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SYNTHESIS AND REACTIONS OF 4-(ARYLHYDRAZINO)COUMARINS

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The interaction of 4-hydroxycoumarin with phenyl-, 2-chlorophenyl- and 4-bromophenyhydrazine hydrochlorides in the presence of triethylamine led in all cases to the corresponding 4-(arylhydrazino)-coumarins and 1-aryl-3-(2-hydroxyphenyl)-2H-pyrazolin-5-ones. 4-(Arylhydrazino)coumarins reacted with 4-chlorobenzaldehyde in the presence of piperidine acetate to give the corresponding 2-aryl-3-(4-chlorophenyl)[1]benzopyrano[4,3-b]pyrazol-4-ones. The reaction of 4-(4-bromophenylhydrazino)-coumarin with 4-chlorobenzaldehyde in the presence of piperidine acetate and an excess of piperidine gave 2-(4-bromophenyl)-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-4-(piperidinocarbonyl)pyrazole, but the reaction of phenyl- and 4-(2-chlorophenylhydrazino)coumarins with 4-chlorobenzaldehyde gave 1-aryl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-4-(1-piperidino)carbonyl-4,5-dihydropyrazoles.

Keywords: 4-(arylhydrazino)coumarins, 1-aryl-3-(2-hydroxyphenyl)-2H-pyrazin-5-ones, aromatic aldehydes, 2,3-diaryl[1]benzopyrano[4,3-*b*]pyrazol-4-ones.

In a development of work on the synthesis of coumarins with heterocycles at the C(3)–C(4) bond [1-3] we have synthesized pyrazolocoumarins by the reactions of 4-(arylhydrazino)coumarins with aromatic aldehydes. We reverted to pyrazolocoumarins [4-6] which, like other 3,4-heteroannelated coumarins, were observed to have biological activity [7-13].

The reactions of phenyl-, 2-chlorophenyl- and 4-bromophenylhydrazine hydrochlorides with 4-hydroxy-coumarin **1** in the presence of triethylamine were carried out by heating in the absent of solvent (1h 30 min, 90-100ºC). In all cases, 1-aryl-3-(2-hydroxyphenyl)pyrazol-5-ones **3a-c** were formed along with the corresponding 4-(arylhydrazino)coumarins **2a-c**. Pyrazolone **3a** was obtained previously [14] by boiling 4-hydroxycoumarin with phenylhydrazine in benzene. On boiling the same reagents in toluene with a catalytic amount of *p*-toluenesulfonic acid we obtained 4-(phenylhydrazino)coumarin (**2a**) as the main product (50%) and the pyrazolone **3a** in a yield of only 18%. Boiling the pyrazolones **3a-c** in acetic anhydride in the presence of *p*-toluenesulfonic acid gave the diacetyl derivatives **4a-c**.

The reaction of (4-arylhydrazino)coumarins **2a-c** with 4-chlorobenzaldehyde in DMF solution in the presence of equimolar catalytic amounts of piperidine and acetic acid gave the corresponding 2-aryl-3-(4-chlorophenyl)[1]benzopyrano[4,3-*b*]pyrazol-4-ones **5a-c**.

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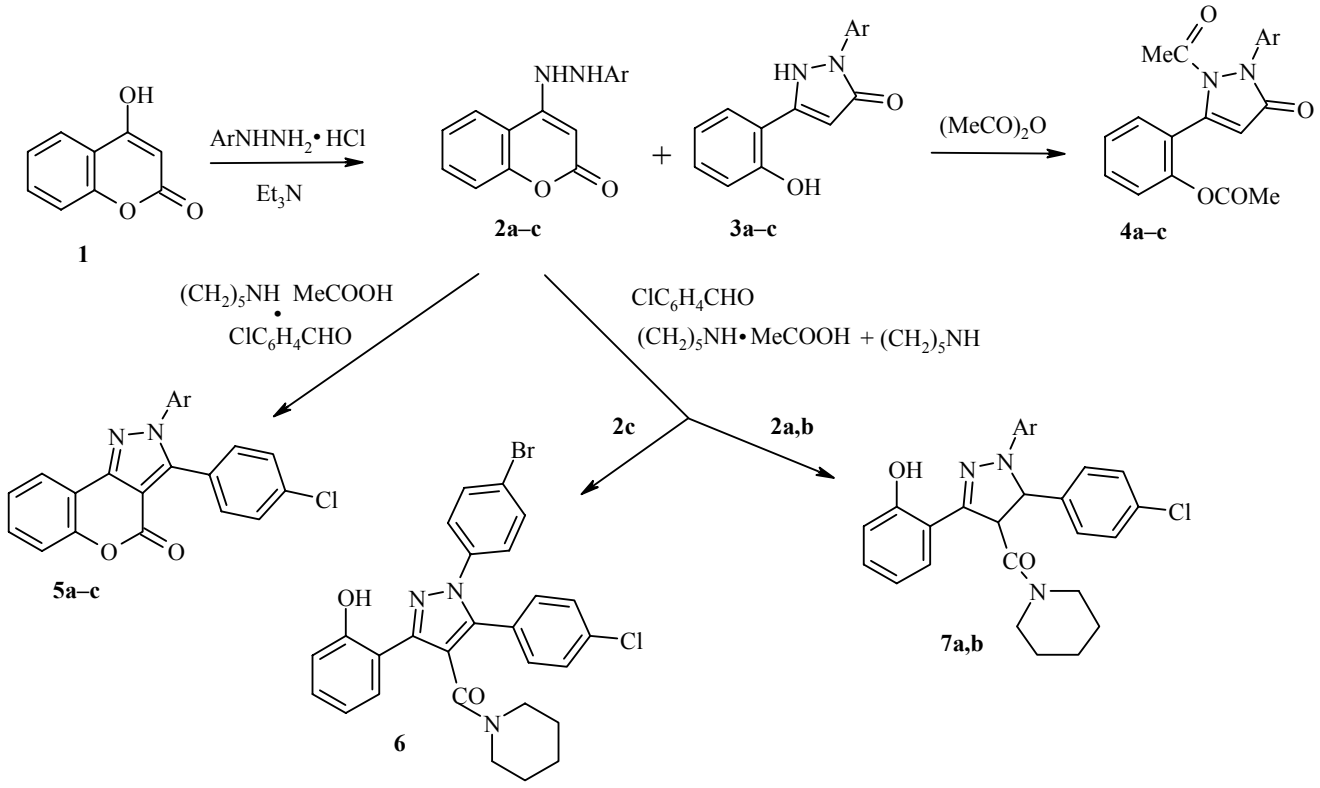

2–5 a Ar = Ph, **b** Ar = 2-ClC_6H_4, **c** Ar = 4-BrC_6H_4; **7 a** Ar = Ph, **b** Ar = 2-ClC_6H_4

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
2a	$C_{15}H_{12}N_2O_2$	71.49 / 71.41	4.69 / 4.80	10.95 / 11.10		245-246	51
2b	$C_{15}H_{11}ClN_2O_2$	62.63 / 62.84	3.80 / 3.87	9.63 / 9.77	12.20 / 12.36	256-257	53
2c	$C_{15}H_{11}BrN_2O_2$	54.20 / 54.40	3.11 / 3.35	8.32 / 8.46	23.90 / 24.13	254-256	52
3a	$C_{15}H_{12}N_2O_2$	71.30 / 71.41	4.66 / 4.80	10.87 / 11.10		119-121	18
3b	$C_{15}H_{11}ClN_2O_2$	62.58 / 62.84	3.71 / 3.87	9.61 / 9.77	12.10 / 12.36	208-210	9
3c	$C_{15}H_{11}BrN_2O_2$	54.18 / 54.40	3.14 / 3.35	8.29 / 8.46	23.95 / 24.13	196-197	15
4a	$C_{19}H_{16}N_2O_4$	67.66 / 67.85	4.70 / 4.80	8.11 / 8.33		90-91	43
4b	$C_{19}H_{15}ClN_2O_4$	61.30 / 61.54	3.92 / 4.08	7.37 / 7.55	9.40 / 9.56	122-123	88
4c	$C_{19}H_{15}BrN_2O_4$	54.72 / 54.96	3.60 / 3.64	6.65 / 6.74	19.00 / 19.24	92-93	64
5a	$C_{22}H_{13}ClN_2O_2$	70.70 / 70.88	3.55 / 3.51	7.40 / 7.51	9.30 / 9.51	201-202	30
5b	$C_{22}H_{12}Cl_2N_2O_2$	64.69 / 64.88	2.99 / 2.97	6.71 / 6.88	17.50 / 17.41	207-208	37
5c	$C_{22}H_{12}BrClN_2O_2$	58.40 / 58.50	2.60 / 2.68	6.14 / 6.20		135-137	40
6	$C_{27}H_{23}BrClN_3O_2$	59.91 / 59.96	4.35 / 4.29	7.60 / 7.77		197-198	70
7a	$C_{27}H_{26}ClN_3O_2$	70.33 / 70.50	5.57 / 5.70	9.11 / 9.14	7.60 / 7.71	221-223	50
7b	$C_{27}H_{25}Cl_2N_3O_2$	65.41 / 65.59	5.00 / 5.10	8.38 / 8.50	14.10 / 14.34	177-178	32

In the reactions of 4-(arylhydrazino)coumarins **2a-c** with 4-chlorobenzaldehyde in the presence of piperidine acetate and an excess of piperidine 1-(4-bromophenyl)-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-4-(piperidinocarbonyl)pyrazole (**6**) was obtained in the case of **2c**, whereas in the cases of **2a,b** under the same conditions the corresponding 1-aryl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-4-(piperidinocarbonyl)- 4,5-dihydropyrazoles **7a,b** were obtained.

The structures of the compounds synthesized were confirmed by IR and ^{1}H NMR spectroscopy and, in the case of the dihydropyrazole **7a**, by X-ray crystallography (Tables 1-3).

The signals of the NH protons for the arylhydrazinocoumarins **2a-c** appear in the ranges δ 8.13-8.35 and δ 9.67-9.77 ppm in the ^{1}H NMR spectra of DMSO solutions, while the signals of the NH and OH protons of the pyrazolones **3a-c** appear correspondingly at δ 10.65-10.83 and δ 11.97-12.34 ppm. The frequencies of the three carbonyl groups of the diacetylpyrazolones **4a-c** were observed at 1740-1750, 1760-1764, and 1775-1777 cm^{-1}.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)
2a	5.35 (1H, s, H-3); 6.76-8.10 (9H, m, C_6H_4, C_6H_5); 8.14 (1H, s, NH); 9.67 (1H, s, NH)
2b	5.25 (1H, s, H-3); 6.77-8.10 (8H, m, $2C_6H_4$); 8.13 (1H, s, NH); 9.77 (1H, s, NH)
2c	5.29 (1H, s, H-3); 6.70-8.10 (8H, m, $2C_6H_4$); 8.35 (1H, s, NH); 9.72 (1H, s, NH)
3a	6.16 (1H, s, H-4); 6.90-7.78 (9H, m, C_6H_4, C_6H_5); 10.84 (1H, s, NH); 12.20 (1H, br. s, OH)
3b	6.11 (1H, s, H-4); 6.88-7.70 (8H, m, $2C_6H_4$); 10.73 (1H, s, NH); 11.95 (1H, br. s, OH)
3c	6.16 (1H, s, H-4); 6.88-7.76 (8H, m, $2C_6H_4$); 10.65 (1H, s, NH); 12.34 (1H, br. s, OH)
4a	2.29 (3H, s, CH_3); 2.33 (3H, s, CH_3); 6.73 (1H, s, H-4); 7.20-7.97 (9H, m, C_6H_4, C_6H_5)
4b	2.19 (3H, s, CH_3); 2.24 (3H, s, CH_3); 6.69 (1H, s, H-4); 7.10-7.92 (8H, m, $2C_6H_4$)
4c	2.28 (3H, s, CH_3); 2.34 (3H, s, CH_3); 6.74 (1H, s, H-4); 7.20-7.96 (8H, m, $2C_6H_4$)
5a	7.45-7.51 (11H, m, $2C_6H_4$, C_6H_5); 7.61 (1H, dt, *J* = 6, *J* = 2, C_6H_4); 8.12 (1H, dd, *J* = 6, *J* = 2, C_6H_4)
5b	7.38-7.62 (10H, m, $3C_6H_4$); 7.88 (1H, m, C_6H_4); 8.10 (1H, dd, *J* = 6.5, *J* = 1.5, C_6H_4)
5c	7.31-7.72 (11H, m, $3C_6H_4$); 8.10 (1H, d, *J* = 7.4, C_6H_4)
6	1.40 (6H, m, $C_5H_{10}N$); 3.02 и 3.41 (4H, m, $C_5H_{10}N$); 6.85-7.64 (12 H, m, $3C_6H_4$); 9.87 (1H, br. s, OH)
7a	1.55 (6H, m, $C_5H_{10}N$); 3.44 (4H, br. s, $C_5H_{10}N$); 5.00 (1H, d, *J* = 5, H-4); 5.45 (1H, d, *J* = 5, H-5); 5.49 (4H, m, $C_5H_{10}N$); 6.76-7.42 (13H, m, $2C_6H_4$, C_6H_5); 10.28 (1H, s, OH)
7b	1.52 (6H, m, $C_5H_{10}N$); 5.21 (1H, d, *J* = 5, H-4); 5.49 (4H, m, $C_5H_{10}N$); 5.58 (1H, d, *J* = 5, H-5); 6.82-7.41 (12H, m, $3C_6H_4$); 10.44 (1H, br. s, OH)

TABLE 3. Basic Bond Lengths (*l*) and Valence Angles (ω) in Molecule **7a**

Bond	*l*, Å	Angle	ω, deg
N(1)–N(2)	1.372(4)	N(2)–N(1)–C(5)	112.1(3)
N(1)–C(5)	1.466(4)	N(2)–N(1)–C(6)	119.2(3)
N(1)–C(6)	1.392(4)	C(5)–N(1)–C(6)	126.5(3)
N(2)–C(3)	1.298(4)	N(1)–N(2)–C(3)	110.9(3)
C(3)–C(4)	1.507(5)	N(2)–C(3)–C(4)	112.6(3)
C(3)–C(12)	1.464(5)	C(3)–C(4)–C(5)	101.9(3)
C(4)–C(5)	1.572(5)	C(4)–C(5)–N(1)	102.4(3)
C(4)–C(19)	1.514(5)	C(12)–C(13)–O(18)	122.2(3)
C(5)–C(27)	1.509(5)		
C(13)–O(18)	1.358(5)		
C(19)–O(20)	1.206(4)		
C(19)–N(21)	1.350(5)		
C(30)–Cl(33)	1.743(4)		

Only signals of the aromatic protons were observed in the ^{1}H NMR spectra of the pyrazolocoumarins **5a-c**, whereas additional signals of the methylene groups of piperidine were observed at δ 1.5 and 3.0-3.5 ppm in the case of the 5-(piperidinocarbonyl) derivative **6**. In compounds **7** doublet signals of the *trans* protons on C(4) and C(5) with a coupling constant of J = 5 Hz were observed. The *trans* positions of the protons on C(4) and C(5) in pyrazolinone **7a** were confirmed by X-ray crystallography (Figure 1, Table 3).

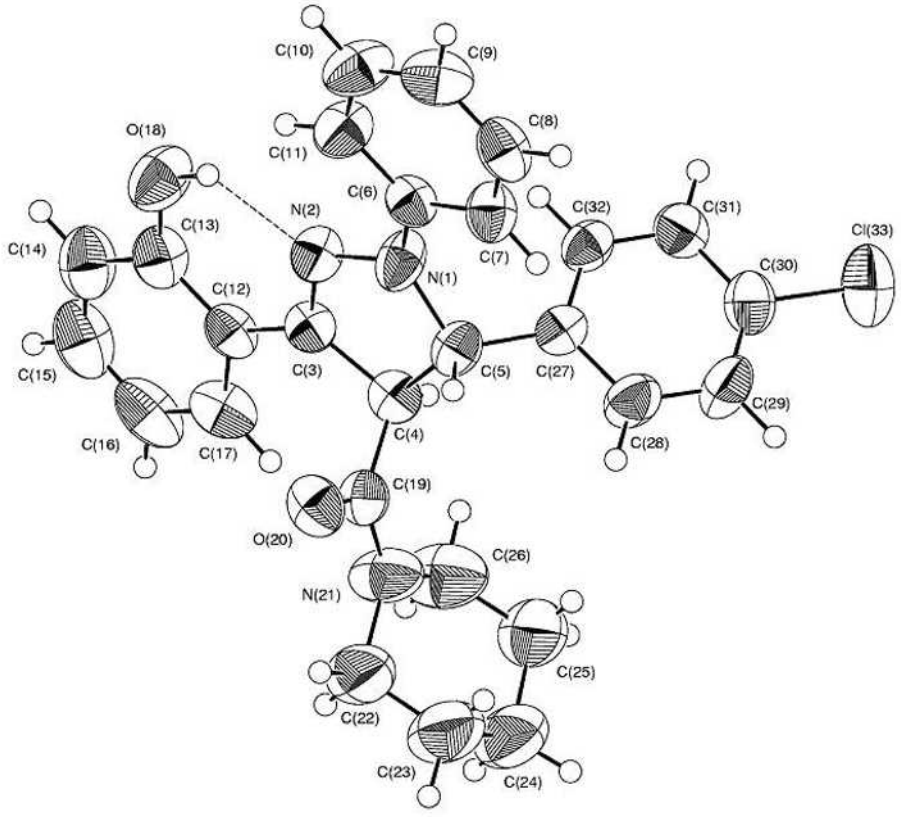

Fig. 1. Spatial model of the molecule **7a** with numbering of atoms and thermal vibrational ellipsoids.

TABLE 4. Crystallographic Data for Compound **7a**

Empirical formula	$C_{27}H_{26}ClN_3O_2$
Molecular mass, M	459.977
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell parameters:	
a, Å	9.3045(3)
b, Å	21.4232(7)
c, Å	11.8452(4)
β, deg	96.661(2)
Unit cell volume, V, Å^3	2345.2(1)
Molecules per unit cell, Z	4
Crystal density, d, g/cm^3	1.303
Coefficient of absorption, μ, mm^{-1}	0.19
Number of independent reflections	6213
Number of reflections with $I > 3\sigma(I)$	2366
Number of parameters refined	298
Final residual factor, R	0.078
Programs used	SIR97 [1], maXus [2]

The five-membered ring in molecule **7a** is planar within the limits of experimental error, despite the two tetrahedral atoms C(4) and C(5). The three phenyl rings of the molecule are also planar. The piperidine ring has a *chair* configuration.

An intramolecular hydrogen bond was observed in the molecule of **7a** with length of 2.620(4) Å (H···N(2) 1.89 Å, angle O(18)-H···N(2) 132°). An additional six-membered ring is formed in the molecule **7a** by the presence of this bond.

EXPERIMENTAL

IR spectra were recorded with a Specord IR-75 instrument with suspensions of the substances in nujol (1800-1500 cm^{-1} range) and hexachlorobutadiene (3600-2000 cm^{-1}). Frequencies of C–H stretching vibrations in the range 3050-2800 cm^{-1} were not recorded. ^1H NMR spectra of $CDCl_3$ and DMSO-d_6 solutions with TMS as internal standard were recorded on a Varian-Mercury BB spectrometer (200 MHz).

4-(2-Phenylhydrazino)- (2a), 4-[2-(2-Chlorophenyl)hydrazino]- (2b), 4-[2-(4-Bromophenyl)-hydrazino]coumarins (2c), and 1-Phenyl- (3a), 1-(2-Chlorophenyl)- (3b), 1-(4-Bromophenyl)-3-(hydroxy-phenyl)-2H-pyrazolin-5-ones (3c). Mixture of 4-hydroxycoumarin **1** (10 mmol) and arylhydrazine hydrochloride (10 mmol) was ground in a mortar, transferred to a flask, triethylamine (20 mmol) was added, and the mixture was heated under reflux on an oil bath at a temperature of 90-100°C for 1 h 30 min. The mixture was cooled, ethanol (30 ml) was added, returned to the boil with shaking, cooled, and compound **2** was filtered off. Dilution of the filtrate with water gave an additional small amount of compounds **2** and **3**. Compounds **3** were dissolved at 20°C in 1% sodium hydroxide solution and precipitate on acidification. Compounds **2a**, **3a-c** were recrystallized from ethanol, **2b** from a mixture of ethanol and DMF, and **2c** from a mixture of ethanol and acetic acid.

1-Phenyl- (4a), 1-(2-Chlorophenyl)- (4b), and 1-(4-Bromophenyl)-2-acetyl-3-(2-acetoxyphenyl)-2H-pyrazolin-5-ones (4c). Pyrazolinone **3** (5 mmol) in acetic anhydride (20 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid was heated for 3 h on a boiling water bath, cooled and poured onto crushed ice. Diacetylated **4** was filtered off and recrystallized from ethanol.

1-Phenyl- (5a), 2-(2-Chlorophenyl)- (5b), and 2-(4-Bromophenyl)-3-(4-chlorophenyl)[1]benzo-pyrano[4,3-*b*]pyrazol-4-ones (5c). A mixture of 4-(arylhydrazino)coumarin (10 mmol), 4-chloro-benzaldehyde (10 mmol), piperidine (4 mmol), and acetic acid (4 mmol) in DMSO (30 ml) was heated on a boiling water bath for 6 h. The mixture was cooled, poured into water, the precipitate of pyrazolocoumarin was filtered off and recrystallized from ethanol.

1-(4-Bromophenyl)-5-(4-chlorophenyl)3-(2-hydroxyphenyl)-4-(piperidinocarbonyl)pyrazole (6). A mixture of 4-(4-bromophenylhydrazino)coumarin (**2c**) (5 mmol), 4-chlorobenzaldehyde (5 mmol), acetic acid (4 mmol), and piperidine (15 mmol) in DMSO (15 ml) was heated on a boiling water bath for 6 h. The mixture was cooled, poured into water, the precipitate of **6** was filtered off, carefully washed with water on the filter and recrystallized from ethanol.

1-Phenyl- and 1-(2-Chlorophenyl)-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-4-(piperidinocarbonyl)-4,5-dihydropyrazoles (7a) and (7b), respectively were obtained analogously to the previous experiment from 4-(arylhydrazino)coumarins **2a,b,** 4-chlorobenzaldehyde, piperidine acetate, and an excess of piperidine. Compounds **7a,b** were recrystallized from ethanol.

X-ray Crystallographic Analysis. The diffraction pattern was taken of a monocrystal of compound **7a**, 0.04×0.06×0.37 mm, on a Nonius KappaCCD automatic diffractometer to $2\theta_{max} = 55°$ ($\lambda_{Mo} = 0.71073$ Å) at room temperature. The basic crystallographic characteristics of compound **7a** and the parameters of the refined structure are given in Table 4. Calculations were carried out using programs [15] and [16].

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