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Reactions of Ethyl Oxamate and Dialkyl Oxalates with Anthranilic Acid Derivatives

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Abstract—Ethyl oxamate reacted with anthranilic acid derivatives at the amide or the ester group leading to the formation of respective esters or amides. A simple method was developed for preparation of alkyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylates.

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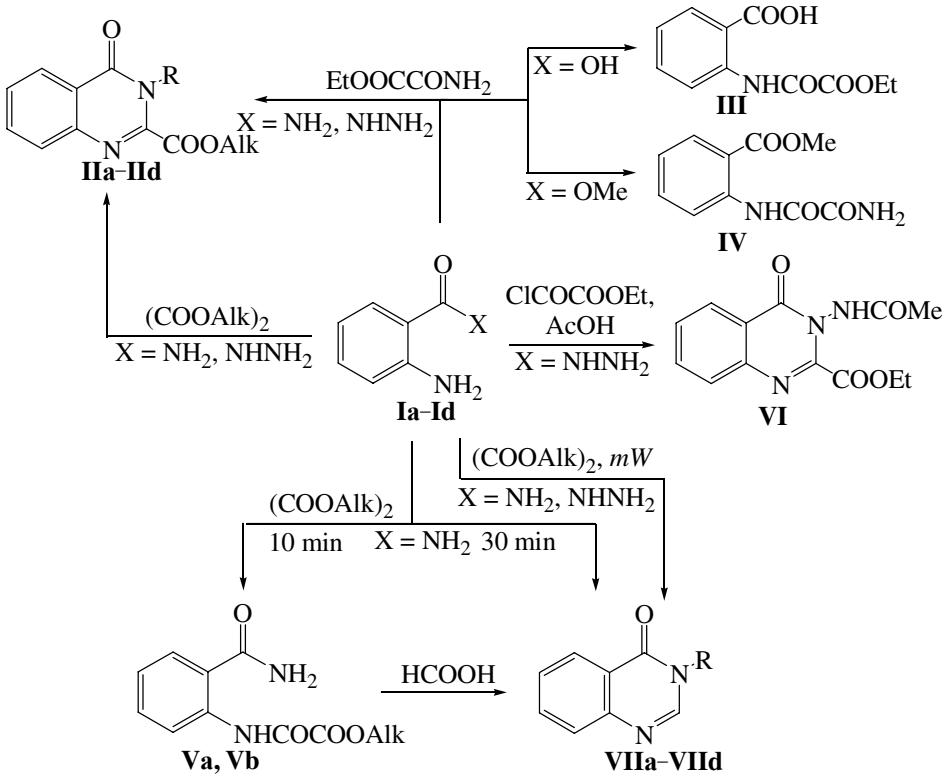
A synthesis was described of ethyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate by heating anthranilohydrazide (**Ia**) with diethyl oxalate at 180°C for 6 h followed by evaporating diethyl oxalate under a vacuum [1]. We attempted to prepare 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid amide by reaction of hydrazide **Ia** with ethyl oxamate using acetic acid as solvent. The result was unexpected since ethyl ester **IIa** was isolated from the reaction mixture; therefore the reaction occurred at the amide instead of ester group, although the oxamic acid esters were known to react [2, 3] with N-nucleophiles by the ester group. The application of a double excess of ethyl oxamate in this reaction did not affect its result and the yield of the product.

The former calculations of the charges on the carbon atoms of the carbonyls in the molecules of the N-substituted oxamic acid esters revealed that in some events the electrophilicity of the amide group is higher than that of the ester one due both to the reciprocal influence of the groups and to the nature of substituents attached to the amide nitrogen [3]. The enhanced reactivity of the amide group in the oxamic acids esters was proved experimentally: In [4] the amination of unsymmetrical *N,N'*-disubstituted oxamides with an ester of an N-substituted oxamic acid gave also a symmetric oxalic acid dialkylamide, a transamination product of oxamide; therewith the ease of the process was mentioned. Yet no reactions of oxamic acids esters with N-nucleophiles were observed occurring at the amide group without affecting the ester group (see the scheme).

The result obtained promoted an extension of our investigations; we used further apart anthranilohydrazide (**Ia**) also anthranilic acid (**Ib**), its methyl ester (**Ic**) and amide (**Id**), and also some dialkyl oxalates. The heating of ethyl oxamate with acid **Ib** and anthranilamide (**Id**) gave rise to the corresponding esters **III** and **IIc**; thus the ethyl oxamate here also reacted at the amide group. With methyl anthranilate (**Ic**) amide **IV** was isolated, therefore here the ester group of the ethyl oxamate proved to be more reactive. It is presumable that the governing factor leading to the amide **IV** was no possibility of intramolecular hydrogen bonds formation in methyl anthranilate molecule (**Ic**) which were present in anthranilic acid (**Ib**) and its other derivatives **Ia** and **Id**. The hydrogen bonds are likely to influence the formation and structure of the transition state and thus determine the character of the leaving group.

By the study of alkylation of anthranilic acid derivatives with dialkyl oxalates we developed a far more easy synthesis of esters **IIa** and **IIb** applying available reagents. Esters **IIa** and **IIb** were obtained by boiling for 30 min of a mixture of anthranilohydrazide (**Ia**) with the corresponding dialkyl oxalate (Alk = Et or Me) in a glacial acetic acid. Yet we failed to isolate under these conditions esters with the other alkyl substituents [reaction was carried out with $(CO_2Alk)_2$ containing Alk = Pr, Bu, C_6H_{13}, C_5H_{11}] even at a longer reaction time. This result is likely due to the lower reactivity of these esters. The reaction of anthranilohydrazide (**Ia**) with ethyl oxalyl chloride in acetic acid in the presence of triethylamine gave 3-*N*-acetylamino-2-carbethoxy-4-oxo-3,4-

Scheme.



I, X = $NHNH_2$ (**a**), OH (**b**), OMe (**c**), NH_2 (**d**); **II**, R = NH_2, Alk = Et (**a**), Me (**b**); R = H, Alk = Et (**c**), Me (**d**); **V**, Alk = Et (**a**), Me (**b**); **VII**, R = H (**a**), NH_2 (**b**).

dihydroquinazoline (**VI**). ^{1}H NMR spectrum of compound **VI** proved to be identical to the spectrum of the same com-pound obtained by another procedure [5]. The participa-tion of the acetic acid in the formation of quinazolinone ring was already reported in [6].

Anthranilamide (**Id**) in the glacial acetic acid formed with diethyl oxalate depending on the reaction time either ester **IIc** or **V** or their mixture; with dimethyl oxalate methyl ester **IId** was obtained. In the formic acid the reaction of anthranilamide (**Id**) with diethyl oxalate gave rise to 4 oxo-3,4-dihydroquinazoline (**VIIa**). This fact may suggest that formic acid was more reactive than diethyl oxalate. However at shorter reaction (10 instead of 30 min) ester **Va** was isolated. Compound **VIIa** was obtained by further heating of the latter in the formic acid. Consequently, first reaction occurred with diethyl oxalate, and the arising ester **Va** then suffered transacylation leading finally to compound **VIIa**. Compounds **VIIa** and **VIIb** were also obtained by microwave irradiation of mixtures of anthranilamide (**Id**) or hydrazide **Ia** with dimethyl and diethyl oxalates; the possibility of this reaction had been reported before. Interestingly, anthranilamide (**Id**) in 1,4-dioxane did not react with diethyl oxalate and ethyl oxamate but only with dimethyl oxalate giving ester **Vb**.

The heating of ethyl oxamate in acetic acid with *p*-toluidine or *o*-phenylenediamine led to the formation of *N,N*' di-(*p*-tolyl)oxamide and 1,4-dihydroquinazoline-2,3-dione respectively.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian M200 (200 MHz) from solutions in DMSO-d_6, internal reference TMS. Microwave irradiation was carried out using an oven of a power 800 W.

Ethyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate (IIa). *a.* In 10 ml of glacial acetic acid 1.51 g (0.01 mol) of hydrazide **Ia** and 1.17 g (0.01 mol) of ethyl oxamate was boiled for 30 min. On cooling the reaction

mixture was diluted with 50 ml of water and left overnight. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.83 g (78%), mp 133–135°C.

b. Analogous procedure was carried out using 0.01 mol of diethyl oxalate. Yield 1.93 g (88%), mp 131–133°C. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3), 4.30 q (2H, CH_2), 5.90 s (2H, NH_2), 7.61 t (1H, H^6), 7.72 d (1H, H^8), 7.87 t (1H, H^7), 8.19 d (1H, H^5) [1].

Methyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate (IIb) was obtained in the same way as compound **IIa** by procedure *b* from 1.51 g (0.01 mol) of amide **Id** and 1.02 g (0.01 mol) of dimethyl oxalate. Yield 1.71 g (84%), mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 3.91 s (3H, OCH_3), 5.90 s (2H, NH_2), 7.60 t (1H, H^6), 7.71 d (1H, H^8), 7.92 t (1H, H^7), 8.18 d (1H, H^5).

Ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate (IIc) was obtained in the same way as compound **IIa** both by procedure *a* from 1.36 g (0.01 mol) of amide **Id** and 1.17 g (0.01 mol) of ethyl oxamate, yield 2.01 g (92%), mp 181–183°C and procedure *b* using 0.01 mol of diethyl oxalate. Yield 1.93 g (88%), mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3), 4.28 q (2H, CH_2), 7.60–8.51 m (4H, C_6H_4), 12.60 s (1H, NH) [7].

Methyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate (IId) was obtained in the same way as compound **IIa** by procedure *b* from 1.36 g (0.01 mol) of amide **^{2}d** and 1.02 g (0.01 mol) of dimethyl oxalate. Yield 1.72 g (84%), mp 192–194°C. ^{1}H NMR spectrum, δ, ppm: 3.80 s (3H, OCH_3), 7.20–8.50 m (4H, C_6H_4), 13.05 s (1H, NH).

2-Carboxyoxanilic acid ethyl ester (III). In a minimal quantity of glacial acetic acid was dissolved 1.37 g (0.01 mol) of anthranilic acid **Ib**, 1.17 g (0.01 mol) of ethyl oxamate was added, and the mixture was heated for 30 min. On cooling the reaction mixture was diluted with 40 ml of cold water and left overnight. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.42 g (60%), mp 178–180°C. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3), 4.30 q (2H, CH_2), 7.20–8.51 m (4H, C_6H_4), 12.50 s (1H, NHCO), 13.05 (1H, OH) [8].

2-Methoxycarbonyloxanilic acid amide (IV) was prepared similarly to compound **III** from 1.51 g (0.01 mol) of ester Ic and 1.17 g (0.01 mol) of ethyl oxamate. Yield 1.31 g (66%), mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H, OCH_3), 7.22–8.65 m (4H, C_6H_4), 8.12 s (1H, $CONH_2$), 8.42 s (1H, $CONH_2$), 12.30 s (1H, NHCO) [9].

2-Carbamoyloxanilic acid ethyl ester (Va). *a.* In a minimal quantity of glacial acetic acid was dissolved 1.36 g (0.01 mol) of amide **Id**, 1.4 ml (0.01 mol) of diethyl oxalate was added, and the mixture was heated for 10 min. On cooling the reaction mixture was diluted with 50 ml of cold water and left overnight. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.07 g (87%), mp 135–137°C.

b. In a minimal quantity of formic acid was dissolved 1.36 g (0.01 mol) of amide **Id**, 1.4 ml (0.01 mol) of diethyl oxalate was added, and the mixture was heated for 10 min. On cooling the reaction mixture was diluted with 50 ml of cold water and left overnight. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.18 g (53%), mp 169–171°C. ^{1}H NMR spectrum, δ, ppm: 1.32 m (3H, CH_3), 4.31 m (2H, CH_2), 7.25–8.52 m (4H, C_6H_4), 7.80 C (1H, $CONH_2$), 8.41 s (1H, $CONH_2$), 13.00 s (1H, NHCO) [10].

2-Carbamoyloxanilic acid methyl ester (Vb). In a minimal quantity of 1,4-dioxane was dissolved 1.36 g (0.01 mol) of amide **Id**, 1.02 g (0.01 mol) of dimethyl oxalate was added, and the mixture was heated for 30 min. On cooling the reaction mixture was diluted with 50 ml of water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.65 g (74%), mp 168–170°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (3H, OCH_3), 7.25–8.51 m (4H, C_6H_4), 7.82 s (1H, $CONH_2$), 8.37 s (1H, $CONH_2$), 13.10 s (1H, NHCO).

3-Acetylamino-2-ethoxycarbonyl-4-oxo-3,4-dihydroquinazoline (VI). In a minimal quantity of glacial acetic acid was dissolved 0.01 mol (1.51 g) of hydrazide **Ia**, 0.01 mol (1.4 ml) of triethylamine was added, and at cooling also 1.2 ml (0.01 mol) of ethyl oxalyl chloride. The reaction mixture was left standing for 1 h, cooled, diluted with 50 ml of water, the separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.73 g (63%), mp 142–144°C. ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, CH_3), 2.50 s (3H, $COCH_3$), 4.05 q (2H, CH_2), 7.05 t (1H, H^6), 7.25 d (1H, H^8), 7.50 t (1H, H^7), 7.70 d (1H, H^5), 11.55 br.s (1H, NHCO) [4].

4-Oxo-3,4-dihydroquinazoline (VIIa). *a.* In a minimal quantity of formic acid was heated for 30 min 1.36 g

(0.01 mol) of amide **Id** and 1.4 ml (0.01 mol) of diethyl oxalate. On cooling the reaction mixture was diluted with 50 ml of water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 0.95 g (56%), mp 220–222°C.

b. In a minimal quantity of formic acid was heated for 30 min 2.36 g (0.01 mol) of ester **Va**. On cooling the reaction mixture was diluted with 50 ml of water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 0.95 g (56%), mp 220–222°C.

c. A mixture of 1.36 g (0.01 mol) of amide **Id** and 0.01 mol of dialkyl oxalate (Alk = CH_3 or C_2H_5) was subjected to microwave irradiation for 10 min. On cooling the reaction mixture was diluted with 50 ml of water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm: 7.51–8.22 m (4H, C_6H_4), 8.13 s (1H, CH), 12.62 s (1H, NH) [11].

3-Amino-4-oxo-3,4-dihydroquinazoline (VIIb). A mixture of 1.51 g (0.01 mol) of hydrazide **Ia** and 1.02 g (0.01 mol) of dimethyl oxalate was subjected to microwave irradiation for 10 min. Yield 1.23 g(76%), mp 205–210°C [6, 12].

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