Chemistry of Heterocyclic Compounds, Vol. 45, No. 4, 2009

MOLECULAR AND CRYSTAL STRUCTURE OF *trans* AND *cis* ISOMERS OF 3-CYANO-4-[2-(4-METHOXYPHENYL)VINYL]-6,6-DIMETHYL-5,6-DIHYDRO-2H-PYRAN*

S. Belyakov[1], M. Fleisher[1], D. Jansone[1], L. Leite[1], and E. Lukevics[1]**

Monocrystals of the trans and cis isomers of 3-cyano-4-[2-(4-methoxyphenyl)vinyl]-6,6-dimethyl-5,6-dihydro-2H-pyran have been obtained and an X-ray structural analysis of them has been carried out. Both compounds have a molecular structure corresponding to symmetry group C_1. The heterocyclic ring is in a distorted envelope conformation. The crystals of the trans isomer are rhombic and have a fir-tree type of packing. The crystal packing of the cis isomer is formed by pairs of molecules, each of which consists of only one enantiomer.

Keywords: 3-cyano-4-[2-(4-methoxyphenyl)vinyl]-6,6-dimethyl-5,6-dihydro-2H-pyran, X-ray structural analysis, AM1.

Many synthetic and natural derivatives of δ-lactones possess a broad spectrum of biological activity, in particular bactericidal [1], cardiotonic [2], and cytotoxic [3] properties, are used in clinical practice as anticonvulsants [4], serve as agents for the treatment of hypercholesterolemia [5], oncological diseases [6], and are also used as plant growth stimulators [7-9]. With the aim of searching for new pharmacologically active compounds of this class, 3-cyano-4-[2-(4-methoxyphenyl)vinyl]-6,6-dimethyl-5,6-dihydro-2H-pyran (**1**) has been synthesized by the condensation of 3-cyano-4,6,6-trimethyl-5,6-dihydro-2-pyranone with 4-methoxybenzaldehyde in EtOH in the presence of catalytic quantities of NaOH. The synthesized compound was identified on the basis of spectral data and elemental analysis [3]. According to data of ^{1}H NMR spectra the vinyl fragment of the compound has a *trans* configuration (J = 15.9 Hz). X-ray structural analysis is the most objective method to establish the three-dimensional structure of chemical compounds in detail. Crystals of two forms were obtained on recrystallizing compound **1** from ethanol, *viz.* pale-green needles and yellow prisms.

Spatial models of molecules of both compounds were obtained by X-ray structural analysis (Fig. 1). The basic geometric characteristics are given in Tables 1 and 2. It was established that the crystals of the first form are *trans* isomers and the crystals of the prismatic form are *cis* isomers of compound **1**. In the condensed phase both isomers have a molecular structure pertaining to the point group of symmetry C_1.

---

* Dedicated to deeply respected Professor Hank van der Plas in connection with his jubilee.

** To whom correspondence should be addressed, e-mail: misha@osi.lv.

[1]Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 535-540, April, 2009. Original article submitted December 5, 2008.

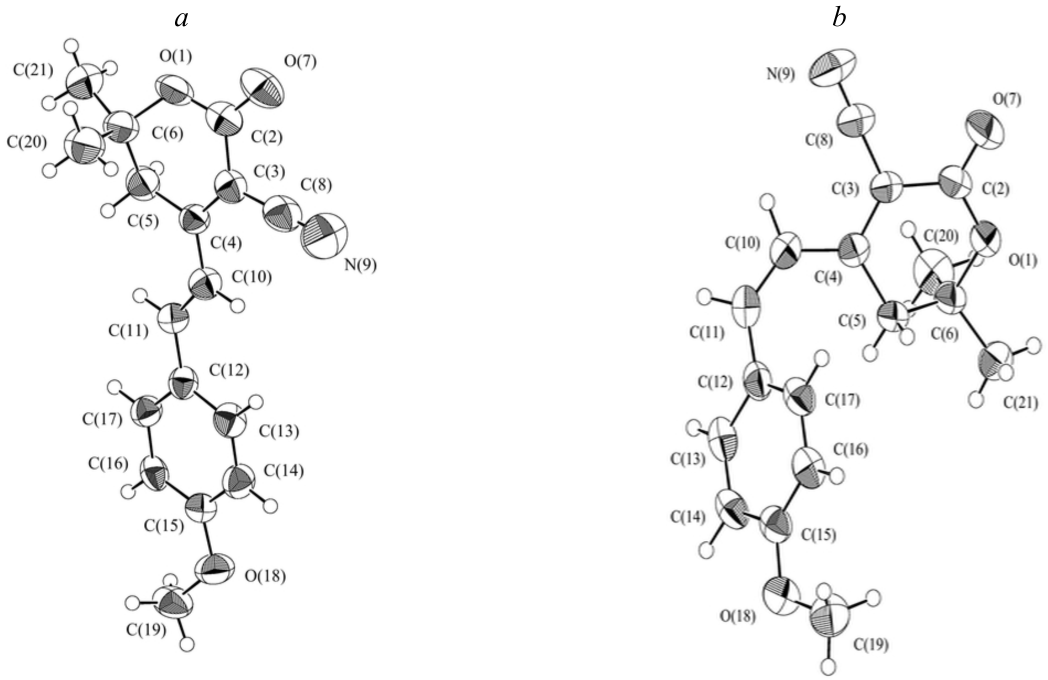

Fig. 1. Spatial models of (*a*) the *trans* isomer and (*b*) the *cis* isomer of the compound **1** molecule according to X-ray structural analysis, with ellipsoids of thermal vibrations and numbering of atoms.

The phenyl ring, the atoms of the vinyl group, the basic atoms of the heterocyclic ring, the cyano group, and the oxygen atom of the carbonyl group of the *trans* isomer lie in one plane. The oxygen atom of the methoxy group occupies the *cis* position relative to the C(15)–C(16) bond. The dihedral angle C(4)–C(10)–C(11)–C(12), characterizing the *trans* form of compound **1**, is equal to 178.9^o.

The heterocyclic ring has the conformation of a distorted *half-chair*. The emergence of atom C(6) from the plane of the other ring atoms was equal to 0.655(6) Å, and the angle of fold of the C(5)–C(6)–O(1) plane was 43.4(4)° The pseudo-plane C(20)–C(6)–C(21), containing the carbon atoms of the methyl groups, was practically orthogonal to the basic plane of the heterocycle (91.7(4)°).

TABLE 1. Main Bond Lengths (*l*) in *trans* and *cis* Isomers of Compound **1**, Determined by X X-ray structural analysis and Calculated by AM1

Bond	*l*, Å			
	trans-**1**		*cis*-**1**	
	X-ray structural analysis	AM1	X-ray structural analysis	AM1
O(1)–C(2)	1.334(6)	1.374	1.340(3)	1.373
C(2)–C(3)	1.478(7)	1.474	1.468(3)	1.475
C(3)–C(4)	1.350(6)	1.360	1.356(3)	1.357
C(4)–C(5)	1.505(6)	1.489	1.504(3)	1.489
C(5)–C(6)	1.511(7)	1.530	1.517(3)	1.529
C(6)–O(1)	1.467(7)	1.442	1.470(2)	1.443
C(4)–C(10)	1.434(7)	1.448	1.452(3)	1.453
C(10)–C(11)	1.336(6)	1.346	1.339(3)	1.340
C(11)–C(12)	1.449(6)	1.449	1.461(3)	1.450
O(18)–C(19)	1.437(6)	1.423	1.429(3)	1.424

TABLE 2. Main Valence Angles (ω) in *trans* and *cis* Isomers of Compound **1**, Determined by X-ray structural analysis and Calculated by the AM1 Method

Angle	ω, deg			
	trans-**1**		*cis*-**1**	
	X-ray structural analysis	AM1	X-ray structural analysis	AM1
C(3)–C(4)–C(5)	116.7(4)	118.7	115.5(2)	119.2
C(4)–C(5)–C(6)	113.1(4)	112.5	111.8(2)	112.4
C(5)–C(6)–O(1)	110.4(4)	111.8	109.3(2)	111.9
C(6)–O(1)–C(2)	119.6(4)	118.3	120.3(2)	118.5
O(1)–C(2)–C(3)	117.7(5)	119.8	117.5(2)	119.7
C(2)–C(3)–C(4)	123.3(5)	120.6	123.6(2)	120.4
C(4)–C(10)–C(11)	125.3(4)	124.0	129.5(2)	127.3
C(10)–C(11)–C(12)	127.0(4)	125.1	130.3(2)	127.7
C(19)–O(18)–C(15)	118.2(4)	116.3	118.1(2)	116.2

In the crystal, the molecules of the *trans* isomer form fir-tree packing, from which significant intermolecular interactions are absent, which causes the relatively low density of the substance (1.211 g/cm^3) (Table 3).

TABLE 3. Crystallographic Characteristics of *trans* and *cis* Isomers of Compound **1** and Refinement Parameters of the Crystal Structures

Parameters	*trans*-**1**	*cis*-**1**
Empirical formula	$C_{17}H_{17}NO_3$	$C_{17}H_{17}NO_3$
Molecular mass	283.327	283.327
Crystal shape	Needles	Prisms
Crystal size, mm	0.05×0.07×0.43	0.12×0.19×0.31
System	Rhombic	Monoclinic
Unit cell parameters:		
a, Å	20.820(2)	12.4206(6)
b, Å	13.8366(11)	8.4972(5)
c, Å	5.3925(4)	14.0206(9)
β, deg	90.0	94.631(2)
Unit cell volume, V, Å^3	1553.5(2)	1474.91(15)
Space group	$Pna2_1$	$P\,2_1/n$
Number of molecules in unit cell, Z	4	4
F(000)	600	600
Density of substance, ρ_{calc}, g/cm^3	1.211	1.276
Maximum angle $2\theta_{max}$, deg	46.0	55.0
Miller index intervals	$-22 \le h \le 22$	$-15 \le h \le 16$
	$-14 \le k \le 15$	$-10 \le k \le 11$
	$-5 \le l \le 5$	$-18 \le l \le 18$
Absorption coefficient, μ, mm^{-1}	0.08	0.09
Number of reflections		
overall	1921	5845
independent	1268	3836
with $I > 3\sigma(I)$	826	1732
R-Factor	0.049	0.048
R-Indexes for all reflections (R_1, wR_2)	0.095, 0.121	0.084, 0.197
Number of parameters refined	190	258
GOOF	1.330	1.267
$(\Delta/\sigma)_{max}$	0.007	0.002

Parameter *c* of the crystal unit cell was significantly less than the two other parameters (Table 3). In similar cases crystal growth occurs preferentially in the direction perpendicular to the small parameter (Gibbs–Currie–Wulff theorem [10]), as a result of which fine needle-shaped crystals are formed.

The molecule of the *cis* isomer of **1** may not have a planar conformation due to the mutual repulsion of the hydrogen atoms at C(5) and C(17), consequently the molecule is characterized by a helical conformation with an absolute value of the C(12)–C(11)–C(10)–C(4) torsion angle of 13.4(2)° (Fig 1*b*). The phenyl ring is turned relative to the plane containing the vinyl group by 33.3(2)°. The heterocyclic ring has, as in the case of the *trans* isomer, the shape of a distorted *half-chair*. The O(1) atom emerges from the plane of the C(3)–C(4)–C(5) atoms by 0.264 Å, and the C(6) atom emerges by 0.755(2) Å in the same direction.

Although the molecule of the *cis* isomer does not have asymmetric atoms it is nonetheless chiral since it may have both a left helical conformation or a right. The crystal consists of a mixture of equal amounts of the two enantiomers (torsion angle C(12)–C(11)–C(10)–C(4) is -13.4(2)° and +13.4(2) °). The special feature of the structure of the crystals of the *cis* isomer is the packing, consisting of pairs of molecules each of which is formed only of one of the enantiomers (Fig. 2). In each pair the molecules are disposed in such a way that the phenyl ring of one of them is almost parallel to the heterocyclic ring of the other (the angle between the planes of the rings is equal to 13.3(2)°).

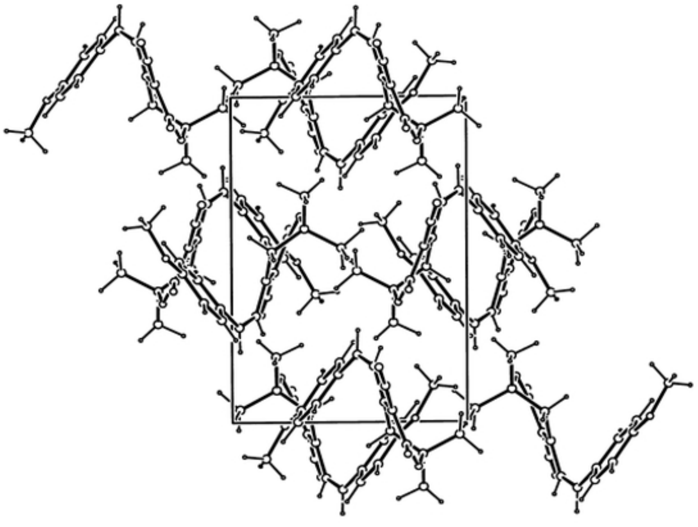

Fig. 2. Projection of the crystal structure of the *cis* isomer of compound **1** along the direction of the *x* axis.

To obtain a representation of the structure of the isolated molecules in the gas phase quantum-chemical calculations were carried out of the isomers with complete optimization of their geometry by the AM1 semiempirical method [11]. Bond lengths and valence angles obtained experimentally (X-ray structural analysis) and found theoretically (AM1) differed insignificantly (Tables 1 and 2). A shortening of the valence bond of the heteroatom to the carbon atom of the carbonyl group on going into the crystalline state amounted to only 0.040 Å for the *trans* isomer and 0.033 Å for the *cis* isomer.

A more significant difference concerned the C(12)–C(11)–C(10)–C(4) torsion angle in the *cis* isomer, describing the extent of rotation of the heterocycle around the C(4)–C(10) bond. According to the calculations this angle is equal to 54.1° in the isolated molecule, while in the crystal, due to the effect of the molecular packing, it was reduced to 13.4(2)°.

EXPERIMENTAL

3-Cyano-4-[2-(4-methoxyphenyl)vinyl]-6,6-dimethyl-5,6-dihydro-2H-pyran (**1**) was synthesized by the procedure reported in [3]. Monocrystals of the *trans* and *cis* isomers of the compound were obtained by recrystallization of the reaction products from ethyl alcohol.

Quantum-chemical calculations were carried out by the AM1 method [11] using the MOPAC2007 set of programs [12]. The optimized structures are minimum points on the potential energy surface of the molecular systems.

The diffraction picture for monocrystals was obtained on a Bruker-Nonius KappaCCD automatic X-ray diffractometer. Interpretation of the crystal structure was carried out by the method developed previously in the Latvian Institute of Organic Synthesis [13]. The initial *R*-factor (after interpretation) obtained for the models of the structures was 25-30%. Further refinement was effected with a full matrix least squares method in an anisotropic approximation for all non-hydrogen atoms using the *maXus* set of programs [14]. Positions of hydrogen atoms were localized on the basis of Fourier difference syntheses of electron density and were refined in an isotropic approximation using a "rider" model. The crystallographic characteristics of the compound **1** isomers and the structural refinement parameters are given in Table 3.

REFERENCES

1. A. Avetisyan and G. Tokmadzhyan, *Khim. Geterotsikl. Soedin.*, 723 (1987). [*Chem. Heterocycl. Comp.*, **23**, 595 (1987)].
2. L. Leite, D. Jansone, M. Veveris, H. Cirule, Y. Popelis, G. Melikyan, A. Avetisyan, and E. Lukevics, *Eur. J. Med. Chem.*, **34**, 859 (1999).
3. L. Leite, D. Jansone, M. Fleisher, H. Kazhoka, J. Popelis, N. Veretennikova, I. Shestakova, I. Domracheva, and E. Lukevits, *Khim. Geterotsikl. Soedin.*, 839 (2004). [*Chem. Heterocycl. Comp.*, **40**, 715 (2004)].
4. R. Kretzschmar and H.-J. Teschendorf, *Chem.-Ztg.*, **98**, 24 (1974).
5. J. A. Tobert, *Am. J. Cardiol.*, **62**, 287 (1988).
6. S. Sirikantaramas, T. Asano, H. Sudo, M. Yamazaki, and K. Saito, *Curr. Pharmaceut. Biotechnol.*, **8**, 196 (2007).
7. A. Avetisyan, G. Melikyan, and S. Sagomonyan, *Biol. Zh. Armen.*, **42**, 959 (1989).
8. A. Avetisyan, A. Galstyan, G. Melikyan, and S. Sagomonyan, *Biol. Zh. Armen.*, **42**, 1006 (1989).
9. G. Melikyan, A. Avetisyan, and V. Sekerka, *Biol. Zh. Armen.*, **44**, 271 (1991).
10. M. P. Shaskol'skaya, *Crystallography* [in Russian], Vyssh. Shkola, Moscow (1984), 376 pp.
11. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
12. J. J. P. Stewart, *Program package MOPAC2007*. http://www.MOPAC2007.com
13. A. F. Mishnev and S. V. Belyakov, *Kristallografiya*, **33**, 835 (1988).
14. 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), Netherlands, MacScience, Japan, University of Glasgow.