for 2 h and at 125° for ~15 min (until $CO_2$ evolution ceased). The volatile products were removed by vacuum distillation, and 100 ml of water was added to the residue. The resulting oily product began to solidify on standing. The solid was removed by filtration, washed with water, refluxed with 20 ml of concentrated HCl for 30 min, and evaporated to dryness. The residue was treated with 10% NaOH, and the insoluble reaction product was removed by filtration, washed with water, and crystallized (Table 2).

Hydrazone of Va. A mixture of 0.2 g (1 mmole) of Va, 2 ml of hydrazine hydrate, and 5 ml of DMF was refluxed for 30 min, after which it was cooled, and the liberated crystals were separated and washed with water to give a light-yellow product that did not melt on heating up to 350°. Found %: N 26.1. $C_{12}H_{12}N_4$. Calculated %: N 26.4.

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# SYNTHESIS OF NAPHTHYRIDINES

## II.* 2,3,9,10-TETRAHYDRO[1,4]BENZODIOXINO[6,7-h][1,6]NAPHTHYRIDIN-4(1H)-ONE


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A method for the preparation of 2,3,9,10-tetrahydro[1,4]benzodioxino[6,7-h][1,6]naphthyridin-4(1H)-one by cyclization of 2,3-dihydro-9-[(2-carboxyethyl)amino][1,4]dioxino[2,3-g]quinoline-8-carboxylic acid in acetic anhydride in the presence of potassium acetate is described.


In the present research we used a new method for the construction of the naphthyridine structure [1] in order to obtain 2,3,9,10-tetrahydro[1,4]benzodioxino[6,7-h][1,6]naphthyridin-4(1H)-ones – the first representative of the benzodioxino[6,7-h][1,6]naphthyridine heterocyclic system.

For this we obtained starting VI from 2,3-dihydro[1,4]benzodioxine (I) via a known scheme [2], which includes nitration of I, reduction of 6-nitro derivative II to corresponding amine III, condensation of the latter with ethoxymethylenemalonic ester to give substituted diethyl malonate IV, thermal cyclization of IV to [1,4]-dioxano[2,3-g]quinoline derivative V, and treatment of V with phosphorus oxychloride.

*See [1] for communication I.


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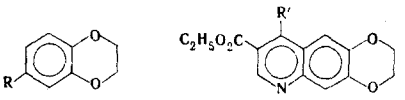


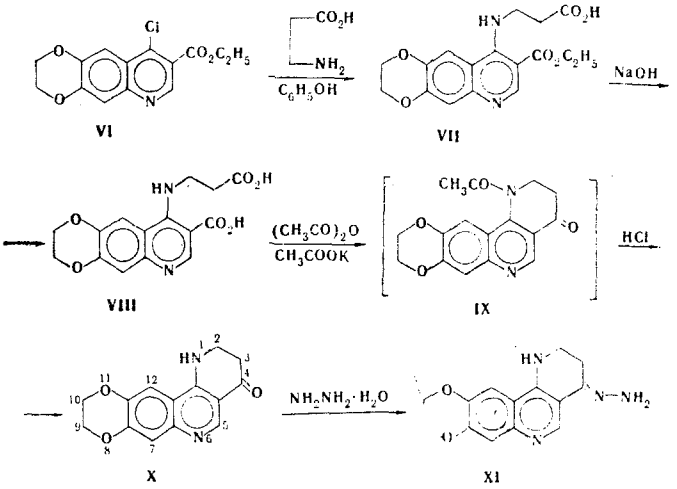
I-IV V, VI

I R = H; II R = $NO_2$; III R = $NH_2$; IV R = NH–CH=C($CO_2C_2H_5$)$_2$;

V R′ = OH; VI R′ = Cl

Changes that simplify the preparation of nitro products II and raise the yield of amino derivative III (see the experimental section) were introduced in the synthesis of derivatives II and III by the methods in [3-5].

2,3,9,10-Tetrahydro[1,4]benzodioxino[6,7-h][1,6]naphthyridin-4(1H)-one (X) was synthesized from VI via the scheme



VI VII VIII IX X XI

Acid VII, which was subsequently converted to dicarboxylic acid VIII by alkaline hydrolysis, was obtained by reaction of VI with β-alanine in phenol. Dicarboxylic acid VIII underwent cyclization in acetic anhydride in the presence of potassium acetate, and the resulting N-acetyl derivative (IX) of the cyclic product was hydrolyzed, without purification, to ketone X.

The presence of a keto group in X was confirmed by the formation of crystalline hydrazone XI and also by the IR spectrum ($\nu_{CO}$ 1663 $cm^{-1}$).

## EXPERIMENTAL

The melting points of the compounds were determined with a Mel-Temp [6] apparatus and were not corrected. The IR spectrum of a mineral oil suspension of IX was recorded with a UR-20 spectrometer. The UV spectrum of an alcohol solution of IX was recorded with a Specord UV-vis spectrophotometer.

6-Nitro-2,3-dihydro[1,4]benzodioxine (II). A mixture of 40.8 g (0.3 mole) of I and 40.8 ml of nitric acid (sp. gr. 1.34) was stirred vigorously at room temperature. After a certain time, the temperature of the reaction mixture began to rise spontaneously. When the temperature had reached 85°, 80 ml of water was added, and the mixture was stirred for 30 min, during which a crystalline precipitate formed. The mixture was then diluted with water, and the precipitate was separated and washed with water to give 51.1 g (94%) of a light-yellow product with mp 119-120° (from alcohol), in agreement with the melting point reported in [3].

6-Amino-2,3-dihydro[1,4]benzodioxine (III). A 36-ml sample of hydrazine hydrate was added gradually with vigorous stirring at 50° to a mixture of 54.3 g (0.3 mole) of nitro compound II (the uncrystallized product was used), 300 ml of alcohol, and ~5.0 g of Raney nickel paste (the reaction mixture effervesced during the addition of the hydrazine hydrate). At the end of the addition, the mixture was refluxed for another 30 min, the catalyst was removed by filtration, and the alcohol was removed by distillation. The residual oil was vacuum distilled to give 39.6 g (87%) of amino compound III as a colorless viscous oil with bp 144-152° (6-7 mm) [bp 165-167° (12 mm) [4]].

Diethyl 6-(2,3-Dihydro[1,4]benzodioxinyl)aminomethylenemalonate (IV). This compound was obtained by the method described in a patent [2] and was used for the next step in the synthesis without purification.

Ethyl 2,3-Dihydro-9-hydroxy[1,4]dioxino[2,3-g]quinoline-8-carboxylate (V). This compound was obtained by thermal cyclization of IV as described in [2] and had mp 308-310° (from DMF), in agreement with the literature value [2].

Ethyl 9-Chloro-2,3-dihydro[1,4]dioxino[2,3-g]quinoline-8-carboxylate (VI). A mixture of 11.0 g (0.04 mole) of V (the uncrystallized product was used) and 30 ml of phosphorus oxychloride was refluxed for 2 h, after which the excess phosphorus oxychloride was removed by vacuum distillation, and a mixture consisting of 20 ml of alcohol and 20 ml of 25% ammonium hydroxide was added to the residue. The resulting viscous oil began to solidify on trituration. The solid product was triturated with ammonium hydroxide, washed with water, and crystallized from aqueous alcohol to give 9.5 g (81%) of light crystals with mp 91-93°. Found %: Cl 12.0; N 4.7. $C_{14}H_{12}ClNO_4$. Calculated %: Cl 12.1; N 4.8.

Ethyl 9-([2-Carboxyethyl)amino]-2,3-dihydro[1,4]dioxino[2,3-g]quinoline-8-carboxylate (VII). A mixture of 11.72 g (0.04 mole) of VI, 7.1 g (0.08 mole) of β-alanine, and 40 ml of phenol was stirred at 120-125° for 4 h, after which the phenol was removed by steam distillation, and the solid product was removed by filtration and washed with water and alcohol. For purification, the product was dissolved in refluxing aqueous $Na_2CO_3$ solution, after which the solution was filtered, and the filtrate was acidified with acetic acid. The resulting colorless precipitate was removed by filtration and washed with water and alcohol to give 10.8 g (78.0%) of a colorless substance with mp 248-250° (dec.). Found %: C 58.6; H 5.1; N 8.2. $C_{17}H_{18}N_2O_6$. Calculated %: C 59.0; H 5.2; N 8.1.

9-[(2-Carboxyethyl)amino]-2,3-dihydro[1,4]dioxino[2,3-g]quinoline-8-carboxylic Acid (VIII). A mixture of 10.38 g (0.03 mole) of VII, 3.6 g (0.09 mole) of sodium hydroxide, 35 ml of water, and 35 ml of alcohol was refluxed for 30 min, after which the resulting solution was concentrated to half its original volume and filtered. The filtrate was acidified with concentrated acetic acid, and the resulting gelatinous mass was immediately converted to a colorless crystalline precipitate, which was removed by filtration and washed with water and alcohol to give 7.8 g (82%) of colorless crystals with mp 260-264° (dec.). Found %: C 56.6; H 4.0; N 8.7. $C_{15}H_{14}N_2O_6$. Calculated %: C 56.8; H 4.1; N 8.8.

2,3,9,10-Tetrahydro[1,4]benzodioxino[6,7-h][1,6]naphthyridin-4(1H)-one (IX). A mixture of 7.93 g (0.025 mole) of dicarboxylic acid VIII, 6.9 g (0.05 mole) of freshly fused potassium acetate, and 120 ml of acetic anhydride was heated at 110° for 1 h (during which carbon dioxide liberation from the reaction mass was observed). The temperature was then raised to 140° in 15 min, after which the acetic anhydride was removed by vacuum distillation, and the residue was diluted gradually with ~20 ml of water. The resulting acetic acid was removed by distillation to dryness. Water (~100 ml) was added to the residual solid product, and two layers – an aqueous layer and an oily layer – were formed. The aqueous layer was removed by decantation, 60 ml of concentrated HCl was added to the residual oil, and the mixture was refluxed for 10 min, during which a bright-yellow precipitate formed. The mixture was evaporated to dryness, and 25% ammonium hydroxide (~25 ml) was added to the solid residue. The solid substance was removed by filtration and washed with water to give 3.7 g (53%) of a yellow substance. Recrystallization from methyl cellosolve gave bright-yellow needles with mp 358-360°.

UV spectrum, $\lambda_{max}$, nm (log ε): 233 (4.12), 247 (4.15), 280 (4.54); 293 (4.45), 313 (4.18), 366 (3.61). Found %: C 65.7; H 4.5; N 10.7. $C_{14}H_{12}N_2O_3$. Calculated %: C 65.5; H 4.7; N 10.9. The hydrochloride was obtained as a yellow crystalline substance with mp > 340° (from 10% HCl). Found %: Cl 11.8; N 9.7. $C_{14}H_{12}N_2O_3 \cdot HCl$. Calculated %: Cl 12.1; N 9.6.

Hydrazone of X. A mixture of 0.26 g (1 mmole) of IX, 2 ml of hydrazine hydrate, and 5 ml of methyl cellosolve was refluxed for 30 min, after which it was allowed to stand at 5° for 24 h. The resulting crystals were removed by filtration and washed with alcohol to give 0.24 g (89%) of shiny yellow-green crystals with mp ~340°. Found %: N 20.3. $C_{14}H_{14}N_4O_2$. Calculated %: N 20.7.

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