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Hydrolytic Opening of the Quinazoline Ring in 3-Furfuryl-4-oxo-3,4-dihydroquinazoline Derivatives

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Abstract—Ethyl 3-furfuryl-4-oxo-3,4-dihydroquinazoline-2-carboxylate extremely readily undergoes hydrolysis in acid, alkaline, or neutral medium with formation of 2-(2-ethoxy-1,2-dioxoethylamino)-*N*-furfurylbenzamide. The reaction of ethyl 3-furfuryl-4-oxo-3,4-dihydroquinazoline-2-carboxylate with phenylmagnesium bromide yields *N*-furfuryl-2-(2-hydroxy-2,2-diphenyl-1-oxoethylamino)benzamide as a result of hydrolytic cleavage of the quinazoline ring.

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With a view to obtain new biologically active compounds we planned to synthesize a series of 4-oxo-3,4-dihydroquinazoline derivatives containing as pharmacophoric fragment a benzilic [hydroxy(diphenyl)acetic] acid residue built in the quinazoline ring. Benzilic acid derivatives are widely used in medical practice; examples are phenytoin, dimenoxadol, and platyphylline [1, 2]. Some widely used medical agents of synthetic (prazozin, doxazozin) and natural origin (deoxypeganine hydrochloride) are derivatives of quinazolinone [3, 4].

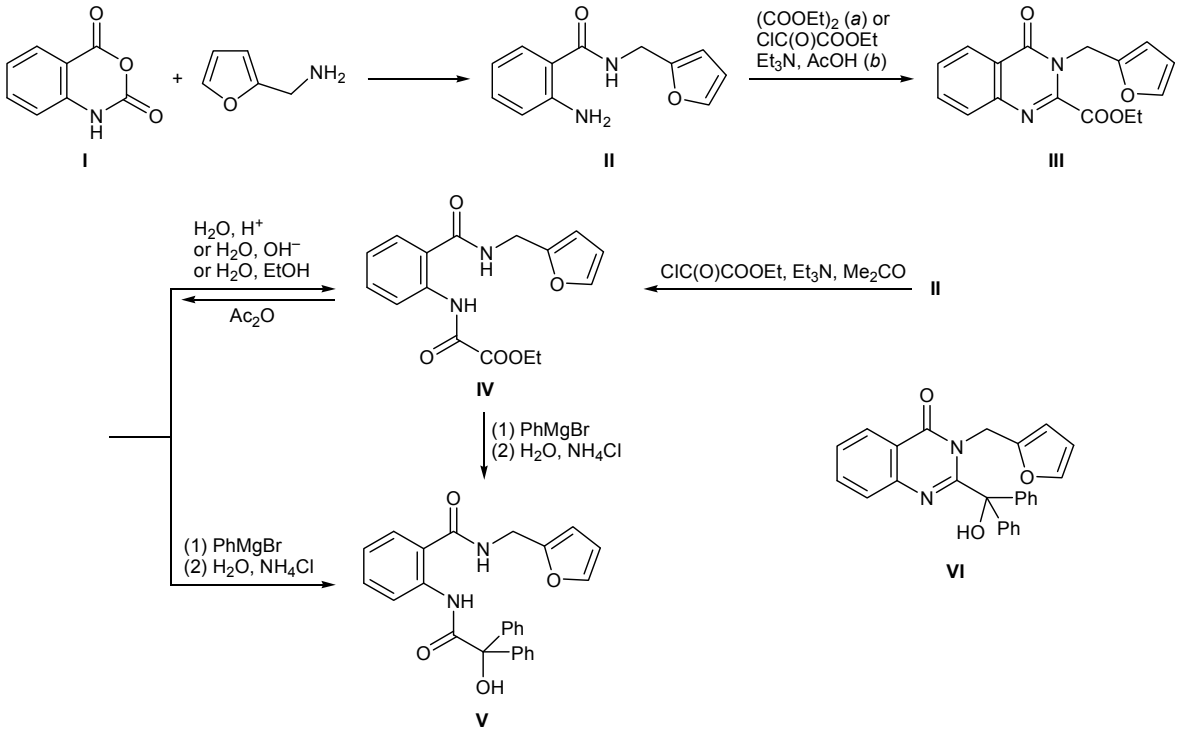
We intended to synthesize ethyl 3-furfuryl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**III**) and examine its reaction with Grignard compounds. As starting compound we used 2-amino-*N*-furfurylbenzamide (**II**) which was prepared by reaction of isatoic anhydride [**I**, 4*H*-3,1-benzoxazine-2,4(1*H*)-dione] with 2-furylmethanamine. Quinazolinone **III** was obtained by heating amide **II** with diethyl oxalate or by reaction of **II** with ethoxalyl chloride in acetic acid. We failed to stop the reaction at the stage of formation of amido ester **IV** and isolate the latter under the above conditions. Compound **IV** was synthesized by carrying out the reaction with ethoxalyl chloride in acetone; on heating in acetic anhydride, compound **IV** underwent cyclization to quinazolinone **III** (Scheme 1).

Published data on reactions of 4-oxo-3,4-dihydroquinazoline derivatives with Grignard compounds are few in number, and they are ambiguous. The results of searching over Beilstein Database showed that the direction of these reactions depends on the substituents in the dihydropyrimidine ring. 4-Oxo-3,4-dihydroquinazoline derivatives having a substituent in the 2-position react with Grignard compounds at the carbonyl group, and the process may be accompanied by opening of the heteroring [5] or not [6, 7]. The formation of 1,3-benzoxazinones is also possible [8]. Quinazolinone derivatives having no substituent on C^2 react with organomagnesium compounds just at that position, and the reaction involves opening of the heteroring [9, 10].

In the reaction of quinazolinone **III** with phenylmagnesium bromide, instead of expected 3-furfuryl-2-[hydroxy(diphenyl)methyl]-3,4-dihydroquinazolin-4-one (**VI**), we isolated *N*-furfuryl-2-(2-hydroxy-2,2-diphenyl-1-oxoethylamino)benzamide (**V**) (Scheme 1). This result may be rationalized assuming that the reaction of the Grignard compound at the ester group is accompanied by cleavage of the dihydropyrimidine ring.

In keeping with published data [11], unsubstituted 3,4-dihydroquinazolin-4-one is very stable to hydrolysis [11]. Alkaline hydrolysis of its substituted derivatives was reported to produce anthranilic acid derivatives [12–14]. There are no published data on the hydrolysis of such compounds in other media. In our case, hydrolytic cleavage of the dihydropyrimidine ring could be related to the presence of excess phenylmagnesium bromide and subsequent addition of dilute hydrochloric acid. However, compound **V** was also formed in the reaction with an equimolar amount of phenylmagnesium bromide, as well as upon replacement of hydrochloric acid by ammonium chloride. Addition of dilute hydrochloric acid to a solution of

Scheme 1.



quinazolinone **III** in tetrahydrofuran led to the formation of 2-(2-ethoxy-1,2-dioxoethylamino)-*N*-furfurylbenzamide (**IV**) as a result of nucleophilic opening of the quinazoline ring. Further examination of the hydrolysis conditions of compound **III** showed that the dihydropyrimidine ring therein undergoes opening not only in weakly acidic but also in weakly alkaline medium. In the latter case, amido ester **IV** was also isolated. Conservation of the ester group suggests high sensitivity of the quinazoline ring in **III** to hydrolysis. Hydrolytic opening of the heteroring also occurred in neutral medium, when compound **III** was heated for a short time in aqueous alcohol. We failed to effect cyclization of amide **V** to compound **VI**, presumably for steric reasons. Compound **V** was also synthesized by reaction of amido ester **IV** with phenylmagnesium bromide.

EXPERIMENTAL

The ^{1}H NMR spectra were measured from solutions in DMSO-d_6 on a Varian M-200 spectrometer (200 MHz) using tetramethylsilane as internal reference. The elemental compositions were determined on a Carlo Erba CHNS-O EA 1108 analyzer.

2-Amino-*N*-(furan-2-ylmethyl)benzamide (II). Furan-2-ylmethanamine, 0.92 ml (0.01 mol), was added to 1.63 g (0.01 mol) of isatoic anhydride (**I**), and the mixture was heated until carbon dioxide no longer evolved. The mixture was cooled, and the product was recrystallized from ethanol. Yield 85%, mp 92°C. ^{1}H NMR spectrum, δ, ppm: 4.30 d (2H, CH_2), 6.20 d (1H, 3′-H), 6.40 m (4H, 4′-H, 5-H, NH_2), 6.70 d (1H, 3-H), 7.20 t (1H, 4-H), 7.50 m (2H, 5′-H, 6-H), 8.60 t (1H, NH). Found, %: C 66.62; H 5.61; N 12.93. $C_{12}H_{12}N_2O_2$. Calculated, %: C 66.64; H 5.60; N 12.96.

Ethyl 3-(furan-2-ylmethyl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (III). *a*. A mixture of 2.16 g (0.01 mol) of amide **II** and 4.2 ml (0.03 mol) of diethyl oxalate was heated for 30 min. The mixture was cooled, 5 ml of ethanol was added, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 80%, mp 105°C.

b. Compound **II**, 2.16 g (0.01 mol), was dissolved in glacial acetic acid on heating. After cooling, 1.4 ml (0.01 mol) of triethylamine and 1.2 ml (0.01 mol) of ethyl 2-chloro-2-oxoacetate were added in succession, and the mixture was heated for 1 h. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 40%, mp 105°C.

c. A mixture of 3.14 g (0.01 mol) of amido ester **IV** and 10 ml of acetic anhydride was heated for 20 min. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 65%, mp 105°C. ^{1}H NMR spectrum, δ, ppm: 1.40 t (3H, CH_3), 4.40 q (2H,

OCH_2), 5.40 s (2H, NCH_2), 6.40 m (2H, 3-H, 4′-H), 7.60–7.70 m (3H, 5′-H, 6-H, 8-H), 7.90 t (1H, 7-H), 8.30 d (1H, 5-H). Found, %: C 66.39; H 4.75; N 9.40. $C_{16}H_{14}N_2O_4$. Calculated, %: C 66.41; H 4.74; N 9.39.

Ethyl 2-[2-(furan-2-ylmethylcarbamoyl)phenylamino]-2-oxoacetate (IV). Compound **II**, 2.16 g (0.01 mol), was dissolved in a minimal amount of acetone, 1.4 ml (0.01 mol) of triethylamine and 1.2 ml (0.01 mol) of ethyl 2-chloro-2-oxoacetate were added in succession, and the mixture was left to stand for 12 h. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 70%, mp 120°C. ^{1}H NMR spectrum, δ, ppm: 1.10 t (3H, CH_3), 4.20 d (2H, NHC**H**$_2$), 4.40 q (2H, OCH_2), 6.20 d (1H, 3′-H), 6.40 m (1H, 4′-H), 7.10 t (1H, 5-H), 7.50 m (2H, 5′-H, 4-H), 7.80 d (1H, 3-H), 8.50 d (1H, 6-H), 9.20 t (1H, N**H**CH_2), 12.80 s (1H, NHCO). Found, %: C 60.75; H 5.13; N 8.84. $C_{16}H_{16}N_2O_5$. Calculated, %: C 60.74; H 5.11; N 8.86.

***N*-(Furan-2-ylmethyl)-2-[(2-hydroxy-2,2-diphenylethanoyl)amino]benzamide (V).** *a*. A solution of 2.96 g (0.01 mol) of compound **III** in freshly distilled tetrahydrofuran was added dropwise to a solution of phenylmagnesium bromide prepared from 0.53 g (0.02 mol) of magnesium and 2.02 ml (0.02 mol) of phenyl bromide in THF [15]. The mixture turned dark brown. It was stirred for 1 h and treated with a saturated solution of ammonium chloride, the organic layer was separated, the solvent was distilled off, and the residue was recrystallized from anhydrous methanol. Yield 70%, mp 180–185°C.

b. A solution of 3.14 g (0.01 mol) of compound **IV** in freshly distilled tetrahydrofuran was added dropwise to a solution of phenylmagnesium bromide prepared from 0.53 (0.02 mol) of magnesium and 2.02 ml (0.02 mol) of phenyl bromide in THF [15]. The mixture turned dark brown. It was stirred for 1 h and treated with a saturated solution of ammonium chloride, the organic layer was separated, the solvent was distilled off, and the residue was recrystallized from anhydrous methanol. Yield 75%, mp 180–185°C. ^{1}H NMR spectrum, ppm: 4.40 d (2H, CH_2), 6.20 d (1H, 3′-H), 6.30 m (1H, 4′-H), 7.10 m (2H, 5-H, OH), 7.30–7.40 m (11H, C_6H_5, 4-H), 7.45 d (1H, 3-H), 7.60 d (1H, 5′-H), 8.50 d (1H, 6-H), 9.10 t (1H, N**H**CH_2), 12.10 s (1H, NHCO). Found, %: C 73.20; H 5.19; N 6.57. $C_{26}H_{22}N_2O_5$. Calculated, %: C 73.21; H 5.21; N 6.57.

Hydrolytic opening of the quinazoline ring in compound III. *a*. Compound **III**, 2.96 g (0.01 mol), was dissolved in tetrahydrofuran, a 1:1 mixture of concentrated hydrochloric acid with water was added on cooling (or a saturated solution of ammonium chloride was added), the organic layer was separated, and the solvent was distilled off. The precipitate of compound **IV** was filtered off, dried, and recrystallized from ethanol. Yield 80%, mp 120°C.

b. Compound **III**, 2.96 g (0.01 mol), was mixed with 100 ml of distilled water, a few drops of a 1% solution of sodium hydroxide were added to pH 8.0–9.0, and the mixture was stirred until complete dissolution and left to stand for 2 h. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 80%, mp 120°C.

c. Compound **III**, 2.96 g (0.01 mol), was dissolved in 30 ml of ethanol, 15 ml of water was added, and the mixture was stirred at 35–40°C until a solid separated. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 85%, mp 120°C.

REFERENCES

1. Bersudsky, Y., *Int. J. Neuropsychopharmacol*., 2006, vol. 9, p. 627.
2. Shabanov, P.D., *Psikhofarmakologiya* (Psychopharmacology), St. Petersburg: Elbi, 2008, p. 416.
3. Kirby, R.S., *Eur.Urol*., 1996, vol. 29, p. 24.
4. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2002, vol. 1, p. 540.
5. Essawya, A., El-Hashash, M.A., and El-Behdy, A.M., *Indian J. Chem*., 1982, vol. 21, p. 593.
6. Upadhyaya, *J. Indian Chem. Soc*., 1950, vol. 27, p. 40.
7. Sen, A.B. and Sidhu, G.S., *J. Indian Chem. Soc*., 1948, vol. 25, p. 437.
8. Elkashef, A.-F.M., *Collect. Czech. Chem. Commun*., 1974, vol. 39, p. 287.
9. Koelsch, C.F., *J. Am. Chem. Soc*., 1945, vol. 67, p. 1718.
10. Kacker, I.K. and Zaheer, S.H., *J. Chem. Soc*., 1956, p. 415.
11. *Heterocyclic Compounds*, Elderfield, R.C., Ed., New York: Wiley, 1957, vol. 6. Translated under the title *Geterotsiklicheskie soedineniya*, Moscow: Inostrannaya Literatura, 1960, vol. 6, p. 268.
12. Poehlmann, H., Theil, F.-P., and Pfeifer, S., *Pharmazie*, 1985, vol. 40, p. 269.
13. Kovac, C.T., Oklobdzija, M., Comissi, G., Decorte, E., and Fajdiga, T., *J. Heterocycl. Chem*., 1983, vol. 20, p. 1339.
14. Reddy, G.M. and Reddy, P.S.N., *Indian J. Chem*., 1997, vol. 36, p. 166.
15. Tietze, L.-F. and Eicher, T., *Reactions and Syntheses in the Organic Chemistry Laboratory*, Mill Valley, California: University Science Books, 1989.