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## REARRANGEMENT OF SUBSTITUTED 1,3-BENZOXAZINES INTO XANTHENE-TYPE COMPOUNDS

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The rearrangement patterns of new 1,3-benzoxazines derivatives obtained by condensation of substituted salicylamides with cyclic ketones under the influence of Vilsmeier-Haack reagent has been studied. The influence of angle strain in a 4-membered spirocycle prevents the rearrangement of spiro [1,3-benzoxazine-2,1'-cyclobutan]-4(3*H*)-one under the action of a formylating agent. 1,3-Benzoxazines derivatives with ring sizes from 5- to 8-membered under the action of a formylating agent have formed formylxanthene derivative. Their formation reaction rate depends on the presence of electronegativity substituents at positions C-6 and C-8 of the aromatic cycle, as well as in the spiroring.

**Key words:** rearrangement, Vilsmeier–Haack reagent, condensation, 1,3-benzoxazine, xanthene derivatives.

*Introduction.* One of the urgent tasks of synthetic chemists is the development of effective synthetic approaches, which allow constructing complex heterocyclic systems from simple and affordable reagents. In the study of formylation, we first showed the possibility of using spiro derivatives of pyrimidines for the synthesis of previously inaccessible derivatives of hydroacridines [1, 2]. To obtain new examples of structurally complex heterocycles, taking into account the concept of molecular diversity, we studied rearrangement to benzothiazine, quinoline [3] and formyl derivatives of xanthenes with various substituents [4-6]. The synthesized formyl derivatives of

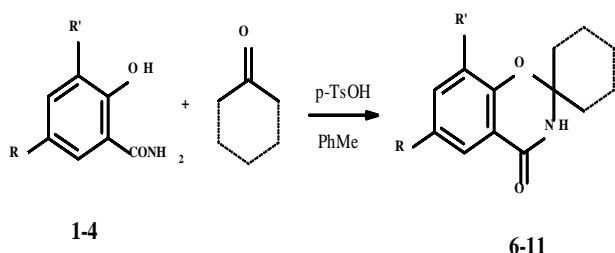
xanthenes exhibit fluoresce in solutions with large Stokes shifts and moderate quantum yields [6, 7]. In [6], the effect of the annulated aliphatic rings on the photophysical properties was studied. It was found that a decrease in the size of this cycle led to an increase in the quantum yield of fluorescence. Modification of the formyl group in the products of rearrangement of 1,3-benz(naphth)oxazines by reaction with aromatic amines, despite the extending of the conjugated chain, does not lead to an increase in fluorescence [8, 9]. The reaction of the formyl derivative of xanthene with hydrazine resulted in a previously unknown aldazine [8]. The interest in these com

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pounds is due to the fact that with a decrease in pH an intense color change is observed, which allows them to be positioned as pH analyzers [10-12]. The initial benzoxazines attract attention not only due to rearrangements under the action of the formulating agent but also due to their biological activity. In particular, we found the presence of antimicrobial activity among derivatives of 1,3-benzoxazines [13].

Given the novelty of the results obtained and the prospects for their practical application, the continuation of research in this direction is an urgent task. This work presents the results of the influence of the size of spirocycle and electronegativity of the substituents on the course of rearrangement.

*Results and Discussion.* New derivatives of 1,3-benzoxazines **5–10** were obtained by condensation of salicylamides **1–4** with cyclic ketones in toluene in the presence of p-TsOH with water removal with a Dean–Stark trap according to the procedure [14] (Scheme 1).



Scheme 1. **1** – R=R'=H; **2** – R=Br, R'=H; **3** – R=R'=Br; **4** – R=R'=H

When the reaction is carried out in acetic acid with propionic anhydride and sulfuric acid the compound **5** is formed (Scheme 2).

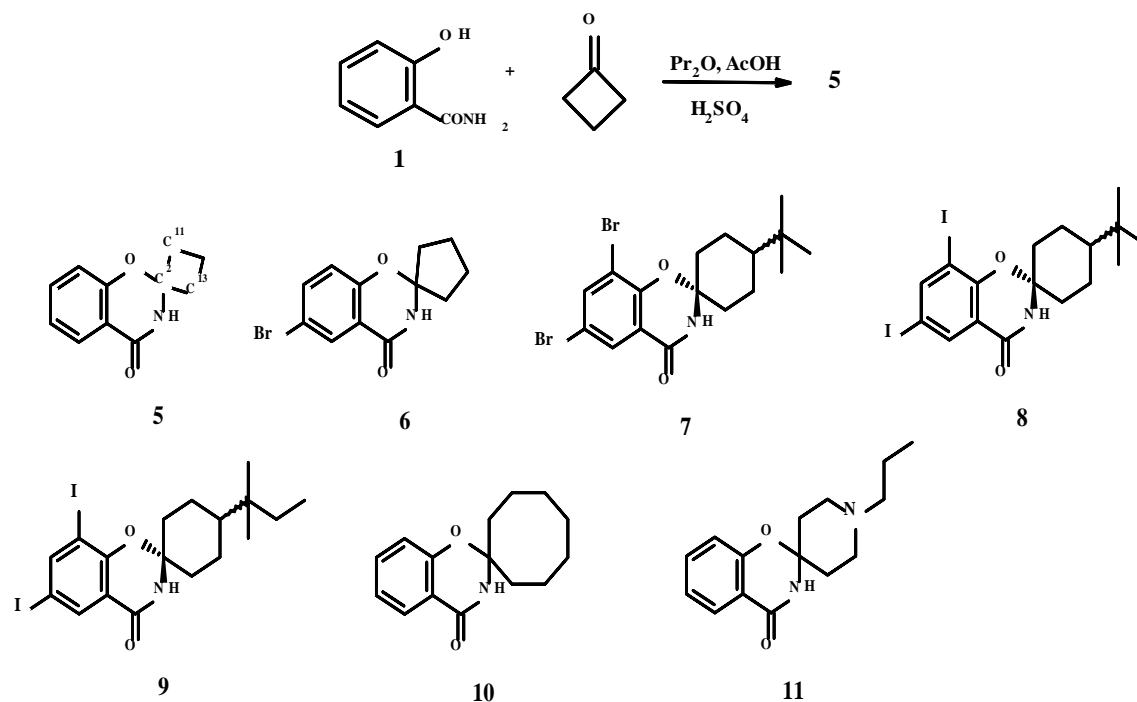
In the case of compound **11**, pyrrolidine was used as a catalyst, and the reaction

time was increased to 16 hours. The structures of the synthesized compounds were established by a complex of spectral methods. Compounds **7–9** were obtained as a mixture of two stereoisomers, which were reacted with a Vilsmeier-Haack reagent without prior separation.

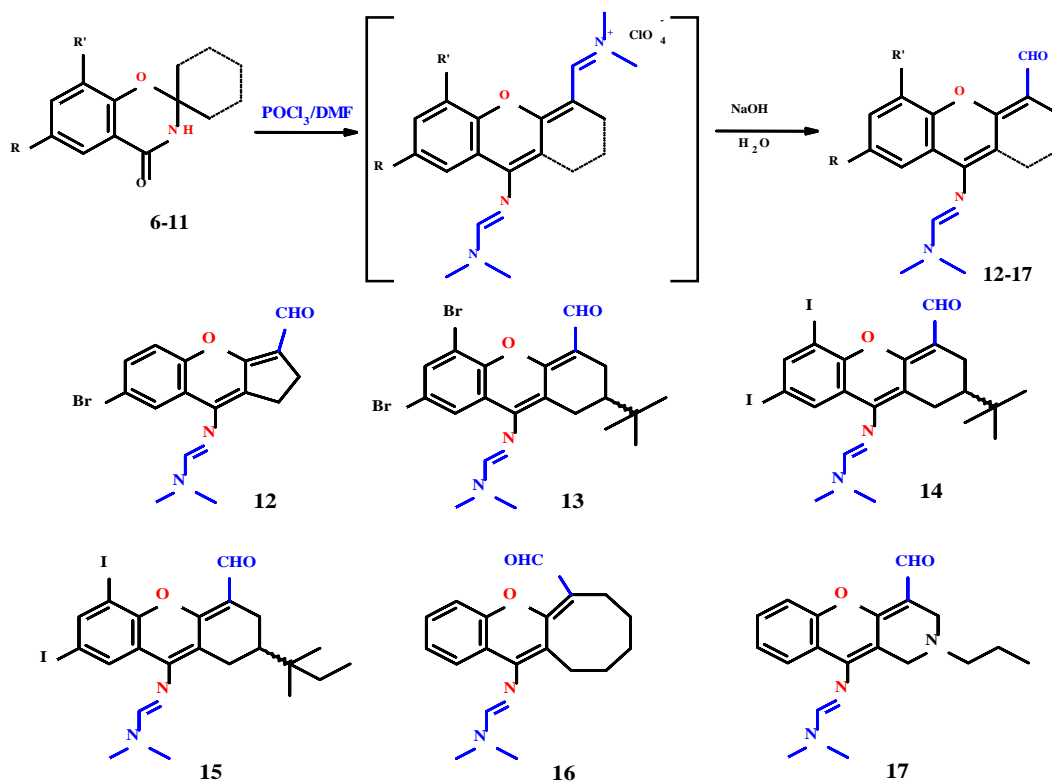
The reaction of spiro derivatives **6–11** with a formylating agent yielded compounds **12–17** (Scheme 3). The reaction products were isolated as intermediate perchlorate salts, which were further subjected to hydrolysis with NaOH solution to obtain relevant formyl derivatives. The structures of the synthesized compounds were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR spectroscopy and mass spectrometric data. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of these compounds have a characteristic signal of the formyl group at ~10.3 ppm and ~187 ppm, respectively. Benzoxazine **5**, during prolonged heating at 100 °C under the conditions of the Vilsmeier-Haack reaction, did not undergo a similar rearrangement, and after alkalinizing the reaction mixture, unreacted compound **5** was isolated.

The key stage of the reaction is the electrophilic disclosure of the oxazine cycle, which flew through the intermediate salt of imidoyl chloride A. The electron lone pair of oxygen atom attacks σ\*-orbital of C–N bond, which leads to breaking of this bond and formation of oxonium cation B (scheme 4). Scheme 3 shows the initial stages of the reaction using compound **6** as an example. For the complete rearrangement mechanism, see [4].

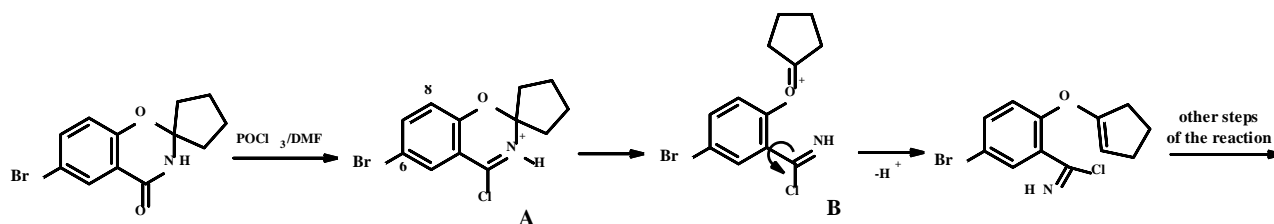
The lack of rearrangement for compound **5** is explained by the strain of the cyclobutane cycle.



Scheme 2



Scheme 3



Scheme 4

In compound **5**, the C11–C2–C13 valence angle was  $90^\circ$ , which was a  $19.5^\circ$  deviation from the perfect tetrahedron angle. In the case of opening of the oxazine cycle, this angle would still be  $90^\circ$ , but hybridization at the C-2 atom would change from  $sp^3$  to  $sp^2$ , and as a result, the strain of the 4-membered cycle would increase, since in this case the deviation of the valence angle from ideal trigonal would already be  $30^\circ$ . Such a transition of hybridization of the C-2 atom in compound **5** would be energetically disadvantageous.

In this regard, compound **5** was not subjected to electrophilic rearrangement under the conditions of the Vilsmeier-Haack reaction even under conditions of prolonged heating at  $100^\circ\text{C}$ .

The increase in reaction time for compounds **7–9** is explained by the influence of the electronegativity of the substituents at positions C-6 and C-8 of the benzoxazine ring. The presence of a bromine atom at position C-6 of spiro compound **6** did not affect the stability of the intermediate cation **B**, so the reaction proceeded under relatively mild conditions (1.5 hours at  $75^\circ\text{C}$ ). The bromine and iodine atoms in the C-8 position of compounds **7–9**, because of their negative inductive effect, destabilized cation **B**, which required more harsh reaction conditions (11 h at  $100^\circ\text{C}$  for compound **7**). Due

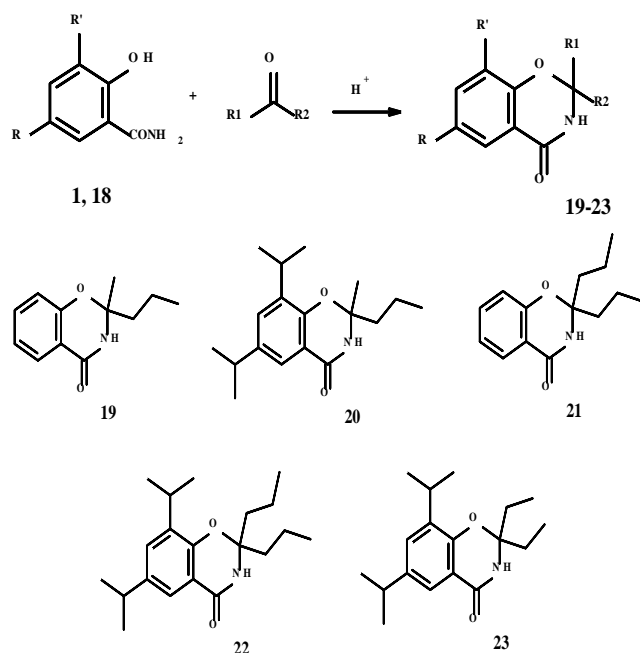
to the negative inductive effect, but of the nitrogen atom presence in the spiro ring, the rearrangement of the spiran **11** was also passing within 11 hours, as in the case of the dibromo-substituted spiran **7**.

The next step in our research was the study of the formylation of compounds **19–23**, with aliphatic substituents instead of a spiro ring. Compounds **19–23** were obtained by condensation of salicylamide derivatives **1, 18** with aliphatic ketones by prolonged boiling for 16–18 h in benzene with the azeotropic distillation of water in the presence of p-TsOH (Scheme 5).

However, the reaction of compounds **19–23** with the Vilsmeier-Haack reagent did not proceed selectively with the formation of resinous products, which were difficult to separate and identify.

The formation of vinyl ethers with different arrangements of double bonds and substituents after the opening of the oxazine cycle is a probable reason for the formation of a complicated mixture of the products. Some of these intermediates react similarly to the previous scheme, others cannot cyclize into the pyran cycle (trans vinyl ethers) and reacted in a different way, which leads to a multicomponent mixture of products with close Rf values.

*Experimental part.*  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance II



**1** – R=R'=H; **18** – R=R'=i-Pr  
Scheme 5

400 spectrometer (400 and 101 MHz, respectively) or a Bruker Avance 600 spectrometer (600 and 151 MHz, respectively; compound **5**) in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> with TMS as internal standard. The <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **7–9** are presented for the predominant isomer. The EI mass spectra were recorded on a Kratos MS 30 instrument with direct injection of the sample, ionization chamber temperature 250°C, ionization energy 70 eV. Elemental analysis was performed on a LECO CHN-900 instrument. Melting points were determined using an Electrothermal 9100 Digital Melting Point apparatus and were uncorrected. Completion of the reactions and purity of the obtained compounds were monitored by TLC on Merck Silica gel 60 F-254 plates, eluent CHCl<sub>3</sub>–MeOH, 9:1.

All reagents of analytical grade were purchased from commercial suppliers and used without any further purification, unless stated otherwise. Compounds **2** [15], **3** [16], **4** [17] and **18** [5, 18] were obtained by known procedures.

*Synthesis of spiro[1,3-benzoxazine-2,1'-cyclobutan]-4(3H)-one (5):* Conc. H<sub>2</sub>SO<sub>4</sub> (1 ml) was added to glacial acetic acid (3 ml), cooled in ice and left for several minutes. A solution of compound **1** (1.37 g, 0.01 mol), cyclobutanone (0.84 g, 0.012 mol), and propionic anhydride (1.5 ml) in glacial acetic acid (3 ml) was prepared separately. The first solution of H<sub>2</sub>SO<sub>4</sub> and AcOH was slowly added to the latter mixture with stirring and cooling with ice, stirred for 12 h at room temperature. Then neutralized to pH ~7 using sodium carbonate solution. The precipitate formed was filtered off and recrystallized from aqueous MeOH. Yield 47%, white powder, mp 158–161°C. <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): δ = 8.43 (1H, s, NH), 7.92 (1H, d, <sup>3</sup>*J*=7.5, Ar), 7.46 (1H, t, <sup>3</sup>*J*=7.4, Ar), 7.08 (1H, t, <sup>3</sup>*J*=7.5, Ar), 7.00 (1H, d, <sup>3</sup>*J*=8.2, Ar), 2.52–2.56 (2H, m, CH), 2.38–2.43 (2H, m, CH), 1.92–1.99 (1H, m, CH), 1.83–1.90 (1H, m, CH). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 163.1, 155.3, 133.9, 127.2, 121.5, 117.2, 116.7, 88.1, 35.1, 11.4. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 189 [M]<sup>+</sup> (3). Found, %: C 69.90; H 5.90; N 7.45. C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>. Calculated, %: C 69.83; H 5.86; N 7.40.

*Synthesis of spirans 6–10 (General method).* A mixture of the corresponding salicylamide **1–4** (0.01 mol), ketone (0.012 mol), and *p*-TsOH·H<sub>2</sub>O (0.03 mol) in PhMe (45 ml) was refluxed for 8 h with continuous removal of water with a Dean–Stark trap.

Then solvent was evaporated to dryness under reduced pressure, the solid residue was washed with 5% aqueous NaOH solution, water and filtered off.

*6-Bromospiro[1,3-benzoxazine-2,1'-cyclopentan]-4(3H)-one (6)*: Yield 68%, white powder, mp 195–196°C (EtOH). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): δ = 8.20 (1H, br. s, NH); 8.00 (1H, s, H-5 Ar); 7.50 (1H, d, <sup>3</sup>*J*=8.6, H-7 Ar); 6.83 (1H, d, <sup>3</sup>*J*=8.6, H-8 Ar); 2.07–2.16 (2H, m, CH); 1.65–1.85 (6H, m, CH). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 162.2; 154.9; 137.3; 130.4; 119.2; 114.2; 96.3, 37.4, 22.4. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 283 [M(<sup>81</sup>Br)]<sup>+</sup> (25), 281 [M(<sup>79</sup>Br)]<sup>+</sup> (24). Found, %: C 51.21; H 4.45; N 5.05. C<sub>12</sub>H<sub>12</sub>BrNO<sub>2</sub>. Calculated, %: C 51.09; H 4.29; N 4.96.

*6,8-Dibromo-4'-tert-butylspiro[1,3-benzoxazine-2,1'-cyclohexan]-4(3H)-one (7)*: Yield 88%, white powder, mp 253–257°C (DMF). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 7.98 (1H, s, NH), 7.80 (1H, s, Ar), 7.28 (1H, s, Ar), 2.31–2.33 (2H, m, CH), 1.55–1.71 (6H, m, CH), 1.13–1.16 (1H, m, CH), 0.91 (9H, s, t-Bu). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 161.6, 154.7, 142.8, 142.6, 132.6, 117.2, 115.1, 92.1, 49.2, 33.3, 35.6, 30.4, 25.9. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 431 [M]<sup>+</sup> (55). Found, %: C 47.51; H 5.05; N 3.38. C<sub>17</sub>H<sub>21</sub>Br<sub>2</sub>NO<sub>2</sub>. Calculated, %: C 47.36; H 4.91; N 3.25.

*4'-tert-Butyl-6,8-diiodospiro[1,3-benzoxazine-2,1'-cyclohexan]-4(3H)-one (8)*: Yield 88%, white powder, mp 228–234°C (DMF). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 8.34 (1H, s, NH), 8.14 (2H, s, Ar), 2.22–2.29 (2H, m, CH), 1.59–1.70 (6H, m, CH), 1.13–1.16 (1H, m, CH), 0.91 (9H, s, t-Bu). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ =

161.6, 155.0, 150.8, 136.6, 119.8, 89.5, 86.3, 84.6, 46.4, 36.3, 32.6, 27.8, 22.8. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 525 [M]<sup>+</sup> (45). Found, %: C 39.05; H 4.15; N 2.82. C<sub>17</sub>H<sub>21</sub>I<sub>2</sub>NO<sub>2</sub>. Calculated, %: C 38.88; H 4.03; N 2.67.

*4'-(1,1-Dimethylpropyl)-6,8-diiodospiro[1,3-benzoxazine-2,1'-cyclohexan]-4(3H)-one (9)*: Yield 90%, white powder, mp 218–223°C (DMF). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): δ = 8.15 (2H, s, Ar), 8.02 (1H, br s, NH), 2.22–2.29 (2H, m, CH), 1.55–1.70 (6H, m, CH), 1.26–1.31 (3H, m, CH), 0.87 (6H, s, 2CH<sub>3</sub>), 0.82 (3H, t, <sup>3</sup>*J*=6.8, CH<sub>3</sub>). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 160.5, 154.0, 149.9, 135.6, 118.8, 88.5, 85.3, 83.6, 42.7, 35.5, 33.9, 31.9, 21.4, 18.9, 7.3. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 539 [M]<sup>+</sup> (35). Found, %: C 40.25; H 4.40; N 2.71. C<sub>18</sub>H<sub>23</sub>I<sub>2</sub>NO<sub>2</sub>. Calculated, %: C 40.10; H 4.30; N 2.60.

*Spiro[1,3-benzoxazine-2,1'-cyclooctan]-4(3H)-one (10)*: Yield 88%, white powder, mp 158–160°C (EtOH). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): δ = 7.89 (1H, d, <sup>3</sup>*J*=7.4, Ar); 7.61 (1H, br. s, NH); 7.42 (1H, t, <sup>3</sup>*J*=7.5, Ar); 7.03 (1H, t, <sup>3</sup>*J*=7.4, Ar); 6.89 (1H, d, <sup>3</sup>*J*=8.1, Ar); 2.20–2.28 (2H, m, CH); 1.96–2.04 (2H, m, CH); 1.51–1.78 (10H, m, 5CH<sub>2</sub>). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 161.2; 154.4; 137.0; 130.0; 119.0; 114.3; 92.1; 39.5; 28.2; 21.2; 20.1. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 245 [M]<sup>+</sup> (10). Found, %: C 73.51; H 7.89; N 5.77. C<sub>15</sub>H<sub>19</sub>NO<sub>2</sub>. Calculated, %: C 73.44; H 7.81; N 5.71.

*Synthesis of 1'-propylspiro[1,3-benzoxazine-2,4'-piperidin]-4(3H)-one (11)*: A mixture of the salicylamide **1** (1.37 g, 0.01 mol), 1-propylpiperidin-4-one (1.69 g, 0.012 mol), and pyrrolidine (2.13 g, 0.03 mol) in

PhMe (45 ml) was refluxed for 16 h with continuous removal of water with a Dean–Stark trap. Then solvent was evaporated to dryness under reduced pressure, the solid residue was washed with 5% aqueous NaOH solution, water and filtered off. Yield 68%, white powder, mp 150–152°C (EtOH).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm ( $J$ , Hz):  $\delta$  = 7.89 (1H, d,  $^3J=6.6$ , Ar); 7.67 (1H, br. s, NH); 7.43 (1H, t,  $^3J=7.1$ , Ar); 7.05 (1H, t,  $^3J=7.5$ , Ar); 6.94 (1H, d,  $^3J=8.2$ , Ar); 2.62–2.72 (2H, m,  $\text{CH}_2$ ); 2.43–2.50 (2H, m, CH); 2.32–2.38 (2H, m, CH); 2.17–2.21 (2H, m, CH); 1.90–2.00 (2H, m, CH); 1.44–1.56 (2H, m,  $\text{CH}_2$ ), 0.89 (3H, t,  $^3J=7.3$ ,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm:  $\delta$  = 161.1; 154.3; 137.0; 130.0; 119.0; 114.1; 89.1; 39.5; 38.2; 37.8; 28.6; 20.1. Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 260  $[\text{M}]^+$  (2). Found, %: C 69.41; H 7.89; N 10.87.  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$ . Calculated, %: C 69.20; H 7.74; N 10.76.

*Synthesis of compounds 12–17 (General method).* The Vilsmeier–Haack reagent was prepared from  $\text{POCl}_3$  (2.75 ml, 0.03 mol) and DMF (4.61 ml, 0.06 mol) with ice-cooling. Compound **6** (2.82 g, 0.01 mol) was added to the Vilsmeier–Haack reagent. The reaction mixture was heated and stirred on a water bath at 80°C for 1.5 h. Then the reaction mixture was cooled to 10°C and treated with an ice-cold 15% aqueous  $\text{NaClO}_4$  solution (10 ml). The precipitate of the organic salt was filtered off, dried, and washed with PhMe. The organic salt was dissolved in hot DMF (5 ml). To the obtained solution, an aqueous 15% NaOH solution (1.5 ml) was added, and the mixture was stirred vigorously at 60–75°C for 5 min. The precipitated solid of compound **12** was filtered off. If no

solid precipitated, the solution was cooled to the room temperature and water was added. For compounds **8** and **9**, the reaction time was increased to 8 h. Compounds **7**, **11** were obtained at 100°C for 11 h.

*N'-(7-Bromo-3-formyl-1,2-dihydrocyclopenta[b]chromen-9-yl)-N,N-dimethylimidoforamamide (12):* Yield 67%, yellow powder, mp 173–175°C (EtOH).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm ( $J$ , Hz):  $\delta$  = 10.21 (1H, s, CHO); 7.61 (1H, d,  $^4J=2.4$ , H-8 Ar); 7.38 (1H, s, CH); 7.37 (1H, dd,  $^3J=8.6$ ,  $^4J=2.4$ , H-6 Ar); 6.95 (1H, d,  $^3J=8.6$ , H-5 Ar); 3.10 (3H, s,  $\text{CH}_3$ ); 3.07 (3H, s,  $\text{CH}_3$ ); 2.75–2.85 (2H, m,  $\text{CH}_2$ ), 2.50–2.55 (2H, m,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm:  $\delta$  = 186.6; 162.7; 153.8; 151.4; 145.5; 132.5; 126.5; 123.1; 116.8; 115.7; 113.4; 111.1; 39.5, 33.5, 23.2, 22.5. Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 348  $[\text{M} (^{81}\text{Br})]^+$  (96), 346  $[\text{M} (^{79}\text{Br})]^+$  (94). Found, %: C 55.45; H 4.40; N 8.05.  $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_2$ . Calculated, %: C 55.35; H 4.35; N 8.07.

*N'-(5,7-Dibromo-2-tert-butyl-4-formyl-2,3-dihydro-1H-xanthen-9-yl)-N,N-dimethylimidoforamamide (13):* Yield 57%, yellow powder, mp 184–186°C (EtOH).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm:  $\delta$  = 10.33 (1H, s, CHO); 7.57 (1H, s, Ar); 7.54 (1H, s, Ar); 7.37 (1H, s, CH); 3.10 (3H, s,  $\text{CH}_3$ ); 3.07 (3H, s,  $\text{CH}_3$ ); 2.75–2.84 (2H, m,  $\text{CH}_2$ ); 1.87–1.93 (2H, m,  $\text{CH}_2$ ); 1.77–1.80 (1H, m, CH); 0.94 (9H, s, *t*-Bu).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm:  $\delta$  = 187.2; 161.6; 153.6; 148.1; 144.4; 135.0; 125.7; 124.0; 115.5; 113.7; 112.0; 109.6; 41.5; 40.0; 34.0; 32.0; 27.2; 26.1; 22.4. Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 496  $[\text{M}]^+$  (100). Found, %: C 51.02; H 8.01; N 5.77.  $\text{C}_{21}\text{H}_{24}\text{Br}_2\text{N}_2\text{O}_2$ . Calculated, %: C 50.83; H 4.87; N 5.65.

*N'*-(2-*tert*-Butyl-4-formyl-5,7-diiodo-2,3-dihydro-1*H*-xanthen-9-yl)-*N,N*-dimethylimidoforamamide (14): Yield 48%, yellow powder, mp 165–168°C (EtOH). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 10.44 (1H, s, CHO), 7.98 (1H, s, Ar), 7.73 (1H, s, Ar), 7.34 (1H, s, CH), 3.12 (3H, s, CH<sub>3</sub>); 3.08 (3H, s, CH<sub>3</sub>); 2.77–2.85 (2H, m, CH<sub>2</sub>); 1.87–1.95 (2H, m, CH<sub>2</sub>); 1.77–1.80 (1H, m, CH); 0.95 (9H, s, *t*-Bu). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 187.5; 161.6; 153.4; 150.8; 146.0; 144.4; 132.5; 123.7; 113.4; 111.0; 86.5; 83.5; 41.6; 40.0; 34.0; 32.1; 27.2; 26.0; 22.5. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 590 [M]<sup>+</sup> (65). Found, %: C 42.90; H 4.15; N 4.85. C<sub>21</sub>H<sub>24</sub>I<sub>2</sub>N<sub>2</sub>O<sub>2</sub>. Calculated, %: C 42.73; H 4.10; N 4.75.

*N'*-[2-(1,1-Dimethylpropyl)-4-formyl-5,7-diiodo-2,3-dihydro-1*H*-xanthen-9-yl]-*N,N*-dimethylimidoforamamide (15): Yield 60%, yellow powder, mp 155–158°C (EtOH). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 10.43 (1H, s, CHO), 7.96 (1H, s, Ar), 7.72 (1H, s, Ar), 7.33 (1H, s, CH), 3.11 (3H, s, CH<sub>3</sub>); 3.07 (3H, s, CH<sub>3</sub>); 2.73–2.84 (2H, m, CH<sub>2</sub>); 1.85–1.93 (2H, m, CH<sub>2</sub>); 1.75–1.80 (1H, m, CH); 1.32–1.40 (2H, m, CH<sub>2</sub>); 0.84 (6H, s, 2Me), 0.79 (3H, t, <sup>3</sup>*J*=7.5 Hz, Me). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 187.4; 161.5; 153.3; 150.7; 146.0; 144.3; 132.4; 123.6; 113.3; 111.0; 86.4; 83.4; 40.1; 39.2; 34.6; 34.3; 32.5; 25.7; 24.2; 23.9; 22.2. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 604 [M]<sup>+</sup> (95). Found, %: C 43.95; H 4.45; N 4.65. C<sub>22</sub>H<sub>26</sub>I<sub>2</sub>N<sub>2</sub>O<sub>2</sub>. Calculated, %: C 43.73; H 4.34; N 4.64.

*N'*-(6-Formyl-8,9,10,11-tetrahydro-7*H*-cycloocta[*b*]chromen-12-yl)-*N,N*-dimethylimidoforamamide (16): Yield 47%, yellow powder, mp 113–116°C (EtOH). <sup>1</sup>H

NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): δ = 10.25 (1H, s, CHO); 7.48 (1H, d, <sup>3</sup>*J*=7.0, Ar); 7.35 (1H, s, CH); 7.27–7.32 (1H, m, Ar); 7.04–7.08 (2H, m, Ar); 3.10 (3H, s, CH<sub>3</sub>); 3.07 (3H, s, CH<sub>3</sub>); 2.60–2.63 (4H, m, 2CH<sub>2</sub>); 1.73–1.85 (6H, m, 3CH<sub>2</sub>). <sup>13</sup>C <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 187.4; 167.3; 153.1; 152.4; 150.3; 130.1; 124.3; 122.6; 120.8; 116.0; 115.0; 110.5; 40.1; 34.3; 28.0; 25.9; 25.3; 19.9; 19.7. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 310 [M]<sup>+</sup> (100). Found, %: C 73.72; H 7.27; N 9.17. C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>. Calculated, %: C 73.52; H 7.14; N 9.09.

*N'*-(4-Formyl-2-propyl-2,3-dihydro-1*H*-chromeno[3,2-*c*]pyridin-10-yl)-*N,N*-dimethylimidoforamamide (17): Yield 52%, yellow powder, mp 127–130°C (EtOH). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): δ = 10.23 (1H, s, CHO); 7.44 (1H, d, <sup>3</sup>*J*=7.0, Ar); 7.33 (1H, s, CH); 7.27–7.30 (1H, m, Ar); 7.02–7.06 (2H, m, Ar); 3.16–3.19 (1H, m, CH); 3.12 (3H, s, CH<sub>3</sub>); 3.09 (3H, s, CH<sub>3</sub>); 2.91–2.94 (1H, m, CH); 2.82–2.89 (1H, m, CH); 2.60–2.65 (1H, m, CH); 2.55–2.59 (2H, m, CH<sub>2</sub>); 1.48–1.58 (2H, m, CH<sub>2</sub>), 0.91 (3H, t, <sup>3</sup>*J*=7.5, CH<sub>3</sub>). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm: δ = 185.2; 155.5; 153.5; 148.1; 144.2; 135.0; 125.5; 124.1; 115.3; 112.9; 112.1; 109.6; 45.5; 44.8; 43.8; 41.5; 40.0; 26.1; 22.4. Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 325 [M]<sup>+</sup> (5). Found, %: C 70.28; H 7.20; N 13.06. C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>. Calculated, %: C 70.13; H 7.12; N 12.91.

*Synthesis of compounds 19–23 (General method).* A mixture of the corresponding salicylamide **1**, **18** (0.01 mol), aliphatic ketone (0.012 mol), and *p*-TsOH·H<sub>2</sub>O (0.03 mol) in benzene (45 ml) was refluxed for 16–18 h with continuous removal of water with



a Dean–Stark trap. Then solvent was evaporated to dryness under reduced pressure, the solid residue was washed with 5% aqueous NaOH solution, water, and filtered off.

*2-Methyl-2-propyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (19)*: Yield (85 %), mp 94–95°C.  $^1\text{H}$  NMR spectrum (DMSO- $d_6$ ),  $\delta$ , ppm ( $J$ , Hz): 8.62 (1H, s, NH); 7.73 (1H, d,  $^3J=7.3$ , H Ar); 7.46 (1H, t,  $^3J=7.3$ , H Ar); 7.04 (1H, t,  $^3J=7.3$ , H Ar); 6.93 (1H, d,  $^3J=7.8$ , H Ar); 1.71–1.73 (2H, m, CH<sub>2</sub>); 1.46 (3H, s, CH<sub>3</sub>); 1.36–1.38 (2H, m, CH<sub>2</sub>); 0.83 (3H, t,  $^3J=6.8$ , CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (DMSO- $d_6$ ),  $\delta$ , ppm: 161.1; 155.4; 134.4; 126.9; 117.2; 116.8; 89.1; 41.5; 25.4; 16.5; 13.9. Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 205 [ $\text{M}$ ]<sup>+</sup> (20), 121 (100). Found, %: C 70.22; H 7.37; N 6.82. C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>. Calculated, %: C 70.33; H 7.26; N 6.69.

*6,8-Diisopropyl-2-methyl-2-propyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (20)*: Yield (70 %), mp 52–54°C.  $^1\text{H}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm ( $J$ , Hz): 8.15 (1H, s, NH); 7.67 (1H, s, H Ar); 7.25 (1H, s, H Ar); 3.25 (1H, sept,  $^3J=6.9$ , CH(CH<sub>3</sub>)<sub>2</sub>); 2.94 (1H, sept,  $^3J=6.9$ , CH(CH<sub>3</sub>)<sub>2</sub>); 1.91–1.93 (2H, m, CH<sub>2</sub>); 1.63 (3H, s, CH<sub>3</sub>); 1.56–1.58 (2H, m, CH<sub>2</sub>); 1.28–1.30 (12H, m, CH(CH<sub>3</sub>)<sub>2</sub>); 0.98 (3H, t,  $J=6.8$ , CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 163.9; 151.2; 141.5; 136.3; 129.8; 122.1; 116.3; 88.7; 42.3; 33.6; 27.1; 25.5; 23.9; 22.6; 22.3; 16.9; 14.0. Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 289 [ $\text{M}$ ]<sup>+</sup> (9). Found, %: C 74.70; H 9.40; N 4.84. C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub>. Calculated, %: C 74.66; H 9.26; N 4.95.

*2,2-Dipropyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (21)*: Yield (70 %), mp 63–65°C (mp 61–63°C [19]).  $^1\text{H}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm ( $J$ , Hz): 8.61 (1H, s, NH); 7.94 (1H, d,  $^3J=8.1$ , H Ar); 7.41 (1H, t,

$^3J=7.3$ , H Ar); 7.03 (1H, t,  $^3J=7.3$ , H Ar); 6.91 (1H, d,  $^3J=8.1$ , H Ar); 1.86–1.88 (4H, m, 2CH<sub>2</sub>); 1.47–1.49 (4H, m, 2CH<sub>2</sub>); 0.91 (6H, m, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 163.3; 156.0; 134.3; 127.3; 121.2; 116.7; 91.2; 40.2; 16.5; 13.9. Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 233 [ $\text{M}$ ]<sup>+</sup> (14), 190 (100). Found, %: C 72.07; H 8.21; N 6.00. C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>. Calculated, %: C 72.01; H 8.34; N 6.15.

*6,8-Diisopropyl-2,2-dipropyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (22)*: Yield (72 %), mp 125–126°C.  $^1\text{H}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm ( $J$ , Hz): 7.74 (1H, s, NH); 7.63 (1H, s, H Ar); 7.22 (1H, s, H Ar); 3.22 (1H, sept,  $^3J=6.9$ , CH(CH<sub>3</sub>)<sub>2</sub>); 2.89 (1H, sept,  $^3J=6.9$ , CH(CH<sub>3</sub>)<sub>2</sub>); 1.80–1.89 (4H, m, CH<sub>2</sub>); 1.47–1.49 (4H, m, CH<sub>2</sub>); 1.25–1.27 (12H, m, CH(CH<sub>3</sub>)<sub>2</sub>); 0.92 (6H, t,  $J=6.8$ , CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 163.7; 151.2; 141.3; 136.1; 129.7; 122.1; 116.2; 90.7; 40.1; 33.6; 26.9; 24.0; 22.5; 16.7; 14.1. Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 317 [ $\text{M}$ ]<sup>+</sup> (1). Found, %: C 75.67; H 9.84; N 4.41. C<sub>20</sub>H<sub>31</sub>NO<sub>2</sub>. Calculated, %: C 75.78; H 9.96; N 4.25.

*2,2-Diethyl-6,8-diisopropyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (23)*: Yield (82 %), mp 80–82°C.  $^1\text{H}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm ( $J$ , Hz): 7.63 (1H, s, NH); 7.56 (1H, s, H Ar); 7.22 (1H, s, H Ar); 3.24 (1H, sept,  $^3J=6.9$ , CH(CH<sub>3</sub>)<sub>2</sub>); 2.89 (1H, sept,  $^3J=6.9$ , CH(CH<sub>3</sub>)<sub>2</sub>); 1.90–1.95 (4H, m, CH<sub>2</sub>); 1.23–1.26 (12H, m, CH(CH<sub>3</sub>)<sub>2</sub>); 1.00 (6H, t,  $J=6.8$ , CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 163.8; 151.2; 141.5; 136.2; 129.8; 122.1; 116.2; 91.3; 33.6; 30.3; 26.9; 24.0; 22.6; 7.7. Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 289 [ $\text{M}$ ]<sup>+</sup> (33), 260 (100). Found, %: C 74.70; H 9.40; N 4.84. C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub>. Calculat-

ed, %: C 74.78; H 9.26; N 4.95.

**Conclusion.** In this work, we presented an effective method for the synthesis of formyl derivatives of xanthenes based on readily available salicylamide. It was found that (spiro[1,3-benzoxazine-2,1'-cyclobutan]-4(3*H*)-one) does not rearrange even under prolonged heating due to the spirocycle strain. The presence of bromine or iodine atoms at positions C-6 and C-8 of the aromatic cycle of 1,3-benzoxazines makes the reaction more difficult, which requires more harsh synthesis conditions.

#### ПЕРЕГРУПУВАННЯ ЗАМІЩЕНИХ 1,3-БЕНЗОКСАЗИНІВ В СПОЛУКИ КСАНТЕНОВОГО ТИПУ

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Вивчено закономірності перегрупування нових похідних 1,3-бензоксазинів, які отримано конденсацією заміщених саліциламідів з циклічними кетонами, під дією реагенту Вільсмайєра-Хаака. Вплив кутового напруження у 4х членному спіроциклі перешкоджає перегрупуванню спіро[1,3-бензоксазин-2,1'-циклобутан]-4(3*H*)-ону під дією формілюючого агента. Похідні 1,3-бензоксазинів з розмірами циклів від 5-ти до 8-и членних під дією формілюючого агента утворюють формілопохідні ксантенів, у яких швидкість реакції залежить від наявності електронегативних замісників у положеннях С-6 і С-8 ароматичного циклу, а також у спіроциклі.

**К л ю ч о в і с л о в а:** перегрупування, реагент Вільсмайєра-Хаака, конденсація, 1,3-бензоксазини, формілопохідні ксантенів.

#### ПЕРЕГРУППИРОВКА ЗАМЕЩЁННЫХ 1,3-БЕНЗОКСАЗИНОВ В СОЕДИНЕНИЯ КСАНТЕНОВОГО ТИПА

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Изучены закономерности перегруппировки новых производных 1,3-бензоксазинов, которые получены конденсацией замещенных салциламидов с циклическими кетонами, под действием Вильсмайера-Хаака. Влияние углового напряжения в 4х членном спироцикле препятствует перегруппировке Spiro[1,3-бензоксазин-2,1'-циклобутан]-4(3*H*)-она под действием формилирующего агента. Производные 1,3-бензоксазинов с размерами циклов от 5-ти до 8-и членных под действием формилирующего агента образуют формилпроизводные ксантенов, в которых скорость реакции зависит от наличия электроотрицательных заместителей в положениях С-6 и С-8 ароматического цикла, а также в спироцикле.

**К л ю ч е в ы е с л о в а:** перегруппировка, реагент Вильсмайєра-Хаака, конденсація, 1,3-бензоксазини, формилпроизводные ксантенов.

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