Synthesis and X-ray diffraction study of 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid

K. A. Krasnov,[a]* *V. G. Kartsev,*[b] *and V. N. Khrustalev*[c]

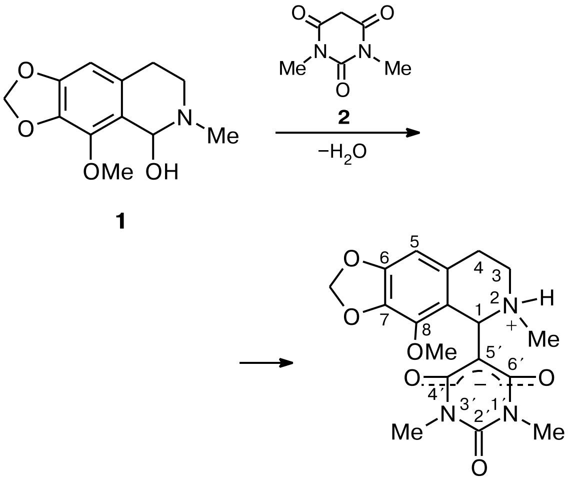
[a]*I. I. Mechnikov St.-Petersburg State Medical Academy,*
47 Piskarevsky prosp., 195067 St.-Petersburg, Russian Federation.
Fax: +7 (812) 350 4428. E-mail: veselkoff@mail.ru
[b]*INTERBIOSCREEN Joint-Stock Company,*
7a Institutskii prosp., 143432 Chernogolovka, Moscow Region, Russian Federation.
Fax: +7 (095) 913 2114. E-mail: screen@ibscreen.ru
[c]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,*
28 ul. Vavilova, 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5085. E-mail: vkh@xrlab.ineos.ac.ru

The reaction of cotarnine with 1,3-dimethylbarbituric acid afforded 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid. Its crystal structure was established by X-ray diffraction analysis and the structure in solution was studied by ^{1}H NMR spectroscopy. This compound has a zwitterionic structure. In the crystal, the molecules are linked in dimers by intermolecular hydrogen bonds, and in solutions, the dimers occur in equilibrium with the monomers.

Key words: cotarnine, 1,3-dimethylbarbituric acid, 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid, X-ray diffraction analysis, NMR spectroscopy.

It is known[1] that many derivatives of pyrimidine-2,4,6-trione (barbituric acid) are prone to various types of prototropic tautomerism, *viz.*, keto-enol, lactim-lactam, *etc.* If a molecule contains a basic group, the proton transfer can lead to the formation of zwitterionic systems, such as 5-amino derivatives[2] and sulfonium ylides of barbituric acid,[3] which belong to internal salts and mesomeric betaines, respectively. Heterocyclic derivatives of pyrimidine-2,4,6-trione, *viz.*, 1,3-dimethyl-5-(3-methyl-1-benzoimidazol-1-yl)barbituric acid,[4] 5-(3-amino-3-deoxy-β-D-glucopyranosyl)barbituric acid,[5] and 3-ethyl-2-(1,3-dimethyl-2,4,6-trioxo-1,3-diazacyclohexan-5-yl)-1,2,3,4,5,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine,[6] have analogous zwitterionic structures.

We found that the reaction of 8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-ol (alkaloid cotarnine) (**1**) with 1,3-dimethylbarbituric acid (**2**) afforded 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid (**3**) as a new zwitterionic heterocyclic system.



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The structure of **3** was studied by mass spectrometry and ^{1}H NMR spectroscopy. The NMR spectra provided evidence for the existence of isomers of **3**, but did not allow us to unambiguously interpret their structures. The crystal structure of compound **3** was established by X-ray diffraction analysis.

Single crystals of **3** were prepared as a 1 : 1 complex with $CHCl_3$.

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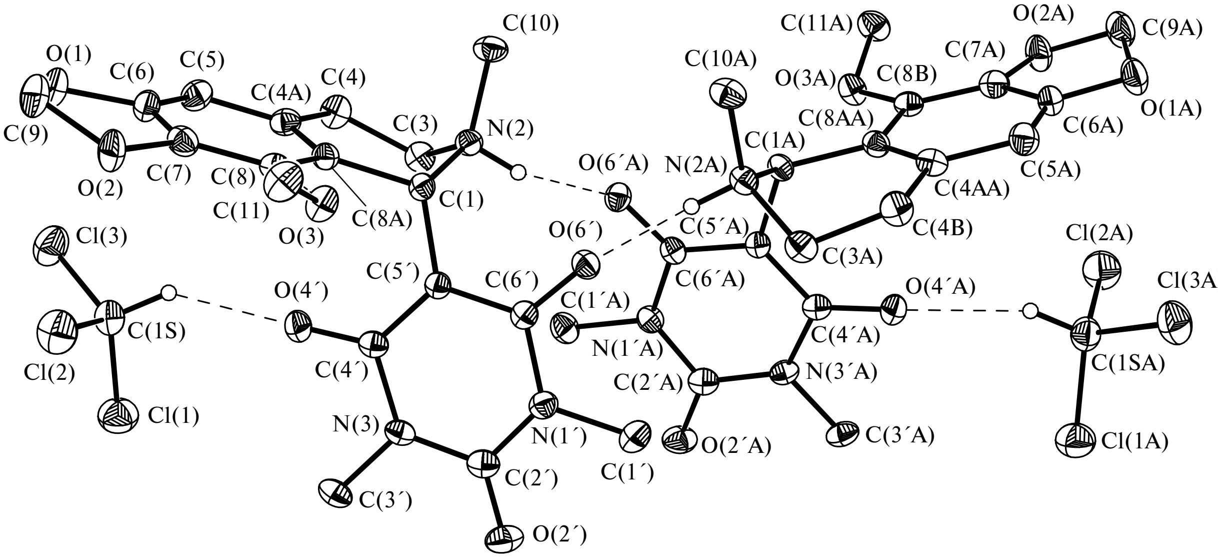


Fig. 1. Structure of the H-bonded dimers of molecules **3** with 50% thermal-motion probability ellipsoids; hydrogen bonds are indicated by dashed lines.

The X-ray diffraction study demonstrated that the three-dimensional structure of compound **3** differs from the zwitterionic systems of the pyrimidine-2,4,6-trione series studied earlier[4—6] in a number of features. The absence of intramolecular hydrogen bonds in molecule **3** was the most unexpected. Only intermolecular hydrogen bonds were observed in the crystal (Fig. 1). It should be noted that the bond lengths in the pyrimidinetrione moiety of compound **3** (Table 1) are virtually identical with those observed in related structures.[4—6]

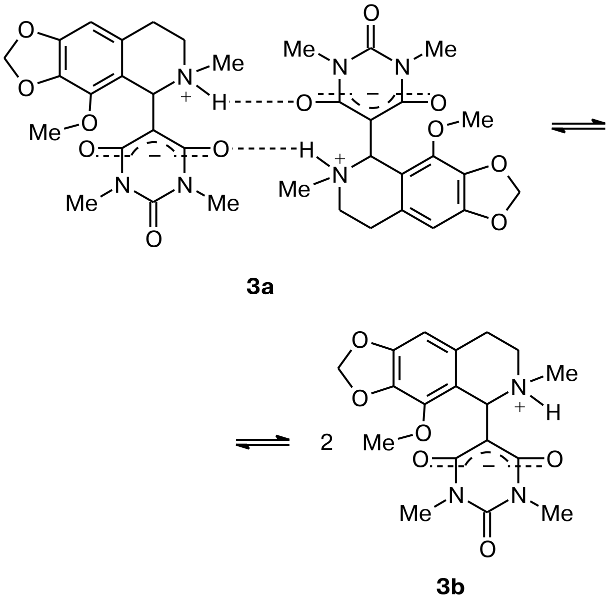
The negative charge in zwitterion **3** is delocalized over the β-dicarbonyl fragment O(4′)—C(4′)—C(5′)—C(6′)—O(6′) of barbituric acid, as evidenced by the bond lengths (Table 1) as well as by the planar structure of the pyrimidine ring (the maximum deviation of the atoms from the mean plane is 0.014 Å).

In molecule **3**, the angle between the planes of the tetrahydroisoquinoline and pyrimidine fragments is close to 90° (91.3°), which is typical of derivatives of barbituric acid containing rather bulky substituents at C(5).[6,7] Apparently, it is the stability of this conformation with the proton of the $N^{(+)}H$ group remote from the O(4′) and O(6′) atoms that is responsible for the fact that intramolecular hydrogen bonding becomes unfavorable and, as a consequence, gives rise to "cross" intermolecular hydrogen bonds observed in the crystal of compound **3**.

Compound **3** is the *rac-R**,*S** diastereomer containing two asymmetric atoms (C(1) and N(2)). The crystal of **3** is a racemate. The molecules related by a twofold axis are linked in dimers (see Fig. 1) by the rather strong N(2)—H...O(6′A) hydrogen bonds ($-x$, y, $-z + 1/2$): N...O, 2.705(3) Å; H...O, 1.89(3) Å; N—H...O, 151(2)°. The geometric parameters of the possible intermolecular N(2)—H...O(6′) interaction (N...O, 3.082(3) Å; H...O, 2.50(3) Å; N—H...O, 124(2)°) indicate that this hydrogen bond is absent. In the crystal, the molecules are packed in

Table 1. Bond lengths (*d*) in the barbituric acid fragment of compound **3**

Bond	*d*/Å	Bond	*d*/Å
N(1′)—C(2′)	1.384(3)	N(3′)—C(3′)	1.465(3)
N(1′)—C(6′)	1.405(3)	C(4′)—O(4′)	1.236(3)
N(1′)—C(1′)	1.469(3)	C(4′)—C(5′)	1.417(3)
C(2′)—O(2′)	1.232(3)	C(5′)—C(6′)	1.409(3)
C(2′)—N(3′)	1.374(3)	C(5′)—C(1)	1.508(3)
N(3′)—C(4′)	1.420(3)	C(6′)—O(6′)	1.252(2)



3a

3b

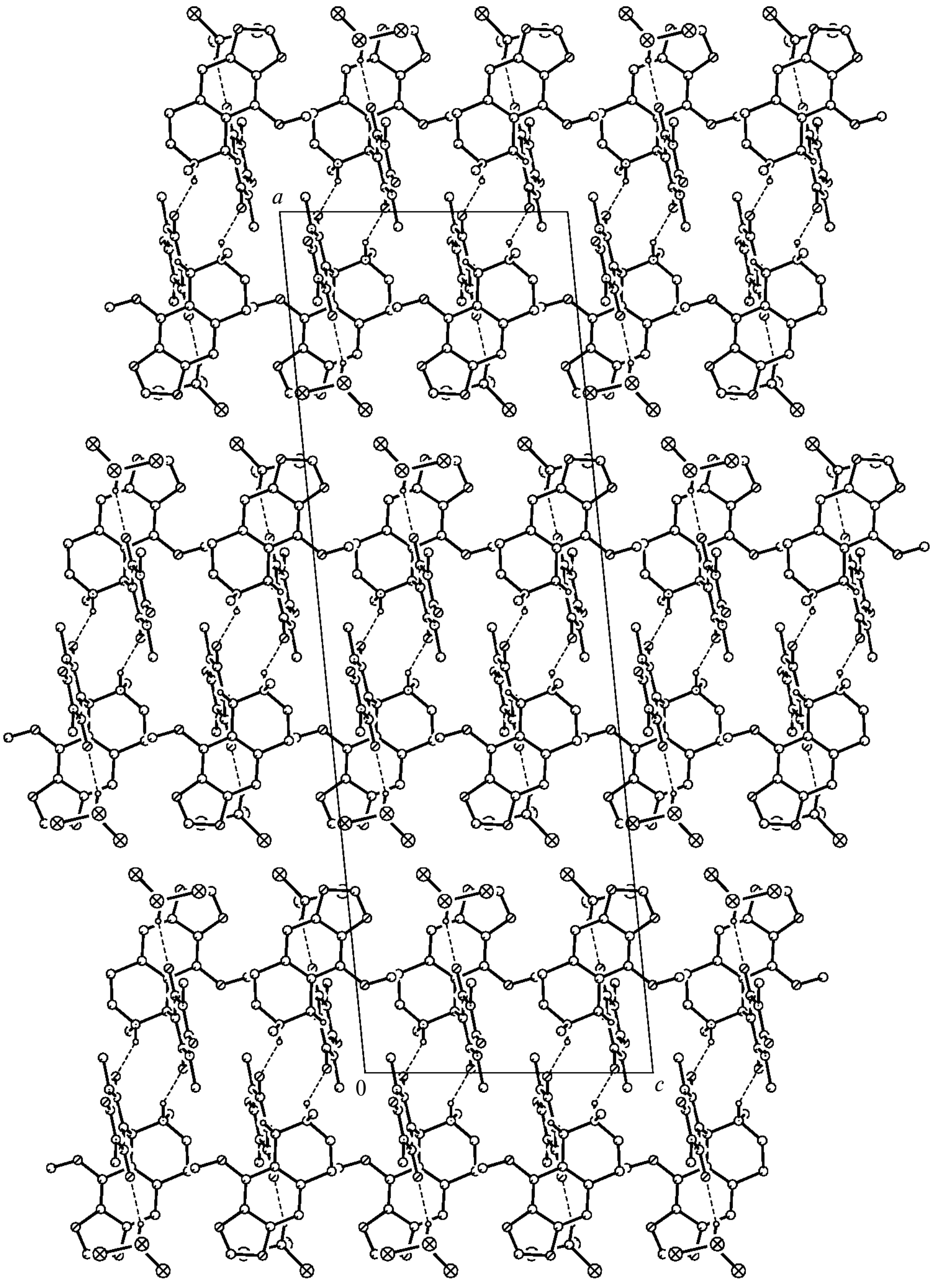


Fig. 2. Packing of molecules **3** in the crystal along the *Y* axis (hydrogen bonds are indicated by dashed lines).

stacks along the *Y* axis (Fig. 2). In the stacks, the homochiral dimers built from opposite enantiomers alternate with each other. The $CHCl_3$ molecules are fixed in the solvate sphere by the weak C(ls)—H...O(4A) hydrogen bonds (C(1s)...O, 3.023(3) Å; H...O, 2.16(3) Å; C—H...O, 143(3)°.

The molecular structure of 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid (**3**) in the crystalline state established by us provided an explanation for the behavior of this compound in solutions. According to the data from ^1H NMR spectroscopy, the structure of compound **3** changes substantially in going from the crystalline state to solution.

The ^1H NMR spectra both in $CDCl_3$ and DMSO-d_6 revealed two equilibrium forms of compound **3**, each giving its own set of signals. We assumed that these forms correspond to dimer **3a** (analogous to that observed in the crystal) and molecule **3b**, which is not involved in a dimer. Taking into account the character of the signals for C(1)H

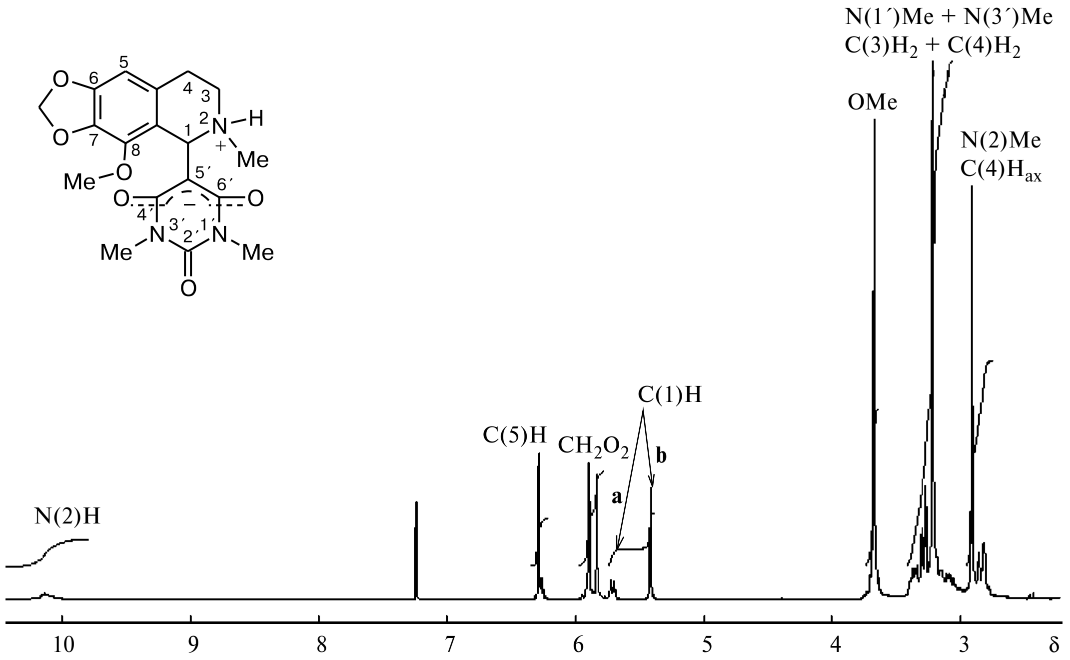


Fig. 3. ^{1}H NMR spectrum of compound **3** (CHCl$_3$, 20 °C, concentration 75 mg mL^{-1}).

in the ^{1}H NMR spectrum in CDCl$_3$, the signals at δ 5.41 and 5.71—5.73 were assigned to form **3b** and dimer **3a**, respectively (Fig. 3). This assumption was confirmed by the pronounced concentration dependence observed in the ^{1}H NMR spectra. Judging from the intensities of the signals for the C(1)H group, solutions in CDCl$_3$ with concentrations of 75, 25, and 10 mg mL^{-1} contained 28% of form **3a** and 72% of **3b**, 13% of **3a** and 87% of **3b**, and 7% of **3a** and 93% of **3b**, respectively, *i.e.*, the change in the percentage of the dimer upon dilution is in keeping with a typical association-dissociation process.

Theoretically, the presence of two asymmetric centers, *viz.*, C(1) and N(2), in molecule **3** could be manifested in the ^{1}H NMR spectra as one more set of signals. However, this type of the isomerism was not found in our investigations due, presumably, to the fact that these stereoisomers are spectroscopically indistinguishable.

At 20 °C, interconversions of the isomeric forms of compound **3** proceed rather slowly, which is manifested only in a slight broadening of the signals for C(1)H. Heating of the sample in DMSO-d$_6$ led to a typical coalescence of the signals with the coalescence temperature of 43—44 °C.

In conclusion, it should be noted that the type of intermolecular hydrogen bonds found in 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid (**3**) is observed in numerous natural molecules (enzymes, proteins, nucleic acids, *etc.*). Hence, compound **3** and its analogs would be expected to exhibit a number of biological effects, particularly, those associated with the selective action on RNA- and DNA-dependent cellular systems.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer (500 MHz). The mass spectra were measured on an MKh-1303 instrument with direct inlet of the sample into the ion source at 150 °C; the ionizing voltage was 70 eV.

8-Methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-ol (cotarnine) (1) was prepared from cotarnine chloride monohydrate (pharm.) by precipitation with KOH, m.p. 130—132 °C (lit. data[8]: m.p. 130 °C).

5-(8-Methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid (3). Dry cotarnine (**1**) (2.36 g, 0.01 mol) was added to a solution of 1,3-dimethylbarbituric acid (**2**) (1.56 g, 0.01 mol) in CHCl$_3$ (20 mL). The reaction mixture was heated under reflux with stirring for 1—2 min, after which the hot solution was filtered through a paper filter. The resulting transparent solution was kept at ~20 °C for one day. The precipitate that formed was separated, washed with CHCl$_3$ and CCl$_4$, and dried in a vacuum desiccator. Compound **3** was obtained in a yield of 3.45 g (92%) as colorless crystals, m.p. 202—204 °C. ^{1}H NMR (CDCl$_3$), δ (20 °C, *C* 75 mg mL^{-1}): 2.82 and 2.91 (both s, 0.9 H and 2.1 H, N(2)Me of forms **a** and **b**); 2.88 (m, 1 H, C(4)H$_{ax}$); 3.24 (s, 6 H, N(1′)Me, N(3′)Me); 3.16 (m, 1 H, C(4)$_{eq}$); 3.33 (m, 1 H, C(3)H$_{ax}$); 3.38 (m, 1 H, C(3)H$_{eq}$); 3.69 (s, 3 H, OMe); 5.41 (s, 0.7 H, C(1)H of form **b**); 5.71 and 5.74 (both s, 0.15 H each, C(1)H of isomers of form **a**); 5.84 and 5.90 (both s, 0.6 H and 1.4 H, OCH$_2$O of forms **a** and **b**); 6.29 (s, 1 H, C(5)H); 10.13 (br.s, 1 H, NH). ^{1}H NMR (DMSO-d$_6$), δ (20 °C, *C* 100 mg mL^{-1}): 2.64 and 2.73 (both s, 0.9 H and 2.1 H, N(2)Me of forms **a** and **b**); 2.77 (m, 1 H, C(4)H$_{ax}$); 2.94 (m, 1 H, C(4)$_{eq}$); 3.06 (s, 6 H, N(1´)Me and N(3´)Me); 3.17 (m, 1 H, C(3)H$_{ax}$); 3.41 (m, 1 H, C(3)H$_{eq}$); 3.57 (s, 3 H, OMe); 5.39 and 5.68 (both s, 0.7 H and 0.3 H, C(1)H of forms **a** and **b**); 5.93 (s, 2 H, OCH$_2$O); 6.46 (s, 1 H, C(5)H); 8.49 and 9.26 (both br.s, 0.7 H and 0.3 H, NH of forms **a** and **b**).

X-ray diffraction study of 3. Crystals were prepared by dissolving compound **3** (100 mg) on heating in CHCl$_3$ (7 mL) followed by the addition of heptane (10 mL) to the hot solution. The solution was transferred into a 25-mL cylinder and kept in the open cylinder at 20 °C with dust protection for 10 days, during which the solution was concentrated to ~1/2 of the initial volume. The crystals that precipitated were separated, washed with CCl$_4$ (2 mL), and dried in air for 30 min.

The crystals of **3** ($C_{18}H_{21}N_3O_6 \cdot CHCl_3$, M = 494.75) are monoclinic, space group $C2/c$, at 110 K, a = 38.230(7), b = 8.6979(16), c = 12.718(2) Å, β = 95.664(5)°, V = 4208.3(14) Å^3, Z = 8, d_{calc} = 1.562 mg cm^{-3}, $F(000)$ = 2048, μ = 0.479 mm^{-1}.

The unit cell parameters and intensities of 21746 reflections were measured on an automated Bruker SMART CCD 1000 diffractometer (T = 110 K, λMoKα, ω scanning technique with a step of 0.3°, the exposition time per frame was 10 s, θ_{max} = 30°). The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. The hydrogen atoms were revealed from difference Fourier syntheses and refined isotropically. The final reliability factors were as follows: R_1 = 0.0660 for 3916 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.1712 for a total of 6103 independent reflections. All calculations were carried out with the use of the SHELXTL PLUS program package (Version 5.10).[9]

The tables of the atomic coordinates, bond lengths, bond angles, torsion angles, and anisotropic thermal parameters for compound **3** were deposited with the Cambridge Structural Database.

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References

1. J. T. Bojarski, J. L. Mokrosz, H. J. Barton, and M. H. Paluchowska, *Adv. Heterocycl. Chem.*, 1985, **38**, 229.
2. B. A. Ivin, V. I. Slesarev, N. A. Smorygo, and E. G. Sochilin, *Zh. Org. Khim.*, 1970, **6**, 1326 [*J. Org. Chem. USSR*, 1970, **6** (Engl. Transl.)].
3. B. A. Ivin, V. I. Slesarev, M. V. Zubkovskii, and E. G. Sochilin, *Zh. Org. Khim.*, 1973, **9**, 2199 [*J. Org. Chem. USSR*, 1973, **9** (Engl. Transl.)].
4. L. Prasad and M. R. Taylor, *Acta Crystallogr.*, *Sect. C*, 1983, **39**, 1686.
5. M. Millan, C. F. Conde, A. Conde, and R. Marquez, *Acta Crystallogr.*, *Sect. C*, 1987, **43**, 1138.
6. J. Antel, G. M. Sheldrick, J. Bachmann, and L.-F. Tietze, *J. Crystallogr. Spectrosc. Res.*, 1988, **18**, 619.
7. E. Vilsmaier, K. Joerg, and G. Maas, *Chem. Ber.*, 1984, **117**, 2947.
8. H. Mohrle and B. Grimm, *Arch. Pharm.*, 1986, **319**, 835.
9. G. M. Sheldrick, SHELXTL, V5.10, Bruker AXS Inc., Madison, WI-53719, USA, 1997.

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