Reaction of 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline with ethyl acetoacetate. The crystal structure and IR spectra of ethyl 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidenehydrazono)-2-oxobutanoate

V. I. Sokol,[a] V. V. Davydov,[b] Yu. V. Shklyaev,[c] V. A. Glushkov,[c] and V. S. Sergienko[a]*

[a]N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 31 Leninsky prosp., 117907 Moscow, Russian Federation. Fax: +7 (095) 954 1279. E-mail: sokol@ionchran.msk.ru
[b]Russian Friendship University, 6 ul. Miklukho-Maklaya, 117198 Moscow, Russian Federation. Fax: +7 (095) 433 1511. E-mail: vdavidov@mx.pfu.edu.ru
[c]Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 116 ul. Bol'shevistskaya, 614000 Perm', Russian Federation

The reaction of 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline with ethyl acetoacetate afforded ethyl 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidenehydrazono)-2-oxobutanoate. The crystal structure of the title compound was established by X-ray diffraction analysis.

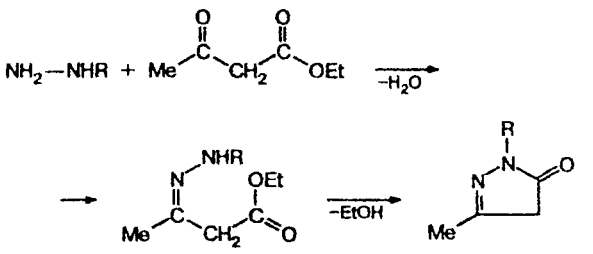
Key words: 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline, ethyl 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidenehydrazono)-2-oxobutanoate, crystal structure, IR spectra.

Derivatives of 3,3-dimethyl-3,4-dihydroisoquinoline and their metal complexes exhibit a broad spectrum of physiological activities.[1,2] In addition, pyrazol-5-one derivatives are widely used in medicine[3,4] and agriculture.[5] In this connection, it was of interest to synthesize and study the structure and properties of 3,3-dimethyl-3,4-dihydroisoquinoline, containing the pyrazolone ring at position 1. One of procedures for the synthesis of pyrazol-5-one derivatives involves the reaction of substituted hydrazines with ethyl acetoacetate (EAA). In this work, we studied the reaction of 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline with ethyl acetoacetate.

Results and Discussion

It is known that EAA reacts with substituted hydrazines as a ketone to form pyrazol-5-one (Scheme 1).[6] Therefore, the reaction of EAA with 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline (**1**) (Scheme 2) would be expected to give the corresponding pyrazolone **3** (pathway *a*). However, the results of elemental analysis ($C_{17}H_{21}N_3O_3$) were inconsistent with the expected composition of the product ($C_{15}H_{17}N_3O$). Besides, the IR spectrum of a polycrystalline sample of the resulting compound had two bands with approximately equal intensities with maxima at 1735 and 1665 cm^{-1} rather than one ν(C=O) band typical of pyrazol-5-one derivatives. In addition, a narrow intense band with a maximum at 3335 cm^{-1} was observed in the region of stretching vibrations of NH and OH groups. This band should be absent in the spectrum of the CH isomer of the expected pyrazolone **3**. This suggested that the reaction under study proceeded according to a scheme different from that assumed.

Scheme 1

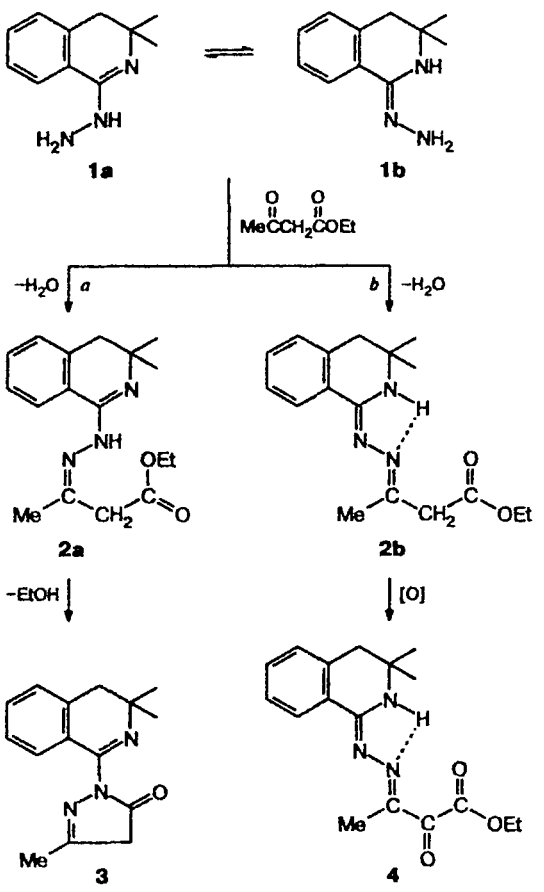


With the aim of establishing the composition and structure of the reaction product, we prepared its single crystal and carried out X-ray diffraction study.

It was established by X-ray analysis that the reaction of 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline (**1**) with EAA afforded ethyl 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidenehydrazono)-2-oxobutanoate (**4**). Consequently, the first stage of the reaction involves condensation to form product **2b**, whose methylene group is oxidized to the carbonyl group in the second stage (see Scheme 2, pathway *b*).

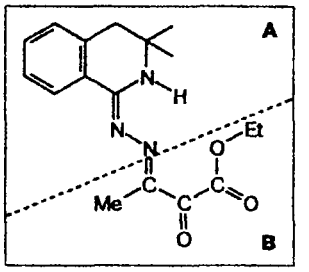
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 5, pp. 966—970, May, 1999.

Scheme 2

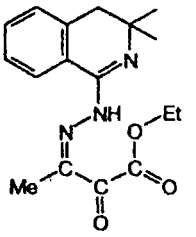


As in the case of other azine derivatives studied by us previously, *viz.*, 3,3-dimethyl-3,4-dihydroisocarbostyryl azine (5)[7] and the protonated form of 5 as its hydronitrate 6,[8] the azine group in molecule 4 (Fig. 1) is in the *cis* position with respect to the endocyclic C(1)—N(1) bond. The C(1)—N(1) and N(2)—N(3) bonds are in a single plane (the N(1)—C(1)—N(2)—N(3) torsion angle is close to 0°).

Compound 4 can exist in two tautomeric forms, *viz.*, the azine (**a**) and hydrazine (**b**) forms.



4a



4b

In crystals of 4, as in 5, the molecules exist in the azine form **a**. The hydrogen atom is localized at the endocyclic N(1) atom. However, the delocalization of the π-electron density over the C—N and N—N bonds in the tetrahydroisoquinolinoazine fragment (A) of molecule 4 is more substantial than that observed in molecule 5 and is somewhat more pronounced than that in 6. Thus, the endocyclic C(1)—N(1) bond (1.333(2) Å) in molecule 4 is nearly identical in length to the exocyclic C(1)—N(2) bond (1.321(2) Å); the difference (Δ) between their lengths is 0.012 Å. In molecule 6, the corresponding C—N bond lengths in fragment B are 1.330(3) and 1.312(3) Å, respectively (Δ = 0.018 Å). In molecule 5, the exocyclic C(1)—N(2) bond (1.300(3) Å) is substantially shorter than the endocyclic C(1)—N(1) bond (1.352(3) Å, Δ = 0.052 Å).

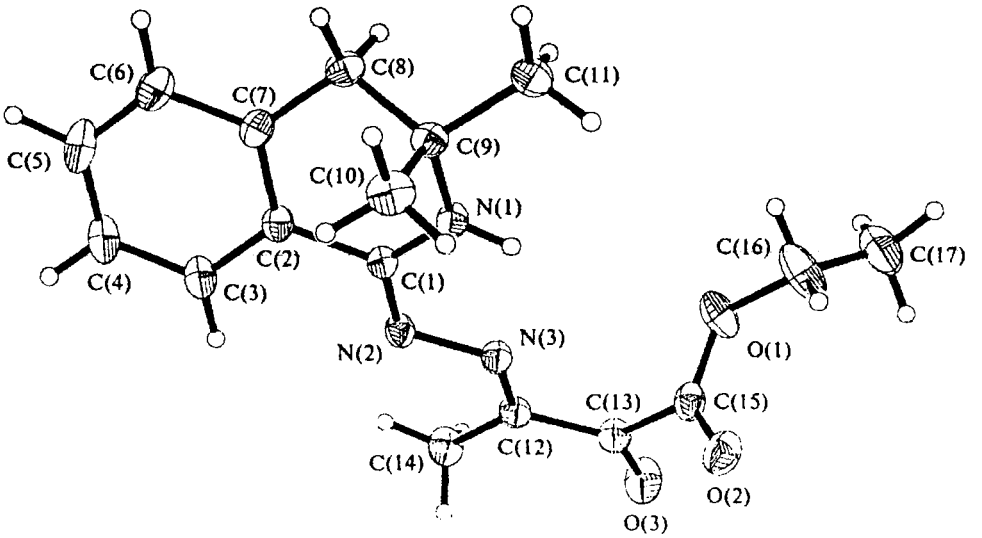


Fig. 1. Molecular structure of compound 4.

Delocalization of the π-electron density in molecule **4** extends also to the N—N bond, which is shortened to 1.369(2) Å. In molecules **5** and **6**, the N—N bond length is 1.410(2) and 1.396(3) Å, respectively. On the whole, the N—N bonds in molecules **4**—**6** are shorter than the standard single N—N bond (1.456 Å).[9] As in molecule **5**, the N atoms of the azine group in molecule **4** are sp^2-hybridized. The C—N—N angle at the N(2) atom (112°) is somewhat smaller than that at the N(3) atom (115°), while the C—N—N angles at the N atoms of the azine group in molecule **5** are 111.5°.

In fragment **A** of molecule **4**, as in molecule **5**, the strong N(1)—H...N(3) intramolecular hydrogen bond occurs, through which the planar (to within ±0.02 Å) five-membered ring is formed. The geometric parameters of this hydrogen bond are as follows: N(1)—H, 0.84 Å; N(1)...N(3), 2.629 Å; and H...N(3), 2.20 Å. Due to the contracting effect of the five-membered ring, the angle at the hydrogen atom (104°) is substantially smaller than the standard value.

The C(12)—N(3) bond that links fragments **A** and **B** in molecule **4** is similar in length (1.299(2) Å) to the double bond and is in the *trans* position with respect to the C(1)—N(2) bond (the C(1)—N(2)—N(3)—C(12) torsion angle is −174°). The N(2)N(3)C(12) and C(12)C(13)O(3) planes in fragment **B** are virtually parallel to each other. The methyl group at the C(12) atom is located symmetrically with respect to the N(3) and C(13) atoms and is in the *cis* position with respect to both the N(2)—N(3) bond and the carbonyl C(13)=O(3) group (the N(2)—N(3)—C(12)—C(14) and O(3)—C(13)—C(12)—C(14) torsion angles are virtually identical and are close to 0°). The same is true for the O(1) and O(2) atoms of the ester group. These atoms are also arranged symmetrically with respect to the C(12)—C(13) bond. The O(1) and O(2) atoms deviate from the C(12)C(13)C(15) plane in opposite directions, the deviations being approximately equal (−1.19 and +1.06 Å). The C(12)C(13)O(3) and O(1)C(15)O(2) planes are nearly perpendicular to each other (the angle between these planes is 88°). The C—C bond lengths in fragment **B** are close to the standard value. The C=O bond lengths in two carbonyl groups (the O(2)—C(15)—C(13)—O(3) torsion angle is −32.6°) also have standard values (C(12)—O(3), 1.211(2) Å; and C(15)—O(2), 1.201(2) Å). One of the C—O bonds, *viz.*, C(15)—O(1), in the ester group is substantially shorter (1.320(3) Å) that the second bond, *viz.*, C(16)—O(1) (1.466(3) Å). The configurations of the bonds about the C(12) and C(15) atoms are planar; the sums of the angles at these atoms are 360°. The bond angles at the C(15) atom are substantially different: the C(13)—C(15)—O(1) angle has the smallest value (111°) and the O(1)—C(15)—O(2) angle is the largest (127°). On the whole, the conformation of fragment **B** is governed by the requirements of the crystal packing of molecules **4** and the possibility of formation of an intermolecular hydrogen bond because this molecule contains the potential donor and acceptor centers, namely, the protonated N(1) atom and the O atoms of the carbonyl groups. The intermolecular N(1)—H...O(2)′ hydrogen bond (−*x*, −*y*, −*z*) exists between two molecules **4** related by an inversion center, as a result of which the crystal structure consists of centrosymmetric pseudodimers (Fig. 2). It should be noted that this hydrogen bond, judging from the geometric parameters (N(1)—H, 0.84 Å; O(2)′...N(1), 3.073 Å; O(2)′...H, 2.34 Å; the N(1)—H—O(2) angle is 146°; the H—O(2)—C(15′) angle is 144°), is substantially weaker than the intramolecular N—H...N hydrogen bond. In the dimer, the bifurcated hydrogen bonds form a tricyclic system, namely, the internal 12-membered heterocycle fused with two five-membered rings.

The tetrahydroisoquinoline fragment of molecule **4** is characterized by standard geometric parameters and adopts a conformation similar to those of other tetrahydroisoquinoline derivatives studied by us previously. Two adjacent atoms of the pyridine ring, *viz.*, the N(1) and C(9) atoms, as usually occurs, deviate from the plane passing through the six atoms of the benzene ring and the C(1) and C(8) atoms attached to this ring (coplanar to within ±0.02 Å) in the same direction by 0.263 and 0.770 Å, respectively (the virtually identical deviations are observed in molecules **5** and **6**: 0.294 and 0.751 Å in **5** and 0.347 and 0.811 Å in **6**). The N atoms of the azine group deviate form this plane in the opposite direction (N(2) by −0.445 Å and N(3) by −0.527 Å). The folding angle between the C(1)—C(8) and C(8)C(9)N(1)C(1) planes is 28°.

The above-considered results and the data obtained previously allow us to make the following conclusion about the pathway of the reaction under study. As in the case of oxidation reported previously,[7] the initial 1-hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline reacts with EAA as hydrazone **1b** to give compound **2b** (see Scheme 2, pathway *b*), which is stabilized through an intramolecular N_{cycle}—H...$N_{exocycle}$ hydrogen bond analogous to the N—H...N bond in the azine 3,3-dimethyl-3,4-dihydroisocarbostyryl.[7] Apparently, the presence of this bond that affects also the overall molecular conformation hinders elimination of an alcohol molecule as a result of which the pyrazolone ring is not formed. The closure of the pyrazolone ring can occur only in the case of *trans* isomer **4** in which the N—N

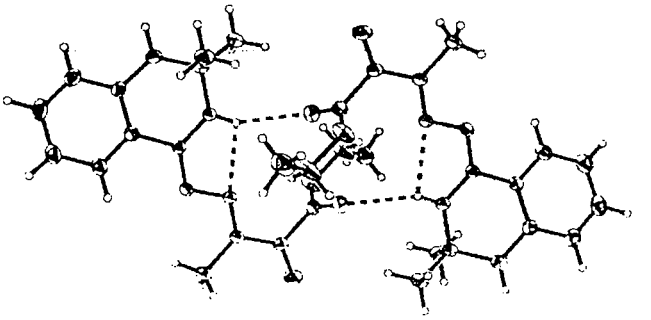


Fig. 2. Centrosymmetric pseudodimer in the structure of **4**.

Table 1. Atomic coordinates ($\times 10^4$; for the H(N(1)) atom, $\times 10^3$) and temperature factors ($U_{eq} \times 10^3$) in the structure of **4**

Atom	*x*	*y*	*z*	U_{eq}/Å^2
O(1)	−536(2)	−2550(2)	678(2)	81(1)
O(2)	1288(2)	−1399(2)	118(2)	77(1)
O(3)	1990(2)	−4225(2)	2364(2)	89(1)
N(1)	−3119(2)	1165(2)	2810(2)	48(1)
N(2)	−1570(2)	−612(2)	4366(2)	47(1)
N(3)	−806(2)	−1187(2)	3239(2)	46(1)
C(1)	−2711(2)	565(2)	4055(2)	42(1)
C(2)	−3656(2)	1223(2)	5220(2)	48(1)
C(3)	−3119(3)	894(2)	6464(2)	61(1)
C(4)	−4030(3)	1453(3)	7562(3)	74(1)
C(5)	−5475(4)	2321(3)	7437(3)	79(1)
C(6)	−6019(3)	2668(3)	6212(3)	69(1)
C(7)	−5105(2)	2132(2)	5077(2)	51(1)
C(8)	−5631(2)	2463(2)	3723(2)	54(1)
C(9)	−4367(2)	2526(2)	2494(2)	49(1)
C(10)	−3840(3)	3899(2)	2251(3)	67(1)
C(11)	−4878(3)	2518(3)	1199(2)	68(1)
C(12)	241(2)	−2424(2)	3512(2)	48(1)
C(13)	1008(2)	−3060(2)	2324(2)	55(1)
C(14)	664(3)	−3214(3)	4908(2)	68(1)
C(15)	588(3)	−2202(2)	912(2)	57(1)
C(16)	−979(5)	−1904(4)	−696(3)	108(1)
C(17)	−931(4)	−3047(4)	−1324(4)	105(1)
H(N(1))	−253(3)	83(3)	215(3)	60(6)

bond in the azine group is in the *trans* position with respect to the C—N bond of isoquinoline, which, in turn, excludes the presence of an intramolecular hydrogen bond and makes possible the formation of the pyrazolone ring. Apparently, the methylene group in compound **2b** was oxidized to the carbonyl group by atmospheric oxygen because no other oxidizing agents were introduced into the reaction mixture.

Experimental

The IR spectra were recorded on a Specord 75-IR spectrophotometer in KBr pellets and as Nujol mulls according to a standard procedure.

Ethyl 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidenehydrazono)-2-oxobutanoate (4). 1-Hydrazino-3,3-dimethyl-3,4-dihydroisoquinoline (1 g, 0.053 mol) was heated in EAA (10 mL) over 5 h, transferred into a beaker, and kept in air. After 10 days, the orange crystals that precipitated were filtered off and recrystallized from Pr^{i}OH (10 mL). Compound **4** was obtained in a yield of 0.57 g (53%), m.p. 118—120 °C. To prove the presence of the α-keto group, the compound obtained was introduced into the reaction with *o*-phenylenediamine. The resulting compound (0.315 g, 0.01 mol) and *o*-phenylenediamine (0.104 g, 0.01 mol) were heated in Pr^{i}OH (3 mL) over 1 h. The crystals that precipitated were filtered off and recrystallized (Pr^{i}OH—dioxane, 5 : 1). Dark-red needle-like crystals were obtained in a yield of 0.29 g (80%), m.p. 227—228.5 °C. Found (%): C, 70.0; H, 6.0; N, 18.94, 19.06. $C_{21}H_{21}N_5O$. Calculated (%): C, 70.17; H, 5.89; N, 19.50. IR, ν/cm^{-1}: 3315 (NH); 1650 (C=O); 1600 (CN); 1540, 1520, 1340, 1295, 1240, 1065, 1030, 985, 940, 860.

X-ray diffraction study. Crystals of compound **4** (prepared by recrystallization from Pr^{i}OH), $C_{17}H_{21}N_3O_3$, are triclinic, a = 9.574(2) Å, b = 9.763(2) Å, c = 10.221(2) Å, α = 73.38(3)°, β = 76.17(3)°, γ = 70.00(3)°, V = 853.4(3) Å^3, d_{calc} = 1.243 g cm^{-3}, μ(Mo) = 0.086 cm^{-1}, Z = 2, space group $P\bar{1}$.

The unit cell parameters and intensities of 3040 reflections were measured on a four-circle automated Enraf Nonius CAD-4 diffractometer (λ(Mo-Kα), graphite monochromator, θ/2θ scanning technique, $2\theta_{max}$ = 60°); 2875 reflections with $I > 2\sigma(I)$ were used in calculations.

The structure was solved by direct methods with the use of the SHELXS-86 program package.[10] The position of the hydrogen atom at the nitrogen atom, H(N(1)), was located from a difference electron density synthesis. The remaining hydrogen atoms (at the C atoms) were calculated geometrically at C—H distances of 0.96 Å. The structure was refined by the full-

Table 2. Bond lengths (*d*) and bond angles (ω) in molecule **4**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
O(1)—C(15)	1.320(3)	N(2)—C(1)	1.321(2)	C(3)—C(4)	1.374(3)	C(9)—C(10)	1.519(3)
O(1)—C(16)	1.466(3)	N(2)—N(3)	1.369(2)	C(4)—C(5)	1.378(4)	C(9)—C(11)	1.519(3)
O(2)—C(15)	1.201(3)	N(3)—C(12)	1.299(2)	C(5)—C(6)	1.381(4)	C(12)—C(13)	1.451(3)
O(3)—C(13)	1.211(2)	C(1)—C(2)	1.480(3)	C(6)—C(7)	1.395(3)	C(12)—C(14)	1.495(3)
N(1)—C(1)	1.333(2)	C(2)—C(7)	1.395(3)	C(7)—C(8)	1.498(3)	C(13)—C(15)	1.521(3)
N(1)—C(9)	1.481(2)	C(2)—C(3)	1.398(3)	C(8)—C(9)	1.524(3)	C(16)—C(17)	1.422(4)
Angle	**ω/deg**	**Angle**	**ω/deg**	**Angle**	**ω/deg**	**Angle**	**ω/deg**
C(15)—O(1)—C(16)	117.1(2)	C(3)—C(2)—C(1)	120.2(2)	N(1)—C(9)—C(10)	109.9(2)	O(3)—C(13)—C(12)	124.8(2)
C(1)—N(1)—C(9)	124.3(2)	C(4)—C(3)—C(2)	119.8(2)	N(1)—C(9)—C(11)	108.2(2)	O(3)—C(13)—C(15)	116.8(2)
C(1)—N(2)—N(3)	112.2(2)	C(3)—C(4)—C(5)	119.8(2)	C(10)—C(9)—C(11)	109.9(2)	C(12)—C(13)—C(15)	118.4(2)
C(12)—N(3)—N(2)	114.6(2)	C(4)—C(5)—C(6)	121.1(2)	N(1)—C(9)—C(8)	107.3(2)	O(2)—C(15)—O(1)	126.8(2)
N(2)—C(1)—N(1)	126.1(2)	C(5)—C(6)—C(7)	120.0(2)	C(10)—C(9)—C(8)	111.3(2)	O(2)—C(15)—C(13)	122.0(2)
N(2)—C(1)—C(2)	116.3(2)	C(2)—C(7)—C(6)	118.6(2)	C(11)—C(9)—C(8)	110.2(2)	O(1)—C(15)—C(13)	111.0(2)
N(1)—C(1)—C(2)	117.6(2)	C(2)—C(7)—C(8)	118.8(2)	N(3)—C(12)—C(13)	114.4(2)	C(17)—C(16)—O(1)	110.3(3)
C(7)—C(2)—C(3)	120.6(2)	C(6)—C(7)—C(8)	122.6(2)	N(3)—C(12)—C(14)	125.8(2)		
C(7)—C(2)—C(1)	119.2(2)	C(7)—C(8)—C(9)	112.6(2)	C(13)—C(12)—C(14)	119.8(2)		

Table 3. Torsion angles (τ) in molecule **4**

Angle	τ/deg
N(1)—C(1)—N(2)—N(3)	0.2
C(1)—N(2)—N(3)—C(12)	−174.1
N(2)—N(3)—C(12)—C(13)	177.6
N(3)—C(12)—C(13)—O(3)	−178.0
C(12)—C(13)—C(15)—O(1)	−88.3
O(2)—C(15)—C(13)—O(3)	−82.6
C(14)—C(12)—C(13)—O(3)	0.6
O(1)—C(15)—C(13)—O(3)	93.0
O(3)—C(13)—C(12)—C(14)	0.6
N(2)—N(3)—C(12)—C(14)	−0.9

matrix least-squares method with anisotropic (for O, N, and C atoms) and isotropic (for H(N(1))) thermal parameters using the SHELXL-93 program package[11] taking into account the fixed positional and thermal parameters of the remaining hydrogen atoms (U_j = 0.08 Å^2). The final values of the R factors were as follows: R_1 = 0.053, wR_2 = 0.159, GOF = 1.077; the extinction coefficient was 0.008(5). The maximum and minimum residual electron density peaks were 0.303 and −0.287 e Å^{-3}, respectively.

The atomic coordinates and thermal parameters are given in Table 1. The interatomic distances and bond angles are listed in Table 2. The torsion angles are given in Table 3.

This work was financially supported by the Federation Target Program "Integration" (Project K0512) and by the Russian Foundation for Basic Research (Project No. 98-03-32689a).

References

1. R. Z. Dautova, V. S. Shklyaev, B. Ya. Syropyatov, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim.-Farm. Zh.*, 1989, **23**, No. 2, 172 [*Chem. Pharm. J.*, 1989, **23**, No. 2 (Engl. Transl.)].
2. E. V. Balebanova, V. V. Davydov, A. N. Zorin, B. Ya. Syropyatov, and Yu. V. Shklyaev, *Khim.-Farm. Zh.*, 1996, **30**, No. 8, 17 [*Chem. Pharm. J.*, 1996, **30**, No. 8 (Engl. Transl.)].
3. G. A. Melent'eva, *Farmatsevticheskaya khimiya* [*Pharmaceutical Chemistry*], Meditsina, Moscow, 1976, **II**, 828 pp. (in Russian).
4. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], Meditsina, Moscow, 1993 (in Russian).
5. N. N. Mel'nikov, K. V. Novozhilov, S. R. Belan, and T. N. Pylova, *Spravochnik po pestitsidam* [*Handbook on Pesticides*], Khimiya, Moscow, 1985, 282 pp. (in Russian).
6. A. N. Nesmeyanov and N. A. Nesmeyanov, *Nachala organicheskoi khimii* [*Fundamentals of Organic Chemistry*], Khimiya, Moscow, 1969, **1**, 415 pp. (in Russian).
7. V. I. Sokol, M. A. Ryabov, N. Yu. Merkur'eva, V. V. Davydov, Yu. V. Shklyaev, V. A. Glushkov, and B. E. Zaitsev, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2468 [*Russ. Chem. Bull.*, 1995, **44**, 2364 (Engl. Transl.)].
8. V. I. Sokol, M. A. Ryabov, V. V. Davydov, N. Yu. Merkur'eva, Yu. V. Shklyaev, V. S. Sergienko, and B. E. Zaitsev, *Kristallografiya*, 1998, **43**, 836 [*Crystallogr. Rept.*, 1998, **43**, No. 5 (Engl. Transl.)].
9. F. M. Allen, O. Konnard, D. Watson, L. Brammer, G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, 91.
10. G. M. Sheldrick, *Acta Crystallogr.*, 1990, **46A**, 467.
11. G. M. Sheldrick, *SHELXL-93, Program for the Refinement of Crystal Structures*, University of Göttingen, Göttingen (Germany), 1993.

Received June 22, 1998