

Synthesis, Molecular and Crystal Structure of 2-[2-(2-Amino-3-cyano-4*H*-chromen-4-yl)-cyclohexylidene]malononitrile

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Abstract—Condensation of salicylaldehyde with cyclohexylidenemalononitrile and hydrazine hydrate results in 2-[2-(2-amino-3-cyano-4*H*-chromen-4-yl)cyclohexylidene]malononitrile, the structure of which was studied by XRD.

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Previously, we have studied the condensation of salicylaldehyde with cyclohexylidencyanothioacetamide affording (*E*)-2-(2-hydroxybenzylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile [1] and the reaction of salicylaldehyde with cyclohexylidenemalononitrile and morpholine leading to 2-(morpholine-5*H*-chromeno[2,3-*d*]pyrimidin-2-yl)phenol [2].

In the present study we investigated the condensation of salicylaldehyde **I** with cyclohexylidenemalononitrile **II** and hydrazine hydrate **III** in anhydrous ethanol at 20°C. This reaction results in a previously unknown 2-[2-(2-amino-3-cyano-4*H*-chromen-4-yl)cyclohexylidene]malononitrile **IV** (method *a*), which is a promising precursor to create antidotes [3, 4], antibacterial [5], anticancer [6], and antidiabetic drugs. [7]

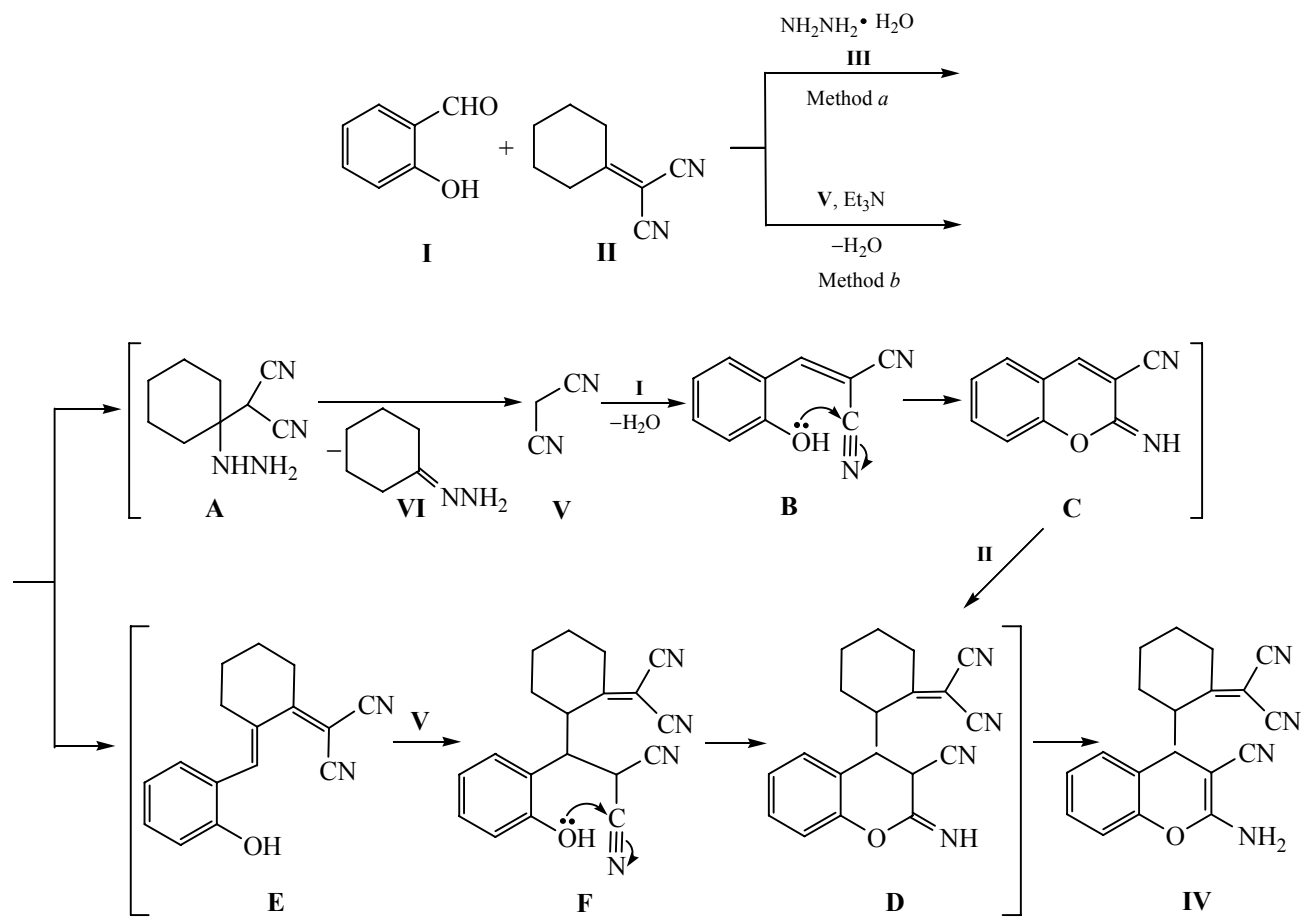
Apparently, the reaction includes the formation of the aza-Michael adduct **A**, which eliminates the malononitrile **V** and is stabilized as a hydrazone **VI**. The presence of amines in the reaction mixture initiates further Knoevenagel reaction to form the corresponding alkene **B**. Under the reaction conditions the latter undergoes the intramolecular cyclization into 2-amino-3-cyano-4*H*-benzo[*b*]pyran **V**, which can easily be formed from salicylaldehyde **I** and malononitrile **V** in a basic medium [8, 9].

Further, an interaction of intermediate **C** with the CH-acid **II** by Michael takes place to give the corresponding adduct **D**, which is unstable under the

reaction conditions and transforms into the substituted 2-amino-4*H*-benzo[*b*]pyran **IV** in 32% yield. The latter can be easily obtained in 69% yield by a three-component condensation of salicylaldehyde **I** with cyclohexylidenemalononitrile **II** and malononitrile **V** in DMF at 20°C in the presence of triethylamine (method *b*). Hypothetical intermediates in the method *b* may be both compounds **B–D** and alkene **E** that can interact with malononitrile **V** to form the Michael adduct **F** followed by intramolecular heterocyclization into the above 2-iminopyran **D**.

A feature of the spectral characteristics of compound **IV** is a doubling with equal intensity of the signal of C⁴H-proton in the ¹H NMR spectrum and the doubling of all the signals in the ¹³C NMR spectrum, which can be attributed to possible conformational isomerism of the cyclohexane substituent.

To establish the univocal structure the product of the above reaction compound **IV** was investigated by X-ray analysis. General view of the molecule is shown in the figure. The independent part of the unit cell contains four molecules of compound **IV** (**A**, **B**, **C** and **D**), which have similar geometrical parameters. The presence of cyclohexane substituent leads to non-planarity of the pyran ring. Its conformation is asymmetrical *boat*. The atoms O¹ and C⁹ are out of the plane of other atoms in the ring by 0.24–0.28 and 0.38–0.46 Å, respectively. The C⁹–C¹⁰ bond is axially oriented relative to the pyran and cyclohexane rings [torsion angles C⁶C¹C⁹C¹⁰ 86.4(3)°–93.6(3)° and



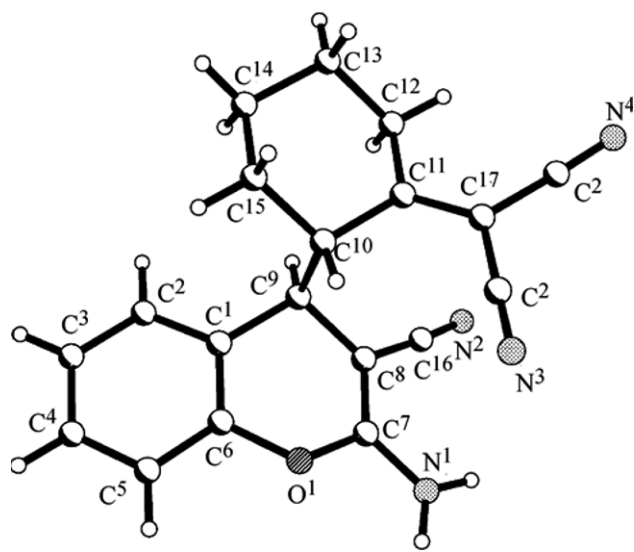
$\text{C}^{14}\text{C}^{15}\text{C}^{10}\text{C}^9$ $72.4(3)^\circ$ – $73.8(3)^\circ$]. The hydrogen atoms at C^9 and C^{10} carbons are *anti*-oriented (torsion angles $\text{H}^9\text{C}^9\text{C}^{10}\text{H}^{10}$ are 166° – 175°). This substituent orientation leads to the location of the dicyanomethylene

moiety in the cyclohexane ring above the cyano group of the pyran ring. The shortened intramolecular contacts $\text{C}^{16}\cdots\text{C}^{17}$ (3.22–3.40 Å, the sum of the van der Waals radii [10] is 3.42 Å) indicates an attractive nonvalence interaction. Asymmetrical conformation of the pyran ring causes a noticeable twist of the endocyclic double bond [torsion angle $\text{N}^1\text{C}^7\text{C}^8\text{C}^{16}$ is in the range of $6.7(3)^\circ$ – $10.0(3)^\circ$].

In the crystal the molecules form centrosymmetric dimers $\text{C}\cdots\text{C}$ and $\text{D}\cdots\text{D}$ and pseudocentrosymmetric dimers $\text{A}\cdots\text{B}$ due to the intermolecular hydrogen bonds $\text{N}^1\text{---H}^{1a}\cdots\text{N}^2$ ($\text{H}\cdots\text{N}$ 2.16–2.23 Å, $\text{N---H}\cdots\text{N}$ 159° – 166°). Also, each of the symmetrically independent molecules forms a weak intermolecular hydrogen bonds $\text{N}^1\text{---H}^{1b}\cdots\text{N}^1$ ($\text{H}\cdots\text{N}$ 2.34–2.51 Å, $\text{N---H}\cdots\text{N}$ 151° – 169°).

EXPERIMENTAL

Crystals of compound **IV** are triclinic, $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}$, at 298 K: a 11.384(2), b 11.640(2), c 25.945(4) Å; α $97.153(16)^\circ$, β $94.358(14)^\circ$, γ $91.374(15)^\circ$; V 3399.3 Å³, M 316.36, Z 8, space group $P1$, d_{calc} 1.236 g cm⁻³, $\lambda(\text{MoK}\alpha)$ 0.08 mm⁻¹, $F(000)$ 1328. The unit cell



General view of the molecules of compound **IV**.

Table 1. Bond lengths (Å) in the structure IV

Bond	A	B	C	D
O ^{1A} -C ^{7A}	1.364(3)	1.366(3)	1.357(3)	1.363(3)
N ^{1A} -C ^{7A}	1.334(3)	1.334(3)	1.333(3)	1.334(4)
N ^{2A} -C ^{16A}	1.145(3)	1.144(3)	1.150(4)	1.145(3)
N ^{3A} -C ^{18A}	1.140(4)	1.139(4)	1.132(4)	1.136(4)
N ^{4A} -C ^{19A}	1.135(4)	1.135(3)	1.138(4)	1.132(3)
C ^{1A} -C ^{2A}	1.380(4)	1.385(4)	1.390(4)	1.386(4)
C ^{1A} -C ^{6A}	1.368(4)	1.379(4)	1.371(4)	1.369(4)
C ^{1A} -C ^{9A}	1.497(3)	1.502(3)	1.504(4)	1.513(3)
C ^{2A} -C ^{3A}	1.371(4)	1.377(4)	1.377(4)	1.388(4)
C ^{3A} -C ^{4A}	1.370(4)	1.371(4)	1.377(4)	1.368(4)
C ^{4A} -C ^{5A}	1.377(4)	1.369(4)	1.373(4)	1.380(4)
C ^{5A} -C ^{6A}	1.377(4)	1.371(4)	1.381(4)	1.372(4)
C ^{7A} -C ^{8A}	1.348(3)	1.338(3)	1.351(4)	1.356(4)
C ^{8A} -C ^{9A}	1.511(3)	1.514(3)	1.513(4)	1.501(4)
C ^{8A} -C ^{16A}	1.404(4)	1.414(4)	1.413(4)	1.414(4)
C ^{9A} -C ^{10A}	1.575(4)	1.571(4)	1.573(3)	1.573(3)
C ^{10A} -C ^{11A}	1.496(3)	1.507(3)	1.507(4)	1.503(3)
C ^{10A} -C ^{15A}	1.527(3)	1.537(3)	1.535(4)	1.531(4)
C ^{11A} -C ^{12A}	1.481(3)	1.489(4)	1.490(3)	1.495(4)
C ^{11A} -C ^{17A}	1.339(4)	1.336(4)	1.340(3)	1.340(4)
C ^{12A} -C ^{13A}	1.526(3)	1.528(4)	1.531(4)	1.532(5)
C ^{13A} -C ^{14A}	1.512(4)	1.520(4)	1.509(4)	1.506(4)
C ^{14A} -C ^{15A}	1.507(4)	1.513(4)	1.523(4)	1.513(5)
C ^{17A} -C ^{18A}	1.433(4)	1.430(4)	1.430(4)	1.431(5)
C ^{17A} -C ^{19A}	1.427(4)	1.433(4)	1.436(4)	1.443(4)

parameters and intensities of 20725 reflections (12029 independent, R_{int} 0.046) were measured on a Xcalibur 3 automatic four-circle diffractometer (MoK α , graphite monochromator, CCD-detector, ω -scanning, $2\theta_{\text{max}}$ 50.0°).

The structure was solved by the direct method using SHELX-97 software [11]. Positions of the hydrogen atoms were geometrically calculated and refined in a *rider* model with $U_{\text{iso}} = 1.2U_{\text{eq}}$ of the carrier atom. The structure was refined by F^2 full-matrix least-square method in the anisotropic approximation for the non-hydrogen atoms to $wR_2 = 0.129$ for 12029 reflections (R_1 0.058 for 5819 reflections with $F > 4\sigma(F)$, S 1.00). The bond lengths and angles are given in Tables 1 and 2, respectively.

The IR spectrum was recorded on a Spectrum One (Perkin Elmer) instrument from KBr pellets. The ¹H

Table 2. Bond angles (deg) in the structure IV

Angle	A	B	C	D
C ^{7A} O ^{1A} C ^{6A}	116.7(2)	117.2(2)	117.4(2)	117.1(2)
C ^{2A} C ^{1A} C ^{9A}	123.7(3)	123.8(3)	123.7(3)	123.1(3)
C ^{6A} C ^{1A} C ^{2A}	117.6(3)	116.5(3)	116.9(3)	118.0(3)
C ^{6A} C ^{1A} C ^{9A}	118.7(3)	119.8(3)	119.4(2)	118.9(3)
C ^{3A} C ^{2A} C ^{1A}	121.1(3)	121.3(3)	120.7(3)	120.3(3)
C ^{4A} C ^{3A} C ^{2A}	119.4(3)	120.4(3)	120.6(3)	119.9(3)
C ^{3A} C ^{4A} C ^{5A}	121.5(3)	119.6(3)	120.0(3)	120.6(3)
C ^{4A} C ^{5A} C ^{6A}	117.3(3)	119.2(3)	118.3(3)	118.4(3)
C ^{1A} C ^{6A} O ^{1A}	120.4(3)	120.9(2)	120.8(3)	121.0(3)
C ^{1A} C ^{6A} C ^{5A}	123.1(3)	123.0(3)	123.5(3)	122.7(3)
C ^{5A} C ^{6A} O ^{1A}	116.5(3)	116.2(3)	115.8(3)	116.3(3)
N ^{1A} C ^{7A} O ^{1A}	110.9(2)	110.1(2)	110.7(3)	110.8(3)
N ^{1A} C ^{7A} C ^{8A}	128.3(3)	128.4(2)	127.8(3)	128.6(3)
C ^{8A} C ^{7A} O ^{1A}	120.9(2)	121.5(2)	121.5(3)	120.6(3)
C ^{7A} C ^{8A} C ^{9A}	119.3(2)	121.0(2)	120.0(3)	120.6(3)
C ^{7A} C ^{8A} C ^{16A}	121.1(2)	118.9(2)	120.7(3)	117.6(3)
C ^{16A} C ^{8A} C ^{9A}	119.6(2)	120.2(2)	119.3(3)	121.7(3)
C ^{1A} C ^{9A} C ^{8A}	107.6(2)	107.9(2)	108.3(2)	107.8(2)
C ^{1A} C ^{9A} C ^{10A}	110.7(2)	112.8(2)	111.6(2)	111.7(2)
C ^{8A} C ^{9A} C ^{10A}	110.1(2)	109.7(2)	110.1(2)	110.4(2)
C ^{11A} C ^{10A} C ^{9A}	108.9(2)	109.0(2)	108.7(2)	108.3(2)
C ^{11A} C ^{10A} C ^{15A}	109.4(2)	109.6(2)	109.7(2)	110.1(3)
C ^{15A} C ^{10A} C ^{9A}	115.6(2)	115.3(2)	114.9(2)	115.7(2)
C ^{12A} C ^{11A} C ^{10A}	116.4(2)	115.9(3)	116.0(2)	115.7(3)
C ^{17A} C ^{11A} C ^{10A}	122.4(3)	122.5(3)	122.3(3)	122.5(3)
C ^{17A} C ^{11A} C ^{12A}	121.1(3)	121.6(3)	121.7(3)	121.8(3)
C ^{11A} C ^{12A} C ^{13A}	110.1(2)	110.8(3)	110.3(3)	111.8(3)
C ^{14A} C ^{13A} C ^{12A}	110.8(2)	110.3(3)	111.5(3)	110.0(3)
C ^{15A} C ^{14A} C ^{13A}	110.5(3)	110.1(3)	111.5(2)	110.9(3)
C ^{14A} C ^{15A} C ^{10A}	113.8(2)	114.0(2)	112.9(3)	114.0(3)
N ^{2A} C ^{16A} C ^{8A}	176.0(3)	178.8(3)	177.0(3)	179.3(4)
C ^{11A} C ^{17A} C ^{18A}	122.2(3)	122.8(3)	122.9(3)	123.9(3)
C ^{11A} C ^{17A} C ^{19A}	122.3(3)	122.0(3)	121.8(3)	121.9(3)
C ^{19A} C ^{17A} C ^{18A}	115.5(3)	115.2(3)	115.3(2)	114.2(3)
N ^{3A} C ^{18A} C ^{17A}	178.4(4)	178.2(4)	177.2(4)	178.1(4)
N ^{4A} C ^{19A} C ^{17A}	177.4(4)	179.9(4)	178.7(4)	179.6(4)

NMR spectrum was registered on a Bruker DR-500 spectrometer (500.13 MHz) from DMSO-*d*₆ solutions relative to internal TMS. The ¹³C NMR spectrum was taken on a Varian VXR-300 spectrometer (125.74 MHz) from DMSO-*d*₆ solutions. The mass spectrum was

recorded on a Chrommass GC/MC (Hewlett Packard) 5890/5972 instrument (column HP-5 MS, 70 eV, CH₂Cl₂ solutions). The melting point was determined on a Koeffler heating block. The reaction progress and individuality of the compounds obtained were monitored by TLC on Silufol UV-254 plates eluting with an acetone–hexane mixture (3:5) and detecting with iodine vapor or UV irradiation.

2-[2-(2-Amino-3-cyano-4*H*-chromen-4-yl)cyclohexylidene]malononitrile (IV). *a.* A mixture of 1.07 ml (10 mmol) of salicylaldehyde **I**, 1.5 g (10 mmol) of cyclohexylidenemalononitrile **II**, and 0.5 ml (10 mmol) of hydrazine hydrate **III** in 20 ml of ethanol was stirred at 20°C for 2 h and then left standing for 48 h. The formed precipitate was filtered off, washed with ethanol and hexane. Yield 1.0 g (32%), white crystals, which fluoresce under the UV irradiation and exhibits a lacrimator properties when heated, mp 165–167°C (*i*-PrOH). IR spectrum, ν , cm⁻¹: 3423, 3328, 3207 (NH₂), 2231, 2184 (C≡N), 1651 (δ_{NH}). ¹H NMR spectrum, δ_{H} , ppm: 1.44–1.71 m (4H, 2CH₂), 1.99–2.18 m (2H, CH₂), 2.85 m (2H, CH₂), 3.01–3.12 m (1H, C¹H), 4.06 d (0.5H, C⁴H, *J* 12.0 Hz), 4.08 d (0.5H, C⁴H, *J* 8.0 Hz), 6.97 d (1H, H_{arom}, *J* 8.0 Hz), 7.15 d (1H, H_{arom}, *J* 8.0 Hz), 7.22–7.38 m (4H, 2H_{arom}, NH₂). ¹³C NMR spectrum, δ_{C} , ppm: 36.60, 37.07, 39.52, 39.69, 39.86, 40.02, 40.11, 40.19, 40.28, 51.33, 52.02, 52.42, 52.66, 83.60, 85.12, 11.15, 112.06, 112.23, 112.59, 116.80, 116.95, 120.68, 121.50, 123.91, 124.06, 124.26, 124.76, 127.93, 128.97, 129.04, 129.60, 129.99, 150.65, 151.17, 164.03, 164.12, 186.19, 186.22. MS, *m/z* (*I*_{rel}, %): 317 (100) [*M* + 1]⁺. Found, %: C 72.01; H 4.95; N 17.62. C₁₉H₁₆N₄O. Calculated, %: C 72.14; H 5.10; N 17.71. *M* 316.366.

b. To a mixture of 1.07 ml (10 mmol) of salicylaldehyde **I** and 1.5 g (10 mmol) of cyclohexylidene-malononitrile **II** in 15 ml of DMF was added 3 drops of triethylamine at 20°C. The mixture was stirred for 2 h and left standing for 24 h. Then to the reaction mixture was added 0.66 g (10 mmol) of malononitrile **V** with stirring for 20 min. The formed precipitate was filtered off, washed with ethanol and hexane. Yield 2.2 g (69%). Melting point and spectral data are identical to the substance synthesized by method *a*.

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