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# SYNTHESIS OF 2,3-DIHYDRO-4(1H)-QUINOLINE DERIVATIVES

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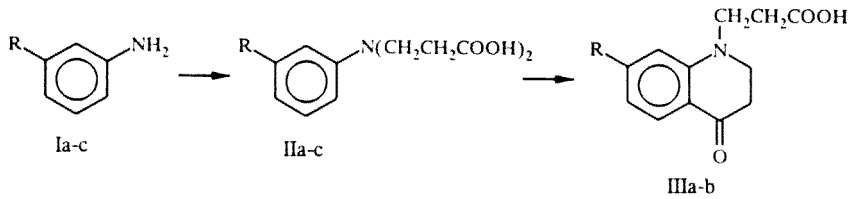
*N-Carboxyethyl-N-(3-R-phenyl)-β-alanines were synthesized by the reaction of m-substituted anilines with acrylic acid; they were cyclized to the corresponding 2,3-dihydro-4(1H)-quinoline derivatives.*

Some 2,3-dihydro-4(1H)-quinolines and their conversion products possess biological activity. They can be produced by the cyclization of N-aryl-substituted β-alanines by polyphosphoric acid [1-6], tin chloride, or phosphorus chloride [3]. In individual cases the secondary amine group is blocked by tosylation for the cyclization of β-alanines, they are treated with phosphorus chloride or anhydrous aluminum chloride, and the tosyl derivative is hydrolyzed [7].

We investigated the cyclization of N-carboxyethyl-N-(3-R-phenyl)-β-alanines II, produced by heating m-substituted anilines I with excess acrylic acid. The presence of electron-donor groups in the m-position of the aromatic ring relative to the substituted amine group, as well as the presence of a carboxyethyl group in compounds II, significantly facilitates the cyclization of these compounds to quinoline derivatives.




Ia-c IIa-c IIIa-b

I—III a R = OH, b R = $OCH_3$, c R = $NHCOCH_3$

It was found that the cyclization of N-(3-hydroxyphenyl)-N-carboxyethyl-β-alanine IIa is catalyzed both by acids and by bases. When hydrochloric or acrylic acid is used as the catalyst, the cyclization of IIa to the corresponding dihydroquinolinone IIIa occurs at the boiling point of benzene, whereas the use of basic-type catalysts — m-aminophenol, pyridine, triethylamine — requires raising the temperature to the boiling point of toluene. Without a catalyst no ring formation is noted under these conditions. In all cases, in the course of the reaction the water liberated was removed with Dean–Stark packing. The presence of weaker electron-donor groups in the aromatic ring of β-alanines IIa-c leads to a decrease in the yield of cyclic products. Thus, for example, 2,3-dihydro-1-carboxyethyl-7-methoxyquinolin-4-one was obtained with a yield of ~ 1%, whereas in the reaction of m-toluidine with acrylic acid under analogous conditions, the cyclic product could not be isolated. Reaction mixtures without the isolation of II can also be used to obtain dihydroquinolinones III, by conducting the cyclization reaction in boiling benzene or toluene.

m-Phenylenediamine IV reacts actively with acrylic acid, forming N,N,N′,N′-tetrakis(carboxyethyl)-m-phenyldiamine (V), which, when heated in dilute acetic acid, cyclizes to 2,3-dihydro-1-carboxyethyl-7,7-bis(carboxyethyl)aminoquinolin-4-one (VI). Boiling compounds V and VI in glacial acetic acid leads to the formation of a tricyclic product VII, in the $^1H$ NMR spectrum of which the aromatic protons form two doublets at 6.2 and 8.07 ppm with J = 10 Hz, while the $[N(CH_2)]_2$ and $[(CH_2CO)_2]_2$ protons give broadened signals at 3.1-3.8 ppm and 2.2-3.0 ppm, respectively.

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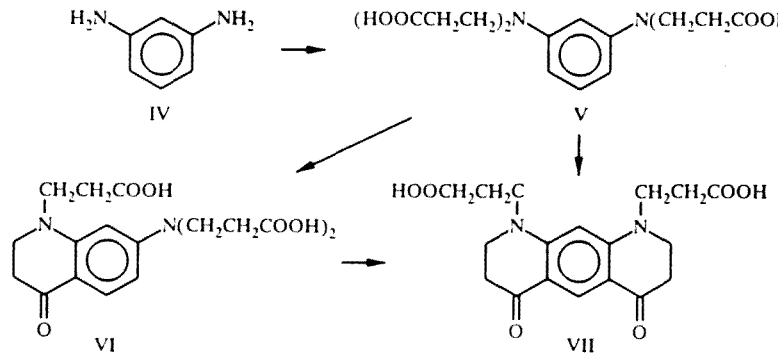

## EXPERIMENTAL

The $^1H$ NMR spectra were recorded on a Tesla BS-487 spectrometer (80 MHz), with internal standard HMDS. The data of the chemical shifts are given in ppm according to the $\delta$ scale. The course of the reaction and purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates. Development in UV light or with iodine.

The data of elementary analysis of compounds II-VII for C, H, and N correspond to those calculated.

**N-(3-Hydroxyphenyl)-N-carboxyethyl-β-alanine (IIa).** A mixture of 10.9 g (0.1 mole) m-aminophenol (I), 10 ml of water, and 21.6 g (0.3 mole) acrylic acid was heated at 70°C for 3 h, cooled, 30 ml of ethanol was added, and the mixture was left at 4°C for 12 h. The crystals of IIa isolated were filtered and washed with ethanol and with ether. Yield 20.7 g (84.8%). mp 149-150°C (from ethanol). $^1H$ NMR spectrum ($CF_3COOH$): 1.6-2.8 [4H, m, $(CH_2CO)_2$], 3.1-4.2 [4H, m, $N(CH_2)_2$], 6.5-7.4 ppm (3H, m, H arom.).

**N-(3-Acetaminophenyl)-N-carboxyethyl-β-alanine (IIc).** A mixture of 7.5 g (0.05 mole) 3-aminoacetanilide (Ic), 10.8 g (0.15 mole) acrylic acid, and 100 ml of water was heated at 100°C for 3 h, cooled, 30 ml of ethanol was added, and the mixture was left at 4°C for 12 h. The crystals of IIc isolated were filtered and washed with ethanol. Yield 13.8 g (93.8%). mp 299-301°C (from ethanol). $^1H$ NMR spectrum ($CF_3COOH$): 1.94 (3H, s, $CH_3$), 2.1-2.7 [4H, m, $(CH_2CO)_2$], 3.4-4.1 [4H, m, $N(CH_2)_2$], 6.8-7.9 (4H, m, H arom.), 8.65 ppm (1H, s, NH).

**2,3-Dihydro-1-carboxyethyl-7-hydroxyquinolin-4-one (IIIa). Method A.** A mixture of 10.9 g (0.1 mole) m-aminophenol (Ia), 18 g (0.25 mole) acrylic acid, and 0.20 g hydroquinone in 150 ml of benzene was boiled for 3 h, then boiling was continued for another 10 h, removing water with Dean–Stark packing. The reaction mixture was cooled, the solvent was decanted, the residue was dissolved with heating in 150 ml of a 10% solution of sodium hydroxide, it was filtered, and the filtrate was acidified with hydrochloric acid to pH 1-2. The crystals of IIIa isolated were filtered and washed with water. Yield 14.8 g (62%). mp 207-208°C (from ethanol). $^1H$ NMR spectrum ($CF_3COOH$): 2.51 and 2.72 [(4H, 2t, $(CH_2CO)$], 3.3-3.8 [4H, m, $N(CH_2)_2$], 6.1-7.7 ppm (3H, m, H arom.).

**Method B.** A mixture of 2.54 g (0.01 mole) of the β-alanine IIa, 0.5 ml conc. HCl, and 30 ml of benzene was boiled for 10 h, removing water. The mixture was cooled, the solvent was decanted, the precipitate was dissolved with heating in 15 ml of a 10% sodium hydroxide solution, it was filtered, and the filtrate was acidified with hydrochloric acid to pH 1-2. The crystals of IIIa isolated were filtered and washed with water. Yield 0.95 g (40.2%).

**Method C.** A mixture of 2.54 g (0.01 mole) of the β-alanine IIa, 0.1 g m-aminophenol, and 30 ml of toluene was boiled for 10 h, removing water. Compound IIIa was isolated analogously to Method B. Yield 0.63 g (26.7%).

**Method D.** A mixture of 2.54 g (0.01 mole) of the β-alanine IIa, 0.5 ml of triethylamine, and 30 ml of toluene was boiled for 10 h, removing water with Dean–Stark packing. Compound IIIa was isolated analogously to Method B. Yield 1.2 g (50.8%).

**2,3-Dihydro-1-carboxyethyl-7-methylquinolin-4-one (IIIb).** A mixture of 37.2 g (0.3 mole) m-anisidine (Ib), 50.4 g (0.7 mole) acrylic acid, and 150 ml of toluene was boiled for 4 h, then boiling was continued for another 10 h, removing water with Dean–Stark packing. The solvent was distilled off under vacuum, and the residue was dissolved with heating in 150 ml of water and 40 ml conc. hydrochloric acid. The crystals of IIIb isolated, after standing for 24 h at 4°C, were filtered

TABLE 1. Analytical Characteristics of the Compounds Obtained

| Compound | Found, % | | | Gross formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|
| | C | H | N | | C | H | N |
| IIa | 56,9 | 6,4 | 5,4 | $C_{12}H_{15}NO_5$ | 56,9 | 6,0 | 5,5 |
| II a | 57,4 | 6,6 | 9,5 | $C_{14}H_{18}N_2O_5$ | 57,1 | 6,2 | 9,5 |
| IIIa | 61,0 | 5,3 | 5,9 | $C_{12}H_{13}NO_4$ | 61,3 | 5,6 | 6,0 |
| IIIb | 62,3 | 5,7 | 5,6 | $C_{13}H_{15}NO_4$ | 62,6 | 6,1 | 5,6 |
| III c | 60,7 | 5,3 | 10,4 | $C_{14}H_{16}N_2O_4$ | 60,9 | 5,8 | 10,2 |
| V | 54,5 | 6,1 | 7,2 | $C_{18}H_{24}N_2O_8$ | 54,5 | 6,1 | 7,1 |
| VI | 57,5 | 6,2 | 7,2 | $C_{18}H_{22}N_2O_7$ | 57,1 | 5,9 | 7,4 |
| VII | 60,5 | 6,1 | 7,6 | $C_{18}H_{20}N_2O_6$ | 60,0 | 5,6 | 7,8 |

and washed with water. Yield 8.1 g (10.8%). mp 137-139°C (from ethanol). $^1$H NMR spectrum ($CF_3COOH$): 2.63 and 2.80 [4H, 2t, $(CH_2CO)_2$], 3.58 (3H, s, $CH_3$), 3.5-3.9 [4H, m, $N(CH_2)_2$], 6.1-7.3 ppm (3H, m, H arom.).

**2,3-Dihydro-1-carboxyethyl-7-acetaminoquinolin-4-one (IIIc).** A mixture of 15.4 g (0.1 mole) m-aminoacetaniline (Ic), 18.0 g (0.25 mole) acrylic acid, and 100 ml of toluene was boiled for 3 h, and boiling was continued for another 10 h with azeotropic distillation of water. The mixture was cooled, and the solvent decanted. Upon standing the mass solidified. We obtained 25.1 g of a mixture, 3 g of which was chromatographed by passing through a column with silica gel L 40/100, collecting the fraction with $R_f$ 0.91 (eluent ethanol–ether, 1:9). We obtained 1.17 g (39%) of compound IIIc in the form of a brown mass. $^1$H NMR spectrum ($CF_3COOH$): 1.89 (3H, s, $CH_3$), 2.1-2.7 [4H, m, $(CH_2CO)_2$], 3.1-4.3 [4H, m, $N(CH_2)_2$], 6.6-8.0 (3H, m, H arom.), 8.65 ppm (1H, s, NH).

**N,N,N′,N′-Tetrakis(carboxyethyl)-M-phenylenediamine (V).** A mixture of 10.9 g (0.1 mole) of m-phenylenediamine (IV), 36 g (0.05 mole) acrylic acid, and 50 ml of acetic acid was heated for 12 h at 50°C. The mass obtained was dissolved with heating in 150 ml of water. After 24 h the crystals of V that separated out were filtered and washed with water. Yield 32 g (81.7%). mp 159-160°C (from ethanol). $^1$H NMR spectrum ($CF_3COOH$): 2.41 [8H, m, $2(CH_2CO)_2$], 3.70 [8H, m, $2N(CH_2)_2$], 7.4-7.8 ppm (4H, m, H arom.).

**2,3-Dihydro-1-carboxyethyl-7,7-bis(carboxyethyl)aminoquinolin-4-one (VI).** A mixture of 10.9 g (0.1 mole) m-phenylenediamine (IV), 28.8 g (0.4 mole) acrylic acid, 10 ml of water, and 40 ml of acetic acid was boiled for 30 min; the mixture was diluted with 150 ml of water and left for 20 h at 4°C. The crystals of VI that separated out were filtered and washed with water. Yield 6.2 g (16.4%). mp 194-195°C (from acetic acid). $^1$H NMR spectrum ($CF_3COOH$): 2.2-2.7 [8H, m, $2(CH_2CO)_2$], 3.2-4.0 [8H, m, $2N(CH_2)_2$], 6.32, 6.47, and 7.71 ppm (3H, s + 2d, J = 8 Hz, H arom.).

**1,9-Dicarboxyethyl-4,6-dioxo-1,2,3,4,5,6,7,8,9-octahydropyrido[2,3-d]quinoline (VII). Method A.** A mixture of 1.89 g (0.005 mole) of compound VI in 15 ml of glacial acetic acid was boiled for 8 h; the liquid fractions were distilled off under vacuum and the residue was dissolved in 8 ml of ethanol. After exposure at 4°C, the precipitate of VII formed was filtered and washed with 5 ml of ethanol. Yield 0.55 g (30.6%). mp 185-187°C (from acetic acid). $^1$H NMR spectrum ($CF_3COOH$): 2.2-3.0 [8H, m, $2(CH_2CO)_2$], 3.1-3.8 [8H, m, $2N(CH_2)_2$], 6.2 and 8.07 ppm (2H, 2d, J = 10 Hz, H arom.).

**Method B.** A mixture of 1.98 g (0.055 mole) of compound V in 15 ml of acetic acid was boiled for 10 h. The liquid fractions were distilled off under vacuum, and the residue was dissolved in 10 ml of ethanol. After exposure at 4°C, the precipitate of VII that formed was filtered and washed with 5 ml of ethanol. Yield 0.45 g (25%).

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