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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 cyclohexylidenecyanothioacetamide 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].

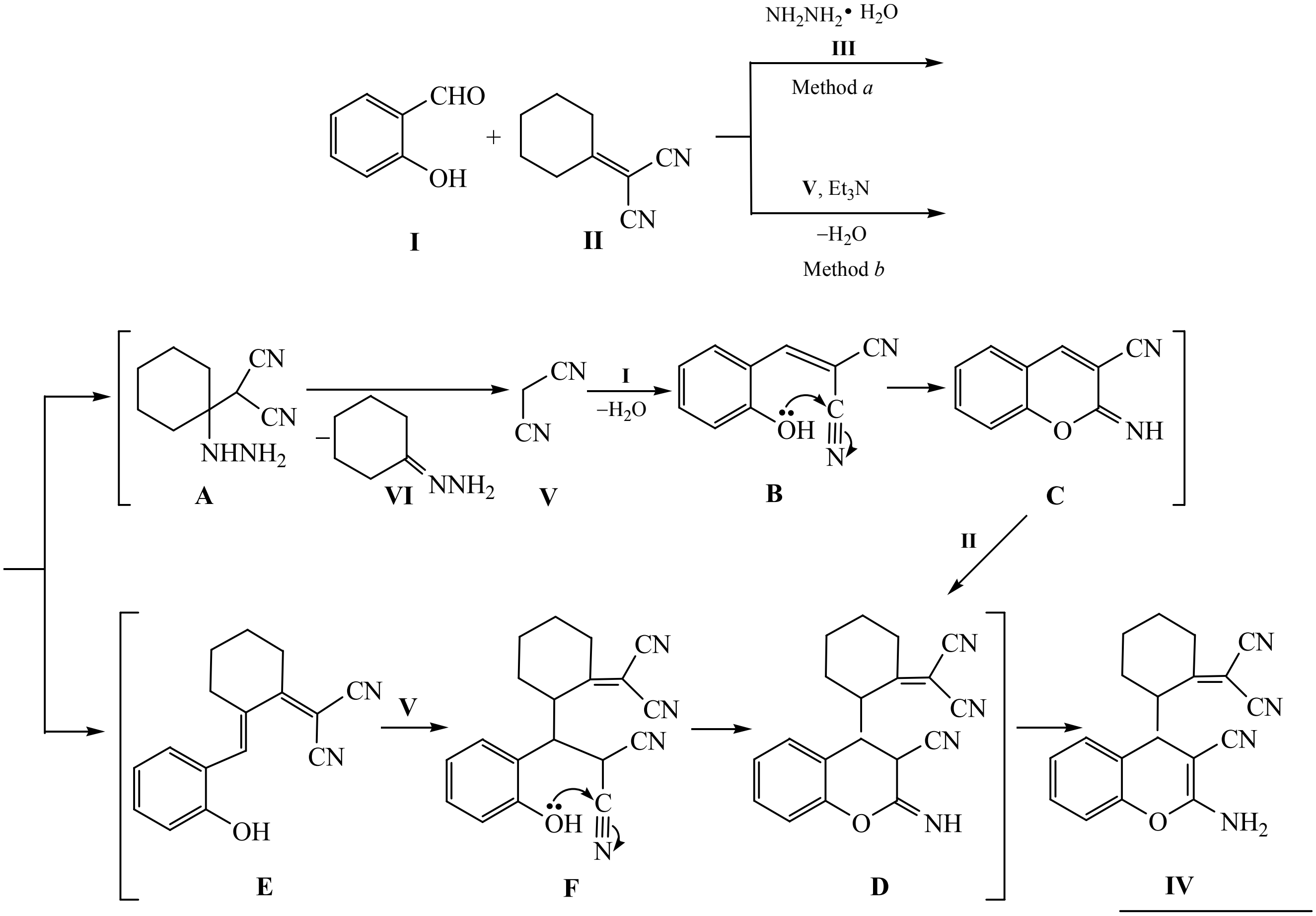
In the present study we investigated the condensation of salicylaldehyde **I** with cyclohexylidenemalononitrile **II** and hydrazine hydrate **III** in anhydrous ethanol at 20°C. This reaction results in a previously unknown 2-[2-(2-amino-3-cyano-4*H*-chromen-4-yl)cyclohexylidene]malononitrile **IV** (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].

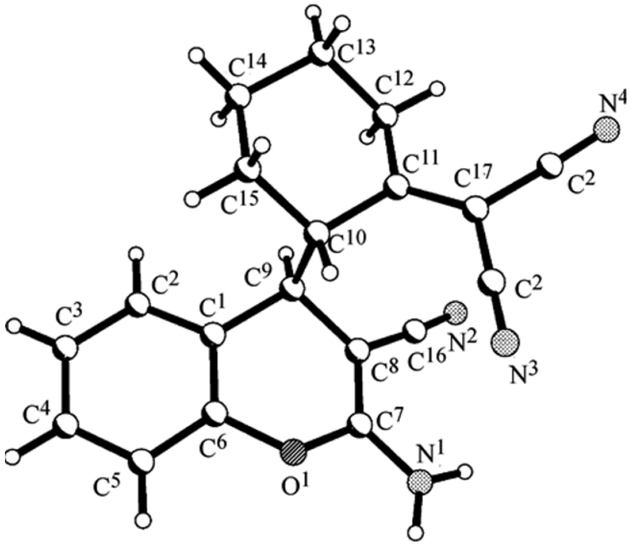
Further, an interaction of intermediate **C** with the CH-acid **II** by Michael takes place to give the corresponding adduct **D**, which is unstable under the reaction conditions and transforms into the substituted 2-amino-4*H*-benzo[*b*]pyran **IV** in 32% yield. The latter can be easily obtained 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 C^4H-proton in the ^1H NMR spectrum and the doubling of all the signals in the ^{13}C NMR spectrum, which can be attributed to possible conformational isomerism of the cyclohexane substituent.

To establish the definite structure of 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 nonplanarity of the pyran ring. Its conformation is asymmetrical *boat*. The atoms O^1 and C^9 are out of the plane of other atoms in the ring by 0.24–0.28 and 0.38–0.46 Å, respectively. The C^9–C^{10} bond is axially oriented relative to the pyran and cyclohexane rings [torsion angles $C^6C^1C^9C^{10}$ 86.4(3)°–93.6(3)° and



$C^{14}C^{15}C^{10}C^{9}$ 72.4(3)°–73.8(3)°]. The hydrogen atoms at C^9 and C^{10} carbons are *anti*-oriented (torsion angles $H^9C^9C^{10}H^{10}$ 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 $C^{16}\cdots C^{17}$ (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 $N^1C^7C^8C^{16}$ is in the range of 6.7(3)°–10.0(3)°].



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

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

EXPERIMENTAL

Crystals of compound **IV** are triclinic, $C_{19}H_{16}N_4O$, at 298 K: *a* 11.384(2), *b* 11.640(2), *c* 25.945(4) Å; α 97.153(16), β 94.358(14), γ 91.374(15); *V* 3399.3 Å^3, *M* 316.36, *Z* 8, space group *P*1, d_{calc} 1.236 g cm^{-3}, λ(MoK_α) 0.08 mm^{-1}, *F*(000) 1328. The unit cell

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)

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

Angle	**A**	**B**	**C**	**D**
$\mathrm{C}^{7A}\mathrm{O}^{1A}\mathrm{C}^{6A}$	116.7(2)	117.2(2)	117.4(2)	117.1(2)
$\mathrm{C}^{2A}\mathrm{C}^{1A}\mathrm{C}^{9A}$	123.7(3)	123.8(3)	123.7(3)	123.1(3)
$\mathrm{C}^{6A}\mathrm{C}^{1A}\mathrm{C}^{2A}$	117.6(3)	116.5(3)	116.9(3)	118.0(3)
$\mathrm{C}^{6A}\mathrm{C}^{1A}\mathrm{C}^{9A}$	118.7(3)	119.8(3)	119.4(2)	118.9(3)
$\mathrm{C}^{3A}\mathrm{C}^{2A}\mathrm{C}^{1A}$	121.1(3)	121.3(3)	120.7(3)	120.3(3)
$\mathrm{C}^{4A}\mathrm{C}^{3A}\mathrm{C}^{2A}$	119.4(3)	120.4(3)	120.6(3)	119.9(3)
$\mathrm{C}^{3A}\mathrm{C}^{4A}\mathrm{C}^{5A}$	121.5(3)	119.6(3)	120.0(3)	120.6(3)
$\mathrm{C}^{4A}\mathrm{C}^{5A}\mathrm{C}^{6A}$	117.3(3)	119.2(3)	118.3(3)	118.4(3)
$\mathrm{C}^{1A}\mathrm{C}^{6A}\mathrm{O}^{1A}$	120.4(3)	120.9(2)	120.8(3)	121.0(3)
$\mathrm{C}^{1A}\mathrm{C}^{6A}\mathrm{C}^{5A}$	123.1(3)	123.0(3)	123.5(3)	122.7(3)
$\mathrm{C}^{5A}\mathrm{C}^{6A}\mathrm{O}^{1A}$	116.5(3)	116.2(3)	115.8(3)	116.3(3)
$\mathrm{N}^{1A}\mathrm{C}^{7A}\mathrm{O}^{1A}$	110.9(2)	110.1(2)	110.7(3)	110.8(3)
$\mathrm{N}^{1A}\mathrm{C}^{7A}\mathrm{C}^{8A}$	128.3(3)	128.4(2)	127.8(3)	128.6(3)
$\mathrm{C}^{8A}\mathrm{C}^{7A}\mathrm{O}^{1A}$	120.9(2)	121.5(2)	121.5(3)	120.6(3)
$\mathrm{C}^{7A}\mathrm{C}^{8A}\mathrm{C}^{9A}$	119.3(2)	121.0(2)	120.0(3)	120.6(3)
$\mathrm{C}^{7A}\mathrm{C}^{8A}\mathrm{C}^{16A}$	121.1(2)	118.9(2)	120.7(3)	117.6(3)
$\mathrm{C}^{16A}\mathrm{C}^{8A}\mathrm{C}^{9A}$	119.6(2)	120.2(2)	119.3(3)	121.7(3)
$\mathrm{C}^{1A}\mathrm{C}^{9A}\mathrm{C}^{8A}$	107.6(2)	107.9(2)	108.3(2)	107.8(2)
$\mathrm{C}^{1A}\mathrm{C}^{9A}\mathrm{C}^{10A}$	110.7(2)	112.8(2)	111.6(2)	111.7(2)
$\mathrm{C}^{8A}\mathrm{C}^{9A}\mathrm{C}^{10A}$	110.1(2)	109.7(2)	110.1(2)	110.4(2)
$\mathrm{C}^{11A}\mathrm{C}^{10A}\mathrm{C}^{9A}$	108.9(2)	109.0(2)	108.7(2)	108.3(2)
$\mathrm{C}^{11A}\mathrm{C}^{10A}\mathrm{C}^{15A}$	109.4(2)	109.6(2)	109.7(2)	110.1(3)
$\mathrm{C}^{15A}\mathrm{C}^{10A}\mathrm{C}^{9A}$	115.6(2)	115.3(2)	114.9(2)	115.7(2)
$\mathrm{C}^{12A}\mathrm{C}^{11A}\mathrm{C}^{10A}$	116.4(2)	115.9(3)	116.0(2)	115.7(3)
$\mathrm{C}^{17A}\mathrm{C}^{11A}\mathrm{C}^{10A}$	122.4(3)	122.5(3)	122.3(3)	122.5(3)
$\mathrm{C}^{17A}\mathrm{C}^{11A}\mathrm{C}^{12A}$	121.1(3)	121.6(3)	121.7(3)	121.8(3)
$\mathrm{C}^{11A}\mathrm{C}^{12A}\mathrm{C}^{13A}$	110.1(2)	110.8(3)	110.3(3)	111.8(3)
$\mathrm{C}^{14A}\mathrm{C}^{13A}\mathrm{C}^{12A}$	110.8(2)	110.3(3)	111.5(3)	110.0(3)
$\mathrm{C}^{15A}\mathrm{C}^{14A}\mathrm{C}^{13A}$	110.5(3)	110.1(3)	111.5(2)	110.9(3)
$\mathrm{C}^{14A}\mathrm{C}^{15A}\mathrm{C}^{10A}$	113.8(2)	114.0(2)	112.9(3)	114.0(3)
$\mathrm{N}^{2A}\mathrm{C}^{16A}\mathrm{C}^{8A}$	176.0(3)	178.8(3)	177.0(3)	179.3(4)
$\mathrm{C}^{11A}\mathrm{C}^{17A}\mathrm{C}^{18A}$	122.2(3)	122.8(3)	122.9(3)	123.9(3)
$\mathrm{C}^{11A}\mathrm{C}^{17A}\mathrm{C}^{19A}$	122.3(3)	122.0(3)	121.8(3)	121.9(3)
$\mathrm{C}^{19A}\mathrm{C}^{17A}\mathrm{C}^{18A}$	115.5(3)	115.2(3)	115.3(2)	114.2(3)
$\mathrm{N}^{3A}\mathrm{C}^{18A}\mathrm{C}^{17A}$	178.4(4)	178.2(4)	177.2(4)	178.1(4)
$\mathrm{N}^{4A}\mathrm{C}^{19A}\mathrm{C}^{17A}$	177.4(4)	179.9(4)	178.7(4)	179.6(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, $2\theta_{\max}$ 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 $U_{\mathrm{iso}} = 1.2U_{\mathrm{eq}}$ of the carrier atom. The structure was refined by F^2 full-matrix least-square method in the anisotropic approximation for the nonhydrogen 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 ^{1}H NMR spectrum was registered on a Bruker DR-500 spectrometer (500.13 MHz) from DMSO-d_6 solutions relative to internal TMS. The ^{13}C 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, CH_2Cl_2 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 (NH_2), 2231, 2184 (C≡N), 1651 (δ_{NH}). ^1H NMR spectrum, δ_H, ppm: 1.44–1.71 m (4H, $2CH_2$), 1.99–2.18 m (2H, CH_2), 2.85 m (2H, CH_2), 3.01–3.12 m (1H, $C^{1'}H$), 4.06 d (0.5H, C^4H, *J* 12.0 Hz), 4.08 d (0.5H, C^4H, *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, $2H_{arom}$, NH_2). ^{13}C 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. $C_{19}H_{16}N_4O$. 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 cyclohexylidenemalononitrile **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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