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Synthesis of 3-Aryl-2-[hydroxy(diaryl)methyl]-4-oxo-3,4-dihydroquinazolines

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Abstract—By heating arylamides of *N*-ethoxalylanthranilic acid in the acetic acid mediun in the presence of triethylamine the corresponding ethyl 3-aryl-4-oxo-3,4-dihydroquinazoline-2-carboxylates were obtained. The latter in the conditions of the Grignard reaction formed 3-aryl-2-[hydroxy-(diaryl)methyl]-4-oxo-3,4-dihydroquinazolines.

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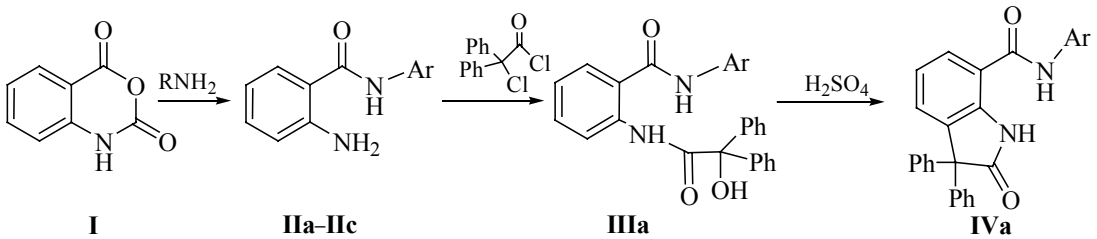
Derivatives of 4-oxo-3,4-dihydroquinazoline are known as a promising class of biologically active compounds [1, 2]. The aim of our study was the preparation of 3-aryl-2-[hydroxy-(diaryl)methyl]-4-oxo-3,4-dihydroquinazolines combining in a single molecule a quinazoline heterocycle and the residue of benzilic acid, two active pharmacophores. To fulfill this task we selected two approaches. The first consisted in the acylation of anthranilic acid arylamides with diarylchloroacetic acids chlorides followed by the reaction products heterocyclization into quinazolinone derivatives. The second approach utilizes the reaction of oxamic acid esters with arylmagnesium halides which are known to stop at the stage of the formation of diarylglycolic acid amides[3]. Therefore we planned proceeding from *N*-ethoxalylanthranilic acid amides to obtain ethyl 3-aryl-4-oxo-3,4-dihydroquinazoline-2-carboxylates and to study their reaction with Grignard reagents.

Initial anthranilamides **II** were obtained from arylamines and isatoic anhydride **I**; the reaction was carried out without solvent or in DMF by procedure [4]. The acylation of amide **IIa** with diphenylchloroacetic acid chloride provided diamide **IIIa** in a low yield (Scheme 1). Inasmuch as the diarylchloroacetic acid, chlorides containing various substituents in the benzene ring are difficultly available this method cannot provide a wide range of diamides **III**. Yet the main disadvantage of the first approach lies in the difficulties in the cyclization of compounds **III** into the corresponding quinazolines due evidently to steric reasons. Initial diamides **III** were isolated at the attempt to carry out the cyclization by boiling in the acetic anhydride in the presence of sodium acetate, and also at heating in the highly boiling solvents (ethylene glycol, diphenyl oxide).

The arylamides of diarylglycolic acids are known to undergo cyclization in the conditions of the acidochromic

Scheme 1.

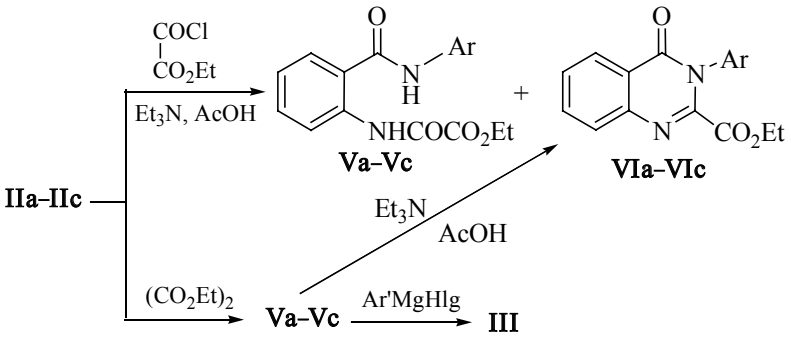


condensation. Diamides **III** in the presence of sulfuric acid easily closed into the corresponding oxindoles **IV**, but in contrast to the published data [5] we did not observe the hydrolysis of the amide group. We avoided the deamination by using for the condensation lesser amount of sulfuric acid than in the previously described procedure.

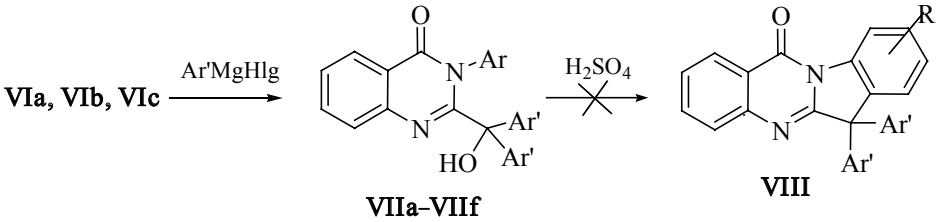
The second way (Scheme 2) presumed the preparation of the target 3-aryl-2-(diarylhydroxymethyl)-4-oxo-3,4-dihydroquinazolines **VII** from ethyl 3-aryl-4-oxo-3,4-dihydro-2-quinazolinecarboxylates. It is known that alkylamides and also hydrazides [6] and hydroxamides of the anthranilic acid [7] reacting with ethoxalyl chloride or with diethyl oxalate readily close into the corresponding ethyl 3-R-4-oxo-3,4-dihydroquinazoline-2-carboxylates; at the same time in the case of arylamides the closure of the quinazoline ring requires additional activation [8]. After acylation anthranilamides **II** with ethoxalyl chloride a mixture was isolated of quinazoline **VI** and acyclic amidoester **V**. The reaction of amides **II** with diethyl oxalate resulted only in acyclic arylamides of N-ethoxalylanthranilic acid **V**. A synthesis was described [8] of initial quinazolines **VI** we required by the cyclization of 2-N-ethoxalylanthranilamides (**V**) by treatment with phosphorus trichloride or by heating in diethyl oxalate. However we failed to obtain pure quinazolinone **VI** from amidoesters **V** under the conditions described in [8]. We also failed to attain the cyclization of obtained compounds **V** with the use of the other common procedures with plausible result: At heating in high boiling solvents (diphenyl oxide, ethylene glycol) cyclic product **VI** formed in a low yield; in acetic anhydride the reaction did not occur, and at adding sodium acetate a mixture formed of cyclic **VI** and acyclic **V** compounds as showed the data of ^{1}H NMR. We remarked that in the acylation of anthranilamides **II** with ethoxalyl chloride in acetic acid in the presence of triethylamine alongside the ethoxalylation formed also quinazoline **VI**. We attempted to carry out the cyclization of amidoesters **V** under analogous conditions; the short heating of the latter in acetic acid medium in the presence of a double excess of triethylamine furnished quinazolinones **VI** in high yields.

The procedures of the synthesis of quinazolinones **VI** were developed by an example of ethyl 3-phenyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**VIa**). It was reported previously that this compound melted at 108–109°C [8]. According to our data the melting point of pure compound **VIa** is 96°C, and the mixture that we have obtained at the acylation of amide **IIa** with ethoxalyl chloride and containing cyclic **VIa** and acyclic **Va** products melted at 109°C.

Scheme 2.



Scheme 3.



Ar = Ar' = Ph (**a**); Ar = 4-MeC$_6$H$_4$, Ar' = Ph (**b**); Ar = 2-MeOC$_6$H$_4$, Ar' = Ph (**c**); Ar = Ph, Ar' = 4-MeC$_6$H$_4$ (**d**); Ar = Ar' = 4-MeC$_6$H$_4$ (**e**); Ar = 2-MeOC$_6$H$_4$, Ar' = 4-MeC$_6$H$_4$ (**f**).

We developed based on compounds **V** an effective synthesis of amides **III** with various substituents in the benzene ring. The readiness of the amidoesters **V** to react with arylmagnesium halides and high yields of the products suggest the use of this method as preparative.

Target 3-aryl-2-[hydroxy(diaryl)methyl]-4-oxo-3,4-dihydroquinazolines **VII** were obtained in up to 85% yield by treating with arylmagnesium halides quinazolinones **VI** (Scheme 3). The reaction occurred exclusively at the ester group, and even the five-fold excess of the reagent did not affect the result of the reaction.

The obtained compounds **VIIa–VIIf** did not enter into the acidochromic condensation apparently due to steric hindrances.

EXPERIMENTAL

^{1}H NMR spectra were measured on a spectrometer Varian M-200 (200 MHz) from solutions in DMSO-d_6, internal reference TMS. Elemental analysis was performed on an analyzer Carlo Erba CHNS-O EA 1108.

2-Amino-*N*-arylbenzamides **IIa–IIc** were obtained from isatoic anhydride and substituted anilines by procedure [4].

2-Hydroxy(diphenyl)methylcarboxamido-*N*-phenylbenzamide (IIIa). A solution of 3.15 g (0.01 mol) of ester **Va** in 50 ml of freshly distilled THF was added dropwise to the solution of phenylmagnesium bromide in 50 ml of THF obtained by procedure [9] from 1.06 g (0.04 mol) of magnesium and 4.04 ml (0.04 mol) of phenyl bromide. The mixture was stirred for 1 h, 300 ml of the saturated solution of ammonium chloride was added, the organic layer was separated and evaporated, the residue was recrystallized from methanol. Yield 3.38 g (80%), mp 240°C. ^{1}H NMR spectrum, δ, ppm: 7.20 m (16H, Ar, OH), 7.90 m (3H, Ar), 8.50 d (1H, Ar) 10.50 s (1H, NHPh), 11.80 s (1H, NHCO). Found, %: C 76.76; H 5.57; N 6.63. $C_{27}H_{22}N_2O_3$. Calculated, % : C 76.75; H 5.26; N 6.63.

2-Oxo-*N*,3,3-triphenylindoline-7-carboxamide (IVa). To a solution of 4.04 g (0,01 mol) of amide **IIIa** in 100 ml of acetic acid was added ~30 ml of concn. H_2SO_4 till the end of appearance of red-brown color, the mixture was poured into 300 ml of water, the precipitate was filtered off and crystallized from ethanol. Yield 2.83 g (70%), mp 205°C. ^{1}H NMR spectrum, δ, ppm: 7.20 m (16H, Ar), 8.00 d (1H, Ar), 8.50 d (1H, Ar), 10.20 s (1H, NHPh), 12.40 s (1H, NHCO). Found, %: C 80.16; H 4.98; N 6.92. $C_{27}H_{20}N_2O_2$. Calculated, % : C 80.17; H 4.99; N 6.93.

Ethyl 2-(phenylcarbamoyl)phenylcarbamoylmethanoate (Va). In 4.2 ml (0.03 mol) of diethyl oxalate 2.12 g (0.01 mol) of amide **IIa** was heated for 30 min. On cooling 5 ml of ethanol was added, the separated precipitate was filtered off, dried, and recrystellized from ethanol. Yield 2.50 g (80%), mp 155°C. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3), 4.20 q (2H, CH_2), 7.10 t (1H, Ar), 7.30 m (3H, Ar), 7.60 m (3H, Ar), 7.90 d (1H, Ar), 8.40 d (1H, Ar), 10.50 s (1H, NHPh), 12.00 s (1H, NHCO). Found, %: C 65.36; H 5.18; N 8.98. $C_{17}H_{16}N_2O_4$. Calculated, % : C 65.37; H 5.17; N 8.97.

Compounds **Vb** and **Vc** were similarly obtained.

Ethyl 2-(*p*-methylphenylcarbamoyl)phenylethanolmethanoate (Vb). Yield 2.45 g (75 %), mp 200°C. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3), 2.20 s (3H, *n*-CH_3), 4.20 q (2H, CH_2), 7.10 t (1H, Ar), 7.30 m (2H, Ar), 7.60 m (3H, Ar), 7.90 d (1H, Ar), 8.40 d (1H, Ar), 10.50 s (1H, NHPh), 12.00 s (1H, NHCO). Found, %: C 66.24; H 5.58; N 8.60. $C_{18}H_{18}N_2O_4$. Calculated, % : C 66.24; H 5.57; N 8.59.

Ethyl 2-(*o*-methoxyphenylcarbamoyl) phenylethanolmethanoate (Vc). Yield 3.08 g (90 %), mp 185°C. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3), 3.80 s (3H, OCH_3), 4.20 q (2H, CH_2), 7.10 t (1H, Ar), 7.30 m (2H, Ar), 7.60 m (3H, Ar), 7.90 d (1H, Ar), 8.40 d (1H, Ar), 10.50 s (1H, NHPh), 12.00 s (1H, NHCO). Found, %: C 63.13; H 5.30; N 8.17. $C_{18}H_{18}N_2O_5$. Calculated, % : C 63.14; H 5.31; N 8.18.

Ethyl 4-oxo-3-phenyl-3,4-dihydroquinazoline-2-carboxylate (VIa). A solution of 2.98 g (0.01 mol) of ester **Va** and 2.8 ml (0.02 mol) of triethylamine in 25 ml of acetic acid was boiled for 40 min. On cooling water was added, the separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.65 g (90 %), mp 95°C. ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3), 3.90 q (2H, CH_2), 7.40 m (5H, Ph), 7.60 t (1H, H^6), 7.80 d (1H, H^8), 7.90 t (1H, H^7), 8.20 d (1H, H^5). Found, %: C 69.37; H 4.81; N 9.51. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.37; H 4.80; N 9.52.

Compounds **VIb** and **VIc** were similarly obtained.

Ethyl 3-(*p*-methylphenyl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (VIb). Yield 2.62 g (85 %), mp 100°C. ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3), 2.40 s (3H, *n*-CH_3), 4.00 q (2H, CH_2), 7.40 m (4H, C_6H_4), 7.60 t (1H, H^6), 7.80 d (1H, H^8), 7.90 t (1H, H^7), 8.20 d (1H, H^5). Found, %: C 70.10; H 5.23; N 9.09. $C_{18}H_{16}N_2O_3$. Calculated, % : C 70.11; H 5.24; N 9.09.

Ethyl 3-(*o*-methoxyphenyl)-4-oxo-3,4-

dihydroquinazoline-2-carboxylate (VIc). Yield 3.08 g (95 %), mp 130°C. ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3), 3.80 s (3H, OCH_3), 4.00 q (2H, CH_2), 6.80 t (1H, Ar), 7.00 d (1H, Ar), 7.40 m (2H, Ar), 7.60 t (1H, H^6), 7.80 d (1H, H^8), 7.90 t (1H, H^7), 8.20 d (1H, H^5). Found, %: C 66.64; H 4.97; N 8.64. $C_{18}H_{16}N_2O_4$. Calculated, %: C 66.65; H 4.98; N 8.64.

2-[Hydroxy(diphenyl)methyl]-4-oxo-3-phenyl-3,4-dihydroquinazoline (VIIa). A solution of 2.62 g (0.01 mol) of ester **VIa** in 50 ml of freshly distilled THF was added dropwise to the solution of phenylmagnesium bromide in 50 ml of THF obtained by procedure [9] from 1.06 g (0.04 mol) of magnesium and 4.04 ml (0.04 mol) of phenyl bromide. After the addition of the Grignard reagent the reaction mixture turned brown-gray. It was stirred with a magnetic stirrer for 1 h, 300 ml of a saturated solution of ammonium chloride was added, the organic layer was separated and evaporated. The residue was recrystallized from methanol. Yield 3.03 g (75%), mp 207°C. ^{1}H NMR spectrum, δ, ppm: 6.60 m (3H, Ar), 6.90 m (2H, Ar), 7.20 m (11H, Ar, OH), 7.60 m (2H, $H^{6,8}$), 7.90 t (1H, H^7), 8.20 d (1H, H^5). Found, %: C 80.16; H 5.00; N 6.93. $C_{27}H_{20}N_2O_2$. Calculated, % : C 80.17; H 4.99; N 6.93.

Compounds **VIIb–VIIf** were similarly obtained.

2-[Hydroxy(diphenyl)methyl]-3-(*p*-methylphenyl)-4-oxo-3,4-dihydroquinazoline (VIIb). Yield 2.93 g (70%), mp 198°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 6.80 m (2H, Ar), 7.20 m (9H, Ar), 7.40–7.60 m (8H, Ar, OH). Found, %: C 80.34; H 5.30; N 6.70. $C_{28}H_{22}N_2O_2$. Calculated, % : C 80.35; H 5.31; N 6.70.

2-[Hydroxy(diphenyl)methyl]-3-(*o*-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline (VIIc). Yield 3.69 g (85%), mp 145°C. ^{1}H NMR spectrum, δ, ppm: 3.20 s (3H, OMe), 6.50 d (1H, Ar), 6.60 m (2H, Ar), 6.70 d (1H, Ar), 7.20–7.30 m (11H, Ar, OH), 7.50 m (2H, $H^{6,8}$), 7.70 t (1H, H^7), 8.20 d (1H, H^5). Found, %: C 77.40; H 5.11; N 6.46. $C_{28}H_{22}N_2O_3$. Calculated, % : C 77.39; H 5.11; N 6.45.

2-[Hydroxy-bis(*p*-methylphenyl)methyl]-4-oxo-3-phenyl-3,4-dihydroquinazoline (VIId). Yield 3.03 g (70%), mp 185°C. ^{1}H NMR spectrum, δ, ppm: 2.10 s (6H, CH_3), 7.20–7.40 m (14H, Ar, OH), 7.60 m (2H, $H^{6,8}$), 8.20 t (1H, H^7), 8.40 d (1H, H^5). Found, %: C 80.51; H 5.60; N 6.47. $C_{29}H_{24}N_2O_2$. Calculated, % : C 80.52; H 5.60; N 6.48.

2-[Hydroxy-bis(*p*-methylphenyl)methyl]-3-(*p*-methylphenyl)-4-oxo-3,4-dihydroquinazoline (VIIe). Yield 3.25 g (75%), mp 145°C. ^{1}H NMR spectrum, δ, ppm: 2.10 s (6H, CH_3), 2.30 s (3H, CH_3), 7.20-7.40 m (11H, Ar, OH), 7.60 m (2H, Ar), 7.80 m (2H, $H^{6,8}$), 8.20 t (1H, H^7), 8.40 d (1H, H^5). Found, %: C 80.67; H 5.87; N 6.26. $C_{30}H_{26}N_2O_2$. Calculated, % : C 80.68; H 5.88; N 6.27.

2-[Hydroxy-bis(*p*-methylphenyl)methyl]-3-(*o*-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline (VIIf). Yield 3.93 g (85%), mp 175°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (6H, CH_3), 3.20 s (3H, OMe), 6.50 d (1H, Ar), 6.60 d (1H, Ar), 6.70 d (1H, Ar), 7.20 m (5H, Ar, OH), 7.3 m (4H, Ar), 7.50 m (2H, $H^{6,8}$), 7.70 t (1H, H^7), 8.20 d (1H, H^5). Found, %: C 77.88; H 5.68; N 6.05. $C_{30}H_{26}N_2O_3$. Calculated, % : C 77.89; H 5.68; N 6.06.

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