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Synthesis of 3-Amino-3,4-dihydroquinazolin-4-one Derivatives from Anthranilic Acid Hydrazide and Dicarboxylic Acids

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Abstract—Treatment of anthranilic acid hydrazide with 2 equiv of ethoxalyl chloride gave the corresponding diester which underwent cyclization in acetic anhydride to produce ethyl 3-(ethoxalylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylate. Acylation of anthranilic acid hydrazide first with succinic anhydride and then with ethoxalyl chloride led to the formation of 4-[2-(2-{[ethoxy(oxo)acetyl]amino}benzoyl)hydrazino]-4-oxobutanoic acid whose cyclization in acetic acid afforded *N*-(2-ethoxycarbonyl-4-oxo-3,4-dihydroquinazolin-3-yl)succinamic acid, while in acetic anhydride ethyl 3-(2,5-dioxopyrrolidin-1-yl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate was obtained. The latter was brought into reactions with amines and hydrazine hydrate and alkaline hydrolysis. Acylation of 2-[2-(2-aminobenzoyl)hydrazinocarbonyl]benzoic acid with ethoxalyl chloride gave ethyl *N*-[2-(phthalimidocarbamoyl)phenyl]oxamate, and with succinic anhydride, 3-[4-oxo-3-phthalimido-3,4-dihydroquinazolin-2-yl]propionic acid. 4-[2-(2-Aminobenzoyl)hydrazino]-4-oxobutanoic acid reacted with phthalic anhydride in boiling acetic acid to give phthalazino[1,2-*b*]quinazoline-5,8-dione via elimination of succinic acid residue.

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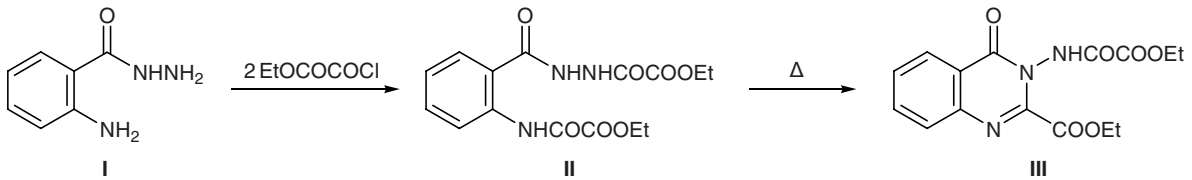
Synthesis of quinazolinones on the basis of anthranilic acid and dicarboxylic acid hydrazides gives rise to structures that are convenient for subsequent chemical modification, in particular for the preparation of tricyclic compounds [1–3]. This is important from the viewpoint of design of biologically active substances and potential drugs since many medical agents incorporate quinazolinone moiety as structural fragment [4, 5].

The goal of the present work was to synthesize 3-amino-3,4-dihydroquinazolin-4-ones from diacyl derivatives of anthranilic acid hydrazide (**I**) containing various dicarboxylic acid moieties (Scheme 1). By acylation of hydrazide **I** with 2 equiv of ethoxalyl chloride we obtained diester **II** which readily underwent cyclization to ethyl 3-[ethoxy(oxo)acetylamino]-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**III**) (Scheme 1).

Ethyl 4-oxo-3-(2,5-dioxopyrrolidin-1-yl)-3,4-dihydroquinazoline-2-carboxylate (**VII**) was synthesized starting from 4-[2-(2-aminobenzoyl)hydrazino]-4-oxobutanoic acid (**IV**) which was prepared according to the procedure described in [3]. The reaction of acid **IV** with ethoxalyl chloride in glacial acetic acid in the presence of triethylamine gave oxamate **V**, and heating of the latter in acetic acid afforded quinazolin-4-one derivative **VI**. By treatment of **VI** with acetic anhydride we obtained the target succinimide **VII**. Compound **VII** can also be obtained directly from ester **V** (without isolation of intermediate acid **VI**) by the action of acetic anhydride (Scheme 2).

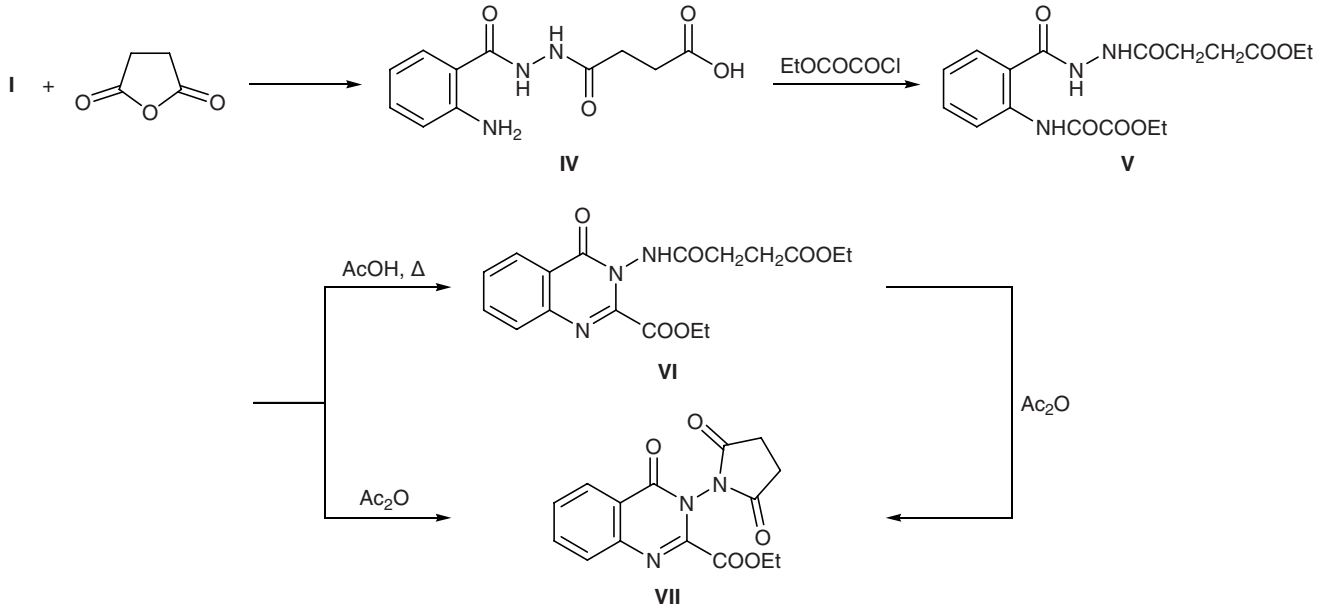
Molecule **VII** possesses ester group and succinimide ring which are capable of readily reacting with nitrogen- and oxygen-centered nucleophiles. Thus imide **VII** reacted with primary amines to produce the corresponding amides **VIIIa–VIIIc** with conservation

Scheme 1.



I II III

Scheme 2.

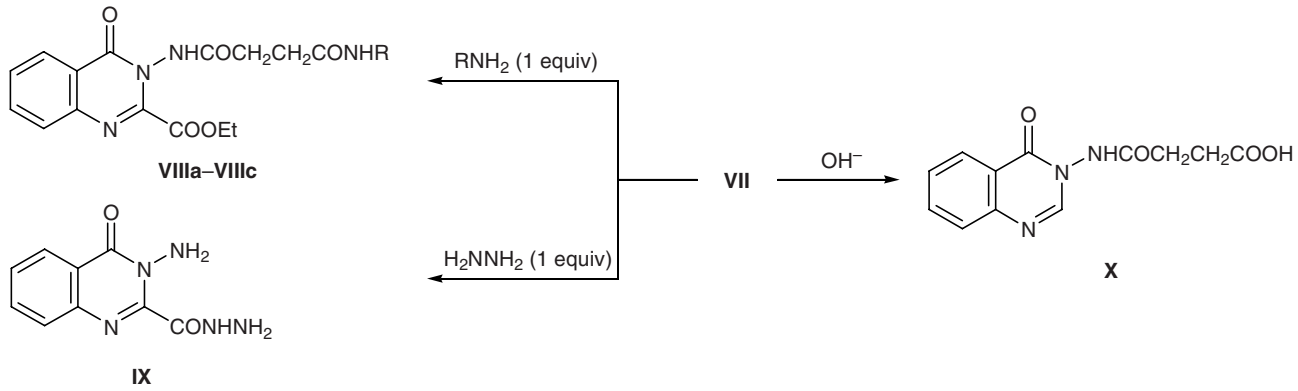


of the ester group (Scheme 3). The product structure indicates higher reactivity of the imide ring toward nucleophiles, as compared to the ester group.

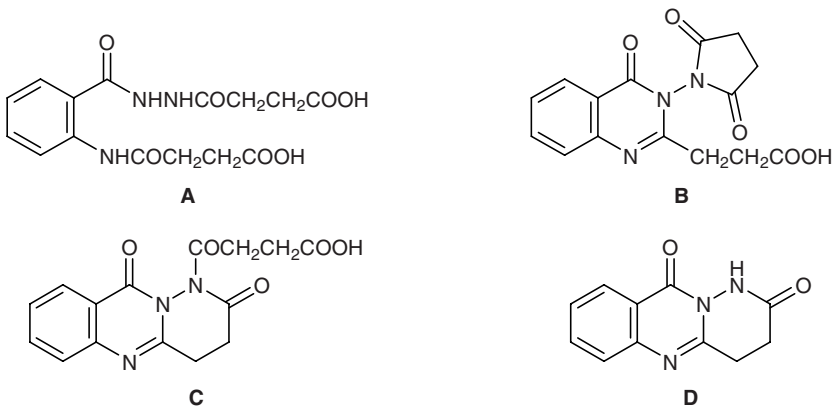
We performed AM1 calculations of electron density on the carbonyl carbon atoms in molecule **VII** with MMX optimization of the geometric parameters [6]. The charge on the ester carbonyl carbon atom was estimated at +0.428, and those on the imide carbonyl carbon atoms, at +0.394 and +0.378. These values suggest higher reactivity of the ester group rather than imide ring. The difference between the charges on the imide carbonyl carbon atom is likely to result from rupture of conjugation therein. An analogous relation was obtained by MINDO/3, MNDO, and PM3 calculations. The fact that the reaction involves the imide ring rather than the ester group may be rationalized in terms of steric factors.

In the reaction of imide **VII** with hydrazine hydrate we isolated ~30% of hydrazide **IX** (Scheme 3). Presumably, the process involves initial opening of the imide ring (as in the reaction with amines), followed by elimination of succinic acid residue. 3-Acylamino-3,4-dihydroquinazolin-4-ones are known to readily lose the acyl group; such transformations were described in [7, 8]. Due to high nucleophilicity of hydrazine, the reaction is accompanied by hydrazinolysis of the ester group. Treatment of imide **VII** with excess alkali led to the formation of acid **X** [9] as a result of decarboxylation of intermediate 4-oxoquinazoline-2-carboxylic acid (Scheme 3).

Scheme 3.



VIII, R = Pr (**a**), $PhCH_2$ (**b**), furfuryl (**c**).

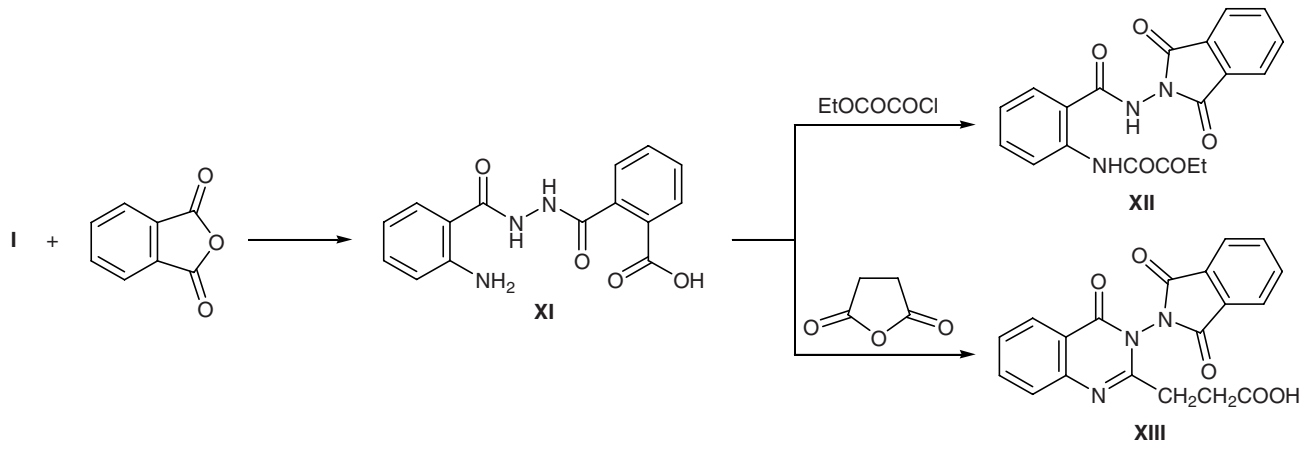


The structure of ester **V** implies that its cyclodehydration could produce both quinazolinone and imide ring. We previously [3] failed to determine the ring closure sequence for analogous structures despite numerous attempts. Preferential formation of quinazolinone structure rather than imide ring on heating of ester **V** in boiling acetic acid is likely to be favored by the presence of a bulky substituent (ethoxalylamino group) in the *ortho* position of the benzene ring, which hinders closure of succinimide ring. We presumed in [10] that the quinazoline and imide rings are formed simultaneously and proposed structure **B** for the cyclodehydration product of bis-acid **A**. The ^{1}H NMR spectrum of the product did not contradict the proposed structure. However, it remained unclear why compound **B** was readily converted into pyrazinoquinazoline **D** even upon crystallization from ethanol whereas it did not change upon crystallization from anhydrous dioxane.

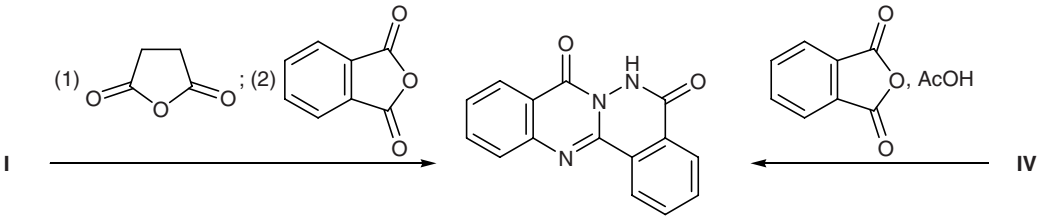
Our present results led us presume that the cyclization of bis-carboxylic acid **A** yields structure **C** as a result of preferential quinazoline ring closure. Intermediate formation of structure **C** explains well the transformation of the cyclodehydration product upon crystallization. An indirect evidence in favor of the formation of structure **C** was obtained by studying cyclodehydration of other diacyl derivatives of anthranilic acid hydrazide, namely those containing oxalic, succinic, and phthalic acid residues. The presence of a phthalic acid moiety turned out to be the main factor determining the cyclization direction; the position of the *o*-carboxybenzoyl substituent is also important. If the latter is attached to the hydrazine fragment, phthalimide ring closure occurs preferentially. In fact, the acylation of acid **XI** [3] with ethoxalyl chloride in the cold gave phthalimide **XII** (Scheme 4). In the reaction of **XI** with succinic anhydride at elevated temperature we isolated compound **XIII**. Phthalic acid is known to readily (as compared to other dicarboxylic acids) undergo imide ring closure; in addition, enhanced nucleophilicity of the hydrazide group in **XI** also favors imide ring closure (α effect) [11].

The reaction takes a different path when the phthalic acid residue is attached to the amino group. The

Scheme 4.



Scheme 5.



acylation of acid **IV** with phthalic anhydride, followed by heating in boiling acetic acid, gave phthalazinoquinazoline **XIV** [3, 10] (Scheme 5). Compound **XIV** can also be obtained by successive acylation of hydrazide **I** with succinic and phthalic anhydrides in acetic acid. Here, the predominant process is closure of quinazoline ring, and subsequent cyclization with formation of phthalazine ring is accompanied by elimination of succinic acid. This reaction scheme not only explains the formation of **XIV** but also provides an indirect proof for intermediacy of structure **C**.

EXPERIMENTAL

The ^{1}H NMR spectra were measured in DMSO-d_6 on a Varian M 200 spectrometer (200 MHz) relative to tetramethylsilane as internal reference.

Ethyl [2-(2-{[ethoxy(oxo)acetyl]amino}benzoyl)-hydrazino]oxoacetate (II). Triethylamine, 3.04 ml (0.02 mol), was added on cooling to a solution of 1.51 g (0.01 mol) of anthranilic acid hydrazide (**I**) in 7 ml of acetic acid, and 2.46 ml (0.02 mol) of ethoxalyl chloride was added dropwise. The mixture was left overnight and diluted with water, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.2 g (63%), mp 156–158°C. ^{1}H NMR spectrum, δ, ppm: 1.36 m (6H, $CH_2C\mathbf{H}_3$), 4.31 m (4H, OCH_2), 7.26 t (1H, 5-H), 7.60 t (1H, 4-H), 7.90 d (1H, 3-H), 8.57 d (1H, 6-H), 10.86 s (1H, NHCOCO), 10.99 s (1H, CON**H**NH), 12.41 s (1H, NHCO). Found, %: C 51.40; H 4.92; N 12.02. $C_{15}H_{13}N_3O_7$. Calculated, %: C 51.28; H 4.88; N 11.96.

Ethyl 3-{[ethoxy(oxo)acetyl]amino}-4-oxo-3,4-dihydroquinazoline-2-carboxylate (III). A solution of 1.0 g (0.05 mol) of diester **II** in a minimal volume of acetic anhydride was heated for 1 h at 70–80°C. Yield 0.48 g (51%), mp 58–60°C. ^{1}H NMR spectrum, δ, ppm: 1.3 m (6H, $CH_2C\mathbf{H}_3$), 4.4 m (4H, OCH_2), 7.73 t (1H, 6-H), 7.84 d (1H, 8-H), 8.00 t (1H, 7-H), 8.23 d (1H, 5-H), 12.45 s (1H, NHCO). Found, %: C 54.20; H 4.68; N 12.70. $C_{15}H_{15}N_3O_6$. Calculated, %: C 54.06; H 4.54; N 12.61.

4-[2-(2-{[Ethoxy(oxo)acetyl]amino}benzoyl)-hydrazino]-4-oxobutanoic acid (V). Triethylamine, 1.4 ml (0.01 mol), was added to a cold solution of 2.5 g (0.01 mol) of acid **IV** in 5 ml of acetic acid, and 1.1 ml (0.01 mol) of ethoxalyl chloride was added dropwise. The mixture was left overnight and diluted with water, and the colorless precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.1 g (60%), mp 178–180°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3), 2.45–2.51 s (4H, CH_2CH_2), 4.3 q (2H, OCH_2), 7.28 t (1H, 5-H), 7.63 t (1H, 4-H), 7.89 d (1H, 3-H), 8.52 d (1H, 6-H), 10.1 s (1H, NHCO), 10.68 s (1H, NHCO), 12.15–12.38 d (2H, NHCO, OH). Found, %: C 51.41; H 4.98; N 12.05. $C_{15}H_{17}N_3O_7$. Calculated, %: C 51.28; H 4.88; N 11.96.

***N*-(2-Ethoxycarbonyl-4-oxo-3,4-dihydroquinazolin-3-yl)succinamic acid (VI).** A mixture of 3.51 g (0.01 mol) of compound **V** and acetic acid was heated for 40 min under reflux and was then left overnight. The mixture was diluted with water, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.9 g (56%), mp 175–177°C. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3), 2.84 t (2H, $COCH_2$), 3.2 t (2H, $C\mathbf{H}_2COOH$), 4.3 q (2H, OCH_2), 7.39 t (1H, 6-H), 7.67 t (1H, 7-H), 8.0 d (1H, 8-H), 8.6 d (1H, 5-H), 12.2 s (1H, NH), 12.4 br.s (1H, OH). Found, %: C 54.19; H 4.67; N 12.71. $C_{15}H_{15}N_3O_6$. Calculated, %: C 54.06; H 4.54; N 12.61.

Ethyl 3-(2,5-dioxopyrrolidin-1-yl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (VII). *a*. A mixture of 0.33 g (0.001 mol) of compound **VI** and excess acetic anhydride was heated for 40 min at 70–80°C and was then left overnight. The mixture was diluted with water, and the precipitate was filtered off. Yield 0.21 g (68%), mp 159°C.

b. A mixture of 0.35 g (0.001 mol) of compound **V** and 0.09 ml (0.001 mol) of acetic anhydride was heated for 20 min at 70–80°C and was then left over-

night. The mixture was diluted with water, and the precipitate was filtered off. Yield 0.23 g (73%), mp 157–159°C. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3), 3.1 s (4H, CH_2CH_2), 4.4 q (2H, OCH_2), 7.75 t (1H, 6-H), 7.95 d (1H, 8-H), 8.05 t (1H, 7-H), 8.21 d (1H, 5-H). Found, %: C 57.26; H 4.22; N 13.41. $C_{15}H_{13}N_3O_5$. Calculated, %: C 57.14; H 4.16; N 13.33.

Ethyl 4-oxo-3-[4-oxo-4-(propylamino)butanoylamino]-3,4-dihydroquinazoline-2-carboxylate (VIIIa). Propylamine, 0.83 ml (0.01 mol), was added to a solution of 3.15 g (0.01 mol) of compound **VII** in a minimal amount of dioxane, and the mixture was refluxed for 1 h and left overnight. The precipitate was filtered off and dried. Yield 2.6 g (71%), mp 108–110°C. ^{1}H NMR spectrum, δ, ppm: 0.9 t (3H, $CH_2CH_2C\mathbf{H}_3$), 1.2–1.5 m (5H, $OCH_2C\mathbf{H}_3$, $CH_2C\mathbf{H}_2CH_3$), 2.51 q (2H, $NHC\mathbf{H}_2$), 4.3 q (2H, $COCH_2$), 7.6–7.9 m (4H, H_{arom}), 8.15 t (1H, $CON\mathbf{H}CH_2$), 11.3 s (1H, NHCO). Found, %: C 57.87; H 5.99; N 15.06. $C_{18}H_{28}N_4O_5$. Calculated, %: C 57.75; H 5.92; N 14.96.

Ethyl 3-[4-(benzylamino)-4-oxobutanoylamino]-4-oxo-3,4-dihydroquinazoline-2-carboxylate (VIIIb) was synthesized in a similar way. Yield 3.1 g (75%), mp 130–132°C. ^{1}H NMR spectrum, δ, ppm: 1.3 t (3H, CH_3), 2.35 t (2H, $COCH_2$), 2.65 t (2H, CH_2CO), 4.2 d (2H, $NHC\mathbf{H}_2$), 4.35–4.4 q (2H, OCH_2), 7.25 m (5H, H_{arom}), 7.6–8.3 m (4H, H_{arom}), 8.4 t (1H, CONH), 11.25 s (1H, NHCO). Found, %: C 62.69; H 5.37; N 13.38. $C_{22}H_{22}N_4O_5$. Calculated, %: C 62.55; H 5.25; N 13.26.

Ethyl 3-[4-(furan-2-ylmethylamino)-4-oxobutanoylamino]-4-oxo-3,4-dihydroquinazoline-2-carboxylate (VIIIc) was synthesized in a similar way. Yield 3.35 g (82%), mp 143–145°C. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3), 2.2–2.8 m (4H, CH_2CH_2), 4.3 d (2H, $NHC\mathbf{H}_2$), 4.4 q (2H, OCH_2), 6.1 d (1H, 3′-H), 6.3 t (1H, 4′-H), 7.5. d (1H, 5′-H), 7.6–8.3 m (4H, H_{arom}), 8.4 t (1H, $N\mathbf{H}CH_2$), 11.4 s (1H, NHCO). Found, %: C 58.39; H 4.97; N 13.68. $C_{20}H_{20}N_4O_6$. Calculated, %: C 58.25; H 4.89; N 13.59.

3-Amino-4-oxo-3,4-dihydroquinazoline-2-carbohydrazide (IX). Hydrazine hydrate, 0.49 ml (0.01 mol), was added to a solution of 3.15 g (0.01 mol) of compound **VII** in ethanol, the mixture was left overnight, and the precipitate was filtered off and dried. Yield 0.66 g (30%), mp 196–198°C [12].

***N*-(4-Oxo-3,4-dihydroquinazolin-3-yl)succinamic acid (X).** A mixture of 3.15 g (0.01 mol) of compound **VII** and 100 ml of a 0.1 M solution of sodium hydroxide was heated until it became homogeneous. The mixture was neutralized with hydrochloric acid, and the precipitate was filtered off. Yield 1.6 g (60%), mp 225°C (from ethanol) [9].

Ethyl *N*-[2-(phthalimidocarbamoyl)phenyl]-oxamate (XII). A solution of 2.9 g (0.01 mol) of compound **XI** in 5 ml of acetic acid was cooled, 1.4 ml (0.01 mol) of triethylamine was added, and 1.1 ml (0.01 mol) of ethoxalyl chloride was added dropwise on cooling. The mixture was left overnight and diluted with water, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.4 g (64%), mp 138–140°C [5, 10]. ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, CH_3), 4.25 q (2H, OCH_2), 7.3–7.87 m (8H, H_{arom}), 11.72 s (1H, NHCO), 12.18 s (1H, CONH). Found, %: C 59.97; H 4.06; N 11.17. $C_{19}H_{15}N_3O_6$. Calculated, %: C 59.84; H 3.96; N 11.02.

3-(4-Oxo-3-phthalimido-3,4-dihydroquinazolin-2-yl)propionic acid (XIII). Succinic anhydride, 1.0 g (0.01 mol), was added to a solution of 2.9 g (0.01 mol) of compound **XI** in acetic acid, the mixture was heated for 30 min under reflux and diluted with water, and the precipitate was filtered off and recrystallized from ethanol. Yield 2.5 g (70%). ^{1}H NMR spectrum, δ, ppm: 2.74 t (2H, CH_2CO), 3.02 t (2H, CH_2), 7.6–8.15 m (8H, H_{arom}), 12.15 s (1H, OH). Found, %: C 62.98; H 3.70; N 11.69. $C_{19}H_{13}N_3O_5$. Calculated, %: C 62.81; H 3.61; N 11.57.

6*H*-Phthalazino[1,2-*b*]quinazoline-5,8-dione (XIV). *a*. Phthalic anhydride, 1.48 g (0.01 mol), was added to a solution of 2.5 g (0.01 mol) of acid **IV** in acetic acid, the mixture was heated for 20 min at 60–70°C and diluted with water, and the precipitate was filtered off and recrystallized from ethanol. Yield 2.2 g (83%), mp 263–265°C. Found, %: C 68.56; H 3.59; N 16.09. $C_{15}H_9N_3O_2$. Calculated, %: C 68.44; H 3.45; N 15.96.

b. Succinic anhydride, 1.0 g (0.01 mol), was added to a solution of 1.51 g (0.01 mol) of hydrazide **I** in acetic acid, the mixture was cooled, 1.48 g (0.01 mol) of phthalic anhydride was added, and the mixture was heated for 30 min under reflux and diluted with water. Yield 1.9 g (75%), mp 260–262°C.

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