

Synthesis of 4-Trifluoromethyl-3,4-dihydro-1,3,5-triazino-[2,1-*a*]isoindol-2-ones by Cyclocondensation of 1-Aryl-1-chloro-2,2,2-trifluoroethyl Isocyanates with 3-Amino-1-arylimino-1*H*-isoindoles

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Received November 22, 2005

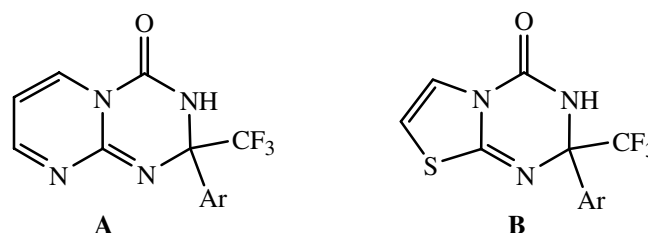
Abstract—4-Trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-ones were prepared by reaction of 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates with 3-amino-1-arylimino-1*H*-isoindoles in the presence of triethylamine. In some events alongside the main product isomeric 2-trifluoromethyl-2,3-dihydro-1,3,5-triazino[2,1-*a*]isoindol-4-ones were obtained. The regioselectivity of the reaction is affected by sterical and electronic characteristics of substituents and by temperature.

DOI: 10.1134/S1070428007020182

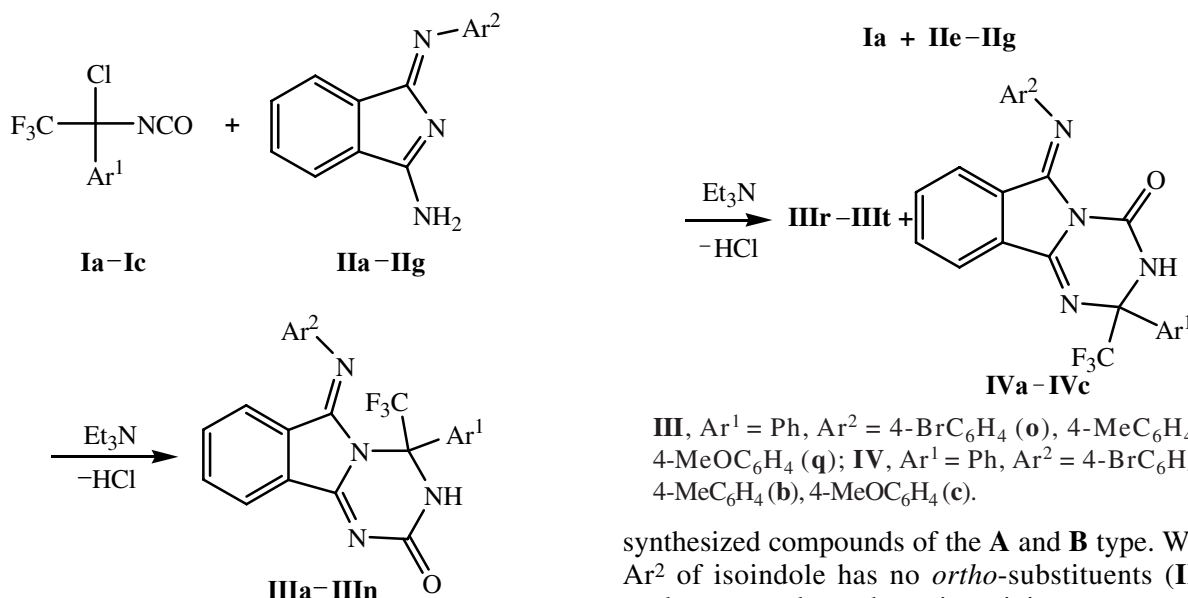
1-Chloroethyl isocyanates are highly reactive bi-electrophilic reagents widely used in syntheses of versatile heterocyclic systems [1, 2]. For instance, their reactions with ambident nucleophiles like ureas [3], amidines [4], and 2-azahetarylamines [5] led to the formation of a series of 1,3,5-triazines derivatives and their pyrido, pyrimido, and triazolo fused analogs. Triazine derivatives, also those containing a CF₃ group, exhibit high biological activity. Among these compounds were found herbicides [6–8], insecticides, fungicides [9, 10], and also compounds with anticonvulsant [11], antiphlogistic, and analgesic action [12].

Derivatives of 3-amino-1*H*-isoindole were established [13–17] to be important initial compounds for the synthesis of fused isoindoles; however, among the latter only some triazinoisoindole derivatives were described [18, 19]. Taking into account the “amidine” character of the aminoisoindole structures their involvement into condensations with 1-chloro-2,2,2-trifluoroethyl isocyanates may constitute a preparatively convenient approach to CF₃-containing triazinoisoindoles, biologically promising substances.

It was shown formerly [5] that 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates **Ia–Ic** reacted with 2-amino-pyridine and 2-aminothiazole via alkylating the exocyclic nitrogen and acylating endocyclic nitrogen providing derivatives of 3,4-dihydropyrido[1,2-*a*]-1,3,5-triazin-4-ones **A** and 3,4-dihydro-1,3,5-triazino[2,1-*b*]thiazol-4-ones **B**.

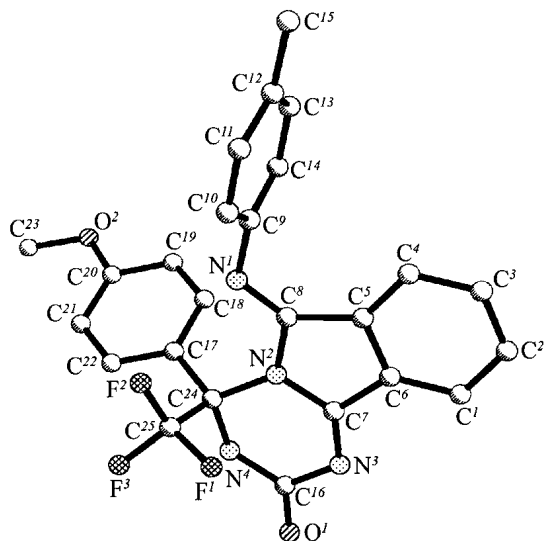


We investigated the reaction of isocyanates **Ia–Ic** with a series of 3-amino-1-arylimino-1*H*-isoindoles **IIa–IIg** that contained substituents Ar² with different sterical parameters. We established that isocyanates **Ia–Ic** notwithstanding the character of substituent Ar¹ reacted with *ortho*-substituted 3-amino-1-arylimino-1*H*-isoindoles **IIa–IId** in toluene at room temperature in the presence



I, Ar¹ = Ph (**a**), 4-MeC₆H₄ (**b**), 4-MeOC₆H₄ (**c**); **II**, Ar² = 2-MeC₆H₄ (**a**), 2-MeOC₆H₄ (**b**), 2,4-Me₂C₆H₃ (**c**), 2,6-Me₂C₆H₃ (**d**), 4-BrC₆H₄ (**e**), 4-MeC₆H₄ (**f**), 4-MeOC₆H₄ (**g**); **III**, Ar¹ = Ph, Ar² = 2-MeC₆H₄ (**a**), 2-MeOC₆H₄ (**b**), 2,4-Me₂C₆H₃ (**c**), 2,6-Me₂C₆H₃ (**d**); Ar¹ = 4-MeC₆H₄, Ar² = 2,4-Me₂C₆H₃ (**e**), 4-BrC₆H₄ (**f**), 4-MeC₆H₄ (**g**), Ar¹ = 4-MeOC₆H₄, Ar² = 2-MeC₆H₄ (**h**), 2-MeOC₆H₄ (**i**), 2,4-Me₂C₆H₃ (**j**), 2,6-Me₂C₆H₃ (**k**), 4-BrC₆H₄ (**l**), 4-MeC₆H₄ (**m**), 4-MeOC₆H₄ (**n**).

of triethylamine to give a single type of compounds from the series of 4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (**III**). Triazinone fragment in these compounds is structurally isomeric to the previously



General view of a molecule of 6-(4-methylphenyl)imino-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (**IIIIm**).

III, Ar¹ = Ph, Ar² = 4-BrC₆H₄ (**o**), 4-MeC₆H₄ (**p**), 4-MeOC₆H₄ (**q**); **IV**, Ar¹ = Ph, Ar² = 4-BrC₆H₄ (**a**), 4-MeC₆H₄ (**b**), 4-MeOC₆H₄ (**c**).

synthesized compounds of the **A** and **B** type. When the Ar² of isoindole has no *ortho*-substituents (**IIe-IIg**) analogous cyclocondensation giving compounds **III****f**, **III****g**, **III****h-III****n** occurred only with isocyanates with the more pronounced donor substituents in Ar¹ (**Ib** and **Ic**).

The reaction of isocyanate **Ia** with 3-aminoisoindoles **IIe-IIg** under the conditions described above alongside compounds **IIIo-IIIq**, as show ¹⁹F NMR spectra, gave rise also in lesser quantity (12–17%) isomeric 2,6-dihydro--1,3,5-triazino[2,1-*a*]isoindol-4-ones **IVa-IVc** that we failed to separate by recrystallization.

We demonstrated by an example of reaction between isocyanate **Ia** and 3-aminoisoindole **IIIf** that the ratio of regioisomers **IIIp** and **IVb** depended on the reaction conditions, in particular, on the temperature. The reaction carried out in toluene at 60–65°C gave predominantly isomer **IIIp** (97%). Raising temperature further we obtained more complex mixture of reaction products as showed the ¹⁹F NMR spectra. In ethyl ether at –78°C the relative amount of compound **IIIp** decreased, and compounds **IIIp** and **IVb** formed in a ratio 0.6:0.4. Regioisomers **IIIp** and **IVb** were successfully separated by column chromatography.

The unambiguous assignment of the structure of isomeric compounds was based on the X-ray diffraction analysis of a single crystal of compound **IIIIm**.

It was established that the repulsion between tolyl substituent and isoindole moiety {shortened intramolecular contacts C⁴...C⁹ 3.15 Å (sum of van der Waals radii 3.42 Å[20]), H⁴...C⁹ 2.67 Å(2.87 Å), and C¹⁴...H⁴ 2.68 Å(2.87 Å)} resulted in some twisting of the double bond N¹=C⁸ [torsion angle C⁹N¹C⁸C⁵ 4.5(4)°]. The tolyl substituent is located virtually normal to the plane of the isoindole fragment [torsion angle C¹⁰C⁹N¹C⁸ 106.1(3)°]

and has *E*-orientation. Triazine ring is present in a *sofa* conformation (folding parameters [21] S 0.29, θ 46.6°, ψ 14.0°). Deviation of C²⁴ from the least-mean square plane of the other atoms in the ring amounts to 0.27 Å. The trifluoromethyl substituent at C²⁴ is axially oriented [torsion angle C²⁵C²⁴N²C⁷ 96.2(2)°] and is so located that F¹ atom is in the +*sc* position with respect to N²–C²⁴ bond [torsion angle F¹C²⁵C²⁴N² 47.3(2)°]. This orientation of the trifluoromethyl substituent results in appearance of shortened intramolecular contacts F²...N¹ 2.79 Å (2.90 Å), F¹...C⁷ 3.01 Å (3.11 Å), F³...C²² 2.94 Å (3.11 Å), and F³...H²² 2.30 Å (2.56 Å). Anisyl substituent at C²⁴ atom is oriented equatorially [torsion angle C¹⁷C²⁴N²C⁷ 138.1(2)°] and is somewhat turned with respect to N²–C²⁴ bond [torsion angle C¹⁸C¹⁷C²⁴N² 15.9(3)°]. Methoxy group is coplanar with the benzene ring C¹⁷...C²² [torsion angle C²³O²C²⁰C²¹ 2.3(4)°] notwithstanding the shortened intramolecular contacts C²¹...H^{23C} 2.74 Å (2.87 Å), C²¹...H^{23B} 2.76 Å (2.87 Å). In the crystal the molecules form centrosymmetrical dimers owing to intermolecular hydrogen bond N⁴–H^{4N}...O¹ (H...O 1.99 Å, N–H...O 168.8°).

We developed a simple and at the same time reliable method of structural identification of the compounds synthesized by means of ¹⁹F NMR spectroscopy based on the structure of compound **III***m* established by X-ray diffraction analysis. Thus compounds of **III** type are characterized by the chemical shift of CF₃ group equal to –74 ppm [22], and in the alternative structures of **IV** type the chemical shift of the corresponding signal is –80 ppm in keeping with the published data for previously obtained fused CF₃-containing 1,3,5-triazin-4-ones **A** and **B** [5].

IR spectra of compounds **III** contain characteristic strong absorption bands of stretching vibrations of C=O groups from the triazinone fragment in the region 1640–1645 cm^{–1}. In contrast, in the IR spectrum of compound **IV***b* the vibrations of the carbonyl group are observed at higher frequencies (1740 cm^{–1}) characteristic of the structurally related derivatives of **A**, **B** type [5]. This difference may be attributed to involvement of the carbonyl group in compounds **III** into a conjugation system which results in the shift of the absorption bands to lower frequencies [23]. The vibrations of NH groups of compounds under study appear as two wide absorption bands in the region 3085–3220 cm^{–1} (isomers **III**) and 3165–3260 cm^{–1} (isomers **IV**) indicating associates formation through intermolecular hydrogen bonds between the amide moieties of the molecules; these

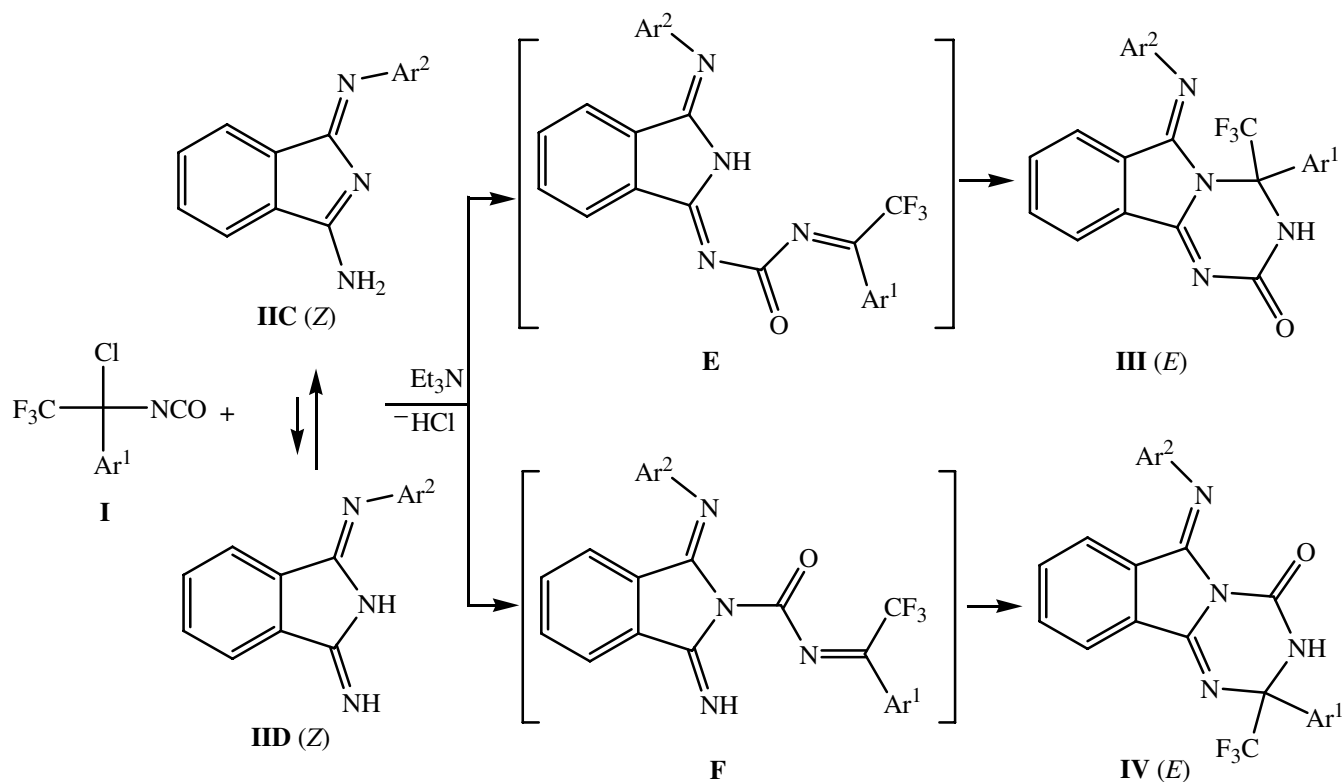
findings are consistent with the X-ray crystallography of compound **III***m*.

As shown by the X-ray crystallography of compound **III***m* the Ar² substituent has *E*-orientation with respect to the exocyclic C=N bond unlike the initial 3-amino-1-(4-methylphenyl)imino-1*H*-isoindole (**II***f*) [24]. Analogous pattern was observed in solutions and was reflected in the ¹H NMR spectra. For instance, solutions of compounds **III***a*–**III***n* and **IV***b* in DMSO-*d*₆ give rise in the ¹H NMR spectra to one-proton doublet in the region 6.4–6.7 ppm belonging to the proton at C⁷ atom of the triazinoisoindole fragment. This upfield shift by 2 ppm compared to initial compounds **II***a*–**II***g* can be ascribed to the shielding effect of the ring current in the Ar² substituent that in its turn can occur only at the *E*-orientation of the substituent.

In the ¹H NMR spectra of compounds **III***a*–**III***e*, **III***h*–**III***k* containing an *ortho*-substituent (CH₃, OCH₃) in Ar² a notably broadened singlet is observed corresponding to the protons of methyl or methoxy group; this fact may be ascribed to the hindered rotation of Ar² owing to sterical hindrances from the substituent in the *ortho*-position. The signal from proton H⁶ in Ar² is also considerably broadened.

Introduction of a second *ortho*-substituent into Ar² hindered its rotation with respect to C–N bond to such extent that in the ¹H NMR spectra of compounds **III***d* and **III***k* appeared two narrow singlets from magnetically nonequivalent methyl groups at 1.3 and 1.9 ppm. Therewith one of the methyl groups occurred in the range of shielding by ring currents from the substituent Ar¹ of the triazinone ring resulting in the upfield shift of this methyl protons by 0.6 ppm compared with the signal from the second methyl group. The magnitude of the diamagnetic shift is in agreement with that calculated by procedure [25].

Taking into account the ambident character of 3-aminoisoindoles **II**, the possible tautomeric equilibrium between amino-imino **II***C* and diimino form **II***D* [24], and also published data [26] on acylation of 2-azahetarylamines the scheme of their reaction with 1-chloroethyl isocyanates **I** may be represented as follows. For compounds **II***a*–**II***d* the most probable primary pathway of reaction independent of the nature of isocyanate **Ia**–**Ic** is the carbamoylation of the exocyclic nitrogen followed by HCl elimination giving intermediates **E**. The alternative carbamoylation of the endocyclic nitrogen by isocyanates **I** that should lead to the formation of intermediates **F** is prevented by the sterical effect of the *ortho*-substituted phenylimino group. Isocyanates **Ib** and **Ic** due to electro-



philicity decreased by the effect of substituent Ar^1 in reaction with less sterically hindered 3-aminoisoindoles **IIe–IIg** also led to carbomoylation of the exocyclic nitrogen. With isocyanate **Ia** possessing enhanced electrophilicity of the heterocumulene group both alternatives of the primary reaction may occur resulting in formation alongside intermediates **E** also intermediates **F** that further undergo cyclization into compounds **IVa–IVc**. The experiments carried out at various temperature suggest that intermediate **E** resulted from the thermodynamical control, and intermediate **F**, from kinetic control.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from KBr pellets. ^1H , ^{13}C , and ^{19}F NMR spectra taken from solutions in $\text{DMSO}-d_6$ were registered on a spectrometer Varian Mercury (400.39, 100.69, 376.71 MHz respectively), internal references TMC (^1H , ^{13}C), C_6F_6 (^{19}F).

Compound **IIIIm** exists in the crystal as a solvate with ethanol. Crystals of compound **IIIIm** triclinic, $\text{C}_{25}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_2 \cdot \text{C}_2\text{H}_5\text{OH}$, at 20°C a 9.975(2), b 10.244(2), c 14.224(3) Å, α 103.12(6), β 101.11(3), γ 112.39(3), V 1244.4(5) Å³, M_r 510.51, Z 2, space group $P\bar{1}$, d_{calc} 1.362 g/cm³, $\mu(\text{MoK}\alpha)$ 0.106 mm⁻¹, $F(000)$ 532. The unit

cell parameters and intensities of 4526 reflections (4270 independent, R_{int} 0.039) were measured on an automatic four-circle diffractometer Siemens P3/PC (MoK α , graphite monochromator, $2\theta/\theta$ -scanning, $2\theta_{\text{max}}$ 50°). The structure was solved by the direct method using software package SHELX97 [27]. The hydrogen atoms positions were revealed from the difference synthesis of the electron density and refined in *rider* model with $U_{\text{iso}} = nU_{\text{eq}}$ of the nonhydrogen atom linked to the given hydrogen ($n = 1.5$ for methyl, 1.2 for the other hydrogen atoms). The ethanol molecule is disordered by two positions with occupancies 59:41% as refined by putting constraints on the length of C–C bonds [1.513(3) Å] and C–O [1.426(3) Å]. The structure was refined with respect to F^2 by the full-matrix least-squares method in anisotropic approximation for nonhydrogen atoms till wR_2 0.135 for 4229 reflections [R_1 0.051 for 2691 reflections with $F > 4\sigma(F)$, S 1.007]. Crystallographic parameters, atomic coordinates, and geometrical parameters of molecules are deposited in Cambridge Structural Database (no. CCDC 287905).

3-Amino-1-arylimino-1*H*-isoindoles were synthesized from phthalonitrile and the corresponding amines along the known method [24]. 1-Chloroalkyl isocyanates were prepared by procedure [28].

4-Aryl-6-arylimino-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-ones IIIa–

III_n. To a dispersion of 3 mmol of 3-amino-1-arylimino-1*H*-isoindole **IIa–IIg** in 10 ml of anhydrous toluene was added 3.6 mmol of triethylamine. Then at stirring was added dropwise a solution of 3 mmol of isocyanate **Ia–Ic** in 5 ml of toluene. The reaction mixture was stirred for 2 h at room temperature. The separated precipitate was filtered off, washed with water to remove triethylamine hydrochloride, and recrystallized from 60% aqueous ethanol.

6-(2-Methylphenyl)imino-4-trifluoromethyl-4-phenyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_a). Yield 89%, mp 180–182°C. IR spectrum, ν , cm^{-1} : 1645 (C=O), 3105, 3220 (N–H). ^1H NMR spectrum, δ , ppm: 1.50 br.s (3H, CH_3), 6.46–6.53 m (2H), 7.01–7.13 m (3H), 7.42–7.50 m (4H), 7.69–7.76 m (3H), 8.09 d (1H, J 7.6 Hz), 9.17 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 17.39 (CH_3), 118.25, 123.71, 124.44, 124.92, 125.33, 126.64, 127.34, 127.95, 128.06, 128.79, 129.79, 131.06, 132.80, 133.68, 134.81, 135.01, 146.29, 147.41, 154.22, 160.50 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.13. Found, %: C 66.22; H 4.11; N 12.83. $\text{C}_{24}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_3 \cdot \text{Bû} \times \text{OCl}_\epsilon\text{-vO}$, %: C 66.36; H 3.94; N 12.90.

6-(2-Methoxyphenyl)imino-4-trifluoromethyl-4-phenyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_b). Yield 79%, mp 230–231°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3100, 3220 (N–H). ^1H NMR spectrum, δ , ppm: 3.52 br.s (3H, OCH_3), 6.39 br.s (1H), 6.70 d (1H, J 7.6 Hz), 6.84 t (1H, J 8 Hz), 6.92 d (1H, J 8.4 Hz), 7.06 t (1H, J 8 Hz), 7.38–7.42 m (3H), 7.50 t (1H, J 7.6 Hz), 7.65 br.s (2H), 7.72 t (1H, J 7.6 Hz), 8.07 d (1H, J 7.6 Hz), 9.11 C (1H, NH). ^{13}C NMR spectrum, δ , ppm: 56.23 (OCH_3), 113.18, 119.91, 121.64, 123.68, 124.27, 125.29, 125.83, 126.60, 127.82, 128.43, 128.62, 129.68, 132.48, 133.60, 134.69, 135.08, 136.37, 148.19, 148.78, 154.23, 160.54 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.17. Found, %: C 63.82; H 4.00; N 12.39. $\text{C}_{24}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_2$. Calculated, %: C 64.00; H 3.80; N 12.44.

6-(2,4-Dimethylphenyl)imino-4-trifluoromethyl-4-phenyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_c). Yield 74%, mp 138–140°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3100, 3205 (N–H). ^1H NMR spectrum, δ , ppm: 1.50 br.s (3H, CH_3), 2.24 s (3H, CH_3), 6.41 br.s (1H), 6.60 d (1H, J 7.6 Hz), 6.93 d (1H, J 8 Hz), 6.98 s (1H), 7.43–7.54 m (3H), 7.59 t (1H, J 7.6 Hz), 7.73–7.78 m (3H), 8.09 d (1H, J 7.6 Hz), 9.27 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 17.38 (CH_3), 20.97 (CH_3), 118.15, 123.72, 124.38, 125.37, 126.63, 126.86, 127.71, 127.91, 128.03, 128.76, 129.75, 131.67, 132.77, 133.60, 133.85, 134.82, 135.02, 143.76, 147.41, 154.24,

160.53 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.17. Found, %: C 67.22; H 4.38; N 12.50. $\text{C}_{25}\text{H}_{19}\text{F}_3\text{N}_4\text{O}$. Calculated, %: C 66.96; H 4.27; N 12.49.

6-(2,6-Dimethylphenyl)imino-4-trifluoromethyl-4-phenyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_d). Yield 94%, mp 225–227°C. IR spectrum, ν , cm^{-1} : 1645 (C=O), 3085, 3215 (N–H). ^1H NMR spectrum, δ , ppm: 1.29 s (3H, CH_3), 1.89 s (3H, CH_3), 6.38 d (1H, J 7.6 Hz), 6.89–7.00 m (3H), 7.41–7.48 m (4H), 7.72–7.76 m (3H), 8.08 d (1H, J 7.6 Hz), 9.18 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 17.68 (CH_3), 17.90 (CH_3), 123.69, 124.28, 124.32, 124.40, 125.17, 126.21, 126.60, 128.15, 128.38, 128.61, 128.75, 128.84, 129.85, 132.32, 133.89, 134.92, 135.46, 145.27, 147.89, 154.19, 160.41 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.17. Found, %: C 66.80; H 4.15; N 12.19. $\text{C}_{25}\text{H}_{19}\text{F}_3\text{N}_4\text{O}$. Calculated, %: C 66.96; H 4.27; N 12.49.

4-(4-Methylphenyl)-6-(2,4-dimethylphenyl)-imino-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_e). Yield 80%, mp 230–231°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3100, 3220 (N–H). ^1H NMR spectrum, δ , ppm: 1.53 br.s (3H, CH_3), 2.28 s (3H, CH_3), 2.37 s (3H, CH_3), 6.36 br.s (1H), 6.60 d (1H, J 7.6 Hz), 6.88 d (1H, J 7.6 Hz), 6.92 C (1H, J 7.6 Hz), 7.20 d (2H, J 8 Hz), 7.47 t (1H, J 7.6 Hz), 7.54 d (2H, J 8 Hz), 7.72 t (1H, J 7.6 Hz), 8.07 d (1H, J 7.6 Hz), 9.07 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 19.73 (CH_3), 20.98 (CH_3), 21.21 (CH_3), 118.16, 123.75, 124.36, 125.36, 126.68, 126.87, 127.72, 127.83, 128.07, 129.21, 131.69, 131.94, 132.75, 133.56, 133.82, 135.00, 139.23, 143.82, 147.45, 154.31, 160.52 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.21. Found, %: C 67.59; H 4.69; N 12.29. $\text{C}_{26}\text{H}_{21}\text{F}_3\text{N}_4\text{O}$. Calculated, %: C 67.52; H 4.58; N 12.11.

6-(4-Bromophenyl)imino-4-(4-methylphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_f). Yield 78%, mp 195–197°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3100, 3215 (N–H). ^1H NMR spectrum, δ , ppm: 2.37 s (3H, CH_3), 6.48 d (2H, J 8.8 Hz), 6.73 d (1H, J 7.6 Hz), 7.19 d (2H, J 8.4 Hz), 7.42 d (2H, J 8.4 Hz), 7.51–7.56 m (3H), 7.75 t (1H, J 7.6 Hz), 8.08 d (1H, J 7.6 Hz), 9.10 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 21.27 (CH_3), 116.94, 121.21, 123.72, 124.54, 125.88, 126.57, 126.64, 127.73, 127.84, 129.16, 129.58, 130.07, 131.44, 131.54, 132.94, 132.97, 133.76, 134.98, 139.21, 146.60, 147.84, 154.16, 160.50 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.45. Found, %: C 55.96; H 3.29; N 11.11. $\text{C}_{24}\text{H}_{16}\text{BrF}_3\text{N}_4\text{O}$. Calculated, %: C 56.16; H 3.14; N 10.91.

4-(4-Methylphenyl)-6-(4-methylphenyl)imino-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-one (IIIg). Yield 82%, mp 158–160°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3095, 3200 (N–H). ^1H NMR spectrum, δ , ppm: 2.32 s (3H, CH_3), 2.38 s (3H, CH_3), 6.42 d (2H, J 8 Hz), 6.69 d (1H, J 7.6 Hz), 7.07 d (2H, J 8 Hz), 7.20 d (2H, J 8 Hz), 7.48 t (1H, J 7.6 Hz), 7.53 d (2H, J 8 Hz), 7.72 t (1H, J 7.6 Hz), 8.07 d (1H, J 7.6 Hz), 9.05 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 21.01 (CH_3), 21.26 (CH_3), 118.78, 123.78, 124.39, 125.81, 126.68, 127.71, 127.87, 129.12, 130.46, 131.77, 132.95, 133.52, 133.84, 134.78, 139.11, 144.95, 147.60, 154.27, 160.61 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.47. Found, %: C 66.99; H 4.35; N 12.22. $\text{C}_{25}\text{H}_{19}\text{F}_3\text{N}_4\text{O}$. Calculated, %: C 66.96; H 4.27; N 12.49.

6-(2-Methylphenyl)imino-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-one (IIIh). Yield 82%, mp 182–183°C. IR spectrum, ν , cm^{-1} : 1645 (C=O), 3100, 3210 (N–H). ^1H NMR spectrum, δ , ppm: 1.52 br.s (3H, CH_3), 3.79 s (3H, OCH_3), 6.45–6.52 m (2H), 6.92 d (2H, J 8.4 Hz), 7.01–7.13 m (3H), 7.46 t (1H, J 7.2 Hz), 7.59 d (2H, J 8.4 Hz), 7.73 t (1H, J 7.2 Hz), 8.07 d (1H, J 7.2 Hz), 9.08 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 17.44 (CH_3), 55.84 (OCH_3), 114.02, 118.25, 123.79, 124.41, 124.88, 125.31, 126.62, 126.71, 126.91, 127.38, 128.12, 129.54, 131.10, 132.78, 133.62, 134.95, 146.42, 147.51, 154.70, 160.30, 160.48 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.42. Found, %: C 64.69; H 4.19; N 11.97. $\text{C}_{25}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_2$. Calculated, %: C 64.65; H 4.12; N 12.06.

4-(4-Methoxyphenyl)-6-(2-methoxyphenyl)-imino-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-one (IIIi). Yield 88%, mp 207–208°C. IR spectrum, ν , cm^{-1} : 1645 (C=O), 3090, 3200 (N–H). ^1H NMR spectrum, δ , ppm: 3.53 br.s (3H, OCH_3), 3.80 s (3H, OCH_3), 6.44 br.s (1H), 6.69 d (1H, J 7.6 Hz), 7.82–7.94 m (4H), 7.05 t (1H, J 8 Hz), 7.49 t (1H, J 7.6 Hz), 7.56 d (2H, J 8.8 Hz), 7.71 t (1H, J 7.6 Hz), 8.05 d (1H, J 7.6 Hz), 9.01 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 55.77 (OCH_3), 56.20 (OCH_3), 113.18, 113.84, 119.88, 121.67, 123.75, 124.24, 125.27, 125.79, 126.55, 126.67, 128.45, 129.43, 132.48, 133.54, 135.02, 136.53, 148.27, 148.81, 154.39, 160.13, 160.49 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.34. Found, %: C 62.59; H 4.17; N 11.60. $\text{C}_{25}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3$. Calculated, %: C 62.50; H 3.99; N 11.66.

6-(2,4-Dimethylphenyl)imino-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-tri-

azino-[2,1-*a*]isoindol-2-one (IIIj). Yield 78%, mp 230–232°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3085, 3205 (N–H). ^1H NMR spectrum, δ , ppm: 1.56 br.s (3H, CH_3), 2.29 s (3H, CH_3), 3.80 s (3H, OCH_3), 6.37 br.s (1H), 6.58 d (1H, J 8.0 Hz), 6.87–6.93 m (4H), 7.47 t (1H, J 7.6 Hz), 7.58 d (2H, J 8.4 Hz), 7.72 t (1H, J 7.6 Hz), 8.06 d (1H, J 7.6 Hz), 9.04 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 17.38 (CH_3), 20.97 (CH_3), 55.83 (OCH_3), 113.99, 118.25, 123.80, 124.34, 125.34, 126.69, 126.79, 127.75, 128.09, 129.49, 131.69, 132.75, 133.54, 133.80, 134.96, 143.89, 147.52, 154.43, 160.27, 160.49 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.47. Found, %: C 65.31; H 4.50; N 11.79. $\text{C}_{26}\text{H}_{21}\text{F}_3\text{N}_4\text{O}_2$. Calculated, %: C 65.27; H 4.42; N 11.71.

6-(2,6-Dimethylphenyl)imino-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino-[2,1-*a*]isoindol-2-one (IIIk). Yield 89%, mp 218–220°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3090, 3200 (N–H). ^1H NMR spectrum, δ , ppm: 1.36 s (3H, CH_3), 1.89 s (3H, CH_3), 3.80 s (3H, OCH_3), 6.37 d (1H, J 7.6 Hz), 6.89–7.01 m (5H), 7.46 t (1H, J 7.6 Hz), 7.63 d (2H, J 8.8 Hz), 7.73 t (1H, J 7.6 Hz), 8.07 d (1H, J 7.6 Hz), 9.10 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 17.71 (CH_3), 17.89 (CH_3), 55.86 (OCH_3), 114.07, 123.76, 124.26, 124.28, 124.35, 125.17, 126.14, 126.69, 128.43, 128.64, 128.75, 129.73, 132.30, 133.83, 135.42, 145.37, 147.94, 154.32, 160.38 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.21. Found, %: C 65.38; H 4.35; N 12.10. $\text{C}_{26}\text{H}_{21}\text{F}_3\text{N}_4\text{O}_2$. Calculated, %: C 65.27; H 4.42; N 11.71.

6-(4-Bromophenyl)imino-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-one (IIIl). Yield 91%, mp 202–203°C. IR spectrum, ν , cm^{-1} : 1645 (C=O), 3100, 3215 (N–H). ^1H NMR spectrum, δ , ppm: 3.81 s (3H, OCH_3), 6.51 d (2H, J 8 Hz), 6.73 d (1H, J 7.6 Hz), 6.90 d (2H, J 8.4 Hz), 7.43 d (2H, J 8 Hz), 7.51–7.58 m (3H), 7.75 t (1H, J 7.6 Hz), 8.08 d (1H, J 7.6 Hz), 9.08 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 55.79 (OCH_3), 113.87, 116.91, 121.21, 123.77, 124.53, 125.88, 126.31, 126.69, 127.85, 129.44, 132.85, 132.98, 133.72, 134.95, 146.68, 147.88, 154.30, 160.15, 160.44 (C=O). ^{19}F NMR spectrum, δ , ppm: –74.46. Found, %: C 54.53; H 3.19; N 10.77. $\text{C}_{24}\text{H}_{16}\text{BrF}_3\text{N}_4\text{O}_2$. Calculated, %: C 54.46; H 3.05; N 10.58.

6-(4-Methylphenyl)imino-4-(4-methoxyphenyl)-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-one (IIIm). Yield 85%, mp 210–212°C. IR spectrum, ν , cm^{-1} : 1640 (C=O), 3080, 3210 (N–H). ^1H NMR spectrum, δ , ppm: 2.33 s (3H, CH_3), 3.81 s (3H, OCH_3), 6.44 d (2H, J 7.6 Hz), 6.68 d (1H, J 7.6 Hz),

6.91 d (2H, *J* 8.4 Hz), 7.08 d (2H, *J* 7.6 Hz), 7.47 t (1H, *J* 7.6 Hz), 7.56 d (2H, *J* 8.4 Hz), 7.71 t (1H, *J* 7.6 Hz), 8.06 d (1H, *J* 7.6 Hz), 9.02 s (1H, NH). ¹³C NMR spectrum, δ , ppm: 21.02 (CH₃), 55.78 (OCH₃), 113.84, 118.77, 123.81, 124.38, 125.81, 126.54, 126.89, 127.88, 129.41, 130.48, 132.95, 133.49, 133.83, 134.76, 145.02, 147.64, 154.40, 160.11, 160.56 (C=O). ¹⁹F NMR spectrum, δ , ppm: -74.43. Found, %: C 64.76; H 4.25; N 12.19. C₂₅H₁₉F₃N₄O₂. Calculated, %: C 64.65; H 4.12; N 12.06.

4-(4-Methoxyphenyl)-6-(4-methoxyphenyl)-imino-4-trifluoromethyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-one (III_n). Yield 79%, mp 223–224°C. IR spectrum, ν , cm⁻¹: 1640 (C=O), 3085, 3215 (N–H). ¹H NMR spectrum, δ , ppm: 7.76 s (3H, OCH₃), 3.80 s (3H, OCH₃), 6.48 d (2H, *J* 8.8 Hz), 6.76 d (1H, *J* 7.6 Hz), 6.83 d (2H, *J* 8.8 Hz), 6.91 d (2H, *J* 8.4 Hz), 7.50 t (1H, *J* 7.6 Hz), 7.56 d (2H, *J* 8.4 Hz), 7.71 t (1H, *J* 7.6 Hz), 8.06 d (1H, *J* 7.6 Hz), 9.14 s (1H, NH). ¹³C NMR spectrum, δ , ppm: 55.76 (OCH₃), 55.78 (OCH₃), 113.82, 115.25, 120.15, 123.81, 124.34, 125.77, 126.64, 126.72, 127.80, 129.41, 132.94, 133.34, 134.80, 140.54, 147.93, 154.45, 156.83, 160.09, 160.60 (C=O). ¹⁹F NMR spectrum, δ , ppm: -74.37. Found, %: C 62.59; H 4.15; N 11.67. C₂₅H₁₉F₃N₄O₃. Calculated, % C 62.50; H 3.99; N 11.66.

6-(4-Methylphenyl)imino-2-trifluoromethyl-2-phenyl-2,3-dihydro-1,3,5-triazino[2,1-*a*]isoindol-4-one (IV_b) was obtained in a mixture with **6-(4-methylphenyl)imino-4-trifluoromethyl-4-phenyl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one (III_p)** by a similar procedure. Yield of isomers mixture 90%. The isomers were separated by column chromatography (silica gel, dichloromethane–acetone, 8:2).

Compound IV_b. mp 262–263°C. IR spectrum, ν , cm⁻¹: 1740 (C=O), 3165, 3260 (N–H). ¹H NMR spectrum, δ , ppm: 2.40 s (3H, CH₃), 6.63 d (1H, *J* 7.6 Hz), 6.78 d (2H, *J* 8.4 Hz), 7.20 d (2H, *J* 8.4 Hz), 7.41–7.55 m (4H), 7.70 t (1H, *J* 7.6 Hz), 7.88 d (2H, *J* 7.6 Hz), 8.12 d (1H, *J* 7.6 Hz), 9.58 s (1H, NH). ¹³C NMR spectrum, δ , ppm: 21.11 (CH₃), 119.02, 123.91, 125.42, 126.13, 127.38, 129.05, 129.32, 130.06, 130.10, 131.81, 133.41, 134.02, 137.84, 146.21, 146.27, 147.57, 152.19 (C=O). ¹⁹F NMR spectrum, δ , ppm: -80.73. Found, %: C 66.57; H 3.90; N 12.77. C₂₄H₁₇F₃N₄O. Calculated, %: C 66.36; H 3.94; N 12.90.

Compound III_p. Mp 262–263°C. IR spectrum, ν , cm⁻¹: 1645 (C=O), 3085, 3190 (N–H). ¹H NMR spectrum, δ , ppm: 2.32 s (3H, CH₃), 6.39 d (2H, *J* 8 Hz), 6.70 d (1H, *J* 7.6 Hz), 7.06 d (2H, *J* 8 Hz), 7.40–7.43 m (3H),

7.48 t (1H, *J* 7.6 Hz), 7.64–7.71 m (2H), 7.73 t (1H, *J* 7.6 Hz), 8.07 d (1H, *J* 7.6 Hz), 9.23 s (1H, NH). ¹³C NMR spectrum, δ , ppm: 21.02 (CH₃), 118.74, 123.68, 124.42, 125.80, 126.67, 127.80, 128.62, 129.73, 130.44, 132.94, 133.55, 133.88, 134.68, 134.81, 144.81, 147.46, 154.25, 160.59 (C=O). ¹⁹F NMR spectrum, δ , ppm: -74.14. Found, %: C 66.49; H 3.81; N 12.92. C₂₄H₁₇F₃N₄O. Calculated, %: C 66.36; H 3.94; N 12.90.

REFERENCES

1. Gorbatenko, V.I. and Samarai, L.I., *Synthesis*, 1980, vol. 2, p. 85.
2. Vovk, M.V. and Bol'but, A.V., *Zh. Org. Farm. Khim.*, 2004, vol. 1, p. 26.
3. Hoover, F.V., Stevenson, H.B., and Rothrock, H.S., *J. Org. Chem.*, 1963, vol. 28, p. 1825.
4. Vovk, M.V. and Tsymbal, I.F., *Khim. Geterotsikl. Soedin.*, 1997, vol. 5, p. 706.
5. Vovk, M.V., Bal'on, Ya.G., Krainikova, L.G., and Samarai, L.I. *Ukr. Khim. Zh.*, 1995, vol. 61, p. 63.
6. Ahrens, H., Dietrich, H., Minn, K., Auler, T., Bieringer, H., Hills, M., Kehne, H., and Menne, H., US Patent 2004157739, 2004; *Chem. Abstr.*, 2004, 141, 152581.
7. Kudis, S., Plath, P., Misslitz, Ul., Menges, M., Witschel, M., Walter, H., and Zagar, C., WO Patent 2001092236, 2001; *Chem. Abstr.*, 2001, vol. 136, 20076.
8. Grossmann, K., Tresch, S., and Plath, P., *J. Biosciences*, 2001, vol. 56, p. 559.
9. Koizumi, K., Yamashita, O., Wakabayashi, K., Tomono, K., and Sasayama, H., WO Patent 970825, 1997; *Chem. Abstr.*, 1997, vol. 127, 95296d.
10. Saito, M., Kubota, M., and Koike, K., WO Patent 9719936, 1997; *Chem. Abstr.*, 1997, vol. 127, 81467y.
11. Kadota, M., Komata, K., and Shirasaka, T., Japan Patent 52083582, 1977; *Chem. Abstr.*, 1978, vol. 88, 89718s.
12. Kadota, M., Umezu, K., Tode, A., Shirasaka, T., and Ozaki, R., Japan Patent 52083581, 1977; *Chem. Abstr.*, 1978, vol. 88, 22985u.
13. Guzzi, U., Omodei-Sale, A., and Galliani, G., German Patent 29432286, 1979; *Chem. Abstr.*, 1980, vol. 93, 186360r.
14. Babichev, F.S., Briks, Yu.L., and Romanov, N.N., *Ukr. Khim. Zh.*, 1981, vol. 47, p. 291.
15. Tytilin, A.K., Lysik, N.A., Demchenko, A.M., and Kovtunencko, V.A., *Khim. Geterotsikl. Soedin.*, 1985, p. 705.
16. Babichev, F.S., Tytilin, A.K., and Kovtunencko, V.A., *Khim. Geterotsikl. Soedin.*, 1980, p. 1693.
17. Gordienko, O.V., Lyubchuk, T.V., Balitskii, Yu.V., and Kornilov, M.Yu., *Khim. Geterotsikl. Soedin.*, 1995, p. 270.
18. Titkov, V., Pletnev, I.D., Torocheshnikova, L.V., and Leina, T.F., DE Patent 1221385, 1966; *Chem. Abstr.*, 1967, vol. 66, 19833.

19. Roth, H. and Schwarz, D., *Arch. Pharm.*, 1973, vol. 306, p. 821.
20. Zefirov, Yu.V. and Zorkii, P.M., *Usp. Khim.*, 1989, vol. 58, p. 713.
21. Zefirov, N.S., Palyulin, V.A., and Dashevskaya, E.E., *J. Phys. Org. Chem.*, 1990, p. 147.
22. Vovk, M.V., Davidyuk, Yu.N., and Chernega, A.N., *Zh. Org. Khim.*, 1992, vol. 28, p. 2042.
23. Bellamy, L.J., *The Infra-red Spectra of Complex Molecules*, London: Methuen, 1958.
24. Spiessens, L. and Anteunis, M., *Bull. Soc. Chim. Belg.*, 1988, vol. 97, p. 431.
25. Johnson, C.E. and Bovey, F.A., *J. Chem. Phys.*, 1958, vol. 29, p. 1012.
26. Mosby, W.L., *Heterocyclic System with Bridgehead Nitrogen Atoms*, New York: Intersci. Publ., 1961, vol. 1, 741 p.
27. Sheldrick, G.M., SHELX97. PC, Version. A, *System of Computer Programs for the Crystal Structure Solution and Refinement*, Rev.2, 1998.
28. Fetyukhin, V.N., Koretskii, A.S., and Gorbatenko, V.I., *Zh. Org. Khim.*, 1977, vol. 13, p. 271.