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# SYNTHESIS AND PHOTOISOMERIZATION OF 3-CYANO-6,6-DIMETHYL-4-(4-NITROPHENYLVINYL)-5,6-DIHYDROPYRAN-2-ONE

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*The condensation of 4-nitrobenzaldehyde with 3-cyano-4,6,6-trimethyl-5,6-dihydropyran-2-one leads to the formation of a crotonization product and a compound of the Michael adduct type. The main product of the photochemical conversion of (E)-3-cyano-6,6-dimethyl-4-(4-nitrophenylvinyl)-5,6-dihydropyran-2-one is the Z-isomer. Investigation of the photoisomerization of 3-cyano-6,6-dimethyl-4-(4-nitrophenylvinyl)-5,6-dihydropyran-2-one by the semiempirical AM1 method showed that in the ground state the E-isomer was thermodynamically more stable than the Z-isomer. E-Z-photoisomerization is effected most probably through the lowest excited singlet state $S_1$.*

**Keywords:** 3-cyano-6,6-dimethyl-4-(4-nitrophenylvinyl)-5,6-dihydropyran-2-one, 4-nitrobenzaldehyde, 3-cyano-4,6,6-trimethyl-5,6-dihydropyran-2-one, aldol condensation, AM1 semiempirical method, *E*-*Z*-photoisomerization.

The biological activity of γ- and δ-lactones is known [1]. With the aim of searching for new pharmacologically active compounds of this class, 3-cyano-6,6-dimethyl-4-(4-nitrophenylvinyl)-5,6-dihydropyran-2-one (**3**) was synthesized by the condensation of 3-cyano-4,6,6-trimethyl-5,6-dihydropyran-2-one (**1**) with 4-nitrobenzaldehyde (**2**) in EtOH in the presence of NaOH. It was discovered that, like the condensation of pyranone **1** with pyridine aldehydes [1], in the reaction with aldehyde **2** a crotonization product **3** was formed and also a compound of the Michael adduct type, *viz*. bis(3-cyano-6,6-dimethyl-2-oxo-5,6-dihydro-4-pyranylmethyl)-4-nitrophenylmethane (**4**).

In the case of benzaldehydes the reaction also proceeds in a manner uncharacteristic for an aldol condensation. The yields of pyranones **3** and **4** at molar ratios of aldehyde **2**–pyranone **1**–NaOH of 1:2:0.06 were 23 and 75% respectively. However, unlike the reaction of pyridine aldehydes with pyranone **1,** when aldehyde predominates in the reaction medium (ratio of aldehyde **2** to pyranone **1** is 1.5:1) only the crotonization product is formed in 60% yield. The yield of reaction products was assessed quantitatively by HPLC without isolating them. Reaction dynamics were studied using TLC. Judging by the TLC results product **4** is formed initially, but pyranone **3** appears in the reaction mixture later. It follows from this that the mechanism proposed by the authors of [2,3] providing for the formation of a compound of the Michael adduct type **4** by addition of a second molecule of pyranone **1** to compound **3** is scarcely probable.

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* Dedicated to the Greatly Respected Academician Janis Stradins on the occasion of his Jubilee.

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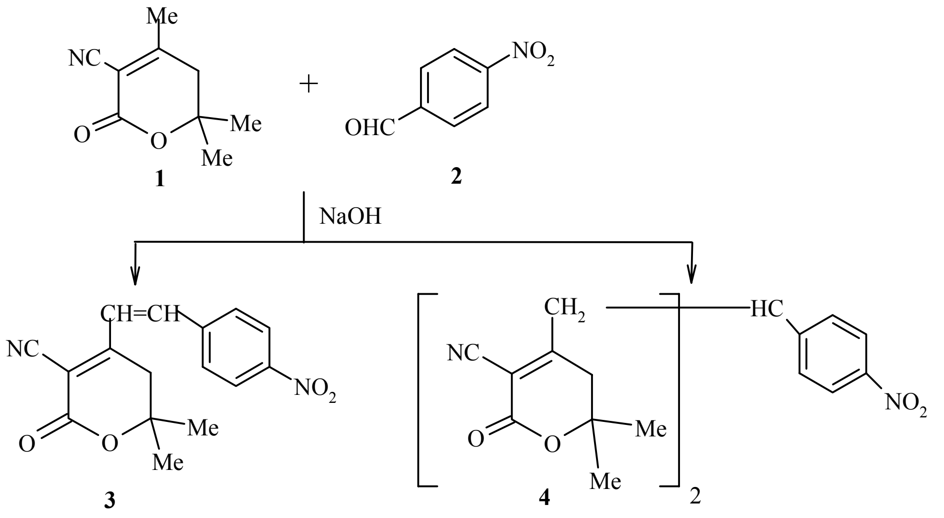

The coupling constant (16.2 Hz) of the vinyl group protons in the $^1$H NMR spectrum of vinylpyranone **3** shows the *E*-configuration of the obtained compound (Table 1).

The biological activity of organic compounds, including lactones, usually depends on their geometric configuration [4]. The photoisomerization of pyranone **3** was studied experimentally and theoretically to obtain further information on the isomerism of the synthesized compounds. One intense absorption band was present at 344 nm in the UV spectrum of a 0.026 mM solution of pyranone **3** in ethanol (Fig. 1). Effects, which were characteristic of $E \rightarrow Z$-isomerism, were observed in the absorption spectrum on irradiating a solution of this compound with sunlight. These effects were a reduction in the intensity of the characteristic band accompanied by a small hypsochromic shift (from 344 to 325 nm), and a some increase in the intensity of the absorption in the high frequency, the so-called "cissoid", region of the spectrum [5,6]. After exposing compound **3** solution to sunlight for 3 h, the content of the *Z*- and *E*-isomers was 80 and 20% respectively, and remained unchanged on further irradiation. In the $^1$H NMR spectrum of the products obtained after irradiation new signals appeared at low field at 6.83 and 7.23 ppm. The coupling constants of the vinylic protons at 11.6 Hz is characteristic of a *Z*-isomer. Isolation of pure *Z*-isomer from the mixture by column chromatography on silica gel 0.06-0.2 mm (Acros) was unsuccessful.

TABLE 1. $^1$H NMR Spectrum of the Synthesized Compounds **3** and **4**

| Compound | $^1$H NMR spectrum, δ, ppm (*J*, Hz)* |
|---|---|
| **3** | 1.55 (6H, s, pyranone $CH_3$); 2.88 (2H, s, pyranone $CH_2$); 7.31 and 7.54 (2H, d, $J = 16.2$, CH=CH); 7.76 (2H, m, $J = 9.0$, phenyl $H_{(2)}$, $H_{(6)}$); 8.3 (2H, m, phenyl $H_{(3)}$, $H_{(5)}$) |
| *E*-**3** + *Z*-**3** | 1.37 (6H, s, $CH_3$ *Z*-isomer); 1.55 (6H, s, $CH_3$ *E*-isomer); 2.39 (2H, s, $CH_2$ *Z*-isomer); 2.88 (2H, s, $CH_2$ *E*-isomer); 6.83 and 7.23 (1H and 1H, d and d, $J = 11.6$, CH=CH *Z*-isomer); 7.31 and 7.52 (1H and 1H, d and d, $J = 16.2$, CH=CH *E*-isomer); 7.41 and 8.27 (2H and 2H $A_2M_2$ m, $J = 9.2$, $C_6H_4$ *Z*-isomer); 7.31 and 7.52 (2H and 2H, $A_2M_2$ m, $J = 9.0$, $C_6H_4$ *E*-isomer) |
| **4** | 1.22 and 1.35 (12H, s, $CH_3$); 2.84 (4H, m, pyranone $CH_2$); 3.11 and 3.71 (5H, m, $CH(CH_2)_2$); 7.68 (2H, d, $J = 9.6$, phenyl $H_{(2)}$, $H_{(6)}$); 8.18 (2H, d, phenyl $H_{(3)}$, $H_{(5)}$) |

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* The $^1$H NMR spectra were taken in $CDCl_3$ (compound **3**) and in DMSO-$d_6$ (compound **4**).

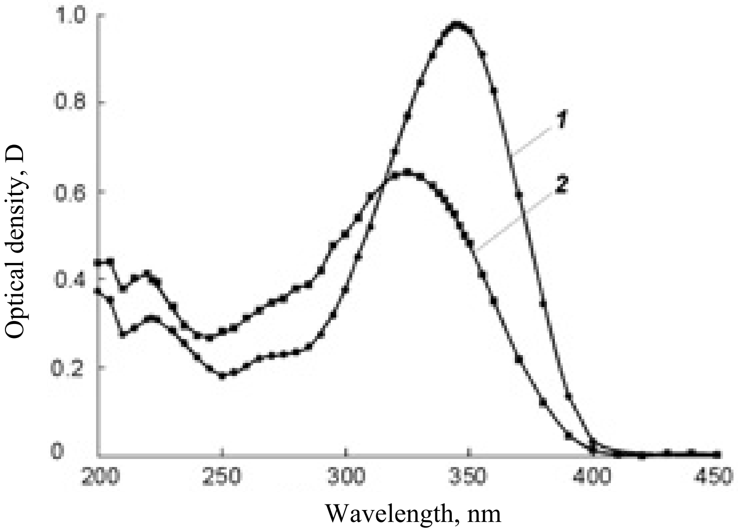


Fig. 1. 1) Absorption spectrum of pyranone **3** in ethanol at 20°C (*E*-isomer) and 2) after irradiation with sunlight for 3 h (20% *E*-isomer + 80% *Z*-isomer).

Quantum-chemical calculations by the AM1 method [7] were carried out by us with the aim of clarifying the mechanism of photoisomerization. Structural and energy characteristics calculated for the ground state as well as mainly for the two lower excited states (Figs. 2-4, Table 2). Taking into consideration the data on the heat of formation, the *E*-isomer is the more stable structure. The photoisomerization process observed by us resulting in the predominance of the thermodynamically less stable *Z*-form is called as an optical pump [8]. Comparison of the calculated values of the C(2)–C(3) bond order indicates that the double bond of the *Z*-isomer is more strong than that one for the *E*-configuration.

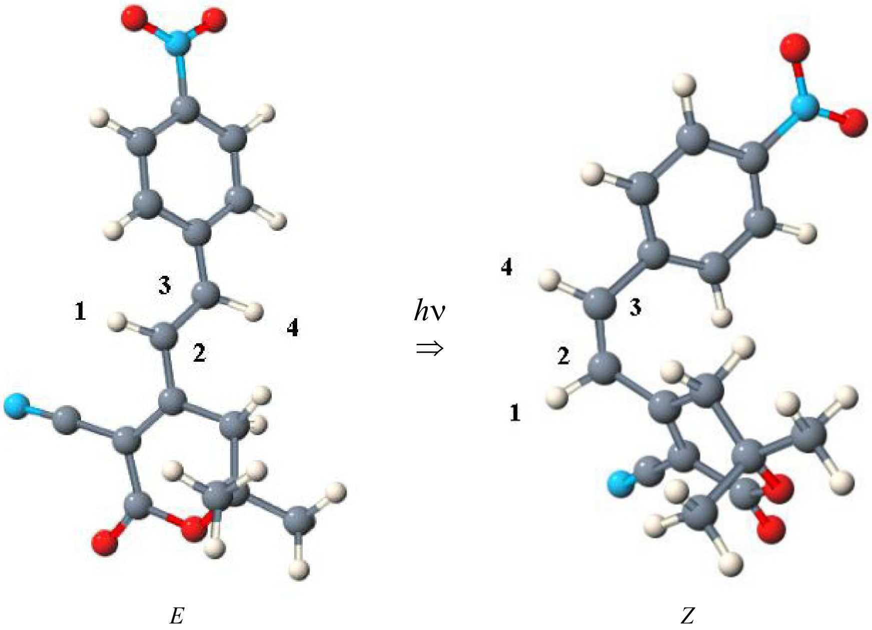
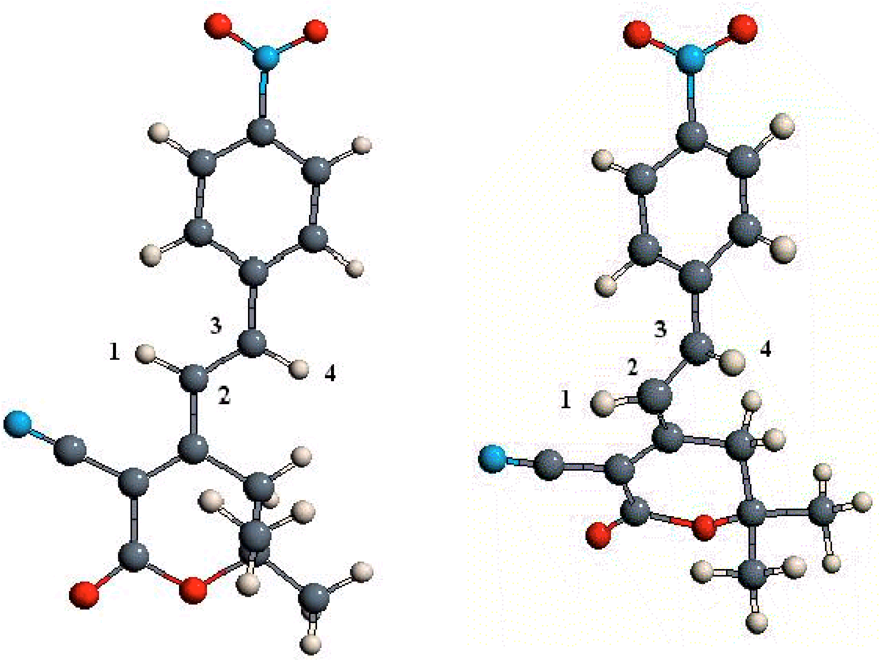


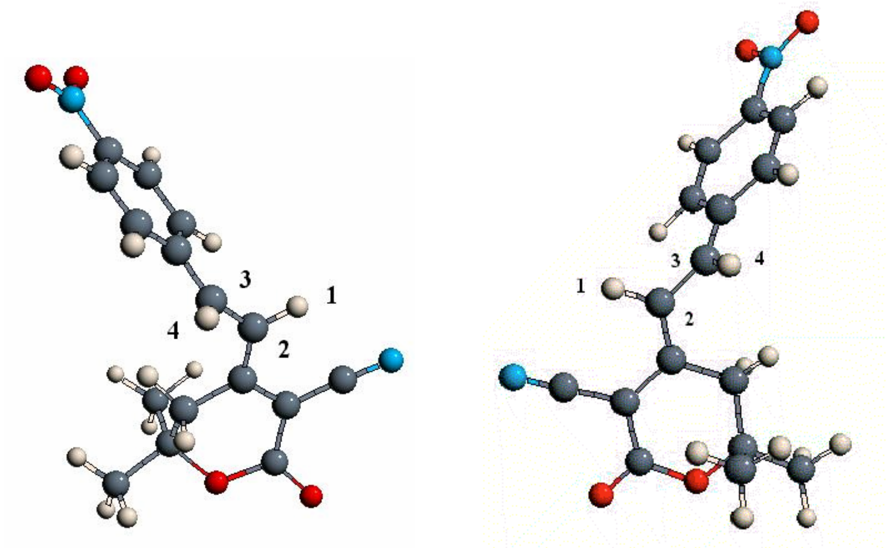
Fig. 2. Geometry of the *E*- and *Z*-isomers of pyranone **3** in the electronic $S_0$ ground state calculated by the AM1 method.

According to the calculations, on going from the ground $S_0$ state to the excited $S_1$ state the *cis* isomer becomes the more stable structure (Table 3, Fig. 3). Comparison of the data of Table 2 shows that the change in dihedral angle H(1)–C(2)–C(3)–H(4) of the *E*-isomer is insignificant while this angle for the *Z*-isomer is changed by approximately 90°. An increase in C(2)–C(3) bond length in relation to the $S_0$ state is specific for



*E* *Z*

Fig. 3. Geometry of the *E*- and *Z*-isomers of pyranone **3** in the $S_1$ state calculated by the AM1 method.



*E* *Z*

Fig. 4. Geometry of the *E*- and *Z*-isomers of pyranone **3** in the $T_1$ state.

TABLE 2. Characteristics of the *Z*- and *E*-Isomers of Compound **3** in the $S_0$, $S_1$, and $T_1$ States Calculated by the AM1 Method

| Calculated characteristics | Figure | State | Isomer | |
|---|---|---|---|---|
| | | | *E* | *Z* |
| Heat of formation, kcal/mol | 2 | $S_0$ | 3.74 | 6.87 |
| | 3 | $S_1$ | 98.16 | 89.40 |
| | 4 | $T_1$ | 38.3 | 38.3 |
| Dihedral angle H(1)–C(2)–C(3)–H(4), deg. | 2 | $S_0$ | 177.6 | -1.96 |
| | 3 | $S_1$ | 166.0 | -89.33 |
| | 4 | $T_1$ | 95.35 | -95.35 |
| Bond order C(2)–C(3) | 2 | $S_0$ | 1.829 | 1.880 |
| | 3 | $S_1$ | 1.140 | 1.093 |
| | 4 | $T_1$ | 1.043 | 1.043 |
| Bond length C(2)–C(3), Å | 2 | $S_0$ | 1.344 | 1.339 |
| | 3 | $S_1$ | 1.390 | 1.378 |
| | 4 | $T_1$ | 1.440 | 1.440 |

the $S_1$ state. A significant reduction of bond order occurs (from 1.829 to 1.140 for the *E*-form and from 1.880 to 1.093 for the *Z*-configuration), which indicates conversion of the multiple bond practically into a single bond, and consequently rotation about this bond is possible. The height of the rotational barrier, found from the reaction coordinates, is 0.21 kcal/mol for the *E*-isomer and 8.97 kcal/mol for the *Z*-isomer. This denotes that the photoexcitation of the *E*-isomer with subsequent transition into the *Z*-isomer is an energetically more favorable process than the reverse conversion and must lead to a predominance of the *Z*-isomer in the photostationary state. The difference in the values of the activation energy is displayed spectroscopically in the hypsochromic shift of the absorption maximum. Calculations show that on deactivation of the $S_1$ state the *E*- and *Z*-isomers are converted respectively into the *E*- and *Z*-isomers in the $S_0$ state of the molecule of **3**.

It has been established for many chemical compounds that *E*–*Z* isomerization occurs with the participation of triplet states [9-12]. As the calculations showed, on transfer to this state the structure of the *E*-isomer is changed most significantly. The dihedral angle H(1)–C(2)–C(3)–H(4) is reduced from 166.0 to 95.35°. The change in angle for the *Z*-isomer is only ~6°. The characteristics obtained (Table 2) and also the visualization of the molecular structures (Fig. 4) indicate that in the triplet state the *E*- and *Z*-configurations of pyranone **3** are mirror antipodes. The further reduction of the order of the C(2)–C(3) bond and the low barrier to rotation about this bond (2.46 kcal/mole) provide an easy interconversion of one isomeric form into the other. Deactivation of the $T_1$ state, unlike the singlet $S_1$ state, leads for both the *E*- and the *Z*-isomer only to one $S_0$ ground state, just to the *E*-isomer.

TABLE 3. Calculated Spectral Characteristics of *E*- and *Z*-Pyranones **3**

| *E*-Isomer | | *Z*-Isomer | |
|---|---|---|---|
| Energy, nm | Oscillator strength | Energy, nm | Oscillator strength |
| 487.2 | 0.0 | 486.4 | 0.0 |
| 413.5 | 0.0 | 413.2 | 0.0 |
| 341.0 | 0.006 | 334.8 | 0.006 |
| 332.2 | 1.327 | 309.1 | 0.711 |
| 296.7 | 0.011 | 292.7 | 0.023 |
| 281.2 | 0.149 | 276.1 | 0.189 |
| 240.3 | 0.022 | 247.5 | 0.091 |
| 239.2 | 0.050 | 238.2 | 0.045 |
| 226.6 | 0.052 | 228.2 | 0.140 |
| 218.6 | 0.029 | 219.6 | 0.171 |

The obtained results therefore point in favor of a singlet mechanism for carrying out the *E*–*Z* photoisomerization of pyranone **3**.

Using the equilibrium geometry of the ground state of the *E*- and *Z*-isomers of compound **3**, spectroscopic parameters, *viz*. transition energies and oscillator strengths (Table 3), were calculated for the isomers by the INDO/S-SCF-CI method [13]. Analysis showed that transitions caused by excitation of an electron from the highest occupied molecular orbital to the lowest vacant molecular orbital ($\pi \rightarrow \pi^*$) were characterized by the greatest intensity.

Based on the data of Table 3 theoretical UV absorption spectra were constructed for the *E*- and *Z*-isomers of pyranone **3** and also for mixtures of them (Fig. 5). Since the absorption spectra of heterocyclic compounds are as a rule unsymmetrical [14,15], a bi-Gaussian function was used to describe the shape [16]. Comparison of the spectra given in Figs. 1 and 5 indicate the good correlation between the experimental data and the theoretical calculations. In particular, the hypsochromic deviation of the position of the absorption maximum of the *E*-isomer of compound **3** in the calculated spectrum from experimental was 12 nm and of its mixture with the *Z*-conformation was 15 nm. The absorption maximum of the *Z*-isomer of pyranone **3** in the calculated spectrum was at 302 nm.

## EXPERIMENTAL

The UV spectra were obtained on a SF 46 spectrophotometer (LOMO) in ethanol. For *E*-pyranone **3** log ε was 4.57. The $^1$H NMR spectra were recorded on a Varian Mercury 200 (200 MHz) instrument, internal standard was TMS. HPLC was carried out on a Gilson 303 instrument on a Waters column (3.9 × 150 mm) packed with Nova-Pak silica sorbent. Eluent (ethyl acetate–hexane, 1:1) flow rate was 1 ml/min with a spectrophotometric detector ($\lambda$ = 254 nm). Analysis by TLC was carried out on Silufol UV 254 plates, eluent was ethyl acetate–hexane, 1:1).

Quantum-chemical calculations were carried out by the semiempirical AM1 method with full optimization of the geometric parameters of both the ground and the two lowest excited states of the *E*- and *Z*-isomers of pyranone **3**. Calculations for the excited states were carried out taking into account for interaction of configurations [keyword of program OPEN (2,2)]. The spectroscopic parameters of the *E*- and *Z*-isomers of pyranone **3**, enabling comparison and prediction of the electronic absorption spectra to be carried out, were calculated by the INDO/S-CI method [13] with the ArgusLab program 3.0 [17]. The theoretical absorption spectra were constructed using program written by us in FORTRAN 77 language. A normalized bi-Gaussian function was used for the shape of the individual spectral peaks [16]. In the case of the *E*-isomer spectrum a mean-square width of 30 nm was chosen for the forepart edge of the peak and 24 nm for the backpart edge. For the *Z*-isomer spectrum the corresponding values were 30 and 26 nm.

Figs. 1-5 were obtained using the programs JPlot [18] and JMol [19].

**Condensation of 3-Cyano-4,6,6-trimethyl-5,6-dihydropyran-2-one with Benzaldehyde 2.** A mixture of pyranone **1**, benzaldehyde **2**, NaOH (molar ratio aldehyde–pyranone–NaOH, 1:2:0.06) in ethanol was stirred vigorously, heated to boiling, and boiled for 4 h. The Michael adduct type product **4** began to precipitate in the course of the reaction, and was filtered off from the hot solution. The crotonization product **3** was precipitated after cooling the reaction mixture to room temperature. Both products were recrystallized from ethanol.

**Pyranone 3.** Mp 224-226°C. Found, %: C 64.40; H 4.67; N 9.35. $C_{16}H_{14}N_2O_4$. Calculated, %: C 64.42; H 4.73; N 9.39.

**Pyranone 4.** Mp 204-207°C (decomp.). Found, %: C 64.65; H 4.42; N 9.03. $C_{25}H_{25}N_3O_6$. Calculated, %: C 64.79; H 5.44; N 9.07.

The $^1$H NMR spectra of compounds **3** and **4** are given in Table 1.

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