Structures of condensation products of *ortho*-aminophenols with ninhydrin

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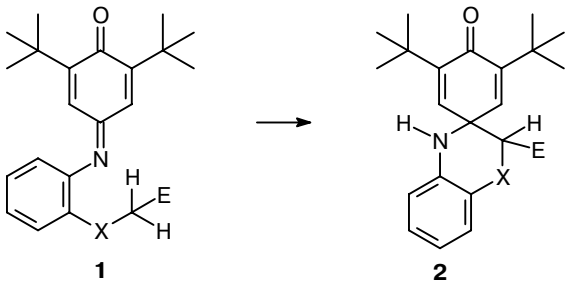
Condensation of *ortho*-aminophenols and *N*-benzylsulfonyl-*o*-phenylenediamine with ninhydrin afforded tetracyclic products, the amino group entering into condensation with the carbonyl group at position 1 of ninhydrin. The structures of the reaction products were established by ^{1}H NMR spectroscopy and X-ray diffraction analysis.

Key words: ninhydrin, benzooxazines, quinoxalines, *ortho*-aminophenols.

Previously,[1,2] we have found that quinoneimines (**1**) undergo thermal intramolecular cyclization in solutions (Scheme 1), which opens broad possibilities for the synthesis of previously inaccessible spiro-fused benzooxazines and quinoxalines of the type **2**.

Scheme 1



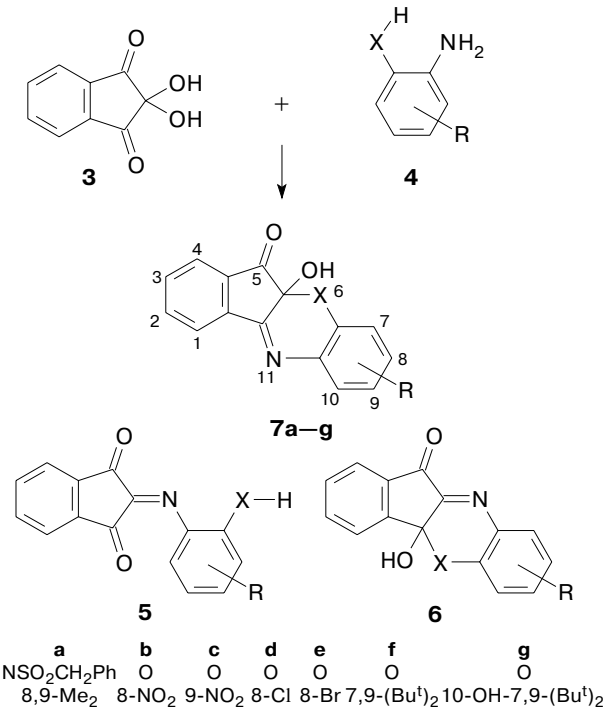
X = O, N—SO_2—R
E = CH=CH_2, Ar

The possibility of the nucleophilic addition of the C—H fragment at the C=N bond to form compounds **2** and the rate of this process depend on the mobility of the methylene protons, which is determined by the electron-withdrawing effect of the substituent E.[1]

When studying the scope of cyclization **1**→**2**, we attempted to synthesize analogs of quinoneimines by the reactions of ninhydrin (**3**) with *N*-substituted *o*-phenylenediamines (Scheme 2) with subsequent alkylation of the reaction products and cyclization analogous to **1**→**2**.

However, the reaction of **3** with *N*-benzylsulfonyl-4,5-dimethyl-*o*-phenylenediamine (**4**, X = $PhCH_2SO_2N$, R = 4,5-Me_2) did not afford the expected product **5a**; instead, we obtained a compound whose chemical and physical properties differed sharply from those of compounds **1** obtained previously. In addition, the methylene protons of the *N*-benzylsulfonyl group are manifested in the ^{1}H NMR spectrum as a characteristic AB quartet at δ 4.7—5.1, which is indicative of their nonequivalence.

Scheme 2



	a	b	c	d	e	f	g
X	NSO_2CH_2Ph	O	O	O	O	O	O
R	8,9-Me_2	8-NO_2	9-NO_2	8-Cl	8-Br	7,9-$(Bu^t)_2$	10-OH-7,9-$(Bu^t)_2$

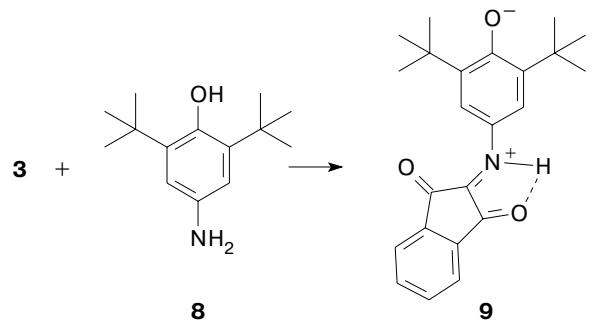
In this connection, we reinvestigated the reactions of ninhydrin with substituted *o*-aminophenols **4** (X = O). Previously, alternative structures (**6**)[3] and (**7**)[4] have been suggested for the reaction products of compound **3** with *o*-aminophenols. The reaction of compound **3** with 4-amino-2,6-di-*tert*-butylphenol (**8**) gave rise to inter-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1020—1023, June, 2001.

1066-5285/01/5006-1064 $25.00

mediate adduct **9** (Scheme 3) stabilized by an intramolecular H-bond in the bipolar NH-tautomer.[5] Hence, in our opinion, the assumption that polycyclic structure **6** is formed in the case of *ortho*-aminophenols is justified.

Scheme 3



Condensation of equimolar amounts of **3** and *o*-aminophenols **4** (X = O) afforded crystalline products in high yields. With the aim of establishing the structures of the reaction products, crystals of compound **7g** were studied by X-ray diffraction analysis. It should be noted that we succeeded in obtaining crystals suitable for X-ray study only after a substantial increase in the lipophilicity of the compounds under study by introducing two *tert*-butyl groups into the *o*-aminophenol molecule. In the crystals, compound **7g** exists as a 1 : 1 solvate with acetone.

The six-membered heterocycle in molecule **7g** has a conformation intermediate between a twist form and a sofa, which is characterized by the following Zefirov—Palyulin's puckering parameters:[6] $\theta = 58.56°$, $\psi = 17.04°$, $S = 0.61$. The five-membered ring adopts an envelope conformation with the C(5a) atom deviating from the plane through the remaining atoms of the ring by 0.231(3) Å. The N atom of the heterocycle forms an intramolecular O—H...N bond with the H atom of the OH group at the C(10) atom (H(10O)...N(11), 2.21(4) Å; O(10)...N(11), 2.713(3) Å; the O(10)—H(10O)...N(11) angle is 124(4)°). In addition, the H atom is involved in intermolecular hydrogen bonding with the O(1S) atom of the acetone molecule of solvation (H(10O)...O(1S), 2.43(4) Å; O(10)...O(1S), 3.057(5) Å; the O(10)—H(10O)...O(1S) angle is 140(4)°).

The second hydroxy group is in the axial position with respect to both the six- and five-membered heterocycles (the C(6a)—O(6)—C(5a)—O(5a) and O(5a)—C(5a)—C(5)—C(4a) torsion angles are −73.7(2)° and 103.0(2)°, respectively) and is involved in intermolecular hydrogen bonding with the O atom of the carbonyl group (H(5aO)...O(5′) (1 − *x*, 3 − *y*, 1 − *z*) 1.91(3), Å; O(15a)...O(5′), 2.782(3) Å; the O(5a)—H(5aO)...O(5′) angle is 164(3)°).

The presence of the bulky *tert*-butyl substituents leads to noticeable steric strain in the aryl fragment of molecule **7g** as evidenced by the shortened intramolecular contacts: C(8)...H(19A), 2.76(1) Å (the sum of the van der Waals radii[7] of the C and H atoms is 2.87 Å); C(10)...H(13A), 2.85(1) Å; C(10)...H(14A), 2.79(1) Å; C(8)...H(15A), 2.78(2) Å; C(8)...H(15C), 2.76(2) Å; C(8)...H(19B), 2.77(1) Å; H(8)...C(15), 2.45(2) Å; H(8)...C(19), 2.46(2) Å; H(8)...H(19A), 2.18(3) Å (the sum of the van der Waals radii[7] of the H atoms is 2.32 Å); H(8)...H(15A), 2.24(3) Å; and H(8)...H(15C), 2.22(3) Å. As a result, the C(6a)—C(7)—C(8)—C(9)—C(10)—C(10a) benzene ring is noticeably nonplanar (the C(10a)—C(10)—C(9)—C(8) and C(8)—C(7)—C(6a)—C(10a) torsion angles are 6.1(3)° and 6.4(3)°, respectively). In addition, the C(7)—C(12) and C(7)—C(16) bond lengths (1.536(3) and 1.543(3) Å, respectively) are larger than the average C(Ar)—C(sp^3) bond length[8] (1.509 Å).

The acetone molecule of solvation is disordered over two positions with the occupancies of 0.7 and 0.3.

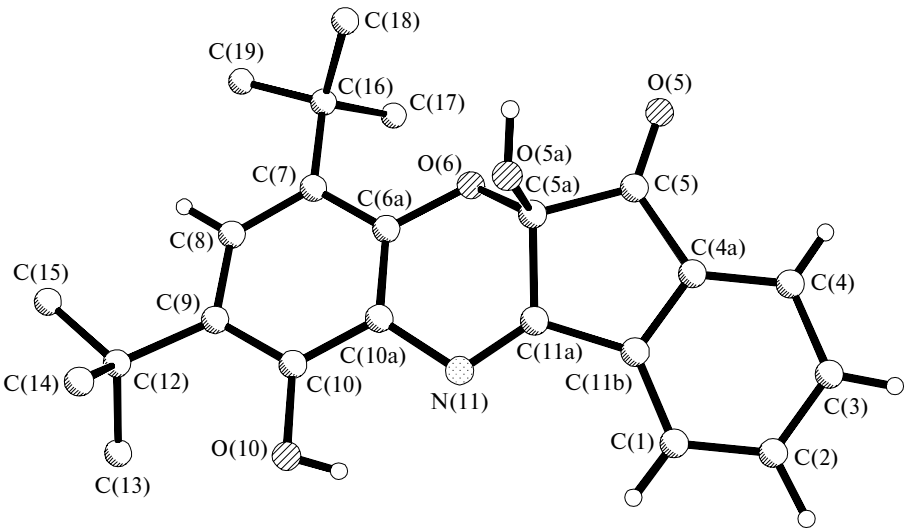


Fig. 1. Structure of molecule **7g** (the hydrogen atoms of the methyl groups are omitted).

The result obtained is against our expectation, which was based on the fact that position 2 in ninhydrin is most reactive in addition—elimination reactions. Apparently, the fact that the O—H or H—N—SO_2R fragment of the reagent rather than the NH_2 group is involved in the nucleophilic attack at position 2 of molecule **3** plays a decisive role in condensation, which is responsible for the regiodirection of cyclization.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DPX-250 spectrometer (250 MHz) at 25 °C. The chemical shifts are given in the δ scale relative to Me_4Si.

Compounds **7a—g** were prepared according to a general procedure by refluxing equimolar amounts of ninhydrin and the corresponding aminophenol in propan-2-ol for 2 h. The precipitate that formed was filtered off and recrystallized from toluene. The yields were 70—85%.

6-Benzylsulfonyl-5a-hydroxy-8,9-dimethyl-5a,6-dihydroindeno[2,1-*b*]quinoxalin-5-one (7a). M.p. 195—198 °C. The yield was 70%. Found (%): C, 66.42; H, 4.68; N, 6.41. $C_{24}H_{20}N_2O_4S$. Calculated (%): C, 66.66; H, 4.66; N, 6.48. ^{1}H NMR ($CDCl_3$), δ: 1.90 and 2.15 (both s, 3 H each, C(8)Me, C(9)Me); 3.48 (br.s, 1 H, OH); 4.59 and 5.04 (both d, 1 H each, CH_2, J = 14.0 Hz); 5.45 (s, 1 H, H(7)); 7.45—7.52 (m, 3 H, Ph); 7.63—7.68 (m, 2 H, Ph); 7.70 (td, 1 H, H(3), J = 7.5 and 1.3 Hz); 7.81 (td, 1 H, H(2), J = 7.5 and 1.3 Hz); 8.06 (d, 1 H, H(1), J = 7.5 Hz); 8.10 (d, 1 H, H(4), J = 7.5 Hz).

5a-Hydroxy-8-nitro-5a*H*-indeno[2,1-*b*]benzo-1,4-oxazin-5-one (7b). M.p. 299—302 °C. The yield was 85%. Found (%): C, 60.16; H, 2.61; N, 9.48. $C_{15}H_8N_2O_5$. Calculated (%): C, 60.81; H, 2.72; N, 9.45. ^{1}H NMR (DMSO-d_6), δ: 7.82 (d, 1 H, H(10), J = 9.3 Hz); 7.92 (td, 1 H, H(3), J = 7.6 and 1.0 Hz); 7.98—8.09 (m, 4 H, H(1), H(2), H(7), H(9)); 8.21 (d, 1 H, H(4), J = 7.6 Hz); 8.97 (br.s, 1 H, OH).

5a-Hydroxy-9-nitro-5a*H*-indeno[2,1-*b*]benzo-1,4-oxazin-5-one (7c). M.p. 315 °C. The yield was 75%. Found (%): C, 60.21; H, 2.63; N, 9.42. $C_{15}H_8N_2O_5$. Calculated (%): C, 60.81; H, 2.72; N, 9.45. ^{1}H NMR (DMSO-d_6), δ: 7.51 (d, 1 H, H(7), J = 9.2 Hz); 7.93 (td, 1 H, H(3), J = 7.5 and 1.1 Hz); 8.02—8.12 (m, 2 H, H(1), H(2)); 8.17—8.26 (m, 2 H, H(4), H(8)); 8.38 (d, 1 H, H(10), J = 3.4 Hz); 9.08 (br.s, 1 H, OH).

Table 1. Principal bond lengths (d) in the structure of **7g**

Bond	d/Å	Bond	d/Å
C(3)—C(4)	1.380(3)	C(7)—C(8)	1.393(3)
C(4)—C(4a)	1.400(3)	C(7)—C(6a)	1.398(3)
C(2)—C(3)	1.390(3)	C(7)—C(16)	1.543(3)
C(1)—C(2)	1.395(3)	C(6a)—O(6)	1.392(3)
C(11a)—N(11)	1.278(3)	O(6)—C(5a)	1.427(3)
C(11a)—C(11b)	1.475(3)	O(5a)—C(5a)	1.396(3)
C(11a)—C(5a)	1.500(3)	C(5)—C(5a)	1.537(3)
C(11b)—C(1)	1.383(3)	O(5)—C(5)	1.221(3)
C(11b)—C(4a)	1.398(3)	C(4a)—C(5)	1.479(3)
N(11)—C(10a)	1.414(3)	C(12)—C(15)	1.534(3)
O(10)—C(10)	1.367(3)	C(12)—C(13)	1.535(3)
C(10)—C(10a)	1.395(3)	C(12)—C(14)	1.536(4)
C(9)—C(10)	1.398(3)	C(16)—C(18)	1.531(3)
C(6a)—C(10a)	1.403(3)	C(16)—C(19)	1.532(3)
C(8)—C(9)	1.402(3)	C(16)—C(17)	1.535(4)
C(9)—C(12)	1.536(4)		

8-Chloro-5a-hydroxy-5a*H*-indeno[2,1-*b*]benzo-1,4-oxazin-5-one (7d). M.p. 290 °C. The yield was 80%. Found (%): C, 62.87; H, 2.75; N, 4.87. $C_{15}H_8ClNO_3$. Calculated (%): C, 63.05; H, 2.82; N, 4.90. ^{1}H NMR (DMSO-d_6), δ: 7.25 (d, 1 H, H(10), J = 8.6 Hz); 7.40 (dd, 1 H, H(9), J = 8.6 and 1.3 Hz); 7.65 (d, 1 H, H(7), J = 1.3 Hz); 7.80—8.15 (m, 4 H, H(1), H(2), H(3), H(4)); 8.93 (br.s, 1 H, OH).

8-Bromo-5a-hydroxy-5a*H*-indeno[2,1-*b*]benzo-1,4-oxazin-5-one (7e). M.p. 305—307 °C. The yield was 80%. Found (%): C, 54.32; H, 2.38; N, 4.21. $C_{15}H_8BrNO_3$. Calculated (%): C, 54.57; H, 2.44; N, 4.24. ^{1}H NMR (DMSO-d_6), δ: 7.21 (d, 1 H, H(10), J = 8.1 Hz); 7.43 (dd, 1 H, H(9), J = 8.1 and 1.5 Hz); 7.78 (d, 1 H, H(9), J = 1.5 Hz); 7.80—8.08 (m, 3 H, H(2), H(3), H(4)); 8.19 (d, 1 H, H(1), J = 7.6 Hz); 8.75 (br.s, 1 H, OH).

7,9-Di-*tert*-butyl-5a-hydroxy-5a*H*-indeno[2,1-*b*]benzo-1,4-oxazin-5-one (7f). M.p. 238—240 °C. The yield was 85%. Found (%): C, 76.17; H, 6.74; N, 3.73. $C_{23}H_{25}NO_3$. Calculated (%): C, 76.01; H, 6.93; N, 3.85. ^{1}H NMR ($CDCl_3$), δ: 1.35 and 1.47 (both s, 9 H each, C(7)Bu^t, C(9)Bu^t); 3.85 (br.s, 1 H, OH); 7.32 (d, 1 H, H(10), J = 3.1 Hz); 7.50 (d, 1 H, H(8), J = 3 Hz); 7.68 (td, 1 H, H(3), J = 7.5 and 1.0 Hz); 7.85 (td, 1 H, H(2), J = 7.5 and 1.0 Hz): 7.96 (d, 1 H, H(1), J = 7.5 Hz); 8.14 (d, 1 H, H(4), J = 7.5 Hz).

Table 2. Bond angles (ω) in the structure of **7g**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(3)—C(4)—C(4a)	117.5(2)	C(6a)—C(10a)—C(10)	120.0(2)	C(6a)—O(6)—C(5a)	112.6(2)
C(2)—C(3)—C(4)	121.3(2)	C(10)—C(10a)—N(11)	117.8(2)	O(5a)—C(5a)—O(6)	112.3(2)
C(1)—C(2)—C(3)	121.4(2)	C(6a)—C(10a)—N(11)	121.8(2)	O(5a)—C(5a)—C(11a)	108.4(2)
N(11)—C(11a)—C(11b)	128.8(2)	C(8)—C(9)—C(10)	115.7(2)	O(6)—C(5a)—C(11a)	110.6(2)
N(11)—C(11b)—C(5a)	122.6(2)	C(10)—C(9)—C(12)	122.5(2)	O(5a)—C(5a)—C(5)	111.1(2)
C(11b)—C(11a)—C(5a)	108.1(2)	C(8)—C(9)—C(12)	121.8(2)	O(6)—C(5a)—C(5)	110.1(2)
C(1)—C(11b)—C(4a)	121.1(2)	C(9)—C(8)—C(7)	126.1(2)	C(4b)—C(5a)—C(5)	104.0(2)
C(1)—C(11b)—C(11a)	129.8(2)	C(8)—C(7)—C(6a)	115.2(2)	O(5)—C(5)—C(4a)	127.7(2)
C(4a)—C(11b)—C(11a)	109.0(2)	C(8)—C(7)—C(16)	122.3(2)	O(5)—C(5)—C(5a)	126.1(2)
C(11b)—C(1)—C(3)	117.5(2)	C(6a)—C(7)—C(16)	122.6(2)	C(4a)—C(5)—C(5a)	106.2(2)
C(11a)—N(11)—C(10a)	114.7(2)	O(6)—C(6a)—C(7)	119.8(2)	C(11b)—C(4a)—C(4)	121.1(2)
O(10)—C(10)—C(10a)	118.7(2)	O(6)—C(6a)—C(10a)	118.6(2)	C(11b)—C(4a)—C(5)	110.4(2)
O(10)—C(10)—C(9)	120.3(2)	C(7)—C(6a)—C(10a)	121.5(2)	C(4)—C(4a)—C(5)	128.4(2)
C(9)—C(10)—C(10a)	121.0(2)				

7,9-Di-*tert*-butyl-5a,10-dihydroxy-5a*H*-indeno[2,1-*b*]benzo-1,4-oxazin-5-one (7g). M.p. 190 °C. The yield was 70%. Found (%): C, 72.74; H, 6.64; N, 3.62. $C_{23}H_{25}NO_4$. Calculated (%): C, 72.80; H, 6.64; N, 3.69. ^{1}H NMR ($CDCl_3$), δ: 1.42 and 1.43 (both s, 9 H each, C(7)Bu^t, C(9)Bu^t); 4.28 (br.s, 1 H, C(5a)OH); 7.19 (s, 1 H, C(10)OH); 7.38 (s, 1 H, H(8)); 7.67 (td, 1 H, H(3), J = 7.7 and 0.9 Hz); 7.84 (td, 1 H, H(2), J = 7.7 and 0.9 Hz); 7.96 (d, 1 H, H(1), J = 7.7 Hz); 8.11 (d, 1 H, H(4), J = 7.7 Hz).

X-ray diffraction study of compound 7g. Crystals of $C_{23}H_{25}O_4N \cdot CH_3C(O)CH_3$ are monoclinic, at 153 K a = 10.873(6) Å, b = 10.095(5) Å, c = 21.57(1) Å, β = 91.52(5)°, V = 2366(2) Å^3, the crystal dimensions are 0.5×0.4×0.3 mm, space group $P2_1/n$, Z = 4, d_{calc} = 1.228 g cm^{-3}, $F(000)$ = 936, μ = 0.085 mm^{-1}.

The intensities of 4402 reflections (4169 independent reflections, R_{int} = 0.055) were measured on an automated four-circle Siemens P3/PC diffractometer (graphite monochromator, Mo-Kα radiation, θ-2θ scanning technique, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the use of the SHELXTL PLUS program package.[9] The positions of all hydrogen atoms, except for those of the MeC(O)Me molecule of solvation, were revealed from the difference electron density synthesis. The positions of the H atoms of the acetone molecule were calculated geometrically. The anisotropic refinement (isotropic refinement for the hydrogen atoms, except for the H atoms of all methyl groups, which were refined using the riding model with fixed $U_{iso} = 1.5U_{eq}$ of the C atoms to which the corresponding H atoms are attached) based on F^2 by the full-matrix least-squares method (363 parameters) using 4104 reflections converged to R_1 = 0.050 (for 2568 reflections with $F > 4\sigma(F)$), wR_2 = 0.136, S = 0.90. In addition, the refinement was performed with restraints imposed on the following bond lengths in the solvate molecule: (O(1S′)—C(2S′), 1.210(2) Å; C(1S′)—C(2S′), 1.500(2) Å; C(2S′)—C(3S′), 1.500(2) Å. The atomic coordinates in the structure of **7g** and the complete tables of the bond lengths and bond angles were deposited with the Cambridge Structural Database. The principal bond lengths and the bond angles in **7g** are given in Tables 1 and 2, respectively.

This work was financially supported by the Russian Foundation for Basic Research (Project Nos. 00-15-97359, 00-03-32807a, 98-03-32903a, and 99-03-33496a).

References

1. L. P. Olekhnovich, V. I. Simakov, N. G. Furmanova, E. P. Ivakhnenko, O. Yu. Rekhlova, T. A. Ryskina, and Yu. A. Zhdanov, *Zh. Obshch. Khim.*, 1992, **62**, 885 [*Russ. J. Gen. Chem.*, 1992, **62** (Engl. Transl.)].
2. L. P. Olekhnovich, S. N. Lyubchenko, I. N. Shcherbakov, S. V. Kurbatov, and V. A. Kogan, *Ros. Khim. Zh.* (*Zh. Ros. Khim. Obshch. im. D. I. Mendeleeva)*, 1996, **40**, 139 [*Mendeleev Chem. J.*, 1996, **40** (Engl. Transl.)].
3. H. J. Roth and W. Kok, *Arch. Pharm.*, 1976, **309**, 81.
4. A. Schonberg and E. Singer, *Chem. Ber.*, 1977, **110,** 3954.
5. L. P. Olekhnovich, S. N. Lyubchenko, V. I. Simakov, A. I. Shif, S. V. Kurbatov, A. V. Lesin, G. S. Borodkin, E. P. Ivakhnenko, and Yu. A. Zhdanov, *Dokl. Akad. Nauk,* 1999, **369**, 632 [*Dokl. Chem.*, 1999 (Engl. Transl.)].
6. N. S. Zefirov, V. A. Palyulin, and E. E. Dashevskaya, *J. Phys. Org. Chem.*, 1990, **3**, 147.
7. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim.*, 1989, **58**, 713 [*Russ. Chem. Rev.*, 1989, **58** (Engl. Transl.)].
8. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. J. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1.
9. G. M. Sheldrick, *SHELXTL PLUS. PC Version, A System of Computer Programs for the Determination of Crystal Structure from X-ray Diffraction Data, Rev. 5.02*, Seimens Analytical X-ray Instruments Inc., Germany, 1994.

Received August 1, 2000;
in revised form January 24, 2001