Chemistry of Heterocyclic Compounds, Vol. 45, No. 5, 2009

INVESTIGATION OF THE STRUCTURE AND PREDICTION OF THE BIOLOGICAL ACTIVITY OF 1,3-BIS(3-CYANO-6,6-DIMETHYL-2-OXO-5,6-DIHYDRO-2H-PYRAN-4-YL)-2-(4-METHOXYPHENYL)PROPANE*

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Single crystals of 1,3-bis(3-cyano-6,6-dimethyl-2-oxo-5,6-dihydro-2H-pyran-4-yl)-2-(4-methoxyphenyl)-propane were prepared, and an X-ray crystallographic analysis was performed. The compound has a molecular structure belonging to the C_1 symmetry group. The heterocyclic rings are in a distorted half-chair conformation. The crystal packing is formed by centrosymmetric dimers, in which the heterocycles turned toward the inversion center are antiparallel. The biological activity of the compound was predicted by the PASS computer system.

Keywords: 1,3-bis(3-cyano-6,6-dimethyl-2-oxo-5,6-dihydro-2H-pyran-4-yl)-2-(4-methoxyphenyl)-propane, X-ray structural analysis, PM6, PASS.

In a continuation of our investigations in the search for new physiologically active compounds of the δ-lactone class the reaction of 3-cyano-4,6,6-trimethyl-5,6-dihydro-2-pyranone with 4-methoxybenzaldehyde in ethanol in the presence of catalytic amounts of NaOH was realized. It was found that together with the expected crotonic condensation product 3-cyano-6,6-dimethyl-2-oxo-5,6-dihydro-4-[2-(4-methoxyphenyl)vinyl]-2H-pyran a compound of the Michael adduct type 1,3-bis(3-cyano-6,6-dimethyl-2-oxo-5,6-dihydro-2H-pyran-4-yl)-2-(4-methoxyphenyl)propane (**1**) is also formed. The synthesized compounds were identified on the basis of spectral data and elemental analysis [1].

Quantum-chemical investigation of the reaction showed that both products are produced from a common protonated intermediate and the difference in the mechanisms of their formation arises from the regioselectivity of the stage involving interaction of the $HetCH_2^-$ carbanion with the intermediate. In the case where attack by the carbanion is directed at the α-carbon atom of the double bond in the intermediate a

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* Dedicated to Highly Respected Academician Andris Strakovs in connection with his jubilee.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 680-685, May, 2009. Original article submitted March 12, 2009.

bimolecular *E*2-elimination reaction occurs with the formation of the crotonic condensation product. If, however, attack is directed to the β-position a spontaneous bimolecular S_N2 nucleophilic substitution reaction occurs, resulting in the formation of a product of the Michael addition type.

In order to obtain objective detailed information on the three-dimensional and geometrical structure of compound **1** we grew crystals suitable for X-ray diffraction investigations and did an X-ray crystallographic analysis of single crystals of this substance (Fig. 1, Table 1).

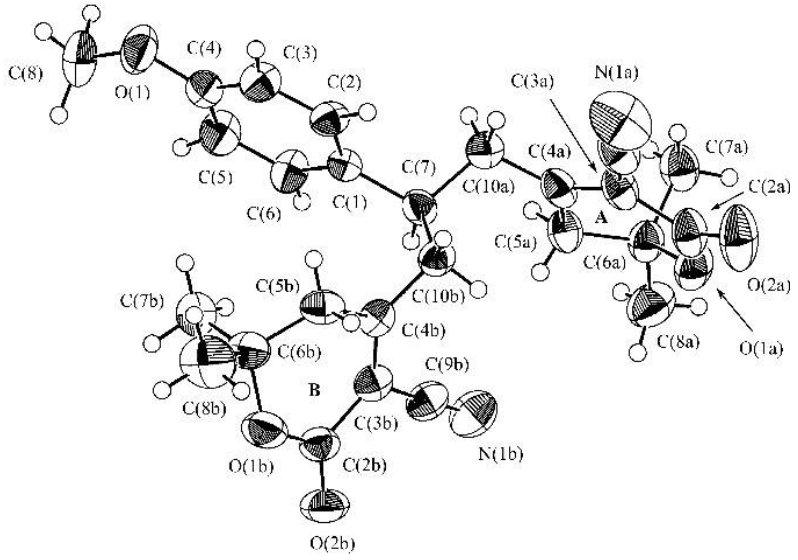

Fig. 1. A general view of the molecule of compound **1** produced by X-ray crystallographic analysis with the thermal vibration ellipsoids and the designations of the atoms.

In the condensed phase the compound has a molecular structure belonging to the C_1 symmetry group. Both heterocycles **A** and **B** exist in a distorted *half-chair* conformation. The projection of the C(6a) atom from the plane of the other ring atoms is 0.566(7) Å, while the bending angle of the C(5a)–C(6a)–O(1a) plane amounts to 41.86°.

The pseudoplane C(8a)–C(6a)–C(7a), containing the carbon atoms of the methyl groups, intersects the base plane of the heterocycle at an angle of 86.61(4)°. In the heterocycle **B** the deviation of the C(6b) atom at the apex of the *half-chair* from the plane of the ring is 0.682(7) Å, while the corresponding bending angle is 41.98°. The base plane of the ring and the pseudoplane C(7b)–C(6b)–C(8b) are orthogonal to each other (89.94°). The oxygen atoms of the carbonyl groups and cyano group are coplanar with the plane of their heterocycles. The oxygen atom of the methoxy group occupies the *cis* position in relation to the C(5)–C(6) bond.

The dihedral angle between the planes of the heterocycles **A** and **B** is 66.99°. The phenyl ring and the heterocycle **A** are practically parallel to each other (the angle between their planes is 1.50°), whereas the angle of inclination of the heterocycle **B** to the plane of the phenyl ring amounts to 68.39°.

In the crystal the molecules of compound **1** are linked into centrosymmetric dimers and are arranged in such a way that the heterocycles **B** turned toward the inversion center are antiparallel (Fig. 2). The distance between the planes of their rings is equal to 3.598(6) Å, while the rings themselves are displaced in relation to each other; the distance between the centroids of the rings amounts to 4.760 Å.

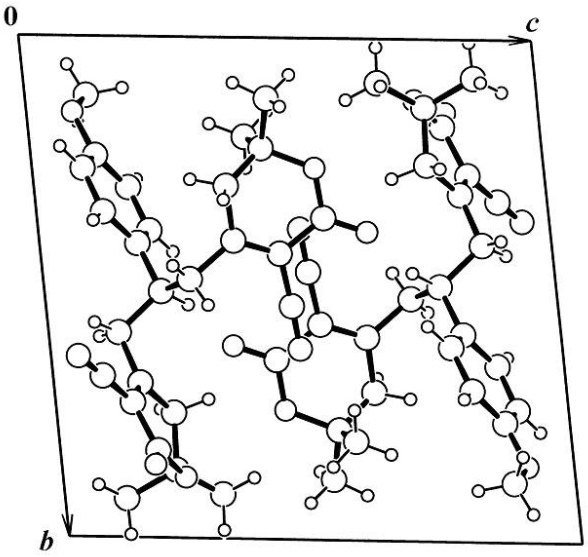

Fig. 2. Projection of the crystal structure of compound **1** along the direction of the *x* axis.

In order to obtain an idea of the structure of the isolated molecule in the gas phase we performed quantum-chemical calculations by the semiempirical PM6 method with full optimization of the geometry [2]. The bond lengths and valence angles obtained experimentally (X-ray structural analysis) and obtained theoretically (PM6) differ little (Table 1). The symmetry of the molecular structure also remains unchanged. In the transition to the crystalline state the shortening of the C(5a)–C(6a) valence bond in heterocycle **A** amounts to only 0.030, while the shortening for the C(5b)–C(6b) bond in heterocycle **B** is 0.035 Å.

TABLE 1. The Principal Bond Lengths (*l*) and Valence Angles (ω) of Compound **1** Determined by X-ray structural analysis and by the PM6 Computational Method

Bond	*l*, Å		Angle	ω, deg.	
	XCA	PM6		X-ray structural analysis	PM6
C(7)–C(1)	1.527(6)	1.512	C(1)–C(7)–C(10a)	110.4 (3)	109.6
C(7)–C(10b)	1.540(6)	1.547	C(1)–C(7)–C(10b)	112.7(3)	111.3
C(7)–C(10a)	1.547(6)	1.546	C(7)–C(10a)–C(4a)	113.0(4)	112.3
O(1a)–C(2a)	1.331(6)	1.375	C(7)–C(10b)–C(4b)	112.9(3)	112.0
O(1a)–C(6a)	1.474(5)	1.471	C(4a)–C(3a)–C(2a)	122.5(5)	121.4
O(1b)–C(2b)	1.341(6)	1.378	C(4b)–C(3b)–C(2b)	123.9(4)	121.6
O(1b)–C(6b)	1.485(6)	1.470	C(3a)–C(2a)–O(1a)	118.1(4)	116.9
C(5b)–C(4b)	1.492(6)	1.492	C(3b)–C(2b)–O(1b)	117.3(4)	116.8
C(5b)–C(6b)	1.508(7)	1.543	C(2a)–O(1a)–C(6a)	119.3(4)	122.1
C(5a)–C(4a)	1.503(6)	1.492	C(2b)–O(1b)–C(6b)	120.7(4)	122.0
C(5a)–C(6a)	1.513(6)	1.543	O(1a)–C(6a)–C(5a)	110.0(4)	109.7
C(3a)–C(2a)	1.487(7)	1.492	O(1b)–C(6b)–C(5b)	110.6(4)	110.0
C(4b)–C(10b)	1.513(6)	1.498	C(6a)–C(5a)–C(4a)	113.4(4)	112.4
C(4a)–C(10a)	1.497(6)	1.498	C(6b)–C(5b)–C(4b)	113.7(4)	112.9
C(3b)–C(2b)	1.465(6)	1.489	C(8)–O(1)–C(4)	118.3(4)	118.0
C(3a)–C(4a)	1.337(6)	1.356	C(5a)–C(4a)–C(3a)	118.0(4)	119.3
C(3b)–C(4b)	1.338(6)	1.358	C(5b)–C(4b)–C(3b)	117.7(4)	119.7

Prediction of the biological activity of compound **1** was realized by means of the PASS computer program (Prediction of Activity Spectra for substance) [3, 4]. The system makes it possible to predict about 3300 types of biological activity for the substance on the basis of its structural formula, including pharmacological effects, molecular mechanisms of action, specific toxicity, and biotransformation. The mean accuracy of the prediction during sliding control with one by one exclusion amounts to ~94%.

The main purpose of the PASS program is to predict the spectrum of biological activity in new previously uninvestigated substances. It makes it possible to "sort out" unpromising compounds (e.g., with a high probability of exhibiting toxicity) at the very early stages of an investigation and to determine what types of biological activity it is expedient to test for candidate substances that have passed this filter.

The results of the prediction (with a threshold probability of more than 0.60) showed that compound **1** can be used for the treatment of ischemic heart disease (probability 0.644), exhibit a cytoprotector effect (0.635), and act as a potential inhibitor of oxidoreductase (0.709), as an inhibitor of ubiquinol-cytochrome c-reductase (0.672), as an agonist of nerve growth factor (0.641), as a stimulator of neutrotropic factor (0.618), as an inhibitor of ubiquinone NADN-dehydrogenase (0.604), and as a substrate of human CYP2C12 enzyme (0.891).

TABLE 2. The Crystallographic Characteristics of Compound **1** and the Refinement Parameters of the Crystal Structure

Parameter	
Empirical formula	$C_{26}H_{28}N_2O_5$
Molecular mass	448.50
Crystal form	Prism
Crystal size, mm	0.09 × 0.11 × 0.36
Crystal system	Triclinic
Unit cell parameters:	
a, Å	6.9750(6)
b, Å	13.0700(13)
c, Å	13.3980(17)
α, deg.	83.331(4)
β,deg.	81.510(4)
γ, deg.	88.511(9)
Unit cell volume, *V*, Å^3	1991.8(2)
Space group	$P\bar{1}$
Number of molecules in cell, *Z*	2
F(000)	476
Density of substance, ρ_{calc}, g/cm^3	1.241
Maximum angle, $2\theta_{max}$, deg	50.0
Ranges of Miller indices	$-8 \le h \le 7$
	$-15 \le k \le 15$
	$-15 \le l \le 15$
Absorption coefficient, μ, mm^{-1}	0.086
Total number of reflections	6233
Number of independent reflections	3858
Number of reflections with $I > 2\sigma(I)$	2426
R-Factor	0.0704
R-Indices for all reflections (R_1, wR_2)	0.0925, 0.1452
Number of refined parameters	298
GOOF	0.970
$(\Delta/\sigma)_{max}$	0.001

EXPERIMENTAL

1,3-Bis(3-cyano-6,6-dimethyl-2-oxo-5,6-dihydro-2H-pyran-4-yl)-2-(2-methoxyphenyl)propane was synthesi-zed by the method described in [1]. Single crystals of the compound were obtained by recrystallization of the reaction product from ethanol. The quantum-chemical calculations were carried out by the PM6 method [2] using the MOPAC2007 software [5]. The optimized structure is the minimum on the potential energy surface of the molecular system.

The diffraction pattern for the single crystals was obtained on an automatic Bruker–Nonius KappaCCD X-ray diffractometer. The crystal structure was interpreted by the method developed previously at the Latvian Institute of Organic Synthesis [6]. The initial *R*-factor of the obtained models (after interpretation) amounts to 25-30%.

Further refinement was realized by full-matrix least-squares treatment in anisotropic approximation using the *maXus* software package [7]. The positions of the hydrogen atoms were located on the basis of Fourier difference electron density syntheses and were refined in isotropic approximation using the "rider" model. the crystallographic characteristics of compound **1** and the structure refinement parameters are given in Table 2. Full crystallographic information has been deposited at the Cambridge structural data bank, No. CCDC 719527.

REFERENCES

1. L. Leite, D. Jansone, M. Fleisher, H. Kazhoka, J. Popelis, N. Veretennikova, I. Shestakova, I. Domracheva, and E. Lukevics, *Khim. Geterotsikl. Soedin.,* 839 (2004). [*Chem. Heterocycl. Comp*., **40**, 715 (2004)].
2. J. J. P. Stewart, *J. Mol. Model*., **13**, 1173 (2007).
3. V. V. Poroikov, D. A. Filimonov, W.-D. Ihlenfeldt, T. A. Gloriozova, A. A. Lagunin, Yu. V. Borodina, A. V. Stepanchikova, and M. C. Nicklaus, *J. Chem. Inf. Comput. Sci.*, **43**, 228 (2003).
4. D. A. Filimonov and V. V. Poroikov, *Ros. Khim. Zh.*, **50**, № 2, 66 (2006).
5. J. J. P. Stewart, *Program Package MOPAC2007*. http://www.MOPAC2007.com
6. A. F. Mishnev and S. V. Belyakov, *Kristallografiya*, **33**, 835 (1988).
7. S. Maskay, C. J. Gilmore, C. Edwards, N. Stewart, and K. Shankland. *maXus*. *Computer Program for the Solution and Refinement of Crystal Structures*, Bruker Nonius, 1999, The Netherlands, MacScience, Japan & The Univ. of Glasgow.