2-SUBSTITUTED [1]BENZOPYRANO[4,3-*d*]PYRIMIDIN-5-ONES

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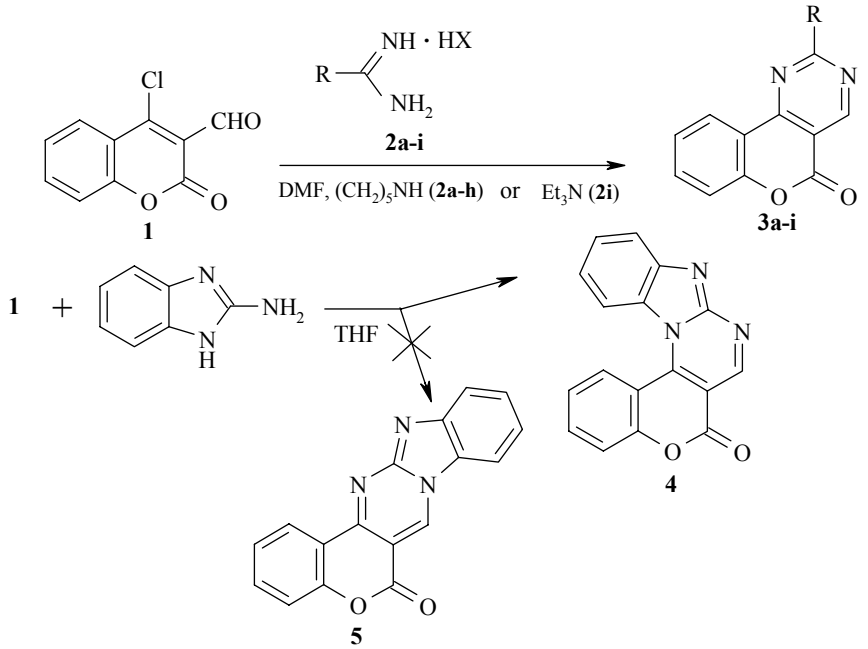
A new method is reported for the synthesis of 2-R-substituted [1]benzopyrano[4,3-d]pyrimidin-5-ones (R = p-phenyl, p-chlorophenyl-, p-carbamoylphenyl-, 3-pyridinyl-, 4-pyridinyl-, 2-pyrazinyl-, pyrrolidino-, morpholino-, 3,6-dimethyl-1-pyrazolyl-) by the reaction of 4-chloro-3-formylcoumarin with salts of the corresponding amidines RC(=NH)NH$_2$HX in DMF in the presence of piperidine or triethylamine. 3-Formyl-4-coumarin and 2-aminobenzimidazole give [1]benzopyrano[2,4:3',4']-pyrimido[1,2-a]-benzimidazol-6-one, whose structure was demonstrated by X-ray diffraction structural analysis.

Keywords: 2-substituted [1]benzopyrano[4,3-*d*]pyrimidin-5-ones, benzene and heterocyclic C- and N-carbamidines, 4-chloro-3-formylcoumarins.

In previous work, we reported the synthesis of the corresponding 3,4-heterofused coumarins from 4-chloro-3-formylcoumarin (**1**) and arylhydrazines, substituted anilines [1], and aminopyridines [2, 3]. In a continuation of this investigation, we studied the reaction of coumarin **1** with amidine salts **2a-i** and also with an asymmetrical amidine analog, namely, 2-aminobenzimidazole.



2,3a R = phenyl; **b** R = *p*-chlorophenyl; **c** R = *p*-carbamoylphenyl; **d** R = 3-pyridinyl; **e** R = 4-pyridinyl; **f** R = 2-pyrazinyl; **g** R = 1-pyrrolidino-, **h** R = morpholino; **i** R= 3,5-dimethyl-1-pyrazolyl

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The reaction of **1** with salts **2a-i** carried out in DMF in the presence of a five-fold excess of piperidine (in the case of salts **2a-h**) or triethylamine (for salt **2i**) gave the corresponding 2-R-[1]benzopyrano [4,3-*d*]pyridin-5-ones **3a-i** in 36-71% yield (Table 1). Petersen [4] and Ghosh [5] have reported the preparation of similar compounds (R = NH_2, 1-pyridinyl) in two steps from 4-oxo-4H-chromene-3-carbaldehyde. The reaction of coumarin **1** with 2-aminobenzimidazole in the presence of triethylamine in THF gave benzopyranopyrimidobenzimidazolone **4** in 36% yield.

TABLE 1. Characteristics of Compounds **3** and **4**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{17}H_{10}N_2O_2$	74.35 / 74.44	3.68 / 3.68	10.19 / 10.21	210-211	50
3b	$C_{17}H_9ClN_2O_2$	66.30 / 66.14	2.91 / 2.94	9.10 / 9.07	255-257	65
3c	$C_{18}H_{11}N_3O_3$	68.41 / 68.13	3.54 / 3.50	13.21 / 13.24	365-367	56
3d	$C_{16}H_9N_3O_2$	69.80 / 69.81	3.29 / 3.30	15.23 / 15.27	240-241	55
3e	$C_{16}H_9N_3O_2$	69.73 / 69.81	3.32 / 3.30	15.38 / 15.27	285-287	36
3f	$C_{15}H_8N_4O_2$	65.01 / 65.22	3.02 / 2.92	20.09 / 20.28	277-278	54
3g	$C_{15}H_{13}N_3O_2$	67.29 / 67.40	4.85 / 4.90	15.67 / 15.72	201-202	57
3h	$C_{15}H_{13}N_3O_3$	63.45 / 63.60	4.63 / 4.62	14.79 / 14.83	191-193	71
3i	$C_{16}H_{12}N_4O_2$	65.68 / 65.74	4.17 / 4.14	19.21 / 19.17	186-187	40
4	$C_{17}H_9N_3O_2$	71.15 / 71.07	3.10 / 3.16	14.52 / 14.63	240-242	36

TABLE 2. Spectral Data for Compounds **3a-i** and **4**

Compound	IR spectrum, ν_{CO} (ν_{NH2}),cm^{-1}	^{1}H NMR spectrum, δ, ppm (SSCS, *J*,Hz)
3a	1740	7.45 (6H, m, H_{arom}); 8.62 (3H, m, H_{arom}); 9.56 (1H, s, H-4)
3b	1743	7.44 (5H, m, H_{arom}); 8.61 (3H, m, H_{arom}); 9.51 (1H, s, H-4)
3c	1738, 1710; (3470, 3180)	8.71 (10H, m, 8H_{arom}, NH_2); 9.51 (1H, s, H-4)
3d	1748	7.44 (3H, m, H_{arom}); 8.04 (1H, dd, J = 6.0, J = 8.0, H_{Het}-5); 8.71 (1H, dd, J_1 = 8.0, J_2 = 2.0, H_{arom}-10); 8.98 (1H, dd, J_1 = 8.0, J_2 = 2.0, H_{Het}-4); 9.58 (1H, dt, J_1 = 6.0, J_2 = 2.0, H_{Het}-6); 9.62 (1H, s, H-4); 10.02 (1H, d, J = 2.0, H_{Het}-2)
3e	1745	7.56-7.82 (3H, m, H_{arom}); 8.53-8.84 (5H, m, H_{arom}); 9.62 (1H, s, H-4)
3f	1750	7.76-7.81 (3H, m, H_{arom}); 8.58 (3H, m, H_{arom}); 9.71 (1H, s, H-4); 9.91 (1H, d, J = 1.5, H_{Het}-3)
3g	1728	2.02 (4H, m, 2CH_2); 3.71 (4H, m, 2CH_2); 7.24-7.61 (3H, m, H_{arom}); 8.33 (1H, dd, J_1 = 8.0, J_2 = 1.5, H-10); 9.07 (1H, s, H-4)
3h	1736	3.73-4.02 (8H, m, 4CH_2); 7.18-7.62 (3H, m, H_{arom}); 8.31 (1H, dd, J = 8, J = 1.5, H_{arom}); 9.07 (1H, s, H-4)
3i	1746	2.28 (3H, s, CH_3); 2.81 (3H, s, CH_3); 6.11 (1H, s, H_{Het}-2); 7.26-7.33 (3H, m, H_{arom}); 8.38 (1H, dd, J_1 = 8.0, J_2 = 1.5, H-10); 9.51 (1H, s, H-4)
4	1738	7.38-8.11 (7H, m, H_{arom}); 8.56 (1H, dd, J = 8, J = 1.5, H_{arom}); 9.13 (1H, s, H-7)

The structure of benzopyranopyrimidinones **3** was supported by spectral data (Table 2). The IR band for the C=O group of the coumarin fragment is seen at 1750-1728 cm^{-1}. The existence of an NH_2 group in **3c** was supported by the bands at 3470 and 3180 cm^{-1}. The ^1H NMR spectra show signals for the protons of all the structural fragments of products **3**. The signal for H-4 characteristic for these compounds is found at 9.07-9.71 ppm. Such a downfield signal may be attributed both to special structural features and the anisotropic effect of the unshared electron pair of the carbonyl oxygen atom. The signals for the protons of the hetaryl substituent, as a rule, coalesce into common multiplets with the aromatic proton signals. However, the spectrum of **3d** (R = 3-pyridinyl) clearly shows signals for the pyridine ring protons. The spectra of **3g** (R = pyrrolidino) and **3h** (R = morpholino) show multiplets for the CH_2 group protons.

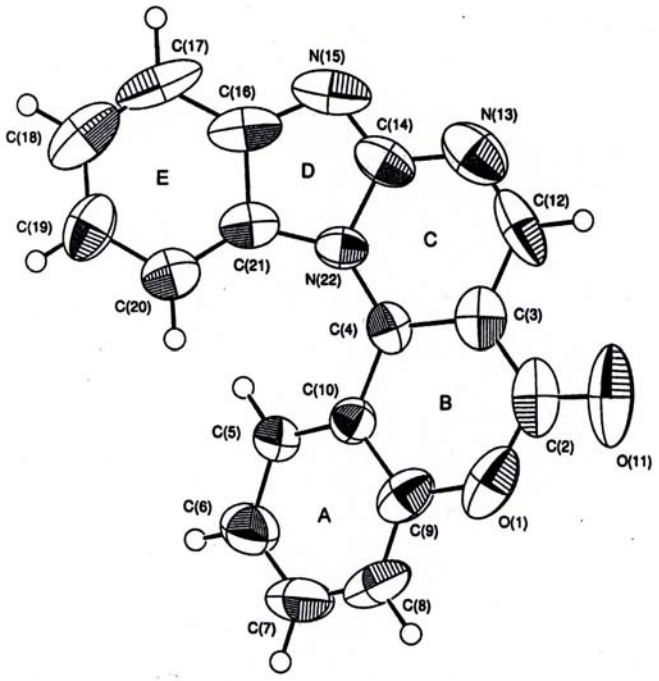

Fig. 1. Three-dimensional model of a molecule of **4** with numbering of the atoms and indication of the rings and thermal vibration ellipsoids.

TABLE 3. Major Bond Lengths (*d*) in Compound **4**

Bond	*d*, Å	Bond	*d*, Å
O(1)–C(2)	1.388(7)	C(9)–C(10)	1.394(6)
O(1)–C(9)	1.390(6)	C(12)–N(13)	1.305(7)
C(2)–O(11)	1.191(7)	N(13)–C(14)	1.338(7)
C(2)–C(3)	1.441(8)	C(14)–N(15)	1.288(7)
C(3)–C(4)	1.382(6)	C(14)–N(22)	1.429(6)
C(3)–C(12)	1.441(8)	N(15)–C(16)	1.391(7)
C(4)–C(10)	1.446(6)	C(16)–C(17)	1.411(9)
C(4)–N(22)	1.374(5)	C(16)–C(21)	1.399(6)
C(5)–C(6)	1.386(6)	C(17)–C(18)	1.375(9)
C(5)–C(10)	1.399(6)	C(18)–C(19)	1.353(8)
C(6)–C(7)	1.387(8)	C(19)–C(20)	1.379(7)
C(7)–C(8)	1.366(9)	C(20)–C(21)	1.381(7)
C(8)–C(9)	1.388(8)	C(21)–N(22)	1.412(6)

TABLE 4. Major Bond Angles (ω) in Compound **4**

Angle	ω, deg	Angle	ω,deg
C(2)–O(1)–C(9)	121.5(4)	C(3)–C(12)–N(13)	123.0(6)
O(1)–C(2)–C(3)	116.6(6)	C(12)–N(13)–C(14)	117.7(5)
O(1)–C(2)–O(11)	116.2(7)	N(13)–C(14)–N(15)	124.5(5)
C(3)–C(2)–O(11)	127.0(7)	N(13)–C(14)–N(22)	121.3(5)
C(2)–C(3)–C(4)	120.3(5)	N(15)–C(14)–N(22)	114.1(6)
C(2)–C(3)–C(12)	119.5(6)	C(14)–N(15)–C(16)	104.6(4)
C(4)–C(3)–C(12)	120.2(5)	N(15)–C(16)–C(17)	128.8(5)
C(3)–C(4)–C(10)	120.0(4)	N(15)–N(16)–C(21)	112.1(5)
C(3)–C(4)–N(22)	114.5(4)	C(17)–C(16)–C(21)	119.3(6)
C(10)–C(4)–N(22)	114.5(4)	C(16)–C(17)–C(18)	118.5(5)
C(6)–C(5)–C(10)	119.5(5)	C(17)–C(18)–C(19)	120.7(6)
C(5)–C(6)–C(7)	120.0(6)	C(18)–C(19)–C(20)	122.8(6)
C(6)–C(7)–C(8)	120.9(5)	C(19)–C(20)–C(21)	117.6(5)
C(7)–C(8)–C(9)	119.6(6)	C(16)–C(21)–C(20)	120.9(5)
O(1)–C(9)–C(8)	117.9(6)	C(16)–C(21)–N(22)	104.7(5)
O(1)–C(9)–C(10)	121.7(4)	C(20)–C(21)–N(22)	133.9(4)
C(8)–C(9)–C(10)	120.4(6)	C(4)–N(22)–C(14)	121.7(5)
C(4)–C(10)–C(5)	124.5(4)	C(4)–N(22)–C(21)	133.9(4)
C(4)–C(10)–C(9)	115.9(4)	C(14)–N(22)–C(21)	104.3(4)
C(5)–C(10)–C(9)	119.3(4)		

The spectrum of **4** features singlets for the two methyl groups. The formation of either isomeric product **4** or **5** is possible in the reaction of coumarin **1** with 2-aminobenzimidazole. The X-ray diffraction structural data indicate the formation of **4** (Fig. 1, Tables 3 and 4).

Figure 1 shows a three-dimensional model of a molecule of **4** with numbering of the atoms (the numbering is in accord with **4** seen as a coumarin derivative). The interatomic distances shown (Table 3) indicate a nonuniform distribution of the π-electron cloud: C(12)-N(13) and C(14)-N(15) are close to double bonds, while C(4)-N(22), C(14)-N(22), C(21)-N(22), and N(15-N(16) approximate single bonds.

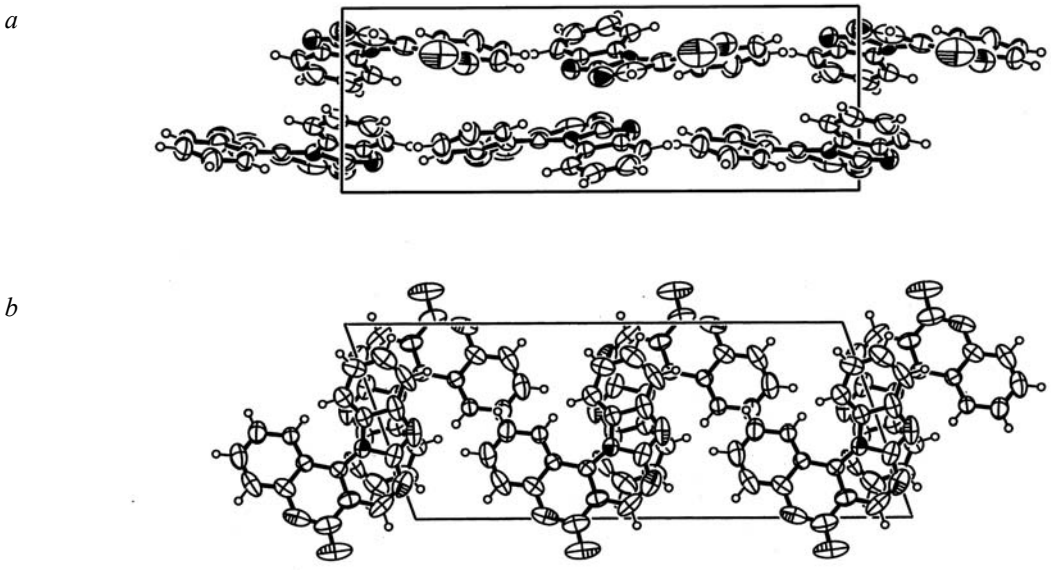

Fig. 2. Projections of the crystal structure of **4** in the *yz* plane (*a*) and *zx* plane (*b*).

Molecule **4** consists of five planar ring fragments, namely, A, B, C, D, and E (Fig 1). The dihedral angles between these rings are as follows: A^B 11.8(2)°, A^C 25.4(2)°, A^D 33.7(2)°, A^E 38.7(2)°; B^C 14.1(2)°, B^D 22.6(2)°, B^E 27.2(2)°; C^D 8.5(2)°, C^E 13.3(2)°; D^E 5.4(3)°. The molecular conformation apparently cannot be planar due to repulsion of the hydrogen atoms at C(5) and C(20). Thus, the dihedral angles between the ring planes are not zero. The dihedral angle between rings A and E (A^E) is virtually equal to the sum of dihedral angles A^B, B^C, C^D, and C^E, while angle B^E is equal to the sum of angles B^C, C^D, and D^E, etc. Hence, the molecule has a helical conformation. The atoms are arranged on the surface of a helicoids with a step of 2.55 Å. Thus, molecules of **4** are chiral even though there are no asymmetric atoms. The crystal structure of **4** has both enantiomers related to each other by centers of inversion and glide planes. Projections of the crystal structure of **4** are shown in Fig. 2.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WH 90/DS spectrometer at 90 MHz in $CDCl_3$ with TMS as the internal standard. The IR spectra were taken on a Specord IR-75 spectrometer for Vaseline mulls (1800-1500 cm^{-1}) and hexachlorobutadiene solutions (3600-2000 cm^{-1}). The C-H stretching bands at 3050-2800 cm^{-1} are not given.

2-Phenyl- (3a), 2-(4-chlorophenyl)- (3b), 2-(4-aminocarbonylphenyl)- (3c), 2-(3-pyridyl)- (3d), 2-(4-pyridyl)- (3e), 2-pyrazinyl- (3f), 2-(1-pyrrolidyl)- (3g), 2-(4-morpholyl)- (3h), and [1]benzopyrano-[4,3-*d*]pyrimidin-5-ones (General Method). A solution of 2 mmol aldehyde **1** in 5 ml DMF was added dropwise with stirring to a solution of 2 mmol amidine **2** and 1.0 ml (10 mmol) piperidine in 3 ml DMF at 20°C. The reaction mixture was maintained for 2 h at 60-70°C. Then, 2 ml water was added and the mixture was left for 24 h in a refrigerator. The precipitate of **3** was filtered off, washed on the filter with ethanol, and recrystallized from DMF.

2-(3,4-Dimethyl-1-pyrazolyl)-[1]benzopyrano[4,3-*d*]pyridin-5-one (3i) was obtained analogously using 1 ml triethylamine instead of piperidine.

[1]Benzopyrano[3,4:3',4']pyrimido[1,2-*a*]benzimidazol-6-one (4). A solution of 2 mmol 2-amino-benzimidazole in 5 ml THF was added dropwise with stirring to a solution of 2 mmol **1** in 5 ml THF at 20°C. The reaction mixture was stirred for an additional 5 h at 20°C. The precipitate of product **4** was filtered off and recrystallized from ethanol.

X-ray Diffraction Structural Analysis of 4. The unit cell parameters of monoclinic crystals of **4** obtained upon recrystallization from ethanol are: a = 9.0103(9), b = 7.244(6), c = 20.841(2) Å, β = 109.276(5), V = 1284.1(2) Å^3, F(000) = 592, μ = 0.10 mm^{-1}, d_{calc} = 1.486 g/cm^3, Z = 4, space group $P2_1/c$.

The intensities of 2833 independent reflections were taken on a Nonius Kappa CCD automatic diffractometer (molybdenum radiation with λ = 0.71073 Å, graphite monochromator) to $2\theta_{max}$ = 55°. A total of 961 reflections were used with $I > 2\sigma(I)$. The structure was solved according to our previous procedure [6]. The refinement was carried out by the method of least squares in the full-matrix anisotropic approximation using the AREN program package [7]. The final R =0.084.

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