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2-CARBETHOXY-4H-3,1-BENZOXAZIN-4-ONE. 2.* HYDRAZINOLYSIS

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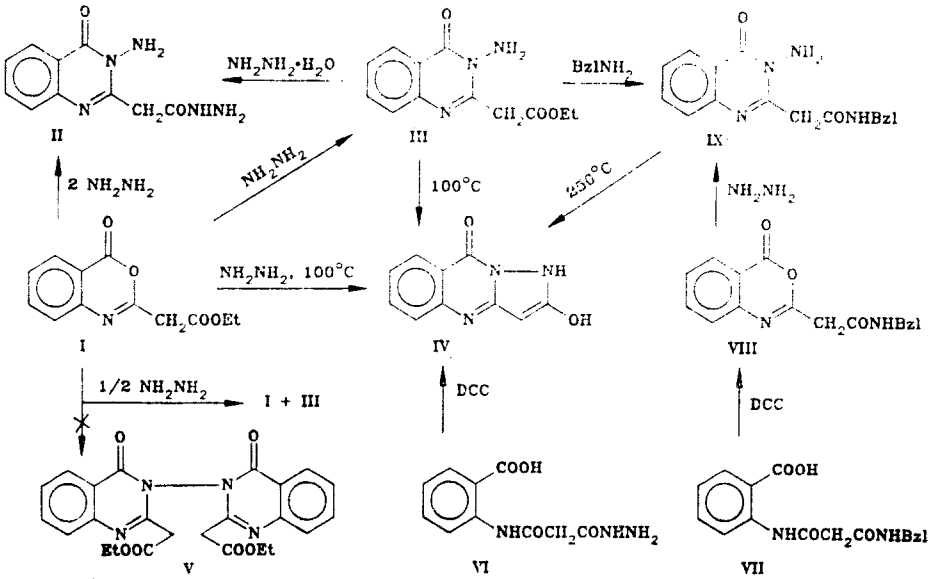
3-Amino-2-carboxymethylquinazolin-4(3H)-one was obtained by hydrazinolysis of 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one. Its transformations into 2-hydroxypyrazolo[5,1-b]quinazolin-9(1H)-one and 3-amino-2-hydrazido-(orbenzylamido)carbonylmethylquinazoline-4(3H)-ones were studied.

The present investigation is addressed to the clarification of the reaction of 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one (I) [1] with hydrazine. With diethyl malonate the anthranilic acid hydrazide forms 2-hydroxypyrazolo[5,1-b]quinazolin-9(1H)-one (IV) [2], which is used in color photography, and 3-amino-2-carbethoxymethylquinazolin-4(3H)-one (III). 3-Aminoquinazolones, which comprise compounds with high antispasmodic [4, 5], hypoglycemic [6], and sedative [7] activity can also be obtained by the reaction of 2-substituted 4H-3,1-benzoxazin-4-ones (acylanthranils) with hydrazine [7].



Acylanthranil I reacts readily with hydrazine in an equimolar ratio in methanol at room temperature. As a result, 3-aminoquinazolinone III was obtained in 91% yield [8]. Increase in the temperature to 100°C is accompanied

*For Communication 1, see [1].

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by cyclization of the intermediate product III into pyrazole IV (method A) [9], the structure of which was proved by countersynthesis: boiling of the preliminarily isolated III in water (method B), pyrolysis of 3-amino-2-benzylamidocarbonylmethylquinazolin-4(3H)-one (IX, method C), or by the reaction of 2-carboxymalonanilic acid hydrazide (VI) with dicyclohexylcarbodiimide (method D). The latter method is distinguished by its simplicity and makes it possible to obtain pyrazole IV in the highest yield.

On melting hydrazine with a double excess of 6-nitroacetylanthranil, 6,6′-dinitro-2,2′-dimethyl-4,4′-diketotetrahydroquinazolyl is formed [10]. Attempts to synthesize a similar product V from acylanthranil I did not give a positive result.

Acylanthranil I reacts with a double excess of hydrazine with the formation of 3-amino-2-hydrazidocarbonylmethylquinazolin-4(3H)-one (II), which was also obtained by treating 3-aminoquinazolinone III with hydrazine hydrate.

EXPERIMENTAL

The PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY spectrometer (100 MHz) in DMSO-D_6, using TMS as internal standard. The IR spectra were run on a Specord IR-75 spectrophotometer in KBr tablets. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates.

The elemental analysis data correspond to the calculated values.

3-Amino-2-carbethoxymethylquinazolin-4(3H)-one (III, $C_{12}H_{13}N_3O_3$). A. 0.32 ml portion (0.01 mole) of anhydrous hydrazine was added to a solution of 2.33 g (0.01 mole) of benzoxazinone I in 5 ml of methanol, and the mixture was allowed to stand overnight. Product III was filtered off and dried, mp 108-110°C, according to the data in [3], 110°C, R_f 0.40 (chloroform—isopropanol, 16:1). IR spectrum: 3300 (NH), 1728, 1684 (C=O), 1666 (C=N), 1186 cm^{-1} (C—O). PMR spectrum: 1.19 (3H, t, CH_3), 3.97 (2H, s, CH_2COOEt), 4.15 (2H, q, CH_2CH_3), 5.61 (2H, s, NH_2), 7.40-7.94 (3H, m, H-6,7,8), 8.14 ppm (1H, d, 4.5). Yield 2.24 g (91%).

B. A 0.16 ml portion (0.005 mole) of anhydrous hydrazine was added to a solution of 2.33 g (0.01 mole) of benzoxazinone I in 10 ml of methanol, and the mixture was boiled for 10 h. The reaction mixture was cooled and separated on a chromatographic column (adsorbent—silica gel L100/250) in the hexane—isopropanol (8:3) system of solvents. Thus, 1.16 g of the starting benzoxazinone I and 1.23 g of quinazolinone III was obtained.

2-Carboxymalonanilic Acid Hydrazide (VI, $C_{10}H_{11}N_3O_4$). A 1.66 g portion (0.011 mole) of ethoxymalonyl chloride [11] was added to a solution of 1.37 g (0.01 mole) of anthranilic acid and 0.89 ml (0.011 mole) of pyridine in 10 ml of methylene chloride, and the mixture was allowed to stand overnight. The solvent was evaporated, the residue was washed with water, and 1.0 ml (0.021 mole) of hydrazine hydrate was added. After 10 h the reaction mixture was acidified with HCl to pH 4-5. The precipitate was filtered off, washed with cold water, and dried. After recrystallization from aqueous alcohol, 2.13 g (90%) of hydrazide VI was obtained, mp 150-152°C, R_f 0.47 (glacial CH_3COOH—n-C_4H_9OH—H_2O, 10:40:1). IR spectrum: 3260, 3180 (NH), 2660-2450 (COOH-dimer), 1700, 1693 cm^{-1} (C=O). PMR spectrum: 3.32 (2H, s, CH_2), 5.58 (2H, s, NH_2). 7.14 (1H, t.d, H-4), 7.56 (1H, t.d, H-5), 7.96 (1H, d.d, H-6), 8.47 (1H, d, H-3), 11.29 ppm (1H, s, NH).

2-Carboxymalonanilic Acid Benzylamide (VII, $C_{17}H_{16}N_2O_4$). A 2.5 ml portion (0.022 mole) of benzylamine was added to a solution of 2.51 g (0.01 mole) of ethyl ester of 2-carboxymalonanilic acid [12] in 10 ml of absolute methanol, and the mixture was boiled under a reflux condenser for 6 h. It was then cooled, washed with 100 ml of water, and acidified with HCl to pH 3-4. The precipitate was filtered off, washed with water, and dried, mp 210-211°C (dioxane). R_f 0.73 (hexane—isopropanol, 8:3). IR spectrum: 3270, 3175 (NH); 2660-2450 (COOH-dimer); 1681 (C=O); 938 cm^{-1} (OH). PMR spectrum: 3.40 (2H, s, CH_2), 4.34 (2H, d, NCH_2), 7.16 (1H, t.d, H-4), 7.30 (5H, s, Ph), 7.61 (1H, t.d, H-5), 8.00 (1H, d.d, H-6), 8.51 (1H, d, H-3), 8.72 (1H, t, NH), 11.33 ppm (1H, s, NH). Yield 2.31 g (74%).

2-Benzylamidocarbonylmethyl-4H-3,1-benzoxazin-4-one (VIII, $C_{17}H_{14}N_2O_3$). A 2.06 g portion (0.01 mole) of DCHC was added to a solution of 3.12 g (0.01 mole) of amide VII in 100 ml of dry methylene chloride, and the mixture was boiled under reflux condenser for 2 h. The mixture was cooled, the precipitate (dicyclohexylurea) was filtered off, and the filtrate was evaporated to dryness, mp 166-168°C (methanol). PMR spectrum: 3.70 (2H, s, CH_2), 4.36 (2H, d, NCH_2), 7.32 (5H, s, Ph), 7.55-7.73 (2H, m, H-6, 8), 7.92 (1H, t.d, H-7), 8.13 (1H, d.d, H-5), 8.76 ppm (1H, t, NH). Yield 2.82 g (96%).

3-Amino-6-benzylamidocarbonylmethylquinazolin-4(3H)-one (IX, $C_{17}H_{16}N_4O_2$). A. Obtained similarly to quinazolinone III by method A, mp 218-220°C (methanol). PMR spectrum: 3.96 (2H, s, CH_2), 4.35 (2H, d, NCH_2), 5.70 (2H, s, NH_2), 7.33 (5H, s, Ph), 7.53 (1H, t.d, H-6), 7.65 (1H, d, H-8), 7.84 (1H, t.d, H-7); 8.15 ppm (1H, d.d, H-5), 8.63 ppm (1H, t, NH). Yield 98%.

B. A solution of 2.47 g (0.01 mole) of quinazolinone III and 1.2 ml (0.011 mole) of benzylamine in 15 ml of methanol was held in a water bath at 50°C for 10 h, then we cooled and diluted with water. The precipitate was filtered off, washed with water, and dried. Yield 2.83 g (92%).

A mixed sample with the compound obtained by method A did not give a depression of the melting point.

2-Hydroxypyrazolo[5,1-b]quinazolin-9(1H)-one (IV, $C_{10}H_7N_3O_2$). A. A solution of 2.33 g (0.11 mole) of benzoxazinone I and 0.49 ml (0.01 mole) of hydrazine hydrate in 10 ml of dioxane was boiled for 30 min, then was cooled and diluted with water. The precipitate was filtered off and dried, mp 270°C (decomp., DMFA), according to the data in [2, 3], >260°C. PMR spectrum: 5.35 (1H, s, CH), 7.21-8.11 (4H, m, H_{arom}), 11.06 (1H, s, OH), 12.00 ppm (1H, s, NH). Yield 1.93 g (96 or 69%, based on the starting anthranilic acid).

B. A 2.47 g portion (0.01 mole) of quinazolinone III was boiled in 20 ml of water for 1 h. The mixture was cooled, the precipitate was filtered off, washed with water, and dried. Yield 1.95 g (97%).

C. A 3.08 g portion (0.01 mole) of quinazolinone IX was held on a metallic bath at 250°C for 10 min, then was cooled, and 20 ml of water acidified with HCl was added. The precipitate was filtered off, washed with water, and dried. Yield 1.95 g (97%).

D. A 2.06 g portion (0.01 mole) of DCHC was added to a solution of 2.37 g (0.01 mole) of hydrazide VI in 10 ml of DMFA. The mixture was allowed to stand at room temperature for 4 h and a solution of 0.6 g (0.015 mole) of NaOH in 20 ml of water was added. The mixture was filtered, the filtrate was acidified with HCl to pH 3-4. The precipitate was filtered off, washed with water, and dried. Yield 1.97 g (98 or 88%, based on the starting anthranilic acid).

The identity of the products obtained by the various methods was established according to the melting point of mixed samples.

3-Amino-hydrazidocarbonylmethylquinazolin-4(3H)-one (II, $C_{10}H_{11}N_5O_2$). A. A 0.67 ml portion (0.021 mole) of anhydrous hydrazine was added to a solution of 2.33 g (0.01 mole) of benzoxazinone I in 5 ml of methanol, and the mixture was allowed to stand overnight. The reaction mixture was diluted with a triple amount of water. The precipitate was filtered off, washed with water, and dried, mp 306°C (decomp., DMFA). PMR spectrum: 3.83 (2H, s, CH_2), 4.45 (2H, s, NH_2), 5.68 (2H, s, NH_2), 7.40-7.91 (3H, m, H-6,7,8), 8.12 (1H, d, H-5), 9.21 ppm (1H, s, NH). Yield 2.21 g (95%).

B. A 0.54 g portion (0.011 mole) of hydrazine hydrate was added to a solution of 2.47 g (0.01 mole) of quinazolinone III in 10 ml of methanol, and the procedure was continued as in the preceding experiment. Yield 2.28 g (98%).

A mixed sample with the compound obtained by method A did not give a depression of the melting point.

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