QUINOLINE-7-CARBOXYLIC ACID DERIVATIVES

IV.* SYNTHESIS OF 1,2,3,4-TETRAHYDRO-4-OXO-6-CHLOROQUINOLINE-7-CARBOXYLIC ACID

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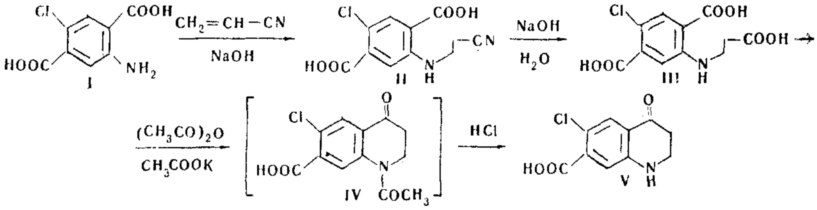
The preparation of 2-amino-5-chloroterephthalic acid and the synthesis from it of 1,2,3,4-tetrahydro-4-oxo-6-chloroquinoline-7-carboxylic acid are described.

This study is devoted to the synthesis of 1,2,3,4-tetrahydro-4-oxo-6-chloroquinoline-7-carboxylic acid (V) by the method developed in [1-3].

The nitrile of N-(2,5-dicarboxy-4-chlorophenyl)-β-alanine (II), obtained by the cyanoethylation of 2-amino-5-chloroterephthalic acid (I), is converted by saponification in alkali to N-(2,5-dicarboxy-4-chlorophenyl)-β-alanine (III). The latter is cyclized in acetic anhydride in the presence of potassium acetate to N-acetyl-1,2,3,4-tetrahydro-4-oxo-6-chloroquinoline-7-carboxylic acid (IV), which was converted, without isolation, to V by acid hydrolysis.



The structure of V was confirmed by the preparation of derivatives of the functional groups and by the IR and UV spectra. The IR spectrum of acid V contains intense absorption bands at 3380 cm^{-1} (N−H) and 1722 cm^{-1} (carboxyl CO) and a split band at 1613-1643 cm^{-1} (CO). The IR spectrum of the ester of V (VI) contains bands at 3374 cm^{-1} (NH), 1723 cm^{-1} ($COOC_2H_5$), and 1684 cm^{-1} (CO). The UV spectra of V and VI were close to the spectra of other 1,2,3,4-tetrahydroquinolones [4].

The starting acid (which is not described in the literature) was obtained via the scheme: dimethyl chloroterephthalate → dimethyl 2-chloro-5-nitroterephthalate → dimethyl 2-amino-6-chloroterephthalate → I. The position of the amino group in the dimethyl ester of I was proved by replacement of it by chlorine via the Sandmeyer reaction; the dimethyl 2,5-dichloroterephthalate thus obtained has physical constants which agree with the data in [5].

EXPERIMENTAL

The IR spectra of crystals and mineral oil pastes of the compounds were obtained with a UR-20 spectrometer. The UV spectra of alcohol solutions were obtained with an EPS-3 recording spectrophotometer.

Dimethyl Chloroterephthalate. Dimethyl aminoterephthalate [209 g (1 mole)] in 700 ml of water and 200 ml of concentrated HCl was diazotized at 0 deg with a solution of 80 g of $NaNO_2$ in 250 ml of water. The resulting solution of diazonium salt was added to a solution of copper catalyst in 540 ml of concentrated

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[*] See [7] for communication III.

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HCl. (The catalyst was obtained according to [6] from 320 g of $CuSO_4 \cdot 5H_2O$, 117 g of NaCl, and 85 g of Na_2SO_3.) The reaction mass was kept on a boiling-water bath for 0.5 h and cooled, the solids were separated, and the residue was vacuum-distilled at 136-166 deg (1 mm) to give 170 g (78.5%) of colorless crystals with mp 59-60 deg (from alcohol), in agreement with the data in [5].

Dimethyl 2-Chloro-5-nitroterephthalate. A nitrating mixture (60 ml of concentrated H_2SO_4 and 60 ml of concentrated HNO_3) was added to a solution of 114 g (0.5 mole) of dimethyl chloroterephthalate in 120 ml of concentrated H_2SO_4 at 20-25 deg. The reaction mass was stirred at this temperature for another 30 min and poured into 2 liter of an ice-water mixture. The resulting solid precipitate was filtered and washed with water, 5% sodium carbonate, and water to give 116.5 g (85%) of colorless crystals with mp 112-113 deg (from alcohol). Found %: Cl 13.0; N 5.2. $C_{10}H_8ClNO_6$. Calc. %: Cl 13.0; N 5.1.

Dimethyl 2-Amino-5-chloroterephthalate. Dimethyl 2-chloro-5-nitroterephthalate [137 g (0.5 mole)] was added with stirring to a solution of 500 g of stannous chloride in 1 liter of methanol containing 200 g of hydrogen chloride, and the mixture was refluxed for 30 min. The solution was cooled and poured into 2.5 liter of water. The resulting precipitate was filtered, washed with water, and crystallized from alcohol to give 108.5 g (89%) of colorless crystals with mp 100-101 deg. Found %: Cl 14.3; N 5.7. $C_{10}H_{10}ClNO_4$. Cl 14.6; N 5.7.

Dimethyl 2,5-Dichloroterephthalate. This was obtained in the same way as dimethyl chloroterephthalate and had mp 137-138 deg, which was in agreement with the data in [5].

2-Amino-5-chloroterephthalic Acid (I). A total of 100 ml of 40% sodium hydroxide was added to a solution of 87.5 g (0.36 mole) of dimethyl 2-amino-5-chloroterephthalate in 100 ml of alcohol. The mixture was refluxed for 30 min, the alcohol was removed by distillation, and the residue was dissolved in water. Acidification of the aqueous solution with 20% sulfuric acid gave a quantitative yield of lemon-yellow crystals with mp 305-306 deg (dec., from water). Found %: C 44.8; H 2.9; Cl 16.6; N 6.5; acid equivalent 219.0 (by titration). $C_8H_6ClNO_4$. Calc. %: C 44.6; H 2.8; Cl 16.5; N 6.5; acid equivalent 215.6.

Nitrile of N-(2,5-Dicarboxy-4-chlorophenyl)-β-alanine (II). Cupric acetate (0.3 g) and 31.8 g (0.6 mole) of acrylonitrile were added to a solution of 32.4 g (0.15 mole) of 2-amino-5-chloroterephthalic acid and 12 g (0.33 mole) of NaOH in 100 ml of water, and the mixture was stirred at 100 deg until a sample of the reaction mixture no longer gave a positive reaction for the presence of a primary amino group (~ 36 h). After this, the reaction mass was diluted with water and acidified with 20% H_2SO_4. The liberated product was separated and washed with water to give 34 g (85%) of yellow crystals with mp 258-259 deg (dec., from aqueous alcohol). Found %: Cl 13.1; N 10.3; acid equivalent 272.0. $C_{11}H_9ClN_2O_4$. Calc. %: Cl 13.2; N 10.4; acid equivalent 268.7.

2,5-Dicarboxy-4-chlorophenyl-β-alanine (III). A solution of 26.9 g (0.1 mole) of II and 16 g (0.4 mole) of NaOH in 45 ml of water was refluxed until ammonia evolution ceased. The mixture was then acidified with 20% H_2SO_4, and the resulting precipitate was filtered, washed with water, and dried to give 25.5 g (95%) of a yellow product with mp 263-264 deg (dec., from aqueous alcohol). Found %: Cl 12.6; N 4.8; acid equivalent 291. $C_{11}H_{10}ClNO_6$. Calc. %: Cl 12.3; N 4.9; acid equivalent 287.7.

1,2,3,4-Tetrahydro-4-oxo-6-chloroquinoline-7-carboxylic Acid (V). A mixture of 20 g (0.075 mole) of III, 20 g (0.22 mole) of freshly fused potassium acetate, and 100 ml of acetic anhydride was stirred at 100 deg until CO_2 evolution had ceased. The solid residue remaining after in vacuo removal of the volatile products was dissolved in water, and the solution was treated with charcoal and acidified with 40 ml of concentrated HCl. After 15 min at 90 deg the reaction mass was concentrated, and the resulting precipitate was separated and washed with cold water. The reaction product was reprecipitated from an alkaline solution with hydrochloric acid and washed with water to give 9 g (52.6%) of orange-red crystals with mp > 340 deg (dec., from water). Found %: C 53.4; H 3.6; Cl 15.5; N 6.0. $C_{10}H_8ClNO_3$. Calc. %: C 53.2; H 3.6; Cl 15.7; N 6.2. UV spectrum, λ_{max}, nm (log ε): 246 (4.27), 327 (3.00), 341 (3.09), 367 (3.29).

Ethyl 1,2,3,4-Tetrahydro-4-oxo-6-chloroquinoline-7-carboxylate (VI). A mixture of 2.26 g (0.01 mole) of acid V, 0.8 ml of sulfuric acid (sp. gr 1.84), and 25 ml of absolute alcohol was refluxed until all of the acid dissolved (3-4 h); the solvent was removed by vacuum distillation; and a saturated solution of Na_2CO_3 was added to the residue. The oily product thus liberated was extracted with ether. The ether extract was dried with Na_2SO_4, purified on a column filled with Al_2O_3, and evaporated to dryness to give 1.38 g (54.3%) of a reddish oil that crystallized on standing to give lemon-yellow crystals with mp 101-102 deg (from aqueous acetone). Found %: Cl 13.8; N 5.8. $C_{12}H_{12}ClNO_3$. Calc. %: Cl 14.0; N 5.6. UV spectrum, λ_{max}, nm (log ε): 244 (4.37), 262-268 (shoulder) (3.95), 374 (3.77). The p-nitrophenylhydrazone was obtained as dark-cherry crystals with mp 255-256 deg (dec., from aqueous alcohol). Found %: Cl 9.0; N 14.6. $C_{18}H_{17}ClN_4O_4$. Calc. %: Cl 9.1; N 14.4.

Ethyl N-Benzoyl-1,2,3,4-tetrahydro-4-oxo-6-chloroquinoline-7-carboxylate. Benzoyl chloride (0.18 g) was added to a solution of 0.25 g (0.001 mole) of ester VI in 3 ml of dichloroethane and 0.5 ml of pyridine. The mixture was refluxed for 3 h, and the solvent was removed by vacuum distillation. The residue was crystallized from aqueous alcohol to give 0.22 g (61%) of light-yellow crystals with mp 103-104 deg. This product depressed the melting point of the starting VI to 77 deg. Found %: Cl 10.0; N 3.9. $C_{19}H_{16}ClNO_4$. Calc. %: Cl 9.9; N 3.9.

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