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Synthesis and crystal structure of 4-hydroxy-3-[(3E)-3-(hydroxyimino)-1-(4-nitrophenyl)butyl]-2H-chromen-2-one

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The structure of 4-hydroxy-3-[(3E)-3-(hydroxyimino)-1-(4-nitrophenyl)butyl]-2H-chromen-2-one was determined by X-ray crystallography. The compound crystallizes in an orthorhombic crystal system and was characterized thus: Pbcn, a = 11.3411(8)Å, b = 10.0843 (14)Å, c = 33.170(3)Å, α = β = γ= 90º, Z = 8, V = 3793.6(7)Å^3. The crystal structure was solved by direct methods and refined by full-matrix least-squares on F^2 to a final R1 of 0.0946.

Key words:4-Hydroxy-3-[(3E)-3-(hydroxyimino)-1-(4-nitrophenyl)butyl]-2H-chromen-2-one, crystal structure, coumarin derivatives

INTRODUCTION

Coumarin is a structural fragment of different natural and synthetic compounds which demonstrated a wide range of pharmacological activities. The coumarin derivatives are of interest because of their properties as oral anticoagulants or rodenticides [1], photosensitizers [2], anti-HIV agents [3,4], and antibiotics [5]. There has been continuous interest in the synthesis of these compounds. The most widely used antithrombotic in European countries is racemic Acenocoumarol (Synthrom, Niffcoumar). Chemical modifications of the Acenocoumarol structure seem to be a promising route to obtain compounds with good biological activity, lower toxicity and fewer side effects.

EXPERIMENTAL

Synthesis and characterization

The title compound (**I**) was obtained according to the reaction scheme 1.

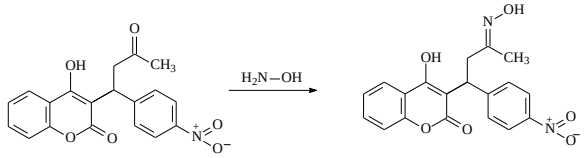

Fig.1. Reaction pathway

Melting point was measured on a Boetius hot plate microscope (Germany) and was uncorrected. IR spectra (nujol) were recorded on an IR-spectrometer FTIR-8101 M Shimadzu. ^{1}H NMR spectra were recorded at ambient temperature on a Bruker 250 WM (250 MHz) spectrometer in [D_6]-acetone. Chemical shifts are given in ppm (σ) relative to TMS used as an internal standard. Mass spectra were recorded on a Jeol JMS D 300 double focusing mass spectrometer coupled to a JMA 2000 data system. The compound was introduced by direct inlet probe, heated from 50 ºC to 400 ºC at a rate of 100 ^{o}/min. The ionization current was 300 mA, the accelerating voltage 3 kV and the chamber temperature 150 ºC. TLC was performed on precoated plates Kieselgel 60 F_{254} Merck (Germany) with layer thickness of 0.25 mm and UV detection (254 nm). Yields of TLC-homogeneous isolated product are given. Elemental analysis was performed at the Faculty of Chemistry, University of Sofia. Analysis data indicated by the symbols of the elements were within ±0.4 % of the theoretical values.

X-ray crystallographic study (general procedure of the diffraction method by single crystal): Measurements [6] were made at 173(2) K on an Enraf-Nonius KAPPA CCD diffractometer with a graphite monochromated Mo- K_α (λ = 0.71069 Å). Crystal unit-cell and orientation parameters were obtained from the auto indexing procedure, as implemented in DENZO [7]. Intensities recorded up to a maximum 2θ value of 45.0° using the ω scan technique, were integrated with DENZO [7], scaled, and then reduced in Scalepack [7] after a

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post-refinement of the unit-cell parameters. The structure was solved by direct methods using SIR97 [8] and refined by full–matrix least–squares techniques on F^2 using SHELX-L 97 [9, 10]. All non-hydrogen atoms were anisotropically and fully refined at the calculated positions.

Acenocoumarol, synthesized by us, was treated with hydroxylamine hydrochloride at a molar ratio of 1:1 to produce the oxime derivative. Acenocoumarol (3.53 g, 10 mmol) was added to 150 ml ethanol containing hydroxylamine hydrochloride (0.7 g, 10 mmol). Three ml pyridine and 0.4 g sodium hydroxide were added to the reaction mixture. The solution was allowed to stand for 12 h and then refluxed for 6 h. After cooling the oxime crystallized out and was filtered off. The crude product was recrystallized from methanol. TLC (toluene/chloroform/acetone, 8:8:1). Yield 2.58 g (70 %), m.p. 191–193 ºC, R_f = 0.15. $C_{19}H_{16}N_2O_6$ (368): IR, cm^{-1}: 2994, 1673, 1620, 1568, 1497, 1452, 1399, 1215, 766. ^{1}H NMR ([D_6]-acetone): 1.84 s (3H), 3.1–3.3 d (2H – side chain), 4.9–5.1 t (1H), 7.2–8.1 m (8H- arom), 10.9 s (2H – two hydroxyl groups). MS: 368 (0.3), 351 (3.2), 310 (0.6), 296 (0.6), 205 (100), 163 (6.4), 162 (52), 159 (58), 143 (20), 142 (15), 120 (77), 92 (46) [11].

RESULTS AND DISCUSSION

We investigated the reaction of 4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2*H*-chromen-2-one (acenocoumarol) with hydroxylamine hydrochloride at a molar ratio of 1:1 in ethanol in the presence of pyridine and sodium hydroxide. The aim of the investigation was to synthesize 4-hydroxy-3-[(3E)-3-hydroxyimino)-1-(4-nitrophenyl) butyl]-2H-chromen-2-one, m. p. 191–193 ºC [10]. It is known that the oximes of the aromatic ketones readily undergo a similar to Beckmann rearrangement to produce different cyclo-derivatives [12]. We established that the only product in this case is the title compound (Fig. 1).

Colourless thin needle-like crystals, sufficiently suitable for X-ray diffraction analysis, were grown by slow evaporation of an ethyl acetate solution. The crystal belongs to the orthorhombic system, chiral space group Pbcn and the structure solution unveils that the asymmetric unit is composed of one diastereomeric molecule corresponding to the title compound, 4-hydroxy-3-[(3E)-3-(hydroxyimino)-1-(4-nitrophenyl)butyl]-2H-chromen-2-one.

An examination of the bond lengths revealed that the atoms retained the character expected for the open-side chain (hydroxyimino) compound.

Table 1. Crystal and experimental data

Empirical formula	$C_{19}H_{16}N_2O_6$
Formula weight	368.34
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Orthorhombic
group	Pbcn
Unit cell dimensions	a = 11.3411(8) Å α = 90º b = 10.0843(14) Å β = 90º c = 33.170(3) Å γ = 90º
Volume	3793.6(7) $Å^3$
Z	8
Calculated density	1.290 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	1536
Crystal size	0.30 × 0.15 × 0.10 mm
θ range for data collection	5.89 to 24.70 deg.
Index ranges	–13≤h≤13, -11≤k≤10, –38≤l≤38
Reflections collected / unique	31770 / 3177 [R(int) = 0.1598]
Completeness to 2 θ = 24.70	86.7%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3177 / 0 / 308
Goodness-of-fit on F^2	1.235
Final R indices [I>2σ (I)]	R1 = 0.0946, wR2 = 0.1667
R indices (all data)	R1 = 0.1339, wR2 = 0.1814
Largest diff. peak and hole	0.222 and –0.175 $e.A^{-3}$

The O21–C2 bond length of 1.348(5)Å is close to that of the phenolic C-O bond. Moreover, the bond lengths between C02–C03 and between C03-C04 are 1.502(6) and 1.490(7), respectively, close to the expected values for C–C bonds adjacent to a C=N-group. In the structure of the investigated compound there is no bond between C03 and O21. Within the coumarin system, the length of the double bond C1-C2, 1.359(6) Å is suitable for a C=C bond conjugated to a carbonyl, and the adjacent C10–C1 bond of 1.437(6) Å is slightly shorter than expected because of resonance. Two near disposed planarities of the coumarin ring system and the aromatic nucleus formed an angle of 110.4(4)º between C11 – C01 – C1. The compound crystallized in the open-chain ketimino form and had only one asymmetric center at C01. No hemiketimino ring was formed in the investigated compound.

All hydrogen atoms were located in different electron-density maps, but refined as riding, with C—H= 0.93 Å and 0.96 Å for the benzene and methyl H atoms, respectively.(Fig. 2).

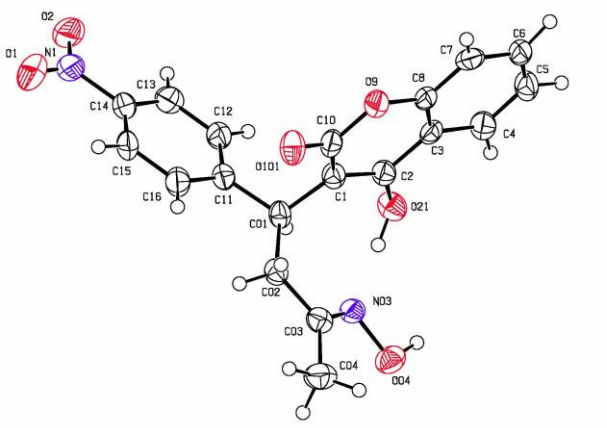

Fig. 2. View of the molecular structure of compound (I), showing the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level and H are shown as small spheres of arbitrary radii.

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (A^2 × 10^3) for the compound. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C 01	5892(4)	–981(5)	3967(1)	32(1)
C 1	6004(4)	–661(4)	3519(1)	33(1)
C 2	6159(4)	–1602(4)	3231(1)	33(1)
C 02	4625(4)	–910(5)	4122(1)	35(1)
C 3	6352(4)	–1240(4)	2817(1)	32(1)
C 03	3843(4)	–2047(5)	4004(1)	35(1)
C 4	6551(4)	–2151(5)	2509(1)	39(1)
C 04	2582(5)	–2014(7)	4128(2)	49(1)
C 5	6719(4)	–1713(6)	2120(1)	42(1)
C 6	6690(4)	–391(6)	2028(1)	42(1)
C 7	6473(4)	527(6)	2328(1)	40(1)
C 8	6320(4)	94(5)	2720(1)	35(1)
C 10	5891(4)	706(5)	3402(1)	36(1)
C 11	6802(4)	-214(4)	4208(1)	32(1)
C 12	7975(4)	-571(5)	4157(1)	39(1)
C 13	8861(5)	65(5)	4364(1)	42(1)
C 14	8556(4)	1061(5)	4625(1)	42(1)
C 15	7414(5)	1448(5)	4681(1)	44(1)
C 16	6526(5)	789(5)	4471(1)	42(1)
N 1	9494(5)	1757(5)	4850(1)	57(1)
N 03	4318(3)	–3009(4)	3811(1)	35(1)
O 1	9209(4)	2671(5)	5071(1)	85(2)
O 2	10515(4)	1384(4)	4797(1)	68(1)
O 04	3514(3)	–4040(3)	3724(1)	45(1)
O 9	6094(3)	1051(3)	3008(1)	39(1)
O 21	6157(3)	–2913(3)	3309(1)	42(1)
O 101	5616(3)	1610(3)	3624(1)	45(1)

Table 3. Selected bond lengths [Å] for the compound.

C 01 – C 11	1.518(6)
C 01 – C 1	1.525(6)
C 01 – C 02	1.528(6)
C 1 – C 2	1.359(6)
C 1 – C 10	1.437(6)
C 2 – O 21	1.348(5)
C 2 – C 3	1.436(6)
C 02 – C 03	1.502(6)
C 03 – N 03	1.280(6)
C 03 – C 04	1.490(7)
C 8 – O 9	1.381(5)
C 10 – O 101	1.214(5)
C 10 – O 9	1.374(5)
C 14 – N 1	1.478(6)
N 1 – O 1	1.219(6)
N 1 – O 2	1.231(6)
N 03 – O 04	1.413(5)

Table 4. Selected bond angles [°] for the compound.

C 11 – C 01 – C 1	110.4(4)
C 11 – C 01 – C 02	116.0(4)
C 1 – C 01 – C 02	113.4(4)
C 2 – C 1 – C 10	119.4(4)
C 2 – C 1 – C 01	123.2(4)
C 10 – C 1 – C 01	117.3(4)
O 21 – C 2 – C 1	123.3(4)
O 21 – C 2 – C 3	115.7(4)
C 03 – C 02 – C 01	115.5(4)
C 4 – C 3 – C 2	123.9(4)
N 03 – C 03 – C 04	124.0(5)
N 03 – C 03 – C 02	117.4(4)
C 04 – C 03 – C 02	118.5(4)
O 9 – C 8 – C 7	116.8(4)
O 9 – C 8 – C 3	121.6(4)
O 101 – C 10 – O 9	115.5(4)
O 101 – C 10 – C 1	125.4(4)
O 9 – C 10 – C 1	119.1(4)
C 16 – C 11 – C 12	119.2(4)
C 16 – C 11 – C 01	123.7(4)
C 12 – C 11 – C 01	117.1(4)
C 13 – C 14 – N 1	119.1(5)
O 1 – N 1 – O 2	124.5(5)
O 1 – N 1 – C 14	118.2(5)
O 2 – N 1 – C 14	117.3(5)
C 03 – N 03 – O 04	112.8(4)
C 10 – O 9 – C 8	120.8(3)

Symmetry transformations used to generate equivalent atoms.

Table 5. Anisotropic displacement parameters ($A^2 \times 10^3$) for the compound. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

	U11	U22	U33	U23	U13	U12
C 01	35(3)	33(3)	29(2)	-6(2)	0(2)	5(2)
C 1	29(2)	39(3)	31(2)	-4(2)	-1(2)	2(2)
C 2	27(2)	39(3)	33(2)	-5(2)	1(2)	3(2)
C 02	35(3)	40(3)	30(2)	-6(2)	3(2)	3(2)
C 3	23(2)	39(3)	34(2)	-7(2)	-4(2)	-5(2)
C 03	31(2)	41(3)	32(2)	7(2)	-1(2)	3(2)
C 4	29(2)	50(3)	38(2)	-9(2)	1(2)	6(2)
C 04	38(3)	56(4)	53(3)	7(3)	4(3)	-4(3)
C 5	34(3)	58(4)	35(3)	-14(2)	1(2)	2(2)
C 6	29(3)	66(4)	30(2)	-7(2)	0(2)	-7(2)
C 7	30(3)	46(3)	44(3)	6(2)	-1(2)	13(2)
C 8	24(2)	50(3)	30(2)	-7(2)	0(2)	-8(2)
C 10	5(3)	41(3)	32(2)	-7(2)	-6(2)	0(2)
C 11	36(3)	34(3)	26(2)	-1(2)	1(2)	1(2)
C 12	36(3)	46(3)	33(2)	-6(2)	2(2)	-1(2)
C 13	33(3)	56(3)	38(2)	8(2)	-2(2)	3(3)
C 14	43(3)	55(3)	27(2)	6(2)	-6(2)	12(2)
C 15	56(3)	47(3)	28(2)	-8(2)	-2(2)	-7(3)
C 16	41(3)	51(3)	34(2)	-5(2)	-2(2)	0(3)
N 1	58(3)	75(4)	38(2)	12(2)	-8(2)	-26(3)
N 03	36(2)	37(2)	33(2)	5(2)	-2(2)	-5(2)
O 1	82(3)	103(4)	70(3)	-32(3)	-3(2)	-39(3)
O 2	46(2)	106(3)	52(2)	17(2)	-16(2)	
O 04	48(2)	35(2)	52(2)	3(2)	-4(2)	-8(2)
O 9	44(2)	37(2)	35(2)	-4(1)	-3(1)	-5(2)
O 21	50(2)	35(2)	40(2)	-3(2)	9(2)	6(2)
O 101	58(2)	37(2)	40(2)	-10(2)	-6(2)	6(2)

Table 6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for the compound.

	X	Y	Z	U(eq)
H 01	6100(3)	1850(4)	3999(11)	22(11)
H 02A	4630(5)	790(6)	4386(17)	72(18)
H 02B	4260(3)	100(4)	4042(11)	21(10)
H 4	6520(4)	3230(5)	2566(13)	43(13)
H 04	4030(7)	4660(8)	3540(2)	130(3)
H 04A	2380(4)	2660(5)	4351(14)	44(13)
H 04B	2050(5)	2170(6)	3921(17)	71(18)
H 04C	2490(6)	1090(9)	4290(2)	120(3)
H 5	6860(4)	2360(5)	1911(14)	46(13)
H 6	6860(4)	50(5)	1756(15)	56(14)
H 7	6410(3)	1360(4)	2268(11)	16(11)
H 12	8220(4)	1240(4)	3989(12)	33(12)
H 13	9630(4)	200(5)	4329(13)	43(14)
H 15	7210(4)	2210(5)	4843(13)	48(14)
H 16	5830(5)	1050(6)	4517(16)	64(19)
H 21	5580(5)	3130(5)	3503(15)	54(15)

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СИНТЕЗА И КРИСТАЛНА СТРУКТУРА НА 4-ХИДРОКСИ-3-[(3E)-3-(ХИДРОКСИИМИНО)-1-(4-НИТРОФЕНИЛ)БУТИЛ]-2H-ХРОМЕН-2-ОН

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(Резюме)

Структурата на 4-хидрокси-3-[(3E)-3-(хидроксиимино)-1-(4-нитрофенил)бутил]-2H-хромен-2-он е определена чрез монокристален рентгеноструктурен анализ. Съединението кристализира в орторомбична кристална система и пространствена група Pbcn, с параметри на елементарната клетка a = 11.3411(8)Å, b = 10.0843 (14)Å, c = 33.170(3)Å, α = β = γ= 90º, Z = 8, V = 3793.6(7)Å^3. Кристалната структура е доказана с директни методи и точно определена с помощта на метода на най-малките квадрати за F^2 до стойност R1 = 0.0946.