Atropoenantiomerism of the *Z*-adduct of 2,3-diethoxycarbonyl-6,6-dimethyl-5,6-dihydro-4-pyridone with dimethyl acetylenedicarboxylate: synthesis and structure in solution and in the crystal

R. G. Kostyanovsky,[a] Yu. I. El'natanov,[a] I. I. Chervin,[a] S. V. Konovalikhin,[b] A. B. Zolotoi,[b] and L. O. Atovmyan[b]*

[a]*N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117977 Moscow, Russian Federation. Fax: 007 (095) 938 2156. E-mail: kost@chph.rc.ac.ru*

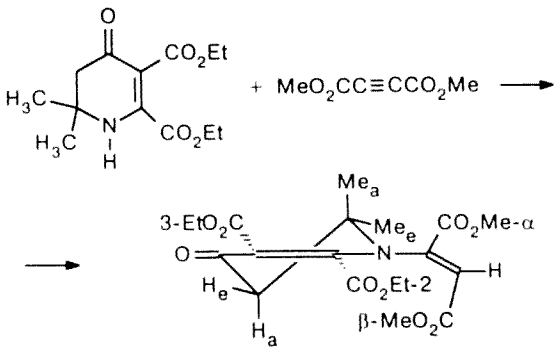
[b]*Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: 007 (095) 265 5714*

The title adduct (**1**) was synthesized, and its conformationally and configurationally rigid chiral structure in solution and in the crystal was established by NMR spectroscopy and by X-ray structural analysis. Atropoenantiomers of **1** were observed by the ^{1}H NMR method in the presence of a chiral shift reagent. A barrier to their interconversion was determined, $\Delta G^{\neq} > 25$ kcal mol^{-1} (200 °C).

Key words: 2,3-diethoxycarbonyl-6,6-dimethyl-5,6-dihydro-4-pyridone, adduct with dimethyl acetylenedicarboxylate, atropoenantiomerism, X-ray structural analysis, interconversion, ^{1}H and ^{13}C NMR.

Atropoisomerism is a rapidly developing division of stereochemistry.[1] In this work, the nature of the atropoisomerism of adduct **1**, which was obtained by the reaction of 2,3-diethoxycarbonyl-6,6-dimethyl-5,6-dihydro-4-pyridone[2] with dimethyl acetylenedicarboxylate, has been studied (Scheme 1).

Scheme 1



1

The composition and the structure of adduct **1** have been unambiguously established by elemental analysis, spectral methods (see the Experimental section), and X-ray structural analysis (Fig. 1).

Based on the value of $^3J_{CH}^{cis} = 4.4$ Hz (the carbonyl carbon atom of the α-CO_2Me group and the olefin proton) it was established that the *N*-substituent at the double bond that formed has a *Z*-configuration because for isomer *E*-**1** the corresponding constant $^3J_{CH}^{trans} = 8.2$ Hz[2] (*cf.* Ref. 3). Based on the data of the ^{1}H and ^{13}C NMR spectra of adduct **1**, it may be concluded that the methylene protons of the ring as well as the protons and carbon atoms of the methyl groups of the ring are nonequivalent. This is attributable to a rigid half-chair conformation of this ring (Scheme 1), which is confirmed by the presence of long-range spin-spin interaction between the protons of one methyl group and one of the methylene protons at C(5), $^4J_{Me_aHa} = 0.8$ Hz. This aspect of the ^{1}H NMR spectrum remained unchanged when a solution of **1** in Ph_2O was heated to 200 °C. Therefore, adduct **1** has a chiral structure, which manifests itself also in the diastereotropicity of the methylene protons in the 2-CO_2Et and 3-CO_2Et groups. In this case, because of hindered rotation about the N—substituent bond, stable atropoenantiomers (rather than atropoisomers with different orientations of the N-substituent with respect to the ring, which has an invariant conformation) occur. The atropoenantiomers were detected by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Eu(tfc)$_3$ from the splitting of the signals of methyl protons at 1.54 ppm ($\Delta\nu = 12$ Hz) and 3.91 ppm ($\Delta\nu = 3$ Hz). The lower limit of the barrier to their interconversion was estimated based on nonequivalence of the protons of the Me_a and Me_e groups ($\Delta\nu = 12.3$ Hz) at 200 °C, $\Delta G^{\neq} > 25$ kcal mol^{-1}.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1796—1799, July, 1996.

1066-5285/96/4507-1707 $15.00

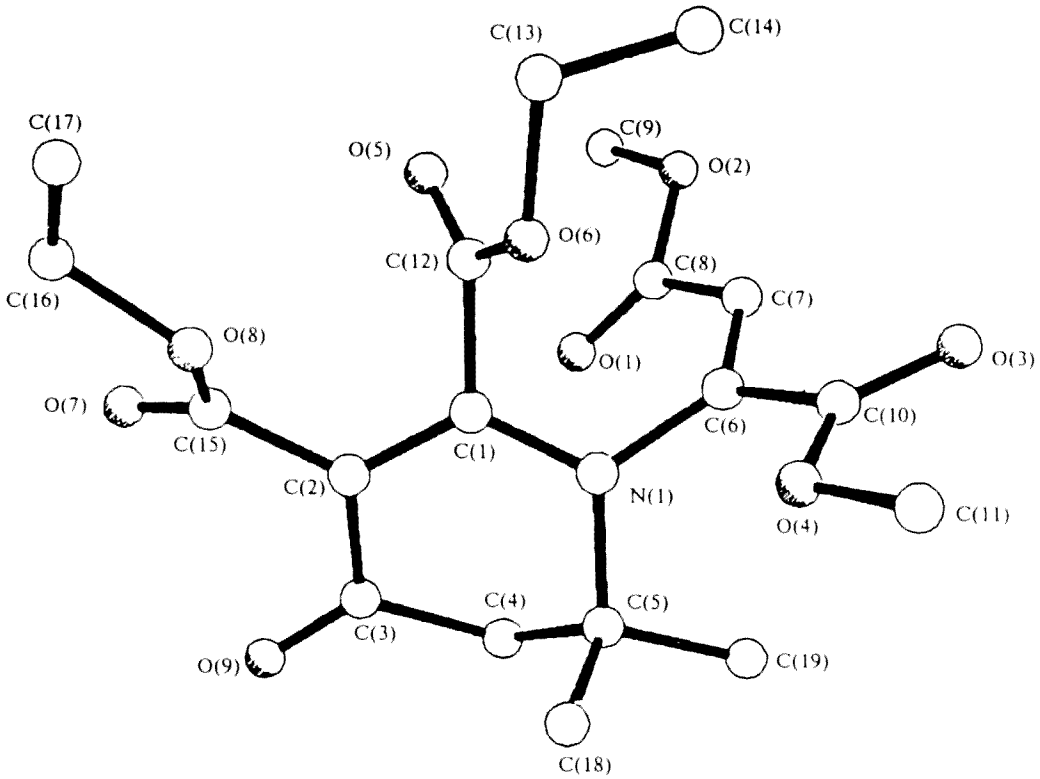
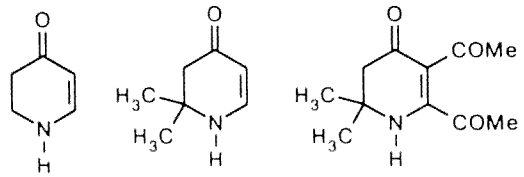


Fig. 1. Overall view of molecule **1**. H atoms were omitted for clarity.

Note that no hindered rotation or conversion of the ring were observed in the initial dihydro-4-pyridone or its analogs[2,3] or in the adducts of dialkyl acetylenedicarboxylates with triacetonamine.[4,5]

With the aim of elucidating the nature of the atropoenantiomerism observed, we carried out an X-ray structural analyis of the crystals of adduct **1** (Figs. 1 and 2, Tables 1—3). It follows from the results obtained that the N-substituent is twisted with respect to the ring; the C(7)C(6)C(10)O(3)O(4)C(11) angle between the N(1),C(1),C(5) and C(9),O(2),C(8),O(1) planes is 66.5 °. Therefore, n—π conjugation with the N-substituent is impossible, and in fact no shortening of the N(1)—C(6) bond occurs.

The conformation of the ring (Fig. 2, Table 3) is close to that shown in Scheme 1. The shortening of the N(1)—C(1) (1.341(3) Å) and C(2)—C(3) (1.439(3) Å) bonds and the elongation of the C(1)=C(2) (1.361(4) Å) and C(3)=O(9) (1.223(4) Å) bonds[6] are indicative of the occurrence of conjugation in the N(1)—C(1)=C(2)—C(3)=O(9) chain. However, the conjugation is weakened because of the nonplanarity of this fragment indicated by the substantial deviations of the endocyclic torsion angles from 0 or 180° (Table 3). To gain an understanding of the reason for these deviations, we carried out calculations of model compounds **2**—**4** by the PM3 method with full optimization of geometry.*



2 **3** **4**

(-2.2 ÷8.0) (-0.3÷21.2) (-19.8÷41.0)

These results demonstrate that the conformation actually observed is determined by spatial interactions between the substituents. An important consequence of these interactions is the occurrence of a virtually eclipsed orientation of the C(6) and C(19) atoms (Table 3) and, apparently, a substantial elongation of the N(1)—C(5) bond caused by this conformation. As a result, the rotation about the N—substituent bond is hindered pri-

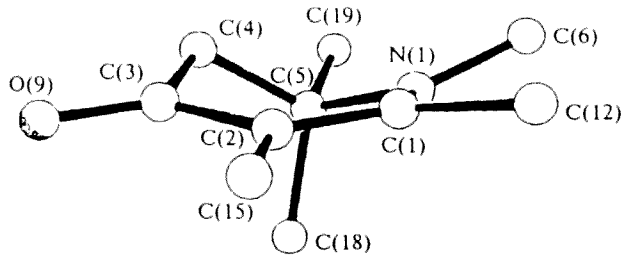


Fig. 2. Conformation of the ring of molecule **1**.

* The ranges of the values of the endocyclic torsion angles (deg.) are given in parentheses.

Table 1. Atomic coordinates in the structure of **1**

Atom	*x*	*y*	*z*
N(1)	−0.0204(2)	0.7529(2)	0.4046(2)
O(1)	−0.0582(3)	0.5659(2)	0.2177(2)
O(2)	0.1520(3)	0.3845(2)	0.1520(2)
O(3)	0.1758(4)	0.5772(2)	0.5725(3)
O(4)	0.1097(3)	0.7715(2)	0.5912(2)
O(5)	0.2843(3)	0.6173(2)	0.0918(2)
O(6)	0.3193(2)	0.7083(2)	0.2743(2)
O(7)	−0.0023(3)	0.8736(2)	0.0319(2)
O(8)	0.1789(3)	0.8814(2)	0.1237(2)
O(9)	−0.3142(3)	0.9666(2)	0.2700(3)
C(1)	0.0464(3)	0.7673(2)	0.2875(2)
C(2)	−0.0428(3)	0.8434(2)	0.2400(3)
C(3)	−0.2231(4)	0.8947(2)	0.3026(3)
C(4)	−0.2944(3)	0.8489(3)	0.4093(3)
C(5)	−0.2004(3)	0.8387(2)	0.4985(3)
C(6)	0.0654(3)	0.6465(2)	0.4258(3)
C(7)	0.1049(4)	0.5336(2)	0.3459(3)
C(8)	0.0533(4)	0.5022(2)	0.2352(3)
C(9)	0.1151(5)	0.3409(4)	0.0363(4)
C(10)	0.1213(4)	0.6604(3)	0.5370(3)
C(11)	0.1650(7)	0.7931(4)	0.6997(4)
C(12)	0.2320(3)	0.6892(2)	0.2048(3)
C(13)	0.5031(4)	0.6327(4)	0.2073(4)
C(14)	0.5472(6)	0.5468(7)	0.2696(8)
C(15)	0.0429(4)	0.8671(2)	0.1203(3)
C(16)	0.2847(6)	0.8884(5)	0.0003(5)
C(17)	0.4335(11)	0.8663(13)	−0.0038(11)
C(18)	−0.2085(4)	0.9620(3)	0.5736(3)
C(19)	−0.2711(4)	0.7826(3)	0.5978(3)
H(1)	0.1842(33)	0.4630(24)	0.3666(27)
H(2)	0.1004(74)	0.4100(55)	−0.0367(62)
H(3)	0.1812(85)	0.2514(61)	−0.0250(70)
H(4)	−0.0094(64)	0.3482(46)	0.0672(51)
H(5)	0.2773(55)	0.7326(41)	0.6727(45)
H(6)	0.2031(56)	0.8681(41)	0.6964(45)
H(7)	0.0664(94)	0.7895(67)	0.7746(74)
H(8)	−0.2902(35)	0.7693(26)	0.3610(29)
H(9)	−0.4145(42)	0.8982(31)	0.4665(36)
H(10)	−0.1340(44)	0.9484(32)	0.6288(36)
H(11)	−0.1397(44)	0.9986(32)	0.5045(36)
H(12)	−0.3314(63)	1.0144(47)	0.6379(52)
H(13)	−0.2059(46)	0.7729(33)	0.6468(38)
H(14)	−0.3909(46)	0.8258(35)	0.6402(39)
H(15)	−0.2606(47)	0.6933(35)	0.5359(39)

Table 2. Bond lengths and bond angles in the structure of **1**

Bond	*d*/Å	Bond	*d*/Å
O(1)—C(8)	1.182(4)	O(2)—C(8)	1.342(2)
O(2)—C(9)	1.448(5)	O(3)—C(8)	1.206(4)
O(4)—C(10)	1.312(3)	O(4)—C(11)	1.443(6)
O(5)—C(8)	1.191(3)	O(6)—C(12)	1.305(2)
O(6)—C(13)	1.484(3)	O(7)—C(15)	1.185(4)
O(8)—C(15)	1.329(4)	O(8)—C(16)	1.462(5)
O(9)—C(4)	1.223(4)	N(1)—C(1)	1.341(3)
N(1)—C(5)	1.506(2)	N(1)—C(6)	1.420(3)
C(1)—C(2)	1.361(4)	C(1)—C(12)	1.510(3)
C(2)—C(3)	1.439(3)	C(2)—C(15)	1.476(4)
C(3)—C(4)	1.499(4)	C(4)—C(5)	1.502(5)
C(5)—C(18)	1.523(4)	C(5)—C(19)	1.522(5)
C(6)—C(7)	1.321(3)	C(6)—C(10)	1.467(4)
C(7)—C(8)	1.457(5)	C(13)—C(14)	1.422(11)
C(16)—C(17)	1.294(12)		

Angle	φ/deg	Angle	φ/deg
C(8)O(2)C(9)	115.2(3)	C(10)O(4)C(11)	117.0(3)
C(12)O(6)C(13)	117.3(2)	C(15)O(8)C(16)	115.1(3)
C(1)N(1)C(5)	118.0(2)	C(1)N(1)C(6)	120.1(2)
C(5)N(1)C(6)	120.7(2)	N(1)C(1)C(2)	124.3(2)
N(1)C(1)C(12)	115.7(2)	C(2)C(1)C(12)	120.1(2)
C(1)C(2)C(3)	119.1(3)	C(1)C(2)C(15)	120.9(3)
C(3)C(2)C(15)	119.9(3)	O(9)C(3)C(2)	124.1(3)
O(9)C(3)C(4)	121.2(3)	C(2)C(3)C(4)	114.7(3)
C(3)C(4)C(5)	112.1(2)	N(1)C(5)C(4)	106.2(3)
N(1)C(5)C(18)	108.6(3)	N(1)C(5)C(19)	110.2(3)
C(4)C(5)C(18)	111.1(2)	C(4)C(5)C(19)	109.4(3)
C(18)C(5)C(19)	111.2(3)	N(1)C(6)C(7)	123.1(3)
N(1)C(6)C(10)	119.2(3)	C(7)C(6)C(10)	117.6(3)
C(6)C(7)C(8)	125.3(3)	O(1)C(8)C(7)	127.8(2)
O(1)C(8)O(2)	122.9(3)	O(2)C(8)C(7)	109.3(3)
O(3)C(10)C(6)	123.2(3)	O(3)C(10)O(4)	123.7(3)
O(4)C(10)C(6)	113.1(3)	O(5)C(12)C(1)	121.3(3)
O(5)C(12)O(6)	126.9(2)	O(6)C(12)C(1)	111.7(3)
O(7)C(15)C(2)	125.3(4)	O(7)C(15)O(8)	123.5(3)
O(8)C(15)C(2)	111.3(2)	O(8)C(16)C(17)	110.3(7)

Table 3. Torsion angles in molecule **1**

Angle	ω/deg
N(1)C(1)C(2)C(3)	−12.5
N(1)C(5)C(4)C(3)	57.6
N(1)C(6)C(7)C(8)	−6.4
C(1)C(2)C(3)C(4)	−4.8
C(1)C(2)C(3)O(9)	177.8
C(2)C(3)C(4)C(5)	41.2
C(2)C(1)C(12)O(5)	−58.1
C(2)C(1)C(12)O(6)	124.3
C(1)C(2)C(15)O(7)	139.3
C(1)C(2)C(15)O(8)	−41.2
C(2)C(1)N(1)C(6)	−159.7
C(1)N(1)C(6)C(7)	−59.4

marily by the Me_c and CO_2Et-2 groups (Scheme 1). In this case, the C(1)—C(12) bond is substantially longer than the C(2)—C(15) bond (Table 2) and is also longer than its normal value (1.470 Å, *cf.* Ref. 6); this elongation occurs, apparently, owing to strong steric interactions in this portion of the molecule.

The CO_2Et groups at the C(1) and C(2) atoms are not involved in conjugation because these groups are rotated with respect to the double bond of the ring by 58.7° and 50.9°, respectively (*cf.* the data in Refs. 2 and 5). The geometrical modeling demonstrates that when the C(1)=C(2) and C(12)=O(5) or C(12)—O(6) bonds are in *cis* orientations, the O atoms of the CO_2Et group at the C(1) atom and the C(6) atom are in proximity (2.45 Å (O(5)...C(6)) or 2.79 Å (O(6)...C(6)). The twist of the CO_2Et group at the C(2) atom results in the occurrence of O(7)...C(12) contact (2.32 Å, for the *cis* orientation of the C(1)=C(2) and C(15)=O(7) bonds)

and O(8)...C(12) contact (2.64 Å, for the *cis* orientation of the C(1)=C(2) and C(15)=O(8) bonds).

In molecules containing planar aminomaleate fragments, which we have studied previously, one of the ester groups is located in the plane of the double bond.[2,5] This conformation is stabilized by n(O)...π^*(C=O) interaction; the steric interactions occurring in this case are offset by an increase in the C=C—C(sp^2) bond angles to 124.8—129.7°. In the structure of adduct **1**, this increase in the exocyclic C(2)C(1)C(12) bond angle would lead to the shortening of the C(12)...C(6) bond, which is already rather short (2.743(4) Å). An increase in the C(1)C(2)C(15) angle would result in the shortening of the C(15)...O(9) bond to 2.874(4) Å. Therefore, the presence of the bulky N-substituent hinders a *cis* orientation of CO_2Et groups with respect to the double bond of the ring. The remaining bond lengths and bond angles have standard values. In the crystal of adduct **1**, no shortened intermolecular contacts are observed. Therefore, it is not surprising that the results of X-ray structural analysis agree with the NMR data for solutions.

Experimental

The NMR spectra were recorded on WM-400 (^{1}H 400.13 MHz; ^{13}C 100.62 MHz) and JNM-C-60-HL (^{1}H, 60 MHz) spectrometers. The mass spectrum of **1** was obtained on a Finnigan 4021 mass spectrometer with an ionizing voltage of 30 eV. The IR spectrum was measured on a UR-20 spectrophotometer using KBr pellets. Elemental analysis was carried out on a CHNOS-1106 analyzer. The melting point was determined on a Boetius PHMK-0.5 table at a heating rate of 4—5 °C/min. The initial dihydro-4-pyridone was obtained by the procedure reported previously.[2]

Dimethyl 2-(2,3-diethoxycarbonyl-6,6-dimethyl-4-oxo-2,4,5,6-tetrahydropyrid-1-yl)fumarate, 1. A mixture of 2,3-diethoxycarbonyl-6,6-dimethyl-5,6-dihydro-4-pyridone (0.54 g, 2 mmol) in MeOH (3 mL) and dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in ether (10 mL) was kept at 20 °C for 1 month. After evaporation of the solvents, the residue was recrystallized from Et_2O. Large, transparent, slightly yellow parallelepiped-shaped crystals were obtained in a yield of 0.52 g (65.7 %), m. p. 93—94 °C. Found (%): C, 55.19; H, 6.05; N, 3.49. $C_{19}H_{25}NO_9$. Calculated (%): C, 55.47; H, 6.08; N, 3.41. IR (KBr pellets), ν/cm^{-1}: 1745, 1720, 1660 (sh), 1645 (CO), 1562 (C=C). Mass spectrum (EI, 30 eV), m/z (I_{rel} (%)): 411 $[M]^+$ (66.6); 396 (11); 366 (28); 352 (54); 338 (64.8); 322 (30); 321 (25.2); 282 (61.2); 278 (25.2); 224 (25); 194 (33.3); 178 (14.4); 83 (100). ^{1}H NMR ($CDCl_3$) δ, J/Hz: 1.21 (t, 3 H, 3-MeCH$_2$O, ^3J = 7.0); 1.28 (t, 3 H, 2-MeCH$_2$O, ^3J = 7.0); 1.29 (s, 3 H, Me$_e$); 1.54 (d, 3 H, Me$_a$, $^4J_{MeaHa}$ = 0.8); 2.21 (d, 1 H, H$_e$, ^2J = −15.3); 3.28 (d.q, 1 H, H$_a$, ^2J = −15.3, ^4J = 0.8); 3.80 and 3.91 (s, 2×3 H, 2 MeO); 4.16 (m, 2 H, 3-MeCH$_2$O, ABX$_3$, $\Delta\nu_{AB}$ = 5.0, ^2J = −11.3); 4.20 (m, 2 H, 2-MeCH$_2$O, ABX$_3$, $\Delta\nu_{AB}$ = 21.0, ^2J = −11.0); 7.04 (s, 1 H, HC=); at 60 MHz in Ph_2O: $\Delta\nu$Me2C/Hz (T/K): 22.5 (293), 18.0 (373), 15.0 (423), 14.2 (443), 12.3 (473).

^{13}C NMR ($CDCl_3$) δ, J/Hz: 13.30 and 13.89 (q.t, MeCH$_2$, ^1J = 127.2, ^2J = 3.6); 22.51 (q.m, Me$_e$, ^1J = 126.4, ^3J = 3.6); 25.68 (q.m, Me$_a$, ^1J = 127.9, ^3J = 4.4); 49.31 (t.m, CH$_2$CO, ^1J = 131.5, ^3J = 4.4); 52.34 and 53.20 (q, MeO, ^1J = 148.5); 60.3 (m, CMe$_2$, ^2J = 4.4); 61.28 and 62.24 (t.q, CH$_2$Me, ^1J = 147.5, ^2J = 4.4); 129.8 (d, CH, ^1J = 167.1); 140.0 (br.s, NC=); 156.4 (s, =CCO); 162.5 and 164.4 (t, CO$_2$Et, ^3J = 3.6); 162.72 (d.q, CO$_2$Me-β, ^2J = ^3J = 4.4); 163.43 (d.q, CO$_2$Me-α, $^3J_1$ = $^3J_2$ = 4.4); 189.02 (t, CO, ^2J = 5.8).

X-ray structural analysis of adduct 1. The principal crystallographic data are as follows: $C_{19}H_{25}NO_9$, M = 411.4, a = 9.211(2), b = 12.347(3), c = 11.101(2) Å, α = 104.11(2)°, β = 12.45(2)°, γ = 71.68(2)°, V = 1059.8(8) Å^3, space group $P\bar{1}$, Z = 2, d_{calc} = 1.29 g/cm^3. A total of 2336 reflections with $I > 3\sigma(I)$ were collected on an automated four-circle RED-4 diffractometer (Cu-K$_\alpha$ radiation, absorption was ignored, μ (Cu-K$_\alpha$) = 8.7 cm^{-1}).

The structure was solved by the direct method; positions of H atoms were located from difference syntheses. The methyl carbon atoms of the CO_2Et groups have large amplitudes of thermal vibrations, and these atoms are involved in shortened C—C bonds, which indicates that these atoms are disordered in the crystal. Because of this, the H atoms at the C(13), C(14), C(16), and C(17) atoms were not located.

The structure was refined by the full-matrix least-squares method with anisotropic thermal parameters for C, N, and O atoms and with isotropic thermal parameters for H atoms. The final value of the R factor was 0.065. All calculations were carried out using the Rentgen-75 program.

Quantum-chemical calculations of model molecules **2**—**4** were carried out by the PM3 method with full optimization of geometry using the MOPAC 6.0 program.

This work was supported by the Russian Foundation for Basic Research (Project No. 94-03-08730).

References

1. M. Oki, in *Topics in Stereochemistry*, Ed. N. L. Allinger, E. L. Eliel, and S. H. Wilen, v. **14**, Scientific Publ., New York, 1983, p. 1.
2. R. G. Kostyanovsky, Yu. I. El'natanov, I. I. Chervin, S. V. Konovalikhin, L. O. Atovmyan, and A. Rauk, *Mendeleev Commun.*, 1996, 106.
3. N. L. Zaichenko, I. I. Chervin, V. N. Voznesenskii, Yu. I. El'natanov, and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 779 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37** (Engl. Transl.)].
4. M. M. Kats, E. F. Lavretskaya, I. I. Chervin, Yu. I. El'natanov, and R. G. Kostyanovsky, *Khim.-Farm. Zh.*, 1987, 675 [*Pharm. Chem. J.*, 1987 (Engl. Transl.)].
5. R. G. Kostyanovsky, Yu. I. El'natanov, I. I. Chervin, S. V. Konovalikhin, A. B. Zolotoi, and L. O. Atovmyan, *Mendeleev Commun.*, 1996, no. 4.
6. F. H. Allen, O. Kennard, D. G. Watson, L. Bramer, A. G. Orgen, and R. Taylor, *J. Chem. Soc., Perkin Trans., 2*, 1987, 1.
7. V. I. Andrianov, Z. Sh. Safina, and B. L. Tarnopol'skii, *Rentgen-75. avtomatizirovannaya systema programm dlya rasshifrovki struktur kristallov* [*Rentgen-75: Automated Program Package for Crystal Structure Determination*], Chernogolovka, 1975 (in Russian).

Received January 22, 1996