Synthesis and properties of a new fused heterocyclic system 12*H*-benzo[5,6][1,2,4]triazepino[3,4-*a*]isoindol-5(6*H*)-one

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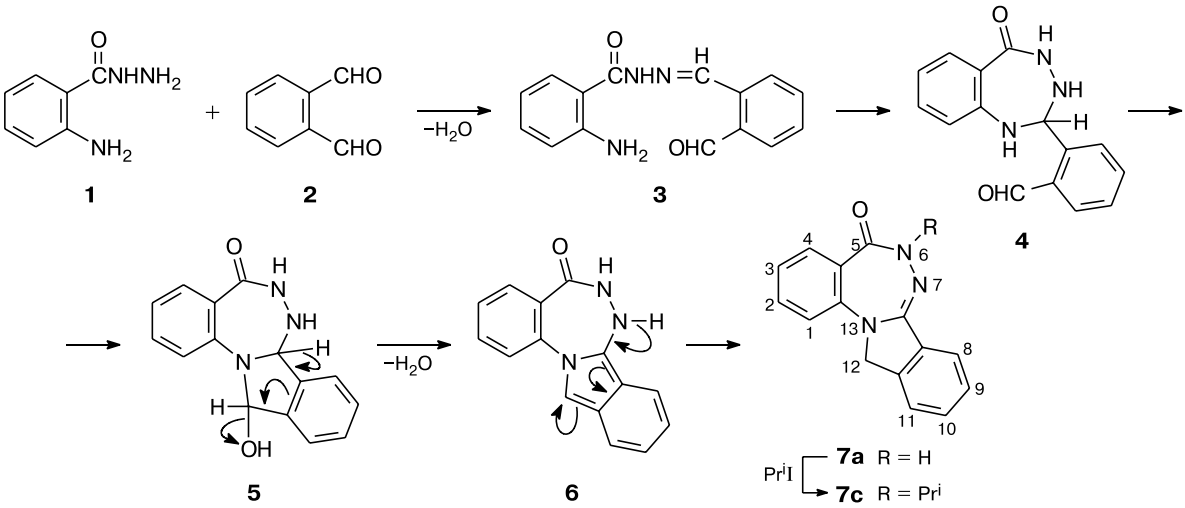
12*H*-Benzo[5,6][1,2,4]triazepino[3,4-*a*]isoindol-5(6*H*)-one was synthesized by the condensation of anthranilic acid hydrazide with *o*-phthalaldehyde. The structure of this compound was established by the X-ray diffraction study of its isopropyl derivative. The mechanism of formation of this compound was suggested and its alkylation reactions were investigated.

Key words: anthranilic acid hydrazide, *o*-phthalaldehyde, 12*H*-benzo[5,6][1,2,4]triazepino[3,4-*a*]isoindol-5(6*H*)-one derivatives.

The reaction of anthranilic acid hydrazide (**1**) with *o*-formylbenzoic acid produces a mixture of two fused heterocyclic systems, 3,4-benzo-1,10-dioxo-1,2,4a,5,10,11-hexahydropyridazino[3,2-*b*]quinazoline and 6-amino-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione.[1] Biological assays showed that the former compound exhibits high analgesic activity.[2] The synthesis of its analogs having high analgesic and antiinflammatory activities was documented.[2—4]

It was of interest to study the reaction of hydrazide **1** with *o*-phthalaldehyde (**2**). To our knowledge, data on this reaction are lacking in the literature. Heating of **1** with aldehyde **2** in Pr^iOH was found to afford a crystalline bright-yellow compound (Scheme 1). The molecular weight of the product is indicative of the condensation of compounds **1** and **2** accompanied by the loss of two water molecules. The ^1H NMR spectrum shows, in addition to signals for aromatic protons, singlets for the NH proton of hydrazide and the protons of the CH_2 group. The X-ray diffraction study demonstrated that the alkylation of this product with isopropyl iodide gave 12*H*-benzo[5,6]-6-isopropyl[1,2,4]triazepino[3,4-*a*]isoindol-5-one (**7c**). The possible mechanism of the reaction is presented in Scheme 1.

Scheme 1



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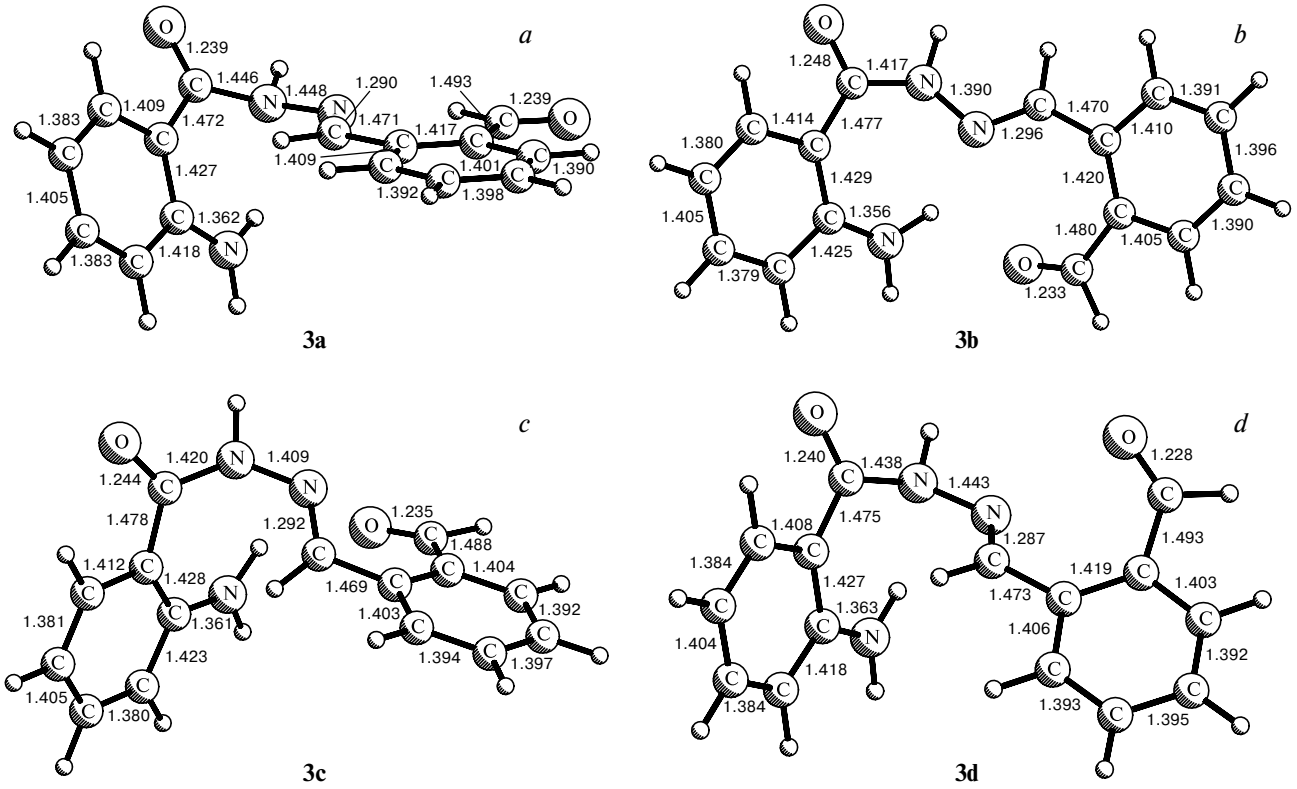


Fig. 1. Geometric characteristics of the most stable conformers **3a** ($\Delta E = 0$) (*a*), **3b** ($\Delta E = 0.51$) (*b*), **3c** ($\Delta E = 3.56$) (*c*), and **3d** ($\Delta E = 7.76$) (*d*) calculated at the B3LYP/3-21G* level of theory. The bond lengths are given in Å.

It is known[1,5] that the hydrazide NH_2 group of compound **1** is the first to react with aldehydes. The reaction of compound **1** with *o*-carboxybenzaldehyde at room temperature produces *o*-carboxybenzaldehyde *o*-aminobenzoylhydrazone. This suggests that the first step of the reaction of hydrazide **1** with phthalaldehyde also affords hydrazone **3**.

According to quantum chemical calculations (at the DFT B3LYP/3-21G* level of theory),[6,7] system **3** can exist as a series of conformational isomers (Fig. 1, Table 1). Conformer **3a** is most stable among these isomers. It is 0.5—7.8 kcal mol^{-1} energetically more favorable than the other conformers. The amino group in conformer **3a** is oriented with respect to the C=N bond so that the system is structurally suitable for further transformation **3**→**4** (the proton transfer from NH_2 to the hydrazone nitrogen atom and the formation of the new C—N bond). The transition **3a**→**4** is exothermic. The aldehyde group in compound **4** can interact with NH at positions 1 or 3 of the tetrahydrotriazepine ring. According to calculations, system **4** also exists as several conformers (Fig. 2), conformer **4a** containing the aldehyde group closely spaced to N(1) and the rather strong (1.792 Å) N(1)H...O hydrogen bond being most stable. Conformer **4b**, in which the aldehyde group points toward the N(3) atom, is 12.2 kcal mol^{-1} less stable than **4a**. Therefore, the interaction between the aldehyde group and NH at position 1 resulting in the transformation into structure **5** is more favorable. The transition **4a**→**5** is exothermic (the energy gain is 7.1 kcal mol^{-1}). Compound **5** undergoes dehydration as a result of the symmetry allowed 1,5-proton shift. However, this reaction produces compound **6** with the nonaromatic isoindole structure, which can be stabilized by the transformation into 12*H*-benzo[5,6][1,2,4]triazepino[3,4-*a*]isoindol-5(6*H*)-one **7a** as a result of the

Table 1. Energy characteristics of systems **3**—**5** (see Scheme 1) calculated at the B3LYP/3-21G* level of theory and corresponding to the energy minima ($\lambda = 0$) on the potential energy surface

Structure	$-E_{tot}$/a.u.	ZPE/a.u.	$\tilde{\omega}_1$/cm^{-1}
3a	889.157410	0.258080	17.6
3b	889.156595	0.257658	15.8
3c	889.151733	0.257327	35.0
3d	889.145043	0.257096	19.8
4a	889.168817	0.261070	26.6
4b	889.162211	0.260523	25.8
4c	889.149293	0.260097	30.7
5	889.180131	0.262212	43.5

Note. E_{tot} is the total energy (1 a.u. = 627.5095 kcal mol^{-1}), ZPE is the zero-point energy, and ω_1 is the lowest harmonic vibrational frequency.

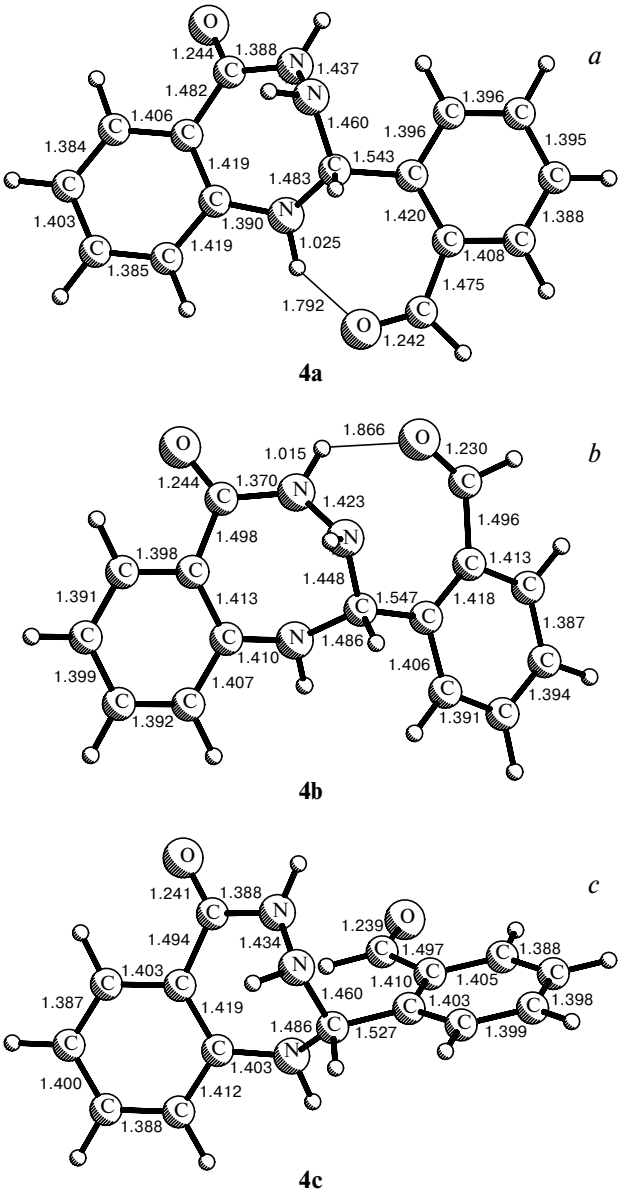


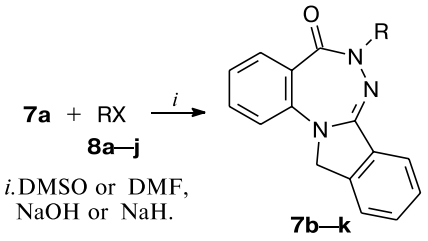
Fig. 2. Geometric characteristics of the most stable conformers **4a** ($\Delta E = 0$) (*a*), **4b** ($\Delta E = 12.25$) (*b*), and **4c** ($\Delta E = 4.14$) (*c*) calculated at the B3LYP/3-21G* level of theory. The bond lengths are given in Å.

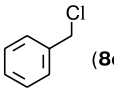
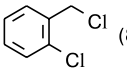
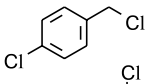
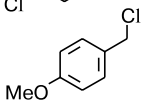
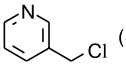
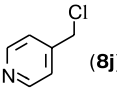
second 1,5-proton shift. These rearrangements proceed very easily in structures analogous to **6**.[8]

Compound **7a** is readily alkylated at the N(6) atom with haloalkyls at room temperature in DMSO or DMF in the presence of NaOH or NaH (Scheme 2).

We failed to replace the H atom at N(6) under these conditions in the reactions with tosyl and mesyl chlorides, ethyl chloroacetate and bromoacetate, and phenacyl bromide. In all cases, only the starting compound **7a** was isolated from the reaction mixture. Compound **7a** does not react with acetic anhydride even under reflux.

Scheme 2



RX	Product	Yield **7** (%)
MeI (**8a**)	**7b**	75
Pr^{i}I (**8b**)	**7c**	67
CH_2=$CHCH_2Br$ (**8c**)	**7d**	99
HC≡$CHCH_2Br$ (**8d**)	**7e**	50
 (**8e**)	**7f**	62
 (**8f**)	**7g**	65
 (**8g**)	**7h**	77
 (**8h**)	**7i**	68
 (**8i**)	**7j**	59
 (**8j**)	**7k**	38

Compound **7c** was characterized by X-ray diffraction (Fig. 3, Tables 2 and 3).

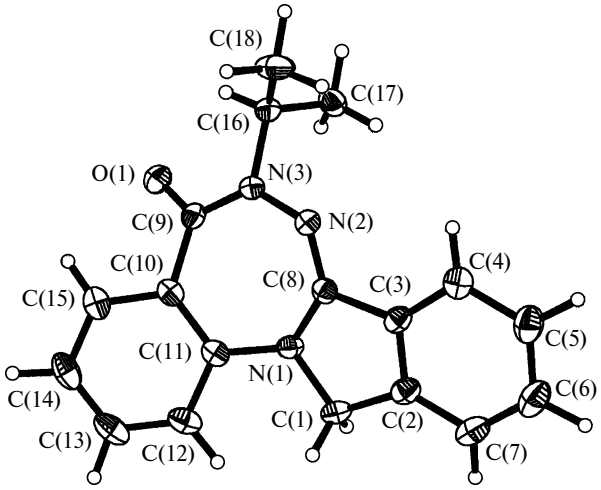


Fig. 3. Molecular structure of compound **7c**.

Table 2. Selected bond lengths (*d*/Å) and bond angles (ω/deg) in molecule **7c**

Parameter	Value	Parameter	Value
Bond length	*d*/Å	Bond length	*d*/Å
N(1)—C(1)	1.485(2)	O(1)—C(9)	1.230(2)
N(1)—C(8)	1.399(2)	C(9)—C(10)	1.505(2)
N(1)—C(11)	1.410(2)	C(10)—C(11)	1.408(2)
N(2)—N(3)	1.397(2)	C(1)—C(2)	1.497(2)
N(2)—C(8)	1.284(2)	C(2)—C(3)	1.386(2)
N(3)—C(9)	1.358(2)	C(3)—C(8)	1.469(2)
Bond angle	ω/deg	Bond angle	ω/deg
C(1)—N(1)—C(8)	110.6(1)	N(2)—N(3)—C(9)	129.8(1)
C(1)—N(1)—C(11)	120.3(1)	C(16)—N(3)—C(9)	119.6(1)
C(8)—N(1)—C(11)	123.6(1)	N(3)—C(9)—C(10)	121.6(1)
N(1)—C(8)—N(2)	133.2(1)	C(9)—C(10)—C(11)	127.1(1)
C(8)—N(2)—N(3)	123.8(1)	C(10)—C(11)—N(1)	122.2(1)
N(2)—N(3)—C(16)	110.6(1)		

Molecule **7c** consists of four fused cyclic fragments. Two benzene rings at the periphery of the molecule are planar, and the dihedral angle between these rings is 29.3°. The five-membered ring fused to the benzene ring C(2)...C(7) is also planar and is coplanar with the benzene ring. The central seven-membered nitrogen-containing heterocycle adopts a twist conformation; the corresponding torsion angles are listed in Table 3.

The N(1) and N(3) atoms have a planar-trigonal configuration. The sums of the bond angles at these atoms are 354.5(3) and 360.0(3)°, respectively. The lengths of the double (N(2)—C(8)) and single (N(2)—N(3)) bonds (1.284(2) and 1.397(2) Å, respectively) are indicative of a substantial localization of the π-electron density on the double bond.

The alkylation of compound **7a** at the oxygen atom is principally possible. However, the presence of carbonyl stretching bands in the spectra of compounds **7b**—**k** (Table 4) confirms that all these compounds are alkylation products at the nitrogen atom.

Experimental

The IR spectra were recorded on a Specord IR-75 instrument in Nujol mulls. The ^{1}H NMR spectra were measured on a Varian UNITY-300 spectrometer. The mass spectra were obtained on a Finnigan MAT INCOS 50 LC-mass spectrometer using a direct inlet probe. The spectroscopic characteristics of the reaction products are given in Table 4. A 57—63% NaH suspension in a mineral oil (Lancaster) and a 80% toluene solution of propargyl bromide (Acros) were used.

12*H*-Benzo[5,6][1,2,4]triazepino[3,4-*a*]isoindol-5(6*H*)-one (7a). A hot solution of aldehyde **2** (2.7 g, 20 mmol) in Pr^{i}OH (10 mL) was added to a hot solution of hydrazide **1** (3 g, 20 mmol) in Pr^{i}OH (15 mL). The mildly exothermic reaction was observed, which was accompanied by the color intensification and the formation of a crystalline precipitate in due course. The reaction mixture was refluxed for 15 min. The hot precipitate was filtered off and washed with hot Pr^{i}OH and petroleum ether. A yellow crystalline compound poorly soluble in most organic solvents was obtained; m.p. 238—240 °C (from propylenecarbonate). The yield was 1.8 g (36%). Positive ion mass spectrum: 249. Found (%): C, 72.16; H, 4.57; N, 17.30. $C_{15}H_{11}N_3O$. Calculated (%): C, 72.28; H, 4.45; N, 16.86.

Table 3. Selected torsion angles (φ/deg) in molecule **7c**

Torsion angle	φ/deg
N(1)—C(11)—C(10)—C(9)	11.6(3)
C(8)—N(1)—C(11)—C(10)	31.4(3)
N(2)—C(8)—N(1)—C(11)	30.1(3)
N(3)—N(2)—C(8)—N(1)	−12.8(3)
C(9)—N(3)—N(2)—C(8)	26.5(3)
C(10)—C(9)—N(3)—N(2)	8.5(3)
C(11)—C(10)—C(9)—N(3)	−37.6(3)

12*H*-Benzo[5,6]-6-methyl[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7b). A suspension of NaH (0.14 g, 3.5 mmol) was dissolved in DMSO (6 mL), heterocycle **7a** (0.75 g, 3 mmol) was added, and the reaction mixture was triturated. The precipitate was dissolved, after which the reaction mixture solidified. Then MeI (0.5 mL, 8 mmol) was added, the mixture was triturated with a rod for 5 min, and MeOH (10 mL) was added. The precipitate was filtered off and recrystallized successively from Pr^{i}OH (75 mL) and CCl_4 (50 mL). A yellow crystalline compound was obtained, m.p. 157—159 °C. The yield was 0.4 g (75%). Found (%): C, 73.28; H, 4.77; N, 15.82. $C_{16}H_{13}N_3O$. Calculated (%): C, 72.99; H, 4.98; N, 15.96.

12*H*-Benzo[5,6]-6-isopropyl-1,2,4]triazepino[3,4-*a*]isoindol-5-one (7c). A suspension of NaH (0.1 g, 2.5 mmol) was added portionwise to a suspension of heterocycle **7a** (0.5 g, 2 mmol) in DMSO (5 mL), the reaction mixture being triturated with a rod. Then Pr^{i}I (0.3 mL, 3 mmol) was added to the solidified mixture, and the mixture was triturated with a rod. The mixture liquefied and warmed up and then again solidified. The precipitate was filtered off and washed with H_2O. A yellow compound was obtained in a yield of 0.3 g. An additional amount of the yellow compound (0.24 g) was precipitated from the filtrate with a 1 : 1 MeOH—H_2O mixture. The precipitates were combined and recrystallized from isooctane (20 mL). A yellow crystalline compound was obtained, m.p. 119—125 °C. The yield was 0.39 g (67%). The structure was established by X-ray diffraction.

12*H*-Benzo[5,6]-6-allyl[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7d). Heterocycle **7a** (0.75 g, 3 mmol) was added to a suspension of NaH (0.14 g, 3.5 mmol) dissolved in DMSO (6 mL), and the reaction mixture was triturated with a rod. The reaction mixture rapidly solidified. Allyl bromide (0.5 mL, 5.7 mmol) was added, and the mixture was triturated until a new precipitate formed. Then 50% MeOH (10 mL) was added, and the precipitate was filtered off, washed with 50% MeOH, and recrystallized from CCl_4 (10 mL). A yellow compound was obtained, m.p. 102—109 °C, in nearly quantitative yield. Found (%): C, 74.51; H, 5.60; N, 14.35. $C_{18}H_{15}N_3O$. Calculated (%): C, 74.72; H, 5.23; N, 14.52.

12*H*-Benzo[5,6]-6-propargyl[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7e). Sodium hydroxide (0.5 g, 1.25 mmol) was triturated under a layer of DMSO (2.5 mL), heterocycle **7a** (0.17 g, 0.7 mmol) was added, and the reaction mixture was triturated with a rod for 10 min. Then a toluene solution of propargyl bromide

Table 4. IR spectra (Nujol mulls) and ^{1}H NMR spectra

Compound	IR, ν/cm^{-1}	Solvent	^{1}H NMR (δ, (J/Hz))
7a	3260, 3127 (NH), 1687, 1640 (CO), 1594, 1487, 1475 (arom.)	DMSO-d_6	4.85 (s, 2 H, CH_2); 6.85 (m, 2 H, SH_{arom}); 7.30—7.50 (m, 4 H, SH_{arom}); 7.55 (br.d, 1 H, SH_{arom}); 7.96 (dd, 1 H, S(10)H, ^3J = 7.5, ^4J = 1.0); 9.68 (s, 1 H, NH)
7b	1687, 1640 (C=O), 1621, 1594, 1567, 1494 (apom)	$CDCl_3$	3.43 (s, 3 H, CH_3); 4.83 (s, 2 H, CH_2); 6.77 (d, 1 H, SH_{arom}, J = 8.3); 6.95 (m, 1 H, SH_{arom}); 7.20—7.60 (m, 5 H, SH_{arom}); 7.72 (d, 1 H, SH_{arom}, J = 7.5); 8.11 (dd, 1 H, S(10)H, ^3J = 7.9, ^4J = 1.75)
7c	1687, 1669 (CO), 1614, 1594, 1567, 1487 (arom.)	$CDCl_3$	1.30 (d, 6 H, 2 SH_3, J = 6.6); 4.82 (s, 2 H, CH_2); 5.04 (quint, 1 H, SH, J = 6.6); 6.75 (d, 1 H, SH_{arom}, J = 8.2); 6.94 (t, 1 H, SH_{arom}, J = 7.5); 7.20—7.60 (m, 4 H, SH_{arom}); 7.76 (d, 1 H, SH_{arom}, J = 7.5); 8.12 (dd, 1 H, S(10)H, ^3J = 7.9, ^4J = 1.75)
7d	1680 (CO), 1614, 1587, 1567, 1487 (arom.)	$CDCl_3$	4.43 (m, 2 H, SH_2); 4.82 (s, 2 H, S(5)H_2); 5.10—5.50 (m, 2 H, =SH_2); 6.03 (m, 1 H, SH=); 6.77 (d, 1 H, SH_{arom}, J = 8.2); 6.95 (m, 1 H, SH_{arom}); 7.20—7.60 (m, 4 H, SH_{arom}); 7.71 (d, 1 H, SH_{arom}, J = 7.4); 8.13 (dd, 1 H, S(10)H, ^3J = 7.9, ^4J = 1.7)
7e	3253 (≡CH); 2167 (C≡C), 1680 (CO), 1621, 1594, 1487 (arom.)	$CDCl_3$	2.26 (t, 1 H, ≡SH, J = 2.4); 4.56 (d, 2 H, SH_2, J = 2.4); 4.82 (s, 2 H, S(5)H_2); 6.77 (d, 1 H, SH_{arom}, J = 8.3); 6.95 (m, 1 H, SH_{arom}); 7.30—7.55 (m, 4 H, SH_{arom}); 7.77 (d, 1 H, SH_{arom}, J = 7.4); 8.17 (dd,1 H, S(10)H, ^3J = 7.9, ^4J = 1.8)
7f	1674 (CO), 1607, 1580, 1555, 1487 (arom.)	$CDCl_3$	4.79 (s, 2 H, S(5)H_2); 5.01 (s, 2 H, SH_2); 6.74 (d, 1 H, SH_{arom}, J = 8.3); 6.94 (m, 1 H, SH_{arom}); 7.10—7.60 (m, 11 H, SH_{arom}); 7.96 (d, 1 H, SH_{arom}, J = 7.4); 8.13 (dd, 1 H, S(10)H, ^3J = 7.9, ^4J = 1.7)
7g	1687, 1634 (CO), 1614, 1587, 1560, 1487 (arom.)	$CDCl_3$	4.84 (s, 2 H, S(5)H_2); 5.16 (s, 2 H, SH_2); 6.79 (d, 1 H, SH_{arom}, J = 8.0); 6.96 (m, 1 H, SH_{arom}); 7.10—7.55 (m, 8 H, SH_{arom}); 7.63 (d, 1 H, SH_{arom}, J = 7.9); 8.16 (dd, 1 H, S(10)H, ^3J = 7.9, ^4J = 1.6)
7h	1687, 1640 (CO), 1620, 1594, 1567, 1487 (arom.)	DMSO-d_6	4.85 (s, 2 H, S(5)H_2); 4.90 (s, 2 H, SH_2); 6.80—7.00 (m, 2 H, SH_{arom}); 7.20—7.50 (m, 8 H, SH_{arom}); 7.58 (d, 1 H, SH_{arom}, J = 7.7); 7.95 (br. dd, 1 H, S(10)H)
7i	1687 (CO); 1620, 1594, 1587, 1567, 1514, 1487 (arom.), 1247, 1228 (S—O)	DMSO-d_6	3.73 (s, 3 H, SH_3); 4.80, 4.88 (both s, 2 H each, SH_2); 6.78 (d, 2 H, SH_{arom}, J = 8.6); 6.90 (m, 2 H, SH_{arom}); 7.20—7.55 (m, 6 H, SH_{arom}); 7.61 (d, 1 H, S(7)H, J = 7.6); 7.94 (dd, 1 H, S(10)H, ^3J = 7.9, ^4J = 1.6)
7j	1687, 1640 (CO), 1620, 1594, 1567, 1487 (arom.)	DMSO-d_6	4.89, 4.90 (both s, 2 H each, SH_2); 6.90 (m, 2 H, SH_{arom}); 7.20—7.50 (m, 6 H, SH_{arom}); 7.61 (d, 1 H, SH_{arom}, J = 7.6); 7.8 (m, 1 H,SH_{arom}); 7.97 (dd, 1 H, S(10)H, ^3J = 7.8, ^4J = 1.6); 8.40 (d, 1 H,SH_{arom}, J = 4.5); 8.60 (c, 1 H, SH_{arom})
7k	1674 (CO), 1634, 1607, 1594, 1587, 1554, 1487 (arom.)	DMSO-d_6	4.89, 4.92 (both s, 2 H each, SH_2); 6.70—7.10 (m, 2 H, SH_{arom}); 7.20—7.70 (m, 7 H, SH_{arom}); 7.95 (d, 1 H, SH_{arom}, J = 7.9); 8.43 (d, 2 H, SH_{arom}, J = 5.8)

(0.12 mL, ~1 mmol) was added, the reaction mixture was triturated and kept for 30 min, H_2O (5 mL) was added, and the precipitate was filtered off, washed with H_2O and MeOH, and recrystallized from CH_3CN (12 mL). A yellow compound was obtained, m.p. 183—184 °C. The yield was 0.1 g (50%). Found (%): C, 74.87; H, 4.89; N, 14.36. $C_{18}H_{13}N_3O$. Calculated (%): C, 75.25; H, 4.56; N, 14.62.

12*H*-Benzo[5,6]-6-benzyl[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7f). Sodium hydroxide (0.16 g, 4 mmol) was triturated in DMSO (3 mL), heterocycle **7a** (0.5 g, 2 mmol) was added, the reaction mixture was triturated for 5 min, and benzyl chloride (0.3 mL, 2.6 mmol) was added with stirring. After 30 min, 50% MeOH (12 mL) was added, and the precipitate (0.6 g) was filtered off and recrystallized from MeCN (15 mL). Yellow crystals were obtained, m.p. 142—143 °C. The yield was 0.42 g (62%). Found (%): C, 77.52; H, 5.34; N, 12.18. $C_{22}H_{17}N_3O$. Calculated (%): C, 77.86; H, 5.05; N, 12.38.

12*H*-Benzo[5,6]-6-(2-chlorobenzyl)[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7g). Sodium hydroxide (0.16 g, 4 mmol) was triturated in DMSO (3 mL), heterocycle **7a** (0.5 g, 2 mmol) was added, and the reaction mixture was triturated for 10 min. Then *o*-chlorobenzyl chloride (0.4 mL, 3 mmol) was added, the reaction mixture was kept for 1 h, and MeOH (5 mL) was added. The precipitate was filtered off (0.7 g) and recrystallized from ethyl acetate (110 mL). A yellow compound was obtained, m.p. 203—205 °C. The yield was 0.49 g (65%). Found (%): C, 70.45; H, 4.63; N, 10.95. $C_{22}H_{16}N_3OCl$. Calculated (%): C, 70.68; H, 4.31; N, 11.24.

12*H*-Benzo[5,6]-6-(4-chlorobenzyl)[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7h). Sodium hydroxide (0.1 g, 2.5 mmol) was triturated in DMF (3 mL), heterocycle **7a** (0.25 g, 1 mmol) was added, the reaction mixture was triturated until solidification took place (~5 min), and a solution of *p*-chlorobenzyl chloride (0.28 g,

Table 5. Crystal parameters and the X-ray diffraction data collection and refinement statistics

Parameter	Value
Molecular formula	$C_{18}H_{17}N_3O$
Molecular weight/kg kmol^{-1}	291.35
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	8.6041(4)
b/Å	10.6309(6)
c/Å	15.9100(8)
V/Å^3	1455.3(1)
Z	4
ρ_{calc}/g cm^{-3}	0.085
F(000)	616
μ(Mo-Kα)/mm^{-1}	0.302
Crystal dimensions/mm	0.34×0.26×0.14
T/K	120.0(2)
Radiation (λ/Å)	Mo-Ka (0.71073)
Scan mode	w
θ-Scanning range/deg	2.30—28.99
Ranges of reflection indices	$-11 \le h \le 11$, $-12 \le k \le 14$, $-21 \le l \le 21$
Number of measured reflections	7920
Number of independent reflections	3782
R_{int}	0.0192
Number of reflections with $I > 2\sigma(I)$	3782
Number of refinement variables	267
R Factors	
based on reflections with $I > 2\sigma(I)$	
R_1	0.0351
wR_2	0.0901
based on all reflections	
R_1	0.0422
wR_2	0.0948
Goodness-of-fit on F^2	1.056
Residual electron density/e Å^3, min/max	−0.191/0.266

1.7 mmol) in DMF (2 mL) was added. Then the reaction mixture was slightly warmed (30—40 °C) and allowed to stand for 2.5 h. The precipitate was filtered off, twice washed with 50% MeOH, and dried. An orange compound was obtained, m.p. 198—202 °C (from MeCN). The yield was 0.29 g (77%). Found (%): C, 70.87; H, 4.42; N, 11.13. $C_{22}H_{16}N_3OCl$. Calculated (%): C, 70.68; H, 4.31; N, 11.24.

12*H*-Benzo[5,6]-6-(4-methoxybenzyl)[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7i). Sodium hydroxide (0.1 g, 2.5 mmol) was triturated in DMSO (2 mL), heterocycle **7a** (0.25 g, 1 mmol) was added, and the reaction mixture was triturated for 10 min. 4-Methoxybenzyl chloride (0.17 mL, 1.2 mmol) was added to the red-brown precipitate. The reaction mixture was triturated and kept for 50 min. Then 50% MeOH (5 mL) was added, and the orange precipitate was filtered off, washed with 50% MeOH, and dried. The product (0.32 g) was recrystallized from MeCN (7 mL), washed with EtOH, and dried. A yellow compound was obtained, m.p. 150—153 °C. The yield was 0.25 g (68%). Found (%): C, 74.48; H, 5.34; N, 11.30. $C_{23}H_{19}N_3O_2$. Calculated (%): C, 74.78; H, 5.18; N, 11.37.

12*H*-Benzo[5,6]-6-(3-picolyl)[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7j). Sodium hydroxide (0.1 g, 2.5 mmol) was triturated in DMF (2 mL), heterocycle **7a** (0.25 g, 1 mmol) was added, and the reaction mixture was triturated for 5 min. A freshly prepared solution of 3-picolyl chloride hydrochloride (0.2 g, 1.2 mmol) in a mixture of DMF (3 mL) and pyridine (0.2 mL) was added to the solidified mixture, and the resulting mixture was slightly warmed (30—40 °C) and kept for 1 h. Then 50% MeOH (10 mL) was added, the mixture was cooled on ice, and the precipitate was filtered off, washed with H_2O and 50% EtOH, and recrystallized from Pr^{i}OH (50 mL). A yellow compound was obtained, m.p. 183—186 °C. The yield was 0.2 g (59%). Found (%): C, 74.32; H, 4.89; N, 16.20. $C_{21}H_{16}N_4O$. Calculated (%): C, 74.10; H, 4.74; N, 16.46.

12*H*-Benzo[5,6]-6-(4-picolyl)[1,2,4]triazepino[3,4-*a*]isoindol-5-one (7k). Compound **7k** was synthesized analogously to **7j** by the addition of 4-picolyl chloride hydrochloride (0.25 g, 1.5 mmol) and recrystallized from Pr^{i}OH (10 mL). A yellow compound was obtained, m.p. 164—167 °C. The yield was 0.13 g (38%). Found (%): C, 74.43; H, 4.95; N, 16.58. $C_{21}H_{16}N_4O$. Calculated (%): C, 74.10; H, 4.74; N, 16.46.

X-ray diffraction study. A single crystal of compound **7c** coated with perfluorinated oil was mounted on a Bruker SMART-CCD diffractometer under a cold nitrogen stream. The experimental X-ray data were collected from a single crystal using the ω-scanning technique and Mo-Kα radiation. The crystallographic parameters and the X-ray diffraction data collection and refinement statistics are given in Table 5. The experimental reflections were processed with the use of the Bruker SAINT software.[9] The structure was solved by direct methods and refined by the full-matrix least-squares method based on F^2 with anisotropic displacement parameters for all nonhydrogen atoms. The hydrogen atoms were located in difference Fourier maps and refined isotropically. All calculations were carried out using the SHELXTL-Plus program package.[10] The atomic coordinates and other experimental data were deposited with the Cambridge Structural Database.*

References

1. M. Ghelardoni, V. Pestellini, *Ann. Chimica (Roma)*, 1974, **64**, 445.
2. V. Pestellini, M. Ghelardoni, G. Volterra, P. Del Soldato, *J. Med. Chim. Ther.*, 1978, **13**, No. 3, 296.
3. G. Bernath, F. Miklos, G. Stajer, *Heterocyclic Chem.*, 1998, **35**, 201.
4. M. Razvi, T. Ramalihgam, P.B. Sattur, *Indian J. Chem.*, 1990, **29B**, 399.
5. Thode, *J. Prakt. Chem.*, 1904, **69**, 92.
6. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V.

* These data can be obtained, free of charge, on application to the Cambridge Crystallographic Data Centre: CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk), refcode 675784.

Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M.W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98 (Revision A.9)*, Gaussian, Inc., Pittsburgh (PA), 1998.

7. J. B. Foresman, E. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Pittsburg: Gaussian, Inc., 1996, 302 p.
8. L. Yu. Ukhin, L. V. Belousova, Zh. I. Orlova, M. S. Korobov, G. S. Borodkin, *Khim. Geterotsikl. Soedin.*, 2002, 1339 [*Chem. Heterocycl. Compd.*, 2002 (Engl. Transl.)].
9. *SAINT, Version 6.02A*, Bruker AXS Inc, Madison Wisconsin, USA, 2001.
10. *SHELXTL-Plus, Release 5.10*, Bruker AXS Inc., Madison, Wisconsin, USA, 1997.

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