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Synthesis of *N*-(4-Oxo-3,4-dihydroquinazolin-3-yl)succinimide and *N*-(4-Oxoquinazolin-3-yl)succinamic Acid Derivatives Based Thereon

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Abstract—The reaction of anthranilic acid hydrazide with diethyl oxalate under microwave irradiation was accompanied by decarboxylation with formation of 3-amino-3,4-dihydroquinazolin-4-one, and acylation of the latter with succinic anhydride gave *N*-(4-oxo-3,4-dihydroquinazolin-3-yl)siccinimide which was converted into various *N*-(4-oxo-3,4-dihydroquinazolin-3-yl)succinamic acid derivatives.

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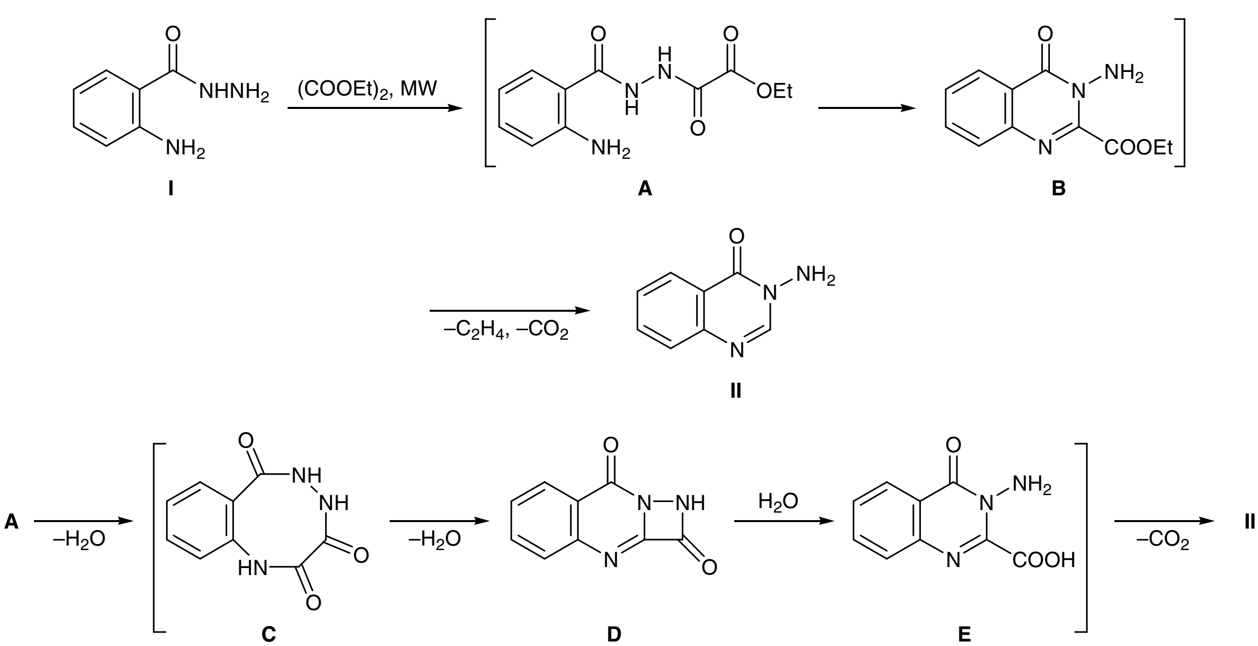
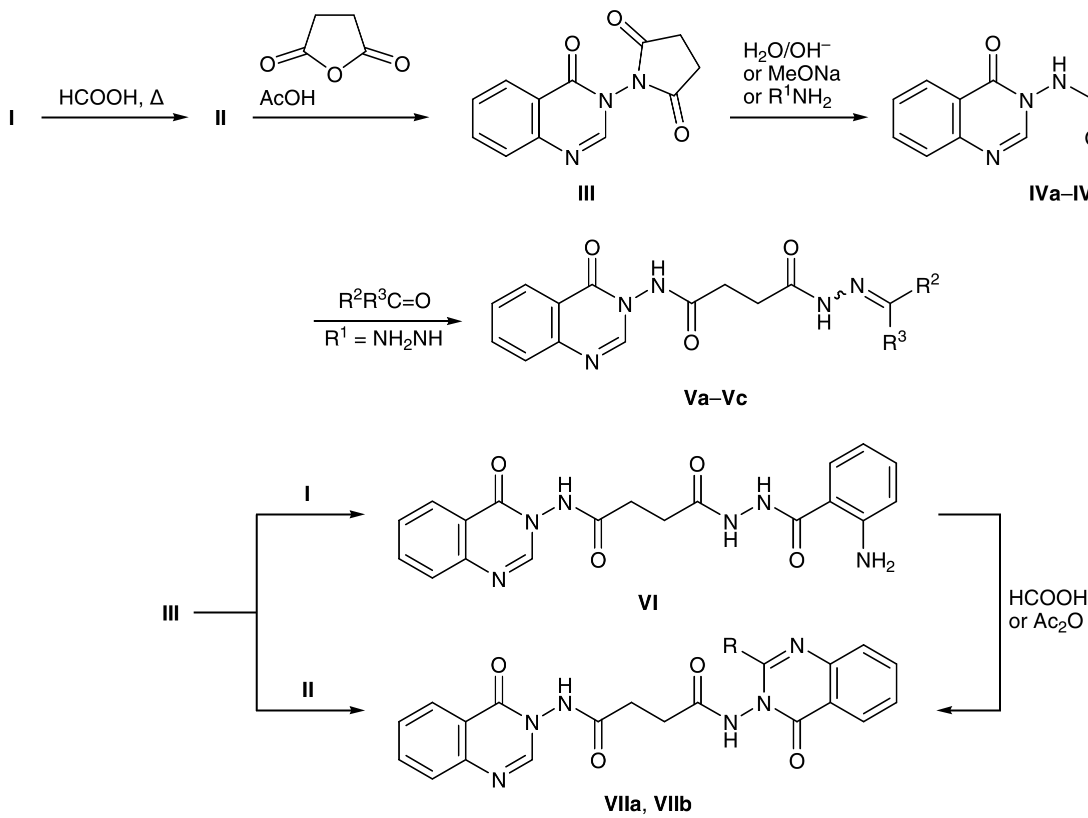
Quinazolin-4-one derivatives have long been known as a promising class of biologically active compounds [1, 2]. Up to now, a great number of various procedures have been proposed for the synthesis of quinazolin-4-ones [3]. Procedures utilizing microwave activation are not laborious and are characterized by high yields; these techniques have also found application for the synthesis of the quinazoline system [4, 5].

The choice of the starting compound in the present work was somewhat accidental. 3-Amino-3,4-dihydroquinazolin-4-one (**II**) was obtained by reaction of anthranilic acid hydrazide (**I**) with diethyl oxalate under microwave irradiation. This result was surprising, for the same reaction performed on heating is known to produce ethyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate [6]. The ^{1}H NMR spectrum of **II** contained a narrow singlet at δ 5.88 ppm from protons of the amino group and a signal at δ 8.37 ppm from 2-H in the pyrimidine ring, while no ethoxy group signals were present.

Scheme 1.



Scheme 2.



IV, R^1 = HO (**a**), MeO (**b**), PrNH (**c**), $PhCH_2NH$ (**d**), NH_2NH (**e**); **V**, $R^2 = R^3$ = Me (**a**), R^2 = H, R^3 = Ph (**b**), 4-$Me_2NC_6H_4$ (**c**); **VII**, R = H (**a**), Me (**b**).

Scheme 1 shows several possible ways for formation of compound **II** from hydrazide **I** and diethyl oxalate. Initially, acylation of hydrazide **I** with diethyl oxalate gives compound **A** which undergoes intramolecular transacylation with formation of ethyl quinazolinecarboxylate **B**. Analogous syntheses of 2-substituted 3-aminoquinazolinones via transacylation of *N*-(2-aminobenzoyl)-*N'*-aroylhydrazines were reported [7–9]. The subsequent decarboxylation of **B** yields final product **II**. An alternative path includes intramolecular acylation of amino ester **A** with formation of 1,4,5-benzotriazocane which is converted into quinazolinone **II** through intermediates **D** and **E**. The latter can also be formed by hydrolysis of ester **B**. In order to verify the possibility for the reaction to follow the first path, we synthesized compound **B** according to the procedure given in [6]. However, the product failed to undergo decarboxylation even under more severe conditions, i.e., under increased microwave irradiation power and time (to 10 min); only the initial compound was recovered from the reaction mixture. Therefore, we believe that the second path is more probable.

We prepared quinazolinone **II** for further transformations by a simpler procedure, by heating hydrazide **I** in formic acid [10]. The reaction of **II** with succinic anhydride on heating in boiling glacial acetic acid for a short time afforded *N*-(4-oxo-3,4-dihydroquinazolin-3-yl)succinimide (**III**) (Scheme 2). The reaction involved intermediate formation of succinamic acid **IVa** which underwent cyclodehydration to imide **III**. The ease of imide ring closure must be noted. Even a slight heating of the reaction mixture resulted in the formation of a mixture of acid **IVa** and imide **III**, the latter prevailing. When the acylation of **II** with succinic anhydride was carried out at room temperature (by stirring for 48 h), a mixture of unreacted compound **II** and acid **IVa** was formed. Therefore, 3-(4-oxo-3,4-dihydroquinazolin-3-ylcarbamoyl)propanoic acid (**IVa**) was synthesized by alkaline hydrolysis of imide **III**.

Imide **III** readily reacts with various nucleophiles. The reaction of **III** with sodium methoxide in boiling methanol gave ester **IVb**, while heating with aliphatic amines in ethanol led to the formation of the corresponding *N*,*N'*-disubstituted succinamides **IVc** and **IVd**. By treatment of **III** with hydrazine hydrate in dioxane we obtained hydrazide **IVe**. The latter can also be synthesized by mixing imide **III** with hydrazine hydrate in a porcelain mortar according to the procedure reported in [11]. However, in this case the reaction is accompanied by partial decomposition of **III** with formation of quinazolinone **II** as an impurity. Hydrazide **IVe** was converted into the corresponding hydrazones **Va**–**Vc** by heating with acetone and aromatic aldehydes in dimethylformamide.

Quinazolin-4-one derivatives **VIIa** and **VIIb** were synthesized from compound **VI** which was prepared by heating imide **III** with hydrazide **I** in dioxane or by fusion of the initial compounds without a solvent. The best results were obtained when the reaction was performed in dioxane. Intramolecular cyclization of the 2-aminobenzohydrazide fragment in **VI** gave compounds **VIIa** and **VIIb**. Symmetric *N*,*N'*-bis(4-oxo-3,4-dihydroquinazolin-3-yl)succinamide (**VIIa**) was obtained by heating compound **VI** in formic acid. Succinamide **VIIa** was also synthesized by fusion of imide **III** with quinazolinone **II**, but the yield was lower, and elevated temperature or prolonged time favored decomposition of the initial compounds. Attempts to react imide **III** with quinazolinone **II** in a solvent were unsuccessful; only the initial compounds were isolated when their mixture was heated in boiling ethanol, dioxane, acetic acid, and DMF. Unsymmetrical succinamide **VIIb** was obtained by heating compound **VI** with an equimolar amount of acetic anhydride in glacial acetic acid (Scheme 2).

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Varian M-200 spectrometer at 200MHz from solutions in DMSO-d_6 relative to tetramethylsilane as internal reference. Microwave-assisted reactions were carried out in a microwave furnace with a power of 800 W.

3-Amino-3,4-dihydroquinazolin-4-one (II). A mixture of 0.01 mol (1.5 g) of anthranilic acid hydrazide (**I**) and 0.01 mol of diethyl oxalate was heated for 7 min in a microwave furnace. After cooling, the melt was crystallized from ethanol. Yield 89%, mp 208–210°C. ^{1}H NMR spectrum, δ, ppm: 5.88 s (2H, NH_2), 7.55 t (1H, 6-H), 7.72 d (1H, 8-H), 7.81 t (1H, 7-H), 8.18 d (1H, 5-H), 8.37 s (1H, 2-H).

1-(4-Oxo-3,4-dihydroquinazolin-3-yl)pyrrolidine-2,5-dione (III). A mixture of 0.01 mol of aminoquinazolinone **II** and 0.01 mol of succinic anhydride in glacial acetic acid was heated for 40 min. The mixture was cooled and diluted with water, and the precipitate was filtered off, dried, and recrystallized from acetic acid. Yield 82%, mp 224°C. ^{1}H NMR spectrum, δ, ppm: 3.0 t (2H, CH_2), 3.06 t (2H, CH_2), 7.69 t (1H, 6-H), 7.83 d (1H, 8-H), 8.00 t (1H, 7-H), 8.22 d (1H, 5-H), 8.36 s (1H, 2-H).

3-(4-Oxo-3,4-dihydroquinazolin-3-ylcarbamoyl)-propanoic acid (IVa). A mixture of 0.01 mol (2.4 g) of compound **III** 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 60%, mp 225°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.5–2.65 m (4H, CH_2CH_2), 7.58 t (1H, 6-H), 7.74 d (1H, 8-H), 7.90 t (1H, 7-H), 8.12–8.20 d (2H, 5-H, 2-H), 11.4–12.0 s (2H, NH, COOH).

Methyl 3-(4-oxo-3,4-dihydroquinazolin-3-ylcarbamoyl)propanoate (IVb). Compound **III**, 0.01 mol (2.4 g), was dissolved on heating in 15 ml of methanol, a solution of 0.01 mol (0.54 g) of sodium methoxide in methanol was added, and the mixture was heated for 1 h. The mixture was cooled and diluted with water, and the precipitate was filtered off and dried. Yield 40%, mp 147°C (from methanol). ^{1}H NMR spectrum, δ, ppm: 2.5 t (2H, CH_2), 3.0 t (2H, CH_2), 3.60 s (3H, CH_3), 7.55 t (1H, 6-H), 7.7 d (1H, 8-H), 7.85 t (1H, 7-H), 8.12 d (1H, 5-H), 8.15 s (1H, 2-H), 11.35 s (NH).

***N*-(4-Oxo-3,4-dihydroquinazolin-3-yl)-*N'*-propylsuccinamide (IVc).** A mixture of 0.01 mol (2.43 g) of compound **III** and 0.01 mol (0.8 ml) of propylamine in 10 ml of ethanol was heated under reflux until it became homogeneous. The mixture was cooled, and the precipitate was filtered off, dried, and recrystallized from water. Yield 63%, mp 212°C. ^{1}H NMR spectrum, δ, ppm: 0.8 t (3H, CH_3), 1.4 m (2H, CH_2), 2.4 m (NCH_2), 2.5 t (2H, $COCH_2$), 3.0 t (2H, $COCH_2$), 7.55 t (1H, 6-H), 7.7 d (1H, 8-H), 7.85–7.9 t (2H, 7-H, CONH), 8.12 d (1H, 5-H), 8.15 s (1H, 2-H), 11.2–11.4 s (NNH).

***N*-Benzyl-*N'*-(4-oxo-3,4-dihydroquinazolin-3-yl)-succinamide (IVd)** was synthesized in a similar way. Yield 67%, mp 201°C. ^{1}H NMR spectrum, δ, ppm: 2.5 t (2H, CH_2), 2.8 t (2H, $COCH_2$), 4.6 d (2H, NCH_2), 7.4 m (5H, C_6H_5), 7.55 t (1H, 6-H), 7.7 d (1H, 8-H), 7.85–7.9 t (2H, 7-H, CONH), 8.12 d (1H, 5-H), 8.15 s (1H, 2-H), 11.2–11.4 s (NNH).

3-Hydrazinocarbonyl-*N*-(4-oxo-3,4-dihydro-quinazolin-3-yl)propanamide (IVe). Compound **III**, 0.01 mol (2.43 g), was dissolved on heating in 10 ml of 1,4-dioxane, and 0.015 mol (0.75 ml) of hydrazine hydrate was added to the hot solution. A solid immediately separated and was filtered off, dried, and recrystallized from water. Yield 65%, mp 237–239°C. ^{1}H NMR spectrum, δ, ppm: 2.2 t (2H, CH_2), 2.7 t (2H, CH_2), 4.15 d (2H, NH_2), 7.55 t (1H, 6-H), 7.7 d (1H, 8-H), 7.85–7.9 t (1H, 7-H), 8.12 d (1H, 5-H), 8.15 s (1H, 2-H), 9.0 t (1H, CONH), 11.2–11.4 s (NNH).

3-(Benzylidenehydrazinocarbonyl)-*N*-(4-oxo-3,4-dihydroquinazolin-3-yl)propanamide (Vb). A mixture of 0.01 mol of compound **IVe** and 0.01 mol (1 ml) of benzaldehyde was heated in DMF. It was then cooled and diluted with water, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 61%, mp 230–232°C. ^{1}H NMR spectrum, δ, ppm: 2.74 s (1H, =CH), 2.6–3.1 m (4H, CH_2CH_2), 7.4–8.4 m (10H, H_{arom}, NH=N), 11.2–11.4 (1H, NHCO).

Compounds **Va** and **Vc** were synthesized in a similar way.

3-(Isopropylidenehydrazinocarbonyl)-*N*-(4-oxo-3,4-dihydroquinazolin-3-yl)propanamide (Va). Yield 55%, mp 187°C. ^{1}H NMR spectrum, δ, ppm: 2.8–2.9 m (4H, CH_2CH_2), 3.2–3.3 s [6H, $(\mathbf{CH}_3)_2C$], 7.55 t (1H, 6-H), 7.7 d (1H, 8-H), 7.85–7.9 t (1H, 7-H), 8.12 d (1H, 5-H), 8.15 s (1H, 2-H), 9.0 s (1H, CONH), 11.2–11.4 s (NNH).

3-(*p*-Dimethylaminobenzylidenehydrazinocarbonyl)-*N*-(4-oxo-3,4-dihydroquinazolin-3-yl)propanamide (Vc). Yield 65%, mp 250°C. ^{1}H NMR spectrum, δ, ppm: 2.65 s (1H, =CH), 2.8–2.9 m (4H, CH_2CH_2), 3.1 m [6H, $N(CH_3)_2$], 7.5–7.9 m (7H, 6-H, 7-H, 8-H, C_6H_4), 8.14 d (2H, 5-H, NH=N), 8.32 s (1H, 2-H), 11.2–11.4 (1H, CONH).

3-(*o*-Aminobenzoylhydrazinocarbonyl)-*N*-(4-oxo-3,4-dihydroquinazolin-3-yl)propanamide (VI). Compound **III**, 0.01 mol (2.43 g), was dissolved on heating in a minimal volume of 1,4-dioxane, the solution was cooled, a solution of 0.01 mol (1.5 g) of anthranilic acid hydrazide (**I**) in 1,4-dioxane was added, and the mixture was left to stand for 3 days. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 52%, mp 244–245°C. ^{1}H NMR spectrum, δ, ppm: 2.4–2.7 m (2H, CH_2CH_2), 6.32 s (2H, NH_2), 6.5–8.2 m (8H, H_{arom}), 9.8 (2H, NHNH), 11.2–11.3 (1H, NH).

***N*,*N′*-Bis(4-oxo-3,4-dihydroquinazolin-3-yl)-succinamide (VIIa).** A mixture of 0.01 mol (3.94 g) of compound **VI** and 5 ml of formic acid was heated to the boiling point. A solid separated and was filtered off, dried, and recrystallized from acetic acid. Yield 68%, mp 241–242°C. ^{1}H NMR spectrum, δ, ppm: 2.7 s (2H, CH_2), 7.6 t (1H, 6-H), 7.72 d (1H, 8-H), 7.9 t (1H, 7-H), 8.18–8.22 t (5-H, 2-H), 11.4 s (1H, NH).

***N*-(2-Methyl-4-oxo-3,4-dihydroquinazolin-3-yl)-*N′*-(4-oxo-3,4-dihydroquinazolin-3-yl)succinamide (VIIb).** A mixture of 0.01 mol (3.94 g) of compound **VI** and 0.01 mol (0.94 ml) of acetic anhydride in glacial acetic acid was heated for 30 min. The precipitate was filtered off, dried, and recrystallized from acetic acid. Yield 65%, mp 230–231°C. ^{1}H NMR spectrum, δ, ppm: 2.5 s (3H, CH_3), 2.9–3.2 m (4H, CH_2CH_2), 7.65 t (2H, 6-H), 7.89 d (2H, 8-H), 7.95 t (2H, 7-H), 8.19 d (2H, 5-H), 8.34 s (1H, 2-H), 11.4 s (2H, NH).

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