agents did not proceed in satisfactory yields. It was, therefore, converted to the styryl base (II) and oxidized with potassium permanganate (2) to give quinoline-4,6-dicarboxylic acid (III) in 76% yield. Hydrogenation of III gave a mixture of the *dl-cis* and *dl-trans* isomers of decahydroquinoline-4,6-dicarboxylic acids (IV). These were separated by virtue of the fact that the *dl-trans* isomer of the ethyl ester (V*b*) forms a solid hydrochloride more readily than the *dl-cis* isomer. The ratio of *dl-cis* to *dl-trans* was 1:4. Varying the conditions and/or the catalyst failed to increase the yield of the *dl-cis* isomer. In one experiment the *dl-cis* isomer (V*a*), obtained as an oil, was heated on an oil bath (3), and the reaction was followed by observing the change in the infrared spectrum. The appearance of the lactam carbonyl peak at 5.96 μ with retention of absorption due to the ester group (Fig. 1) suggested that the reaction proceeded to form VI as shown in Scheme I. Under similar conditions the *dl-trans* isomer (V*b*), as the free base, failed to react.

The low yield of the *dl-cis* isomer and the failure to obtain the lactam (VI) in a pure state precluded further studies in this area.

EXPERIMENTAL[1]

4 - Methylquinoline - 6 - carboxylic Acid.—A mixture of 42.9 Gm. (0.315 mole) of *p*-aminobenzoic acid, 135.1 Gm. of (0.5 mole) $FeCl_3 \cdot 6H_2O$, 10 Gm. of zinc chloride (anhydrous), and 250 ml. of ethyl alcohol was heated with stirring at 60–65°. To this mixture was added 17.5 Gm. (0.25 mole) of methyl vinyl ketone over a 2-hr. period. The mixture was allowed to reflux for an additional 2 hr. and left overnight at room temperature. Excess ethyl alcohol was removed under vacuum, and the residue was treated with 300 ml. of 20% sodium hydroxide solution. The mixture was filtered, and the filtrate was acidified with glacial acetic acid to pH 5. The light brown precipitate was washed with water and alcohol. Recrystallization from absolute alcohol gave 32 Gm. (54.1%) of 4-methylquinoline-6-carboxylic acid, m.p. 280–282°. $\lambda_{max.}^{KBr}$ 5.87 μ; 6.3 and 6.4 μ.

Anal.—Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 71.00; H, 5.36; N, 7.16.

4-Styrylquinoline-6-carboxylic Acid.—A mixture of 14.0 Gm. of 4-methylquinoline-6-carboxylic acid, 78.7 Gm. of benzaldehyde, and 6.6 Gm. of anhydrous zinc chloride was heated on an oil bath for 5 hr. at a temperature of 180–190°. The reaction mixture was cooled and poured into 300 ml. of 25% sulfuric acid. Ethyl ether (1 L.) was added to the mixture and the styryl quinoline sulfate was filtered off. The precipitate was washed successively with 25% sulfuric acid, alcohol, and ether to give 18.6 Gm. of the salt. Recrystallization from absolute alcohol gave yellow crystals, m.p. 250–252°. The styryl sulfate (18.6 Gm.) was treated with 15% sodium hydroxide solution and filtered. The filtrate was acidified with glacial acetic acid and the buff-colored precipitate was filtered. Recrystallization from absolute alcohol gave 13.4 Gm. (65%) of 4-styrylquinoline-6-carboxylic acid, m.p. 292–293°.

Anal.—Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.35; H, 5.07; N, 5.27.

Quinoline - 4,6 - dicarboxylic Acid.—To a mixture of 10.0 Gm. of 4-styrylquinoline-6-carboxylic acid in 250 ml. of 50% aqueous pyridine was added 14.0 Gm. of potassium permanganate over a period of 2 hr. The mixture was maintained at 0° throughout the addition. Stirring was continued for 2 hr., and the mixture was allowed to come to room temperature. It was allowed to stand overnight, and then 20 ml. of 20% potassium hydroxide solution was added. The solution was then treated with sodium bisulfate until there was a complete change

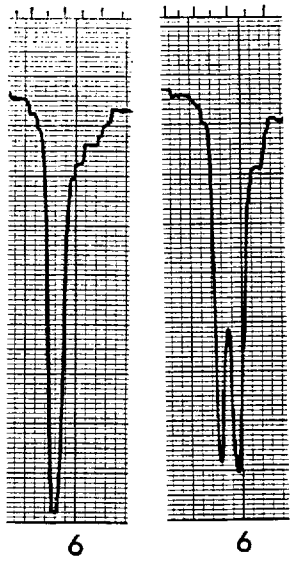

Fig. 1.—Infrared spectrum of *cis*-diethyl decahydroquinoline-4,6-dicarboxylate (V*a*) (left) and the cyclized lactam (VI).

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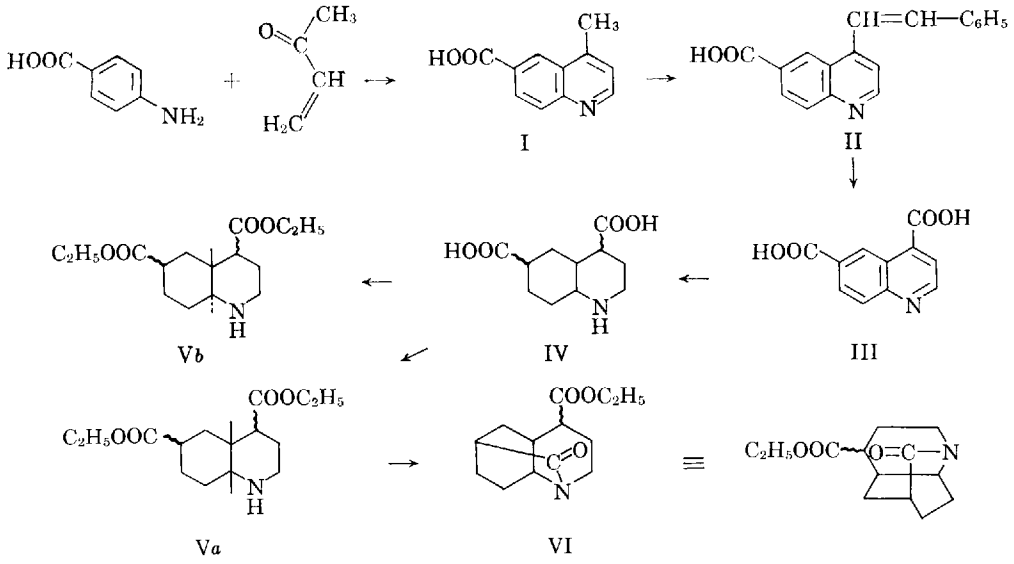
[1] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The infrared and ultraviolet spectra were determined on a Perkin-Elmer Infracord spectrophotometer and a Beckman DB spectrophotometer, respectively. Elemental analyses were performed by Weiler and Strauss, Oxford, England.



Scheme I

in the color of the solution. It was filtered, and the filtrate was acidified with concentrated hydrochloric acid to pH 5. The precipitate was washed successively with water, alcohol, and then dried to give 6.0 Gm. (76%) of quinoline-4,6-dicarboxylic acid. Recrystallization from alcohol–acetonitrile gave an analytically pure sample, m.p. >300°.

Anal.—Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.29; H, 3.45; N, 6.68.

Decahydroquinoline - 4,6 - dicarboxylic Acid Hydrochloride.—Quinoline-4,6-dicarboxylic acid (3.7 Gm.) was treated with 20 ml. each of water, HCl, and acetic acid, and 500 mg. platinum dioxide. The mixture was hydrogenated at 60° for a period of 36 hr. The catalyst was removed by filtration, and the filtrate was evaporated under vacuum to give white crystals of decahydroquinoline-4,6-dicarboxylic acid hydrochloride. Recrystallization from acetonitrile gave an analytically pure sample, m.p. 280–285°. The yield was 4.0 Gm. (90%) λ_{max}^{KBr} 5.85.

Anal.—Calcd. for $C_{11}H_{18}ClNO_4$: C, 50.09; H, 6.87; N, 5.31. Found: C, 50.83; H, 7.30; N, 5.16.

Diethyl Decahydroquinoline-4,6-dicarboxylate Hydrochloride.—Decahydroquinoline - 4,6 - dicarboxylic acid (2.7 Gm.) was added to a mixture of 15 ml. of alcohol, 20 ml. of benzene, and 2.5 ml. of concentrated sulfuric acid. It was refluxed for 20 hr., and the water formed was continuously removed. Excess solvent was removed under vacuum and the residue was treated with ammonium hydroxide until neutral to litmus and extracted with benzene–ether. The extracts were dried over sodium sulfate. Anhydrous hydrogen chloride was passed through the solution, and the solvent was removed leaving an oily residue. Addition of ether to this oily residue gave 2.6 Gm. (80%) of *dl-trans*-decahydroquinoline-4,6-dicarboxylic acid diethylester hydrochloride, m.p. 154–156°. The *dl-cis* isomer remains as an oil.

Anal.—Calcd. for $C_{15}H_{26}ClNO_4$: C, 56.32; H, 8.19; N, 4.37. Found: C, 56.31; H, 8.36; N, 3.81.

Cyclization of dl-cis-Diethyl Decahydroquinoline-4,6-dicarboxylate to VI.—The free ester of the *cis*-isomer was obtained by dissolving the above oil in 1.0 ml. of 5% sodium hydroxide and extracting with 10 ml. of ethyl acetate. The organic layer was washed with water, dried, and evaporated. The diethyl ester, obtained as an oil, was cyclized by heating in a distillation flask to 190–200°. The reaction was followed by observing the change in the infrared spectrum in the lactam region. After 15–20 min. the flask was cooled and the residue was chromatographed on neutral alumina. Elution with benzene gave the desired lactam VI. $\lambda_{max.}^{CHCl_3}$ 5.96 μ.

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