ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 8, pp. 1984–1986. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © V.L. Gein, M.I. Kazantseva, T.M. Zamaraeva, L.F. Gein, P.A. Slepukhin, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 8, pp. 1397–1399.

LETTERS TO THE EDITOR

Synthesis of 9-Aryl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones

V. L. Gein[a], M. I. Kazantseva[b], T. M. Zamaraeva[a], L. F. Gein[b], and P. A. Slepukhin[c]

[a] *Perm State Pharmaceutical Academy of the Ministry of Health of the Russian Federation, ul. Polevaya 2, Perm, 614990 Russia*
e-mail: geinvl48@mail.ru

[b] *Perm State Medical University, Perm, Russia*

[c] *Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, Yekaterinburg, Russia*

Received April 2, 2015

Keywords: three-component reaction, 1,3-cyclohexanedione, dimedone, aromatic aldehyde, 5-aminotetrazole monohydrate, 9-aryl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one

DOI: 10.1134/S1070363215080332

It has been earlier found that the reaction of keto acids esters with a mixture of an aromatic aldehyde and 5-aminotetrazole leads to the formation of fused heterocyclic systems [1]. Reaction of methyl esters of acylpyruvic acids with 5-aminotetrazole in the presence of an aromatic aldehyde has yielded 5-aryl-6-acyl-7-methoxycarbonyl-5,8-dihydrotetrazolo[1,5-*a*]-pyrimidines [2]. The reaction with 3-amino-1,2,4-triazole proceeds similarly to give 4-aryl-3-benzoyl-2-methoxycarbonyl-1,4-dihydropyrimidino[1,2-*d*]tetrazoles [3]. It has been found that the fusion of various acetylacetates with a mixture of aromatic aldehyde and 5-aminotetrazole affords dihydrotetrazolo[1,5-*a*] pyrimidine derivatives [4], being the only reaction product when using *N*-substituted amides of acetylacetic acid as the dicarbonyl compound [5]. 5-Aminotetrazole is known to be a part of certain drugs such as korazol, cefazolin, and cefoperazonum [6].

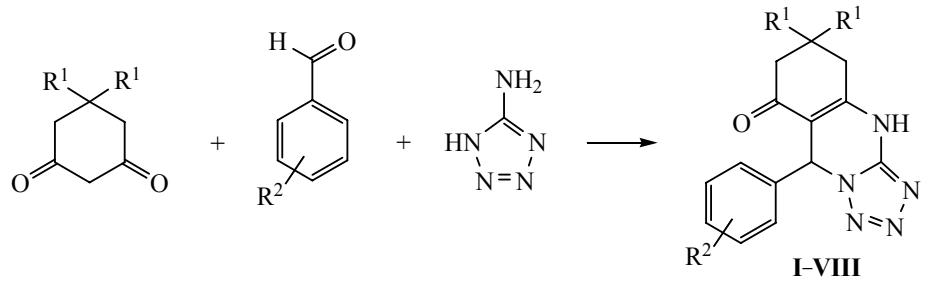
Aiming to synthesize new heterocyclic compounds with potential biological activity containing 5-aminotetrazole fragment, we used 1,3-cyclohexanedione and dimedone as the dicarbonyl components instead of esters of acetylacetic and acylpyruvic acids.

Reaction of equimolar amounts of 1,3-cyclohexanedione or dimedone, an aromatic aldehyde, and 5-aminotetrazole monohydrate in bulk at 160–170°C during 10–12 min gave 9-aryl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]-quinazolin-8(4*H*)-ones **I**–**IV** and 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones **V**–**VIII** (Scheme 1).

The resulting compounds **I**–**VIII** were pale-yellow crystalline solids, soluble in ethanol, and insoluble in water.

IR spectra of compounds **I**–**VIII** contained absorption bands assigned to stretching of the C=C (1580–

Scheme 1.



I–**VIII**

R^1 = H, R^2 = H (**I**), 4-Cl (**II**), 4-MeO (**III**), 4-NO_2 (**IV**); R^1= Me, R^2= H (**V**), 4-Cl (**VI**), 4-OMe (**VII**), 4-NO_2 (**VIII**).

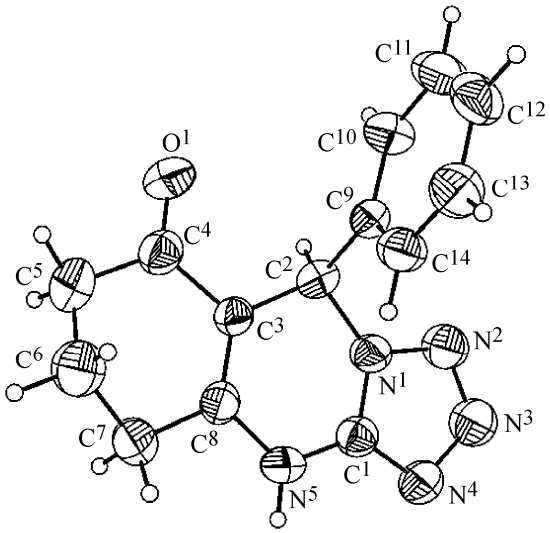
1588 cm^{-1}), C=O (1641–1654 cm^{-1}), and N–H bonds (3251–3290 cm^{-1}).

^{1}H NMR spectra of compounds **V**–**VIII** contained the signals of aromatic fragments and related groups along with the following characteristic signals: two singlets of two methyl groups in position 6 at 0.80–0.83 and 1.02–1.04 ppm, four doublets of the protons H^5 and H^7 at 1.87–1.90, 2.04–2.06, 2.20–2.23, and 2.35–2.37 ppm, the signal of the H^9 proton at 6.39–6.65 ppm, and the signal of NH group at 11.40–11.89 ppm. The spectra of compounds **I**–**IV** contained multiplets of the methylene protons in position 6 (1.70–1.78 ppm) and of protons at positions 5 (1.83–1.92 ppm) and 7 (2.11–2.25 ppm).

To determine the spatial structure of the obtained compounds, we performed X-ray diffraction analysis of crystal of compound **I** grown via slow crystallization from dioxane (see figure). The results were fully consistent with the proposed structure. According to the XRD analysis, compound **I** crystallized as a 1 : 1 solvate with 1,4-dioxane. Most of the bond lengths and bond angles were close to the normal values. The deviations were as follows. The formal single bond C^3–C^4 was shortened to 1.461 Å due to the effect of conjugation in the vinyl ketone moiety and the expected alignment of the bond lengths of the tetrazole ring. Cyclohexene ring had a *sofa* conformation, and C^6 atom was out of the ring plane. The molecules formed dimers in the crystal, due to the paired intermolecular hydrogen bonding NH···N between NH group of the pyrimidine moiety and the N^4 atom of the tetrazole ring.

9-Phenyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinozolin-8(4*H*)-one (I) *(general procedure).* A mixture of 1.12 g (0.01 mol) of 1,3-cyclohexanedione, 1.06 mL (0.01 mol) of benzaldehyde, and 1.03 g (0.01 mol) of 5-aminotetrazole monohydrate was incubated during 10–12 min at 160–170°C until the evolution of water vapor ceased, and the reaction mixture solidified. After cooling, the residue was treated with ethanol; the resulting crystals were filtered off and dried. Yield 2.2 g (62%), mp 234–236°C (EtOH). IR spectrum, ν, cm^{-1}: 1580 (C=C), 1648 (C=O), 3280 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.70–1.76 m (2H, C^6H_2), 1.85–1.92 m (2H, C^5H_2), 2.15–2.25 m (2H, C^7H_2), 6.46 s (1H, C^9H), 7.03–7.30 m (5H, C_6H_5), 11.40 s (1H, NH). Found, %: C 62.77; H 4.62; N 26.49. $C_{14}H_{13}N_5O$. Calculated, %: C 62.91; H 4.90; N 26.20. *M* 267.29.

Compounds **II**–**VIII** were obtained similarly.



General view of the molecule of compound **I**.

9-(4-Chlorophenyl)-5,6,7,9-tetrahydrotetrazolo-[5,1-*b*]quinazolin-8(4*H*)-one (II). Yield 2.9 g (68%), mp 245–247°C (EtOH). IR spectrum, ν, cm^{-1}: 1584 (C=C), 1646 (C=O), 3288 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.73–1.76 m (2H, C^6H_2), 1.85–1.92 m (2H, C^5H_2), 2.11–2.25 m (2H, C^7H_2), 6.54 s (1H, C^9H), 7.10 s (4H, C_6H_4Cl), 11.60 s (1H, NH). Found, %: C 55.57; H 4.32; N 23.43. $C_{14}H_{12}ClN_5O$. Calculated, %: C 55.73; H 4.01; N 23.21. *M* 301.74.

9-(4-Methoxyphenyl)-5,6,7,9-tetrahydrotetrazolo-[5,1-*b*]quinazolin-8(4*H*)-one (III). Yield 2.4 g (64%), mp 215–218°C (EtOH). IR spectrum, ν, cm^{-1}: 1586 (C=C), 1641 (C=O), 3290 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70–1.74 m (2H, C^6H_2), 1.83–1.92 m (2H, C^5H_2), 2.15–2.25 m (2H, C^7H_2), 3.65 s (3H, $C_6H_4O\underline{CH_3}$), 6.43 s (1H, C^9H), 6.65 d and 7.00 d (4H, $\underline{C_6H_4}OCH_3$, *J* 8.4), 11.50 s (1H, NH). Found, %: C 60.37; H 4.92; N 23.78. $C_{15}H_{15}N_5O_2$. Calculated, %: C 60.60; H 5.09; N 23.55. *M* 297.32.

9-(4-Nitrophenyl)-5,6,7,9-tetrahydrotetrazolo-[5,1-*b*]quinazolin-8(4*H*)-one (IV). Yield 3.2 g (73%), mp 233–235°C (EtOH). IR spectrum, ν, $см^{-1}$: 1580 (C=C), 1648 (C=O), 3280 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.73–1.78 m (2H, C^6H_2), 1.83–1.92 m (2H, C^5H_2), 2.15–2.25 m (2H, C^7H_2), 6.68 s (1H, C^9H), 7.73 d and 8.08 d (4H, $C_6H_4NO_2$, *J* 9.3), 11.34 s (1H, NH). Found, %: C 53.97; H 3.92; N 26.88. $C_{14}H_{12}N_6O_3$. Calculated, %: C 53.85; H 3.87; N 26.97. *M* 312.30.

9-Phenyl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo-[5,1-*b*]quinazolin-8(4*H*)-one (V). Yield 2.78 g (68%),

mp 196–198°C (EtOH). IR spectrum, ν, cm^{-1}: 1588 (C=C), 1652 (C=O), 3256 (N–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.80 s and 1.02 s (6H, CH_3), 1.90 d (1H, H_A^5, *J* 16.1), 2.06 d (1H, H_B^5, *J* 16.1), 2.23 d (1H, H_A^7, *J* 16.0), 2.37 d (1H, H_B^7, *J* 16.1), 6.64 s (1H, C^9H), 6.85–7.23 m (5H, C_6H_5), 11.46 s (1H, NH). Found, %: C 65.28; H 5.52; N 23.85. $C_{16}H_{17}N_5O$. Calculated, %: C 65.07; H 5.80; N 23.71. *M* 295. 34.

9-(4-Chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (VI). Yield 3.28 g (74%), mp 193–195°C (EtOH). IR spectrum, ν, cm^{-1}: 1581 (C=C), 1650 (C=O), 3258 (N–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.83 s and 1.02 s (6H, CH_3), 1.87 d (1H, H_A^5, *J* 16.1), 2.06 d (1H, H_B^5, *J* 16.1), 2.20 d (1H, H_A^7, *J* 16.0), 2.37 d (1H, H_B^7, *J* 16.1), 6.56 s (1H, C^9H), 6.90 d and 7.21 d (4H, C_6H_4Cl, *J* 7.5), 11.67 s (1H, NH). Found, %: C 58.48; H 4.62; N 21.15. $C_{16}H_{16}ClN_5O$. Calculated, %: C 58.27; H 4.89; N 21.23. *M* 329.79.

9-(4-Methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (VII). Yield 3.32 g (76%), mp 183–185°C (EtOH). IR spectrum, ν, cm^{-1}: 1585 (C=C), 1654 (C=O), 3251 (N–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.82 s and 1.02 s (6H, CH_3), 1.87 d (1H, H_A^5, *J* 16.1), 2.06 d (1H, H_B^5, *J* 16.1), 2.20 d (1H, H_A^7, *J* 16.0), 2.35 d (1H, H_B^7, *J* 16.1), 3.65 s (3H, $C_6H_4O\underline{CH_3}$), 6.39 s (1H, C^9H), 6.77 d and 7.08 d (4H, $\underline{C_6H_4}OCH_3$, *J* 8.5), 11.46 s (1H, NH). Found, %: C 62.57; H 5.62; N 21.75. $C_{17}H_{19}N_5O_2$. Calculated, %: C 62.76; H 5.89; N 21.52. *M* 325.37.

9-(4-Nitrophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (VIII). Yield 3.6 g (79%), mp 180–182°C (EtOH). IR spectrum, ν, cm^{-1}: 1588 (C=C), 1654 (C=O), 3256 (N–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.80 s and 1.02 s (6H, CH_3), 1.87 d (1H, H_A^5, *J* 16.1), 2.06 d (1H, H_B^5, *J* 16.1), 2.20 d (1H, H_A^7, *J* 16.0), 2.35 d (1H, H_B^7, *J* 16.1), 6.65 s (1H, C^9H), 7.85 m and 8.23 m (4H, $C_6H_4NO_2$), 11.89 s (1H, NH). Found, %: C 56.67; H 4.53; N 24.85. $C_{16}H_{16}N_6O_3$. Calculated, %: C 56.47; H 4.74; N 24.69. *M* 340.35.

IR spectra (mineral oil) were recorded with a Specord M-80 spectrophotometer. ^1H NMR spectra were registered using a Bruker 500 instrument (500.13 MHz, DMSO-d_6) relative to internal TMS reference. Elemental analysis was performed with a Perkin Elmer 2400 instrument. Melting points were determined using an M-565 apparatus. X-Ray diffraction analysis was performed with an automated four-circle diffractometer Xcalibur S via the standard procedure [MoK_α radiation, 295(2) K, ω/2θ-scanning with step of 1°]. Solution and refinement of the structure was carried out using SHELXTL software package [7]. Main crystallographic parameters were as follows: triclinic crystal system, space group *P*-1, a = 6.1005(8), b = 11.2632(17), c = 12.595(3) Å, α = 107.36(2)°, β = 103.928(17)°, γ = 101.369(12)°, μ = 0.093 mm^{-1}. 5967 reflections were collected over the range of reflection angles of 3.11° < θ < 28.28°, 3605 of them being independent (R_{int} 0.0235), including 1531 with $I > 2\sigma(I)$, *GooF* 1.004, R_1 0.1085, wR_2 0.0576 (for all reflections), $\Delta\rho_{\bar{e}}$ = 0.212/–0.188 $e/Å^{-3}$.

The XRD data were deposited in the Cambridge Structural Database (CCDC 1,410,335).

ACKNOWLEDGMENTS

This work was financially supported by the Russian Science Foundation (project no. 15-13-10029).

REFERENCES

1. Zhidovinova, M.S., Rusinov, G.L., and Ovchinnikova, I.G., *Russ. Chem. Bull*., 2003, vol. 52, no. 8, p. 1768. DOI: 10.1023/A:1026052603951.
2. Gein, V.L., Tsyplyakova, E.P., Rozova, E.A., and Gein, L.F., *Russ. J. Org. Chem*., 2003, vol. 39, no. 5, p. 753. DOI: 10.1023/A:1026002522354.
3. Gein, V.L., Gein, L.F., and Tsyplyakova, E.P., *Chem. Heterocycl. Compd*., 2003, vol. 39, no. 6, p. 821. DOI: 10.1023/A:1025671818256.
4. Gein, V.L., Vladimirov, I.N., Kurbatova, A.A., Nosova, N.V., Krylova, I.V., Vakhrin, M.I., and Fedorova, O.V., *Russ. J. Org. Chem*., 2010, vol. 46, no. 5, p. 699. DOI: 10.1134/S1070428010050180.
5. Gein, V.L., Zamaraeva, T.M., Zorina, A.A., Levandovskaya, E.B., Nosova, N.V., and Vakhrin, M.I., *Russ. J. Org. Chem*., 2009, vol. 45, no. 6, p. 942. DOI: 10.1134/S1070428009060256.
6. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2010.
7. Sheldrick, G.M., *Acta Crystallogr. (A)*, 2008, vol. 64, p. 112. DOI: 10.1107/S0108767307043930.