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BENZO[*f*][1,2,4]TRIAZINO[2,3-*d*][1,4]DIAZEPINES – A NEW HETEROCYCLIC SYSTEM: SYNTHESIS AND SPECTRAL CHARACTERISTICS

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Abstract

Benzodiazepines are an important group of heterocyclic compounds in organic and medicinal chemistry due to their wide range of biological activity and application in medical practice, significant potential for functionalization and synthesis of various compounds with fused cycles. In this work, we present simple methods for the synthesis of a new system of benzo[f]1,2,4]triazino[2,3-d][1,4]diazepines by acylation of 3-(2-aminophenyl)-6-R-1,2,4-triazine-5(2H)-ones with chloroacetyl chloride. The peculiarities of the reaction, the optimal conditions for the synthesis of the new heterocyclic system, namely the ratio of reagents, solvents, temperature and duration of the reaction, have been established. It has been shown that the starting compounds containing donor-acceptor groups in the reaction in question form a mixture of two structural isomers. An alternative synthetic method has been developed, namely nucleophilic ring expansion of the corresponding 3-R-6-chloromethyl-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones, and the probable mechanism of this reaction has been discussed. Structural confirmation was achieved using ^{1}H and ^{13}C NMR, LS-MS and X-ray.

Keywords: benzo[*f*][1,2,4]triazino[2,3-*d*][1,4]diazepines; acylation; cycle expansion; spectral data; X-Ray study.

БЕНЗО[*f*][1,2,4]ТРИАЗИНО[2,3-*d*][1,4]ДІАЗЕПІНИ – НОВА ГЕТЕРОЦИКЛІЧНА СИСТЕМА: СИНТЕЗ ТА СПЕКТРАЛЬНІ ХАРАКТЕРИСТИКИ

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Анотація

Бензодіазепіни є важливою групою гетероциклічних сполук у органічній та медичній хімії завдяки різносторонньому спектру біологічної активності та застосування в медичній практиці, значному потенціалу для функціоналізації та синтезу різноманітних конденсованих систем. У цій роботі ми пропонуємо прості методи синтезу нової системи бензо[*f*]1,2,4]триазино[2,3-*d*][1,4]діазепінів шляхом ацилювання 3-(2-амінофеніл)-6-R-1,2,4-триазин-5(2H)-онів хлорацетилхлоридом. Визначено особливості реакції, оптимальні умови синтезу нової гетероциклічної системи, а саме співвідношення реагентів, розчинників, температуру та тривалість реакції. Показано, що вихідні сполуки, які містять донорно-акцепторні групи, у даній реакції утворюють суміш двох структурних ізомерів. Розроблено альтернативний синтетичний метод, а саме нуклеофільне розширення циклу відповідних 3-R-6-хлорметил-2H-[1,2,4]триазино[2,3-c]хіназолін-2-онів та обговорено ймовірний механізм цієї реакції. Структурне підтвердження отримано за допомогою ^{1}H та ^{13}C ЯМР, LS-MS та рентгеноструктурного аналізу.

Ключові слова: бензо[*f*][1,2,4]триазино[2,3-*d*][1,4]діазепіни; ацилювання; розширення циклу; спектральні дані; рентгеноструктурне дослідження.

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Introduction

Diazepines are an important group of heterocyclic compounds which, due to their broad spectrum of biological activity, are regarded as "privileged structures" in medicinal chemistry [1–4]. Among diazepines, benzene-condensed derivatives are currently of particular importance. Most structural analogues (1,2-, 1,3-, 1,4-, 1,5-, 2,3-, and 2,4-benzodiazepines) exhibit versatile biological activities, including antipsychotic, anxiolytic, anticonvulsant, muscle relaxant, analgesic, antibacterial, antifungal, anticancer, and antituberculosis effects, among others [5–13]. Heterocondensed benzodiazepine derivatives are comparatively less studied. However, they also represent promising biologically active compounds. It has been demonstrated that annulation of azoles and azines to the benzodiazepine core is a rational modification strategy and can lead to both the retention of known biological activities and the emergence of new ones [12; 14–16]. Importantly, many of these compounds display a high affinity for the benzodiazepine–GABA receptor complex [12; 15–17] and are used in medical practice as anxiolytics, sedatives, anticonvulsants, hypnotics, muscle relaxants, as well as antagonists (antidotes) in cases of benzodiazepine drug overdose (Fig. 1).

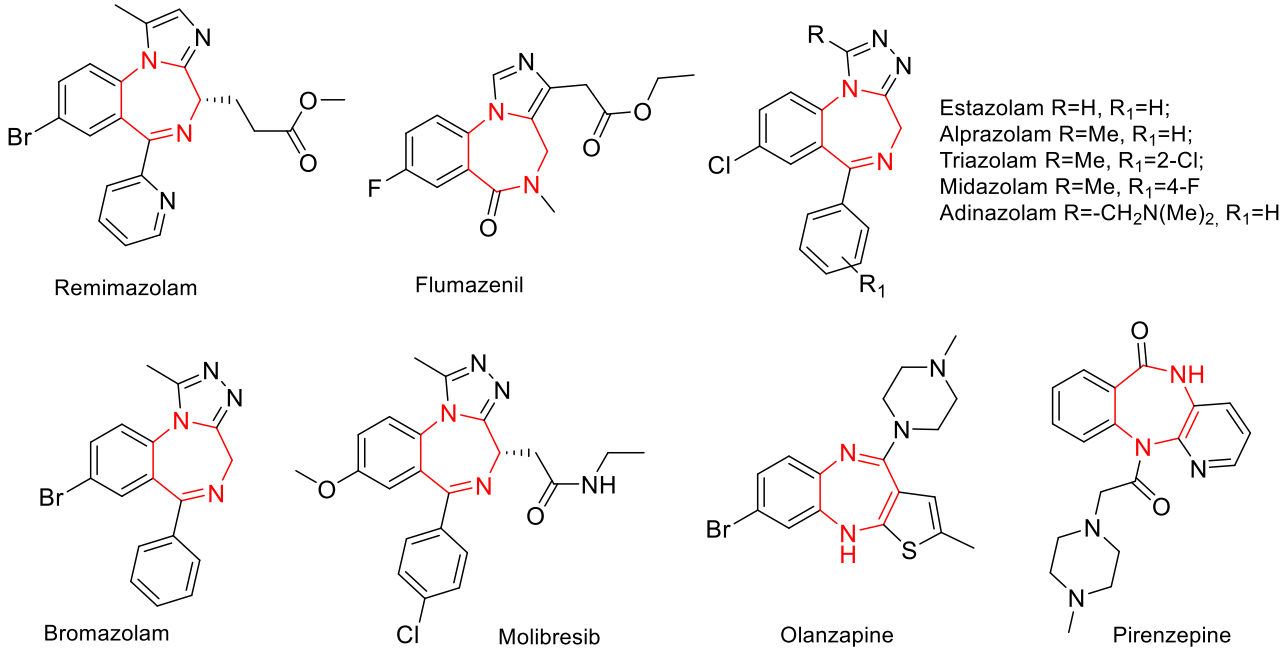

Fig. 1. Drugs among azolo-(azino-)benzodiazepines used in medicine

At present, given the medical significance of benzodiazepines and their analogues, approaches to their synthesis have also undergone substantial development. Condensation of 1,3-dicarbonyl compounds or α,β-unsaturated carbonyl compounds with o-phenylenediamines remain one of the most established methods of synthesis [5, 18]. In addition, alternative synthetic strategies have been reported, such as ring expansion reactions [19], click chemistry [20], Ugi condensation [21], azo-Michael cyclization [22], Friedel–Crafts reactions [23], Pd-catalyzed processes [24], and others. Despite the availability of studies devoted to the synthesis of condensed benzodiazepines, research in this field remains relevant due to the considerable promise of condensed benzodiazepine systems as biologically active compounds. Among these, compounds incorporating a triazine ring fused to a benzodiazepine fragment have been insufficiently explored. The development of synthetic methods for such compounds is justified, since the introduction of a triazine moiety into the benzodiazepine framework may result in modification of existing biological properties or the emergence of new pharmacological effects.

Thus, this study aims to develop accessible synthetic methods, to characterize their course, and to investigate the physicochemical properties of a new condensed system, benzo[*f*][1,2,4]triazino[1,5-*d*][1,4]diazepines.

Materials and methods

Melting points were determined in open capillary tubes in a «Mettler Toledo MP 50» apparatus and were uncorrected. The elemental analyses (C, H, N) were performed using the ELEMENTAR vario EL cube analyzer (USA). Analyses were indicated by symbols of the elements or functions within ±0.3 % of the

theoretical values. ^{1}H NMR (300 MHz) and ^{13}C NMR (76 MHz) spectra were recorded on a Varian-Mercury 300 (Varian Inc., Palo Alto, CA, USA) spectrometers with TMS as internal standard in DMSO-d_6 solution. LC-MS data were acquired using a chromatography/mass spectrometric system comprising the high-performance liquid chromatography «Agilent 1260 Infinity II» (Agilent, Palo Alto, CA, USA) equipped with a 6135 LC/MSD XT detector and a ZORBAX Eclipse Plus C18 column (2.1×50 mm, 1.8 μm). The sample (0.5 μL) was injected once; detection was performed by chemical ionization. The retention time of the analyte was 6.00 min.

3-(2-Aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-one (**1.1-1.6**) were synthesized using known methods and constants corresponding to the literature data [25]. Synthetic studies were conducted according to general approaches using reagents from Enamine (Kyiv, Ukraine), Merck (Darmstadt, Germany), and Sigma-Aldrich (Missouri, USA), which were used without additional purification.

Method for synthesizing 6-chloromethyl-3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones (**2.1**, **2.2**).

To 0.01 M of 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-ones (**1**) in 30 ml of glacial acetic acid, 1.47 g (0.013 M) chloroacetyl chloride is added and stirred on a magnetic stirrer at a temperature of 80–100 °C for up to 1 hour (reaction control by TLC). The reaction mixture is cooled, poured into water, the precipitate is filtered off and washed with water. For additional purification, the obtained substance was recrystallized from acetone.

6-Chloromethyl-3-methyl-2*H*-[1,2,4]triazino-[2,3-*c*]quinazoline-2-ones (**2.1**). Light yellow crystals, yield: 89.0 %, mp 120-122°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, *J* = 7.7 Hz, 1H, H-11), 7.99 (t, *J* = 7.1 Hz, 1H, H-9), 7.88 (d, *J* = 8.0 Hz, 1H, H-8), 7.77 (t, *J* = 7.6 Hz, 1H, H-10), 5.06 (s, 2H, -CH_2Cl), 2.46 (s, 3H, -CH3); LC-MS, m/z = 261 [M+1]; Anal. Calcd for $C_{12}H_9ClN_4O$: C, 55.29; H, 3.48; N, 21.49; Found: C, 55.34, H, 3.52; N, 21.51.

6-Chloromethyl-3-phenyl-2*H*-[1,2,4]triazino–[2,3-*c*]quinazoline-2-ones (**2.2**). Yellow crystalline compound, yield: 93.4 %, mp 223–225 °C (according to literature data [26] 218–220 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, *J* = 7.9 Hz, 1H, H-11), 8.35 (d, *J* = 7.3 Hz, 2H, Ph H-2, 6), 8.04 (t, *J* = 7.5 Hz, 1H, H-9), 7.94 (d, *J* = 8.0 Hz, 1H, H-8), 7.82 (t, *J* = 7.4 Hz, 1H, H-10), 7.69–7.43 (m, 3H, Ph H-3, 4, 5), 5.19 (s, 2H, CH_2Cl); LC-MS, m/z = 323 [M+1]; Anal. Calcd for $C_{17}H_{11}ClN_4O$: C, 63.31; H, 3.49; N, 17.41;Found: C, 63.38; H, 3.53; N, 17.44.

Methods for synthesizing 3-R-benzo[*f*][1,2,4]triazino[2,3-*d*][1,4]diazepine-2,7–(6*H*,8*H*)-diones (**3.1**, **3.2**).

Method A. In a 50 mL flask, mix 0.0025 M of the corresponding 3-(aminophenyl)-6-R-1,2,4-triazine-5(2*H*)-one (**1**), 10 ml of dioxane (anhydrous) and 0.97 g (0.0075 M) of N,N-diisopropylethylamine (DIPEA). To the reaction mixture, with constant stirring on a magnetic stirrer, add 0.31 g (0.00275 M) of freshly distilled chloroacetyl chloride in 10 ml of dioxane (anhydrous) in the temperature range from –5 °C to +20 °C at a rate of 15–20 drops per minute. Stirring is continued for 2 hours (**3.1**) to 48 hours (**3.2**) (reaction control by TLC). The reaction mixture is cooled, the precipitates are filtered off and washed with water and acetone. The filtrate is poured into water, the additional precipitates are filtered off, washed with water and acetone. For additional purification, the obtained substances were recrystallized from acetic acid.

Method B. In a 50 ml flask containing 10 ml of propanol-2, add 0.0025 mol of the corresponding 3-R-6-chloromethyl-2*H*-[1,2,4]triazine[2,3-*c*]quinazolin-2-one (**2.1**, **2.2**), 0.97 g (0.0075 M) of N,N-diisopropylethylamine (DIPEA), 2-3 drops of water, and boil for 6 to 48 hours (reaction control by TLC). The reaction mixture is cooled, diluted with water, and acidified to pH 5–6. It is cooled, the precipitate is filtered, washed with water, and dried. For additional purification, the obtained substances were recrystallized from acetic acid.

3-Methylbenzo[*f*][1,2,4]triazino[2,3-*d*][1,4]–diazepine-2,7(6*H*,8*H*)-dione (**3.1**). White crystalline compound; yield: 82 % (Method A), 76 % (Method B); mp 312–314 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H, NH), 7.97 (d, *J* = 8.0 Hz, 1H, H-12), 7.59 (t, *J* = 7.7 Hz, 1H, H-10), 7.31 (t, *J* = 7.6 Hz, 1H, H-11), 7.25 (d, *J* = 8.1 Hz, 1H, H-9), 4.59 (s, 2H, CH2), 2.24 (s, 3H,CH3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 162.1, 157.6, 152.8, 137.8, 133.5, 131.4, 124.6, 122.8, 121.7, 58.9, 16.9; Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13; Found: C, 59.55; H, 4.21; N, 23.18.

3-Phenylbenzo[*f*][1,2,4]triazino[2,3-*d*][1,4]–diazepine-2,7(6*H*,8*H*)-dione (**3.2**). Yellow crystalline compound; yield: 87 % (Method A), 72 % (Method B); ^{1}H NMR (302 MHz, DMSO-d_6) δ 10.97 (s, 1H, NH), 8.20–8.09 (m, 2H, 2,6-Ph), 8.01 (d, *J* = 7.1 Hz, 1H, H-12), 7.69 (t, *J* = 6.7 Hz, 1H, H-10), 7.60-7.44 (m, 3H, 3,4,5-Ph,), 7.40 (t, *J* = 6.9 Hz, 1H, H-11), 7.27 (d, *J* = 7.3 Hz, 1H, H-9), 4.79 (s, 2H, CH2); ^{13}C NMR (76 MHz, DMSO- d_6) δ 167.5, 160.9,

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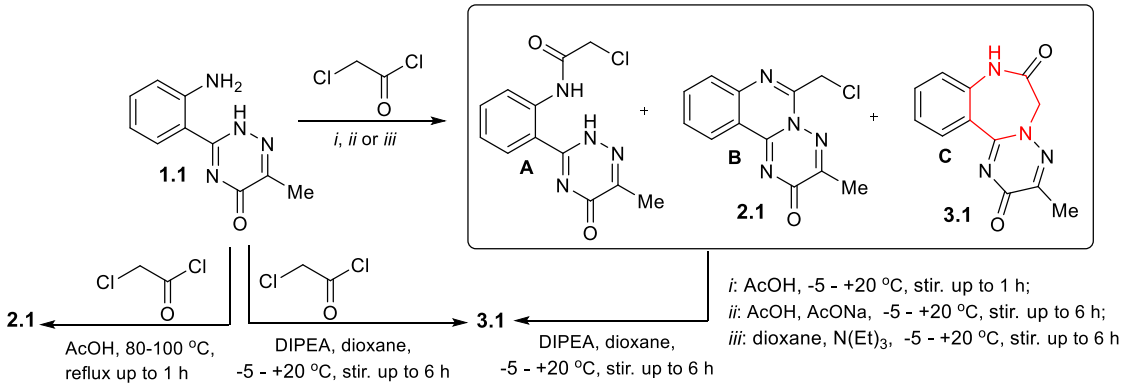
156.9, 148.2, 137.9, 133.7, 131.9, 131.7, 130.6, 128.7, 128.3 (2C), 124.6 (2C), 122.5, 121.8, 59.4; Anal. Calcd for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41; Found: C, 67.16; H, 4.02; N, 18.46.

X-ray crystallographic study of 3-methylbenzo[*f*][1,2,4]triazino[2,3-*d*][1,4]–diazepine-2,7(6*H*,8*H*)-dione (**3.1**). Colourless crystals of compound **3.1** from acetic acid existing as a monohydrate ($C_{12}H_{10}N_4O_2 \cdot H_2O$) are monoclinic. At 173 K a = 8.3441(2), b = 16.3657(3), c = 9.1961(2) Å, β = 108.485(2)°, V = 1191.00(5) Å^3, Mr = 260.26, Z = 4, space group P21/c, dcalc=1.451 g/cm^3, μ(MoKα)=0.108 mm^{-1}, F(000) = 544. Intensities of 15205 reflections (2094 independent, Rint=0.0391) were measured on the Bruker APEX II diffractometer (graphite monochromated MoKα radiation, CCD detector, φ- and ω-scanning, 2Θmax = 50°). The structure was solved using OLEX2 [27] package with SHELXT [28] and SHELXL modules [29]. Positions of the hydrogen atoms were located from electron density difference maps and refined using "riding" model with Uiso = nUeq of the carrier atom (n = 1.5 for methyl group and n = 1.2 for other hydrogen atoms). Hydrogen atoms of the NH group and water molecule are refined using isotropic approximation. Full-matrix least-squares refinement against F2 in anisotropic approximation for non-hydrogen atoms using 2094 reflections was converged to wR2 = 0.0922 (R1 = 0.0352 for 1783 reflections with F > 4σ(F), S = 1.068). The final atomic coordinates, and crystallographic data for molecule **3.1** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2501224).

Results and Discussion

In this study, we were interested in developing practical and accessible synthetic routes that provide access to a new heterocyclic system that could be used for further structural modification and the search for biologically active compounds for drug development. In our search for convenient methods for obtaining new condensed benzodiazepines, we drew attention to previous works in which the creation of these systems is based on the acylation of the corresponding binucleophiles or their synthesis by ring expansion.

At the beginning of the study, we examined the conditions for the synthesis of compound **3.1**. It was found that the interaction of 3-(2-aminophenyl)-6-methyl-1,2,4-triazin-5(2*H*)-ones (**1.1**) with chloroacetyl chlorides at temperatures ranging from −5 to +20 °C in acetic acid in the absence of a base (Scheme 1, condition *i*) leads to the formation of a mixture of compounds, namely 2-chloro-*N*-(2-(6-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)acetamide (A), 6-(chloromethyl)-3-methyl-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-one (**2.1**, B) in a ratio of 1:3.5 and trace amounts of benzotriazinodiazepines (**3.1**, C). It is important that an increase in the temperature of the reaction mixture shifts the equilibrium towards the formation of compound **2.1** (B), and complete conversion occurs in the temperature range of 80–100 °C and a reaction time of up to 1 hour (Scheme 1). The addition of nucleophilic bases (sodium acetate, $N(Et)_3$) at temperatures from −5 to +20 °C (Scheme 1, conditions *ii and iii*) shifts the reaction equilibrium towards the formation of compound **3.1** (C), but impurities of compound **2.1** (B) are present in the reaction mass in a ratio of ≈ 3:1 and trace amounts of compound A. Currently, complete conversion of the starting compound **1.1** to the corresponding benzotriazinodiazepines (**3.1**) occurs in the presence of non-nucleophilic bases (DIPEA, DBU) (Scheme 1, Table 1).



Scheme 1. Synthetic approaches for benzo[*f*][1,2,4]triazino[2,3-*d*][1,4]diazepines

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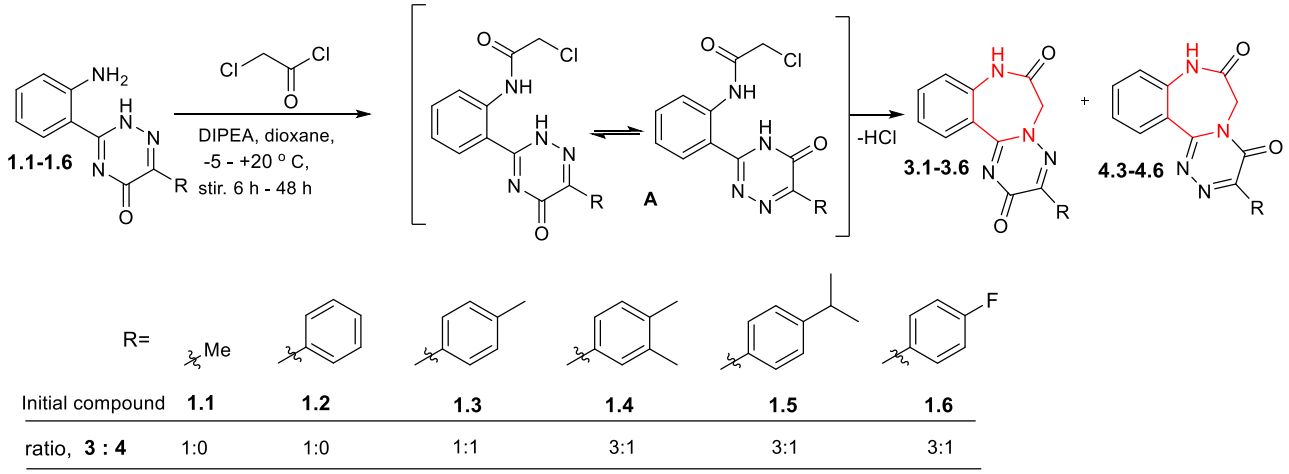
Optimization of synthesis conditions to determine the effect of the ratio of reagents, solvents, non-nucleophilic bases, and temperature showed (Scheme 2, Table 1) that the optimal conditions for the synthesis of **3.1** are the ratio of reagents (starting compound, chloranhydride, and DIPEA, 1:1, 1:3), dioxane solvent, and a temperature of –5 to +20 °C. The solvent also plays an important role in this reaction, namely, conducting it in dioxane leads to the formation of a precipitate, which is an individual compound **3.1**. We also found that the mixture of reaction products (method A) containing the corresponding chloroacetylanilide (A) is converted to benzotriazinodiazepines (**3.1**) under the above conditions (Scheme 1) with a low yield (10 %).

Table 1

Optimization of synthesis conditions for compound 3.1

№	Conditions	Yield, %
1	1 eq, $ClCH_2C(O)Cl$, 2 eq. DIPEA, dioxane, –5–0 °C, 30 min	<15
2	1 eq. $ClCH_2C(O)Cl$, 2 eq. DIPEA, dioxane, –5–0 °C, 1 h	<35
3	1 eq. $ClCH_2C(O)Cl$, 2 eq. DIPEA, dioxane, –5–0 °C, 1,5 h	56
4	1 eq. $ClCH_2C(O)Cl$, 2 eq. DIPEA, dioxane, –5–0 °C, 2 h	74
5	1,1 eq. $ClCH_2C(O)Cl$, 3 eq. DIPEA, dioxane, –5–0 °C, 2 h	80
6	1,3 eq. $ClCH_2C(O)Cl$, 4 eq. DIPEA, dioxane, –5–20 °C, 2 h	74
7	1,3 eq. $ClCH_2C(O)Cl$, 3 eq. DIPEA, dioxane, –5–20 °C, 6 h	82
8	1,1 eq. $ClCH_2C(O)Cl$, 3 eq. DIPEA, ТГФ, –5–0 °C, 6 h	52
9	1,1 eq. $ClCH_2C(O)Cl$, 3 eq. DIPEA, DMF, –5–0 °C, 48 h	40
10	1,1 eq. $ClCH_2C(O)Cl$, 3 eq. DBU, dioxane, –5–0 °C, 6 h	43

As a next step, we introduced a wider range of 3-(2-aminophenyl)-6-aryl-1,2,4-triazin-5(2*H*)-ones (**1.2-1.6**) into a similar reaction to obtain compounds **3.2-3.6**. The peculiarities of this reaction include, first, the reaction time increased to 48 hours; second, according to spectral data, the reaction results in a mixture of two structural isomers compounds **3** and **4** (Scheme 2). The formation of isomers can be explained by the existence of both the starting compounds **1** and the intermediate 2-chloro-N-(2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)acetamides (A) in the main medium in the form of two prototropic forms: 2*H*- and 4*H*-tautomers. Thus, in a nucleophilic attack on the carbon atom of the chloromethylene group (electrophilic center), both the N2 and N4 atoms of the triazine ring can be involved. It is important that donor-acceptor substituents in position 6 make a certain contribution to the isomer ratio.



Scheme 2. Formation of isomeric condenced derivatives and their ratio

Since benzotriazino-diazepines are a new class of compounds and are of interest as building blocks for further structural modification and the search for biologically active compounds, we attempted to develop alternative methods for their synthesis (**3**) from the corresponding 6-(chloromethyl)-3-R-2*H*-[1,2,4]triazino[2,3-*c*]–quinazolin-2-ones (**2**). In our opinion, nucleophilic expansion of the heterocycle will promote the formation of one of the structural isomers. For the synthesis of compounds **3**, we modeled the preliminary reaction conditions (Scheme 2), but the reaction was carried out in a protonic solvent of propanol-2 and a small amount of water was added to the reaction mass to create a certain activity of hydroxide ions. It was found that refluxing of compounds **2.1** and **2.2** in propanol-2 in the presence of DIPEA and water leads to the

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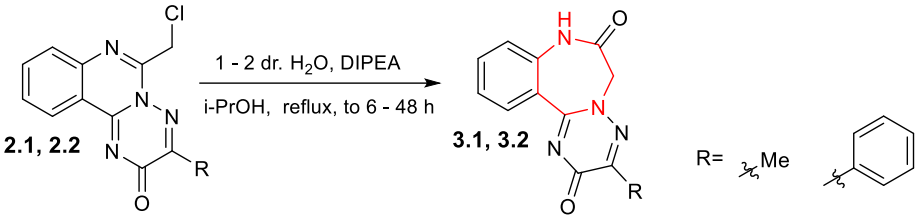
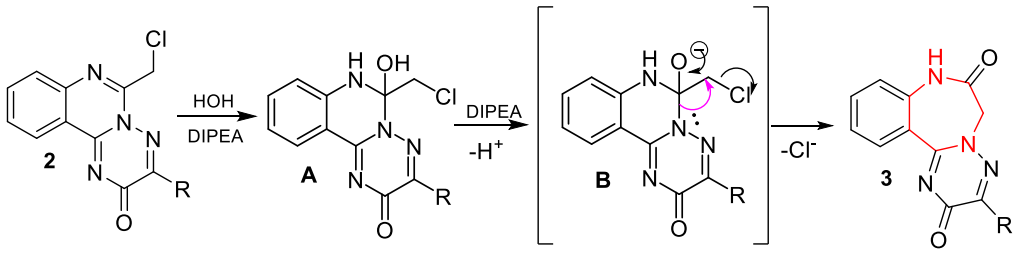
formation of individual compounds **3.1** and **3.2** (Scheme 3). We were unable to extend the method to other representatives of this class. In all cases, we isolated degradation products that did not contain a benzotriazine-diazepine fragment. Modification of the method by changing the solvent (dioxane, TGA, acetonitrile) and increasing the reaction time (over 48 hours) did not lead to a significant increase in the yield of the final products. However, it can be stated that structures **2.1** and **2.2** under the above conditions are capable of undergoing rearrangement accompanied by the expansion of the pyrimidine fragment. This method is preparative for compounds **3.1** and **3.2**, but has not been extended to other representatives of this series due to the absence of conversion even after prolonged heating. This fact is probably related to the electronic effects of the substituent in position 6.



Scheme 3. Synthesis of the target compounds by cycle expansion approach

As for the probable mechanism of nucleophilic ring expansion, in our opinion, it involves a nucleophile (HOH) attack at position 6, followed by attachment at the 6–7 bond to form intermediate A (Fig. 2). The latter, in the presence of a base (DIPEA), removes a proton to form adduct B, which undergoes intramolecular rearrangement with elimination of the chloride anion and cleavage of the 5–6 bond. This transformation can occur either as a synchronous one-step process with 1, 2 nucleophilic shift (B) followed by attack of the nucleophilic atom N1 of the triazine fragment on the electrophilic carbon atom of the chloromethylene group. Currently, this leads to the formation of a benzotriazinodiazepine cycle (3).



Scheme 4. Probable mechanism of molecular rearrangement of 6-(chloroalkyl)-3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones

The structure and purity of the obtained compounds were confirmed by a set of physicochemical methods, including elemental analysis, ^{1}H and ^{13}C NMR, X-ray diffraction analysis. The 1H NMR spectra of compounds 3 are characterized by a single proton broad singlet at 10.97–10.90 ppm (NH group) and a two-proton singlet proton at position 6 of the heterocycle at 4.79–4.59 ppm. In the ^{1}H NMR spectra of compounds **3**, a significant diamagnetic shift of the ABCD system of the tricyclic fragment was observed compared to the corresponding triazinoquinazoline systems [26]. Thus, these signals appear as two doublets (H-12, H-9) at 8.01–7.97 ppm and 7.27–7.25 ppm and two triplets (H-10, H-11) at 7.75–7.59 ppm and 7.40–7.31 ppm. Obviously, such a spectral pattern indicates that these compounds are not fully aromatic. In addition, ^{1}H NMR spectra of compounds **3** show signals of protons of functional groups in position 2 of the heterocycle, with corresponding multiplicity and chemical shift [30]. The results of the ^{13}C NMR spectral study of compounds 3 also confirmed our assumption, as the characteristic signals in this case are those of two carbon atoms -C=O of heterocyclic groups at 167.6–167.5 ppm and 162.1–160.9 ppm, and a significant paramagnetic shift of the sp^{3}-hydrid carbon atom at position 6 to 59.4–58.9 ppm. These facts give reason to assume that the compounds we obtained represent a new benz[*f*][1,2,4]triazino-diazepine system.

The spectral data presented (^{1}H and ^{13}C NMR spectra) allowed us to establish the structure of compounds **3**, but did not provide a reasonable answer to a number of questions, namely, to differentiate the formed benzo[*f*][1,2,4]triazino[2,3-*d*][1,4]diazepines

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system from its structural [4, 3-*d*]-isomer. Therefore, it was decided to conduct an X-ray diffraction study of compound **3.1** to further confirm the peculiarities of its structure.

The compound **3.1** was found in the crystalline phase as a monohydrate (Fig. 2). The partially saturated diazepine cycle adopts a boat conformation where the N1, C7, N2 and C11 atoms lie within a plane with an accuracy of 0.018 Å while the deviations of the C1, C6 and C8 atoms from this plane are –0.663(2) Å, –0.650(2) Å and –0.7027(18) Å, respectively.

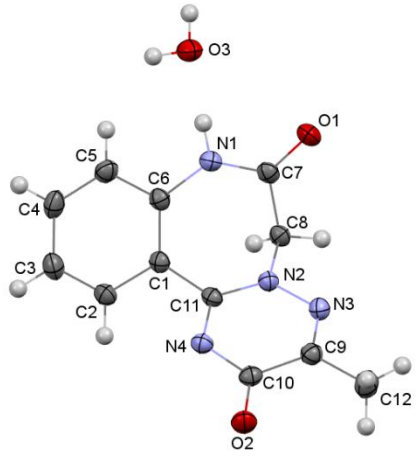

Fig. 2. Molecular structure of compound 3.1 monohydrate according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50 % probability level

In the crystal phase, molecules **3.1** are bound through the bridged water molecules forming centrosymmetric tetramer (Fig. 3a) due to the intermolecular hydrogen bonds N1–H…O3' (symmetry operation x,y,z; H…O distance 1.87(2) Å, N–H…O bond angle 171(2)°) and O3–H…O1' (symmetry operation -x,1-y,-z; H…O distance 1.99(2) Å, N–H…O bond angle 173(2)°). Tetramers are bound by the intermolecular hydrogen bonds O3–H…O2' (symmetry operation x-1,0.5-y,z-0.5; H…O distance 1.89(2) Å, N–H…O bond angle 166(2)°) forming a layer (Fig. 3b).

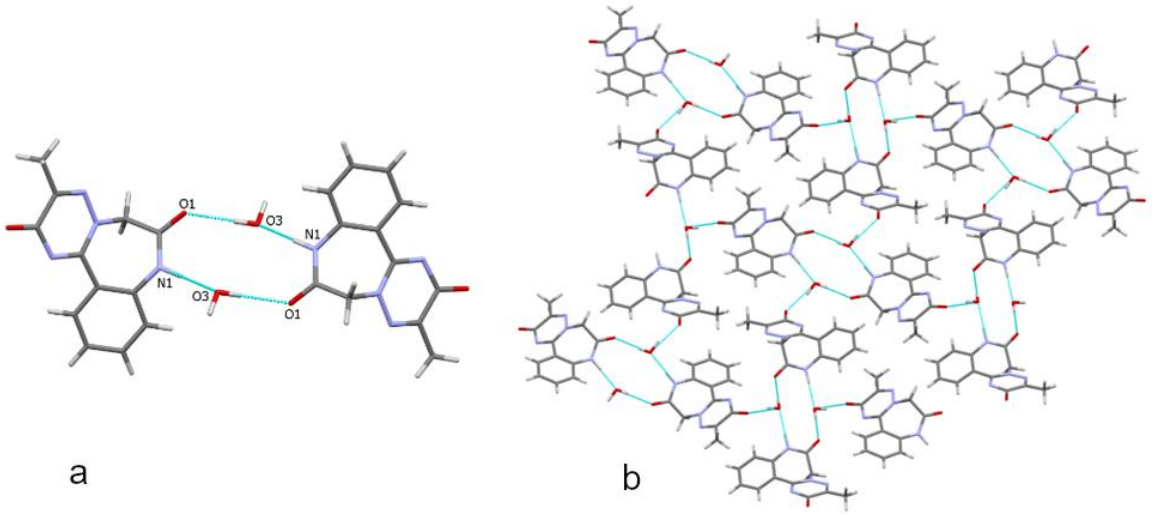

Fig. 3. Packing of molecules 3.1 in the crystal phase: a) tetramer with water molecules: b) hydrogen bonded layer

Conclusions

Thus, the present work is devoted to the development of a new benzo[*f*][1,2,4]triazino[2,3-*d*][1,4]diazepines system using simple and available synthesis methods. It should be noted that 3-(2-aminophenyl)-6-aryl-1,2,4-triazin-5(2*H*)-ones, which contain electron-donating and electron-withdrawing groups, in an acylation reaction in the presence of a non-nucleophilic base formed a mixture of two structural isomers. Alternative methods of benzo[*f*][1,2,4]triazino[2,3-*d*][1,4]diazepines from the corresponding 6-(chloromethyl)-3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones by nucleophilic expansion of the pyrimidine cycle of the molecule were developed, which contributed to the formation of one of the structural isomers ([2, 3-*d*] – series). Given the potential use of anellated benzdiazepines in medicine, further progress in this direction concerns the

functionalization of said heterocycles. In the case of a significant effect on neurodestructive damage to the central nervous system, the separation of isomers by chromatographic methods is promising.

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