Synthesis of isobornylphenol-containing 3-aryl-1,2,4-triazin-5(4*H*)-ones*

I. N. Egorov,[a] O. N. Chupakhin,[a,b] M. V. Berezin,[b] G. L. Rusinov,[b] V. L. Rusinov,[a] E. V. Buravlev,[c] I. Yu. Chukicheva,[c] and A. V. Kuchin[c]*

[a] *Ural Federal University named after the First President of Russia B. N. El´tsin, 19 ul. Mira, 620002 Ekaterinburg, Russian Federation. Phone: +7 (343) 375 4501. E-mail: i.n.egorov@gmail.com*

[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Phone: +7 (343) 374 1189. E-mail: chupakhin@ios.uran.ru*

[c] *Institute of Chemistry, Komi Research Center, Ural Branch of the Russian Academy of Sciences, 48 ul. Pervomaiskaya, 167982 Syktyvkar, Komi Republic, Russian Federation. Fax: +7 (821 2) 43 6677. E-mail: chukicheva-iy@chemi.komisc.ru*

A method for modification of 3-aryl-1,2,4-triazin-5(4*H*)-ones with isobornylphenols was proposed. The influence of various acylating agents on the reaction pathway was studied.

Key words: 1,2,4-triazin-5(4*H*)-ones, isobornylphenols, nucleophilic addition, arylation, valine.

Terpenophenols are physiologically active broad-spectrum compounds produced in plant biosynthesis.[1,2] Alkylphenols are well known for their antioxidant[3,4] and antibacterial properties;[5] they also exhibit antiatherosclerosis activity.[6] These compounds have found use in diverse areas: *e.g.*, 2,6-di(*tert*-butyl)-4-methylphenol (ionol) is employed as a stabilizer and an antioxidant in the production of foods, lubricating oils, *etc*.[4] A search for new active compounds among alkylphenols is of great practical interest. Some azine derivatives of borneol and isoborneol are known to exhibit antiviral properties.[7] Modification of terpenophenols with a 1,2,4-triazine fragment is important for further target synthesis of products combining antioxidant and/or antiviral properties.

Previously, we have reported on successful introduction of a number of C-nucleophiles[8,9] (in particular, alkylphenols[10] and crown ethers[10,11]) into the 1,2,4-triazine ring under acylation conditions. For instance, dissolution of 1,2,4-triazin-5(4*H*)-ones in trifluoroacetic or acetic acid results in the formation of triazinium salts, which readily react with 2,6-dimethylphenol and resorcinol at room temperature.[9] This reversible reaction produces C(6)-adducts that are stable only in strongly acidic solutions and detected by ^{1}H NMR spectroscopy (the presence of a resonance signal for the methine proton at the sp^3-hybridized C atom in the spectrum of the reaction mixture). Any attempts to isolate these adducts in the individual state result in their quantitative decomposition into the starting reagents. Acylation provides a possible way of stabilizing such adducts.[9]

In the present work, we studied reactions of 3-aryl-1,2,4-triazin-5(4*H*)-ones **1a,b** with racemic 2-isobornyl-6-methylphenol (**2**) and 2-isobornyl-4-methylphenol (**3**) as C-nucleophiles. We found that compound **2** forms adducts in both pure acid anhydride and its mixture with a carboxylic acid (Scheme 1, Table 1). The reactions gave *N*(1)-acetyl (**4a**, **4c**) and *N*(1)-isobutyroyl derivatives (**4b**) in moderate yields. Reflux of 3-(2-pyridyl)-1,2,4-triazin-5(4*H*)-one **1b** with compound **2** in trifluoroacetic acid—trifluoroacetic anhydride for 1.5 h afforded adduct **4d** containing the trifluoroacetyl residue (see Scheme 1).

X-ray diffraction study of a crystal of compound **4a** isolated from the reaction mixture revealed the presence of two pairs of diastereomers in a ratio of ~1 : 3 (Fig. 1). However, the specific rotation of a solution of compound **4a** is zero, which suggests that each of the diastereomers is a racemate.

Attempted addition of compound **3** as a C-nucleophile to the 1,2,4-triazine ring in acetic anhydride or its mixture with acetic acid failed. In the case of AcOH—Ac_2O, the reaction gave compound **5** in 37% yield *via* the addition of water to the imine fragment followed by N-acylation (Scheme 2). The source of water molecules in this reaction may be acetic acid.

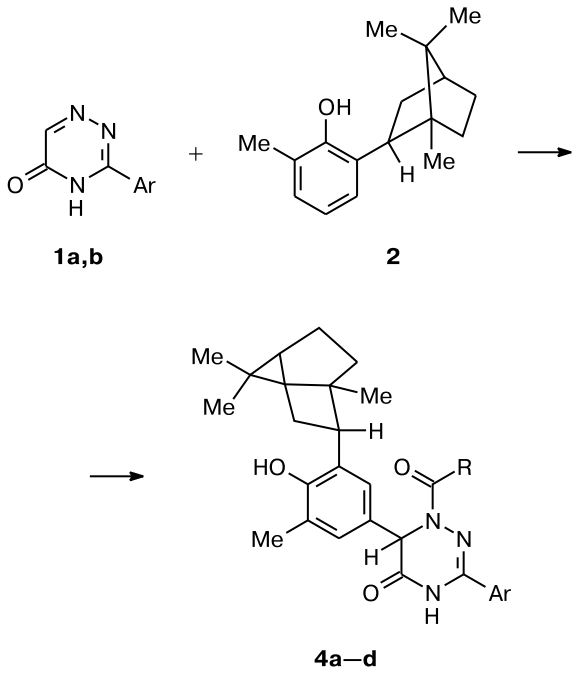
When analyzing possible causes behind the different reactivities of two isomeric isobornylphenols **2** and **3**, we noticed that reflux of compound **5** in acetic acid—acetic anhydride in the presence of 2-isobornyl-6-methylphenol (**2**)

* Dedicated to Academician V. N. Charushin on the occasion of his 60th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 893—897, May, 2011.

1066-5285/11/6005-914

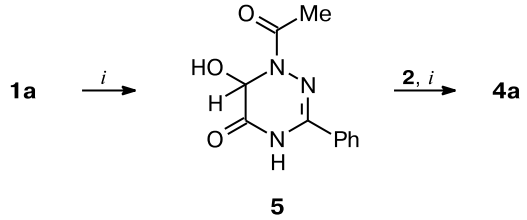
Scheme 1



1: Ar = Ph (**a**), 2-pyridyl (**b**)
4: R = Me, Ar = Ph (**a**); R = $CHMe_2$, Ar = Ph (**b**); R = Me, Ar = 2-pyridyl (**c**); R = CF_3, Ar = 2-pyridyl (**d**)

results in replacement of the OH group at the sp^3-hybridized C atom by the isobornylphenol residue, giving compound **4a** (see Scheme 2). However, a similar reaction

Scheme 2



i. AcOH, Ac_2O, reflux.

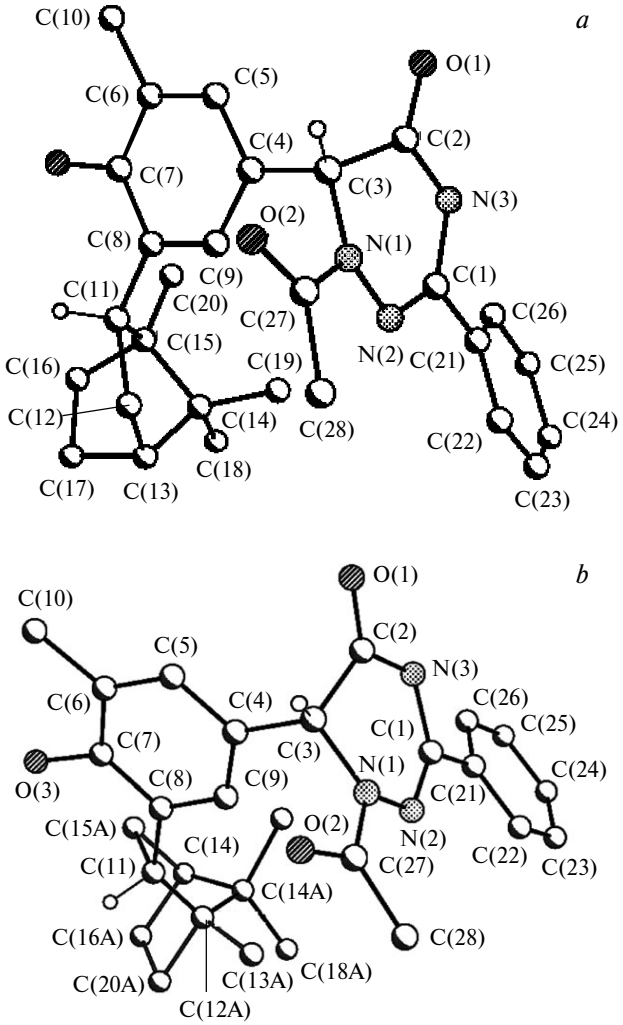


Fig. 1. Crystal structures of the major (*a*) and minor diastereomers (*b*) of compound **4a** (X-ray diffraction data).

with 2-isobornyl-4-methylphenol (**3**) failed. This is evidence that isobornylphenol **2** is a more reactive C-nucleophile than its isomer **3**.

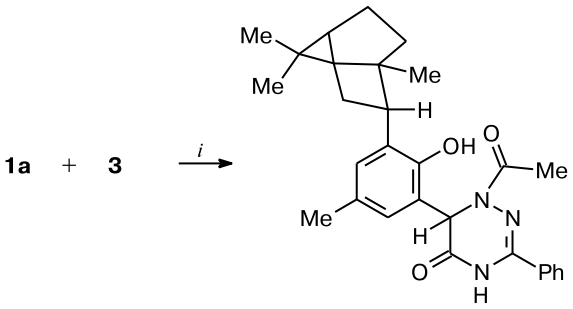
On further optimization of the reaction conditions, we found that a reaction of triazinone **1a** with compound **3**

Table 1. Reaction conditions for the synthesis of compounds **4a—d**

Starting compound	Acylating agent	*T*/°C	Product	Yield (%)
1a	Ac_2O	140	**4a**	32
1a	AcOH, Ac_2O	Reflux	**4a**	30
1a	CF_3COOH, Ac_2O, CH_2Cl_2	25	**4a**	27
1a	$(Me_2CHCO)_2O$	100	**4b**	8
1b	CF_3COOH, Ac_2O	Reflux	**4c**	45
1b	CF_3COOH, Ac_2O	25	**4c**	30
1b	AcOH, Ac_2O	Reflux	**4c**	55
1b	CF_3COOH, $(CF_3CO)_2O$	Reflux	**4d**	85

in CH_2Cl_2 in the presence of trifluoroacetic acid—acetic anhydride affords compound **6** as a sole product (Scheme 3).

Scheme 3



i. CF_3COOH, Ac_2O, CH_2Cl_2

We also studied the possibility of a diastereoselective synthesis similar to documented[12] reactions of compound **1a** with indoles. For this purpose, we used *N*-Ts-L-valine acid chloride **7** instead of acetic anhydride as an acylating agent. However, in contrast to the earlier employed indoles, phenols **2** and **8a,b** proved to be inert under these conditions and the reaction gave compounds **9a,b** in low yields (14—16%; Scheme 4), following much the same pattern as described for compound **5** (see Scheme 2). In this case, the water source is incompletely dehydrated THF. The ^{1}H NMR spectra of compounds **9a,b** show one set of signals, which is indicative of the formation of only one of two possible diastereomers. It should be noted that compound **1a** reacts with acid chloride **7** alone (without phenols) to give compound **9b** in 13% yield.

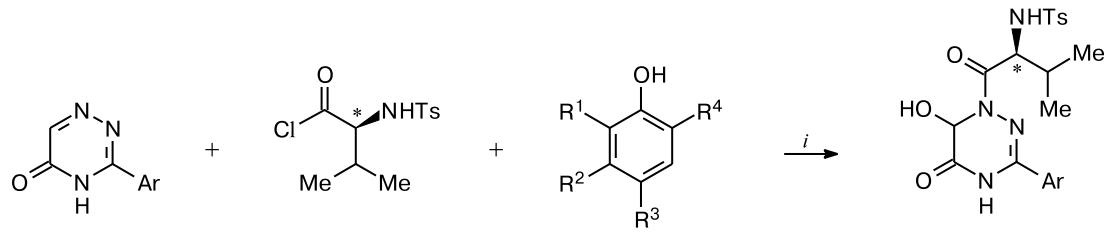
To sum up, we demonstrated the fundamental possibility of modifying isobornylphenols with azines. The next steps will include reactions of enantiomerically pure isobornylphenols and testing of the products for antioxidant properties.

Experimental

The starting compounds 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1a**), 3-(4-methylphenyl)-1,2,4-triazin-5(4*H*)-one (**1c**) (see Ref. 13), 2-isobornyl-6-methylphenol (**2**), and 2-isobornyl-4-methylphenol (**3**) (see Ref. 14) were prepared according to known procedures. The other starting materials are commercially available. The course of the reaction was monitored, and the purity of the products was checked, by TLC on Merck Silica Gel 60 F_{254} plates; spots were visualized under UV light. Column chromatography was carried out on Silica Gel 60 (Merck). ^{1}H NMR spectra were recorded on a Bruker DRX-400 instrument. Melting points were determined on a Boetius instrument. Specific rotation was measured on a Perkin—Elmer 341 polarimeter. An X-ray diffraction study of compound **4a** was carried out on an Oxford Diffraction Xcalibur S CCD diffractometer with the CrysAlisPro software.[15] The structure was solved by direct methods with the SHELXS-97 program and refined by the full-matrix least-squares method on F^2 with the SHELXL-97 program.[16] Selected crystallographic parameters and the data collection and refinement statistics are summarized in Table 2. The atomic coordinates and the comprehensive X-ray diffraction data have been deposited with the Cambridge Crystallographic Data Center (CCDC 763851) and available on www.ccdc.cam.ac.uk/data_request/cif.

3-(2-Pyridyl)-1,2,4-triazin-5(4*H*)-one (1b). Hydrazine hydrate (15 mL, 0.3 mol) was added to a solution of 2-cyanopyridine (5.2 g, 0.05 mol) in methanol (9 mL). The reaction mixture was stirred at room temperature for 2 h and diluted with an equal amount of water. The product was extracted with diethyl ether (8×20 mL). The combined organic extracts were dried with $CaCl_2$ and concentrated to a colorless precipitate. The yield of pyridine-2-carboxamidrazone was 1.5 g (22%). In subsequent experiments, this compound was used without further purification. Pyridine-2-carboxamidrazone (1.5 g, 0.011 mol) was dissolved in ethanol (50 mL). Then glyoxylic acid monohydrate (1.2 g, 0.013 mol) in cooled ethanol (10 mL) was added at −20 °C. The reaction mixture was kept at this temperature for 18 h and con-

Scheme 4



1a,c **7** **2, 8a,b** **9a,b**

i. $AlCl_3$, THF, 0 °C.

Ar = Ph (**1a**, **9a**), 4-MePh (**1c**, **9b**)
2: R^1 = Me, R^2 = R^3 = H, R^4 = isobornyl
8: R^1 = R^2 = R^3 = R^4 = H (**a**); R^1 = R^4 = H, R^2 = R^3 = Me (**b**)

Table 2. Crystallographic parameters and the data collection and refinement statistics for structure **4a**

Parameter	Value
Molecular formula	$C_{28}H_{33}N_3O_3$
Molecular mass	459.57
Crystal system	Triclinic
Space group	*P*-1
a/Å	10.6821(17)
b/Å	10.697(2)
c/Å	11.225(3)
α/deg	74.656(18)
β/deg	89.429(16)
γ/deg	88.641(14)
V/Å^3	1236.5(4)
Z	2
d_{calc}/g cm^{-3}	1.234
μ/mm^{-1}	0.081
F(000)	492
Crystal dimensions/mm	0.34×0.29×0.21
θ/deg	2.72—26.42
Number of measured reflections	11970
Number of independent reflections	5008
R_{int}	0.0381
Number of reflections with $I > 2\sigma(I)$	1894
R_1 ($I > 2\sigma(I)$)	0.0503
wR_2 ($I > 2\sigma(I)$)	0.1208
Residual electron density (ρ_{min}/ρ_{max})/e Å^{-3}	−0.173/0.165

centrated. The resulting oily residue was dissolved in DMF (7 mL) and refluxed for 1 h. The precipitate that formed was crystallized from ethanol. The yield was 86%, gray crystalline powder, m.p. 244 °C. ^{1}H NMR (DMSO-d$_6$), δ: 14.37 (br.s, 1 H, NH); 8.80—8.82 (m, 1 H, C(6)H); 8.30—8.32 (m, 1 H, Py); 8.12—8.13 (m, 1 H, Py); 8.10—8.11 (m, 1 H, Py); 7.73—7.75 (m, 1 H, Py). Found (%): C, 55.10; H, 3.38; N, 31.95. $C_8H_6N_4O$. Calculated (%): C, 55.17; H, 3.47; N, 32.17.

1-Acetyl-6-[4-hydroxy-3-methyl-5-(1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl)phenyl]-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (4a). ***A.*** Acetic anhydride (3 mL) was added to triazinone **1a** (1.2 mmol) and phenol **2** (1.2 mmol). The reaction mixture was refluxed for 1 h and kept at room temperature for 24 h. The resulting colorless crystals were filtered off and washed with a small amount of acetic anhydride and diethyl ether. The yield was 32%, m.p. > 260 °C, R_f 0.8 (ethyl acetate), $[\alpha]_D^{20}$ 0 (*c* 1.0, DMF). ^{1}H NMR (DMSO-d$_6$), δ: 11.44 (s, 1 H, OH); 7.95 (s, 1 H, NH); 7.84—7.89 (m, 2 H, Ph); 7.38—7.47 (m, 3 H, Ph); 6.88—6.90 (m, 1 H); 6.76—6.78 (m, 1 H); 5.89 (s, 1 H, C(6)H); 3.15—3.20 (m, 1 H, CH); 2.34—2.35 (m, 3 H); 2.15 (s, 3 H); 1.68—1.88 (m, 3 H); 1.43—1.52 (m, 3 H); 1.23—1.30 (m, 1 H); 0.72—0.75 (m, 3 H); 0.62—0.68 (m, 6 H). Found (%): C, 73.34; H, 7.52; N, 9.35. $C_{28}H_{33}N_3O_3$. Calculated (%): C, 73.18; H, 7.24; N, 9.14.

B. Acetic acid (3 mL) and acetic anhydride (1 mL) were added to triazinone **1a** (1.2 mmol) and phenol **2** (1.2 mmol). The reaction mixture was refluxed for 1 h and kept at room temperature for 24 h. The resulting colorless crystals were filtered off and washed with acetic acid and diethyl ether. The yield was 30%.

C. A solution of compound **5** (150 mg, 0.64 mmol) (see below) in a mixture of acetic acid (3 mL) and acetic anhydride (1 mL) was refluxed for 2 h. The solution was concentrated and the residue was chromatographed on silica gel with ethyl acetate as an eluent. The yield was 25%. The crystals obtained were examined by X-ray diffraction.

D. Trifluoroacetic acid (0.1 mL) and acetic anhydride (0.5 mL) were added to a suspension of triazinone **1a** (1.2 mmol) and phenol **2** (1.2 mmol) in CH_2Cl_2 (8 mL). The resulting solution was stirred at room temperature for 24 h. The precipitate that formed was filtered off and washed with CH_2Cl_2. The yield was 27%.

6-[4-Hydroxy-3-methyl-5-(1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)phenyl]-1-isobutyroyl-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (4b). Isobutyric anhydride (2 mL) was added to triazinone **1a** (1.2 mmol) and phenol **2** (1.2 mmol). The reaction mixture was stirred at 100 °C for 3 h and kept at room temperature for 24 h. The colorless crystals that formed were filtered off and washed with diethyl ether. The product was chromatographed on silica gel with ethyl acetate as an eluent. The yield was 8%, m.p. > 260 °C, R_f 0.8 (ethyl acetate). ^{1}H NMR (DMSO-d$_6$), δ: 11.41—11.43 (m, 1 H, OH); 7.93 (s, 1 H, NH); 7.84—7.88 (m, 2 H, Ph); 7.40—7.43 (m, 3 H, Ph); 6.87—6.91 (m, 1 H); 6.75—6.76 (m, 1 H); 6.87—6.88 (m, 1 H, C(6)H); 3.54—3.64 (m, 1 H, CH); 3.15—3.20 (m, 1 H); 2.14—2.15 (m, 3 H); 1.85—1.90 (m, 1 H); 1.68—1.78 (m, 2 H); 1.39—1.52 (m, 3 H); 1.22—1.31 (m, 1 H); 1.12—1.17 (m, 6 H); 0.55—0.74 (m, 8 H). Found (%): C, 73.72; H, 7.32; N, 8.67. $C_{30}H_{37}N_3O_3$. Calculated (%): C, 73.89; H, 7.65; N, 8.62.

1-Acetyl-6-[4-hydroxy-3-methyl-5-(1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl)phenyl]-3-(2-pyridyl)-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (4c). ***A.*** Triazinone **1b** (0.574 mmol) and phenol **2** (0.631 mmol) were refluxed in a mixture of AcOH (1 mL) and Ac_2O (1 mL) for 1.5 h. The solvents were removed and the oily residue was triturated with a small amount of water. The resulting colorless powder was crystallized from methanol. The yield was 55%, m.p. 239—241 °C. ^{1}H NMR (DMSO-d$_6$), δ: 11.16 (s, 1 H, OH); 8.66 (s, 1 H, NH); 8.21—8.22 (m, 1 H, Py); 8.11—8.14 (m, 1 H, Py); 7.96—8.00 (m, 1 H, Py); 7.58 (s, 1 H, Py); 6.83—6.89 (m, 2 H, Ph); 5.91 (s, 1 H, C(6)H); 2.35 (s, 3 H, MeCO); 2.22 (s, 3 H, Me); 1.90—1.91 (m, 3 H); 1.09—1.11 (m, 3 H); 1.07—1.08 (m, 1 H); 0.69 (s, 3 H); 0.57 (s, 3 H); 0.54 (s, 3 H). Found (%): C, 70.33; H, 7.00; N, 12.01. $C_{27}H_{32}N_4O_3$. Calculated (%): C, 70.41; H, 7.00; N, 12.16.

B. Triazinone **1b** (0.287 mmol) and phenol **2** (0.319 mmol) were refluxed in a mixture of CF_3COOH (1 mL) and Ac_2O (1 mL) for 1.5 h. The solvents were removed and the oily residue was triturated with a small amount of water. The resulting colorless powder was crystallized from methanol. The yield was 45%.

C. Triazinone **1b** (0.287 mmol) and phenol **2** (0.319 mmol) were stirred in CF_3COOH (1 mL) at room temperature for 12 h. Then Ac_2O (1 mL) was added and stirring was continued for an additional 12 h. The solvents were removed and the oily residue was triturated with a small amount of water. The resulting colorless powder was crystallized from methanol. The yield was 30%.

6-[4-Hydroxy-3-methyl-5-(1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)phenyl]-3-(2-pyridyl)-1-trifluoroacetyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (4d). Triazinone **1b** (0.287 mmol) and phenol **2** (0.319 mmol) were refluxed in a mixture of CF_3COOH (1 mL) and trifluoroacetic anhydride (1 mL) for 1.5 h. The solvents were removed and the oily residue was triturated with a small amount of water. The resulting colorless powder was

crystallized from methanol. The yield was 85%, m.p. 189—191 °C. ^{1}H NMR (DMSO-d_6), δ: 11.50 (br.s, 1 H, OH); 8.70—8.71 (m, 1 H, NH); 8.36—8.37 (m, 1 H, Py); 8.02—8.07 (m, 2 H, Py); 7.62—7.64 (m, 1 H, Py); 6.93—6.94 (m, 2 H, Ph); 5.80 (s, 1 H, C(6)H); 3.17—3.33 (m, 1 H); 2.16 (s, 3 H, Me); 1.65—1.73 (m, 3 H); 1.49.—1.52 (m, 3 H); 1.40—1.47 (m, 1 H); 0.71 (s, 1 H); 0.66 (s, 2 H); 0.63 (s, 2 H); 0.59 (s, 1 H); 0.57 (s, 2 H); 0.50 (s, 1 H). Found (%): C, 63.21; H, 5.74; N, 10.68; F, 10.55. $C_{28}H_{33}N_4O_3F_3$. Calculated (%): C, 63.38; H, 6.27; N, 10.56; F, 10.74.

1-Acetyl-6-hydroxy-3-phenyl-1,6-dihydro-4*H*-[1,2,4]triazin-5-one (5). Acetic acid (3 mL) and acetic anhydride (1 mL) were added to 3-phenyl-1,2,4-triazin-5-one (**1a**) (1.2 mmol). The reaction mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate—chloroform (1 : 1) as an eluent. The yield was 42%, colorless crystalline powder, m.p. 195 °C, R_f 0.4 (AcOEt—$CHCl_3$, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 11.44 (s, 1 H, NH); 7.89—7.91 (m, 2 H, Ph); 7.41—7.46 (m, 3 H, Ph); 7.20 (d, 1 H, OH, J = 6.3 Hz); 5.92 (d, 1 H, C(6)H, J = 6.3 Hz); 2.36 (s, 3 H, MeCO). Found (%): C, 56.61; H, 4.72; N, 18.04. $C_{11}H_{11}N_3O_3$. Calculated (%): C, 56.65; H, 4.75; N, 18.02.

1-Acetyl-6-[2-hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl)phenyl]-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (6). Trifluoroacetic acid (0.1 mL) and acetic anhydride (0.5 mL) were added to a suspension of triazinone **1a** (1.2 mmol) and phenol **3** (1.2 mmol) in CH_2Cl_2 (8 mL). The resulting solution was stirred at room temperature for 24 h. The precipitate that formed was filtered off. The yield was 24%, colorless crystalline powder, m.p. > 260 °C, R_f 0.8 (AcOEt). ^{1}H NMR (DMSO-d_6), δ: 11.92—11.95 (m, 1 H, OH); 8.76—8.79 (m, 1 H, NH); 7.93—7.96 (m, 2 H, Ph); 7.45—7.51 (m, 3 H, Ph); 6.98 (s, 1 H); 6.42 (s, 1 H); 6.10—6.11 (m, 1 H, C(6)H); 3.27—3.33 (m, 1 H, CH); 2.38—2.39 (m, 3 H); 2.06—2.14 (m, 4 H); 1.79—1.85 (m, 2 H); 1.47—1.55 (m, 3 H); 1.29—1.36 (m, 1 H); 0.81—0.83 (m, 6 H); 0.70—0.73 (m, 3 H). Found (%): C, 73.12; H, 7.28; N, 9.09. $C_{28}H_{33}N_3O_3$. Calculated (%): C, 73.18; H, 7.24; N, 9.14.

Triazine derivatives of valine (9). Aluminum trichloride (0.01 mmol) and *N*-Ts-L-valine acid chloride **7** (1.2 mmol) were added at −5 to 0 °C to THF (3 mL). The solution was stirred for 5 min. Then triazinone **1** (1.2 mmol) and, after 5 min, an appropriate phenol **8a**,**b** or **2** (1.2 mmol) were added. The reaction mixture was stirred at 0—5 °C for 1 h and then at room temperature for 1 h and poured into cooled water (50 mL). The product was extracted with ethyl acetate (2×30 mL). The combined extracts were dried with Na_2SO_4, concentrated on a rotary evaporator, and chromatographed on silica gel with ethyl acetate as an eluent.

6-Hydroxy-1-(3-methyl-2(*S*)-tosylaminobutanoyl)-3-phenyl-5,6-dihydro-1,2,4-triazin-5(4*H*)-one (9a). Colorless crystalline powder, m.p. 229—230 °C, R_f 0.8 (ethyl acetate), $[\alpha]_D^{20}$ −29.7 (*c* 1.0, DMF). ^{1}H NMR (DMSO-d_6), δ: 11.32 (s, 1 H, NH); 7.87—7.89 (m, 2 H, Ph); 7.64 (d, 1 H, NH, J = 10.4 Hz); 7.45 (d, 2 H, Ts, J = 8.2 Hz); 7.48—7.51 (m, 3 H, Ph); 7.14 (d, 1 H, OH, J = 6.9 Hz); 7.05 (d, 2 H, Ts, J = 8.2 Hz); 5.38 (d, 1 H, C(6)H, J = 6.8 Hz); 4.66 (dd, 1 H, CH, J_1 = 7.7 Hz, J_2 = 10.4 Hz); 2.32 (s, 3 H, Me); 1.99—2.07 (m, 3 H, CH); 1.01 (d, 3 H, Me, J = 6.8 Hz); 0.93 (d, 1 H, Me, J = 6.8 Hz). Found (%): C, 56.88; H, 5.63; N, 12.40. $C_{21}H_{24}N_4O_5S$. Calculated (%): C, 56.74; H, 5.44; N, 12.60.

6-Hydroxy-3-(4-methylphenyl)-1-(3-methyl-2(*S*)-tosylaminobutanoyl)-5,6-dihydro-1,2,4-triazin-5(4*H*)-one (9b). Colorless crystalline powder, m.p. 225 °C, R_f 0.8 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 11.28 (s, 1 H, NH); 7.77 (d, 1 H, 4-MeC_6H_4, J = 8.2 Hz); 7.43 (d, 2 H, 4-MeC_6H_4, J = 8.2 Hz); 7.31 (d, 2 H, Ts, J = 8.1 Hz); 7.16 (d, 1 H, OH, J = 6.8 Hz); 7.04 (d, 2 H, Ts, J = 8.1 Hz); 5.35 (d, 1 H, C(6)H, J = 6.8 Hz); 4.65 (dd, 1 H, CH, J_1 = 7.8 Hz, J_2 = 10.4 Hz); 2.43 (s, 3 H, Me); 2.33 (s, 3 H, Me); 2.02 (m, 1 H, CH); 1.01 (d, 3 H, Me, J = 6.7 Hz); 0.92 (d, 3 H, Me, J = 6.7 Hz). Found (%): C, 57.80; H, 5.90; N, 11.97. $C_{22}H_{26}N_4O_5S$. Calculated (%): C, 57.63; H, 5.72; N, 12.22.

This work was financially supported by the Council on Grants at the President of the Russian Federation (State Support Program for Leading Scientific Schools of the Russian Federation, Grant NSh-65261.2010.3) and the Ministry of Education and Science of the Russian Federation (State Contract No. 02.740.11.0260).

References

1. E. V. Kuzakov, E. N. Shmidt, *Khim. Prir. Soedin.*, 2000, 198 [*Chem. Nat. Compd.* (*Engl. Transl.*), 2000, **36**, 245].
2. A. A. Semenov, *Ocherk khimii prirodnykh soedinenii* [*Essay on the Chemistry of Naturally Occurring Compounds*], Nauka, Novosibirsk, 2000, 664 pp. (in Russian).
3. V. V. Plemenkov, *Vvedenie v khimiyu prirodnykh soedinenii* [*Introduction to the Chemistry of Naturally Occurring Compounds*], Kazan, 2001, 376 pp. (in Russian).
4. V. V. Ershov, G. A. Nikiforov, A. A. Volod´kin, *Prostranstvenno-zatrudnennye fenoly* [*Sterically Hindered Phenols*], Khimiya, Moscow, 1972, 352 pp. (in Russian).
5. Z. M. Petrykina, A. N. Polin, I. S. Belostotskaya, N. L. Komissarova, V. B. Vol´eva, L. G. Plekhanova, V. V. Ershov, *Antibiot. Khimioter.* [*Antibiotics and Chemotherapy*], 1998, **43**, No. 8, 11 (in Russian).
6. P. K. Witting, B. J. Wu, M. Raftery, P. Southwell-Keely, R. Stocker, *J. Biol. Chem.*, 2005, **280**, 15612.
7. US Pat. 5 166 348A; *Chem. Abstr.*, 1993, **115**, 183354.
8. V. L. Rusinov, G. V. Zyryanov, T. L. Pilitcheva, O. N. Chupakhin, H. Neunhoeffer, *J. Heterocycl. Chem.*, 1997, **34**, 1013.
9. O. N. Chupakhin, G. L. Rusinov, D. G. Beresnev, H. Neunhoeffer, *J. Heterocycl. Chem.*, 1997, **34**, 573.
10. G. L. Rusinov, D. G. Beresnev, N. A. Itsikson, O. N. Chupakhin, *Heterocycles*, 2001, **12**, 2349.
11. N. A. Itsikson, D. G. Beresnev, G. L. Rusinov, O. N. Chupakhin, *ARKIVOC*, 2004, **12**, 6.
12. I. N. Egorov, G. V. Zyryanov, E. N. Ulomsky, V. L. Rusinov, O. N. Chupakhin, *Tetrahedron Lett.*, 2006, **47**, 7485.
13. V. Uchutilova, P. Fiedler, M. Prystas, J. Gut, *Collect. Czech. Chem. Commun.*, 1971, **36**, 1955.
14. I. Yu. Chukicheva, A. V. Kuchin, *Ross. Khim. Zh.*, 2004, **48**, 21 [*Mendeleev Chem. J.* (*Engl. Transl.*), 2004, **48**, No. 3].
15. *CrysAlisPro* (*Version 171.31.8*), *CrysAlisRed* (*Version 1.171.31.8*), Oxford Diffraction, Ltd., Abingdon, Oxfordshire, England, 2007.
16. G. M. Sheldrick, *Acta Crystallogr. A: Found. Crystallogr.*, 2008, **64**, 112.

Received October 13, 2010