

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 **Ila** 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 **Ila** and **Ilb** applying available reagents. Esters **Ila** and **Ilb** 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 (CO₂Alk)₂ containing Alk = Pr, Bu, C₆H₁₃, C₅H₁₁] 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*-acetyl-amino-2-carbethoxy-4-oxo-3,4-

The reaction scheme illustrates the synthesis of 2-alkoxycarbonyl-4-alkoxy-1,2,3,4-tetrahydroquinazolin-6(1H)-one (IIa-IId) from 2-amino-1-phenylethan-1-one (Ia-Id). The scheme includes several reaction pathways:

- Reaction of Ia-Id with (COOAlk)₂ and X = NH₂, NHNH₂:** This reaction leads to the formation of IIa-IId.
- Reaction of Ia-Id with ClCOCOOEt and AcOH, X = NHNH₂:** This reaction leads to the formation of VI.
- Reaction of Ia-Id with (COOAlk)₂ and X = NH₂, NHNH₂ for 10 min:** This reaction leads to the formation of Va, Vb.
- Reaction of Ia-Id with (COOAlk)₂ and X = NH₂, NHNH₂ for 30 min:** This reaction leads to the formation of VIIa-VIIId.
- Reaction of Ia-Id with (COOAlk)₂ and X = NH₂, NHNH₂ for 10 min, followed by HCOOH:** This reaction leads to the formation of VIIa-VIIId.
- Reaction of Ia-Id with EtOOCCONH₂ and X = OH:** This reaction leads to the formation of III.
- Reaction of Ia-Id with EtOOCCONH₂ and X = OMe:** This reaction leads to the formation of IV.

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. ¹H NMR spectrum, δ , ppm: 1.25 t (3H, CH₃), 4.30 q (2H, CH₂), 5.90 s (2H, NH₂), 7.61 t (1H, H⁶), 7.72 d (1H, H⁸), 7.87 t (1H, H⁷), 8.19 d (1H, H⁵) [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. ¹H NMR spectrum, δ , ppm: 3.91 s (3H, OCH₃), 5.90 s (2H, NH₂), 7.60 t (1H, H⁶), 7.71 d (1H, H⁸), 7.92 t (1H, H⁷), 8.18 d (1H, H⁵).

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. ¹H NMR spectrum, δ , ppm: 1.25 t (3H, CH₃), 4.28 q (2H, CH₂), 7.60–8.51 m (4H, C₆H₄), 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 **Id** and 1.02 g (0.01 mol) of dimethyl oxalate. Yield 1.72 g (84%), mp 192–194°C. ¹H NMR spectrum, δ , ppm: 3.80 s (3H, OCH₃), 7.20–8.50 m (4H, C₆H₄), 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. ¹H NMR spectrum, δ , ppm: 1.35 t (3H, CH₃), 4.30 q (2H, CH₂), 7.20–8.51 m (4H, C₆H₄), 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. ¹H NMR spectrum, δ , ppm: 3.90 s (3H, OCH₃), 7.22–8.65 m (4H, C₆H₄), 8.12 s (1H, CONH₂), 8.42 s (1H, CONH₂), 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. ¹H NMR spectrum, δ , ppm: 1.32 m (3H, CH₃), 4.31 m (2H, CH₂), 7.25–8.52 m (4H, C₆H₄), 7.80 c (1H, CONH₂), 8.41 s (1H, CONH₂), 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. ¹H NMR spectrum, δ , ppm: 3.87 s (3H, OCH₃), 7.25–8.51 m (4H, C₆H₄), 7.82 s (1H, CONH₂), 8.37 s (1H, CONH₂), 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. ¹H NMR spectrum, δ , ppm: 1.05 t (3H, CH₃), 2.50 s (3H, COCH₃), 4.05 q (2H, CH₂), 7.05 t (1H, H⁶), 7.25 d (1H, H⁸), 7.50 t (1H, H⁷), 7.70 d (1H, H⁵), 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 = CH₃ or C₂H₅) 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. ¹H NMR spectrum, δ, ppm: 7.51–8.22 m (4H, C₆H₄), 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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