SYNTHESIS OF 2*H*-1-BENZOPYRAN-2,4(3*H*)-DIONE-3-CARBOXAMIDE AND 2*H*,3*H*-[1]BENZOPYRANO[4,3-*b*]PYRANO-2-HYDROXY-3-CARBOXAMIDE-4,5-DIONE DERIVATIVES *VIA* CARBON SUBOXIDE

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Abstract - The reaction of substituted 2-hydroxybenzamides with carbon suboxide is described. By varying the weight ratio of the reagent, this reaction leads to the coumarin and/or pyranocoumarin derivatives in one step and with satisfactory yields.

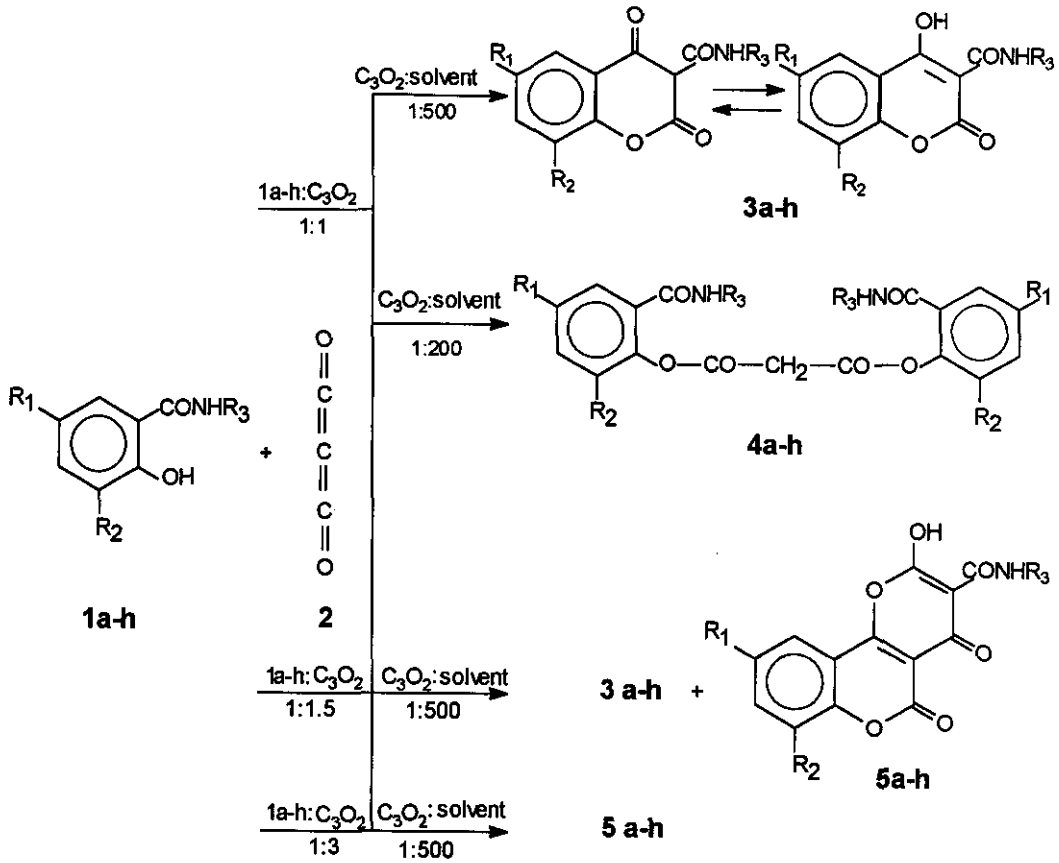
The synthesis[1] and pharmacological activity[2] of several coumarin derivatives obtained in one step *via* carbon suboxide and with high yields has been reported in previous works.

Coumarin derivatives are known to be an interesting class of natural or synthetic compounds, whose biological activity varies according to the substituents on the benzopyran ring.[3] To this purpose, following along this research, in the present study we prepared the synthesis of new 2*H*-1-benzopyran-2,4(3*H*)-dione-3-carboxamide derivatives, structurally correlable to analogous coumarins, whose pharmacological activity is reported in the literature.[4]

Starting from 0.014 moles of substituted 2-hydroxybenzamides (**1a-h**) and 0.016 moles of carbon suboxide (**2**), the derivatives 2*H*-1-benzopyran-2,4(3*H*)-dione-3-carboxamides (**3a-h**) were obtained in anhydrous acetone (C_3O_2:solvent = 1:500) in a one step procedure and with high yields.

Since the attack of **2** to the nucleophilic sites of **1a-h** was slowed down by a hydrogen bond that is present in their structure, a slight excess of **2** (about 15%) was used in this reaction, in order to prevent a longer reaction time from favouring a partial loss of carbon suboxide, that is a very volatile compound at room temperature. Moreover from a preliminary study of the reaction, it was seen that the weight ratio of the reagent and the more or less dilute solution play a very important role. In fact, at the described conditions, but in a more concentrated acetone solution (C_3O_2:solvent = 1:200), only the substituted propanedioic esters (**4a-h**) were isolated and an unidentified gummy product, probably macrocyclic or polymeric in nature, was also obtained.

On the other hand, by reacting **1a-h** and **2** in a 1:1.5 molar ratio in anhydrous acetone (C_3O_2:solvent = 1:500), we mainly obtained derivatives (**3a-h**) and small quantities of new 2*H*,3*H*-[1]benzopyrano[4,3-*b*]pyrano-2-hydroxy-3-carboxamide-4,5-dione derivatives (**5a-h**); while by reacting the same reagents in a 1:3 molar ratio, we only obtained **5a-h** in satisfactory yields (Sheme[5]). The new synthesized compounds were characterised by MS, ^{1}H NMR, FTIR and analytical studies. Particularly, the most significant fragmentations of the mass spectra of compounds (**5a-h**) have been reported in Table 3, since they further confirm the hypothesized structures.[6]



a:R_1=R_2=R_3= H
b:R_1=R_2= H, R_3= C_6H_5
c:R_1=R_2=H, R_3= CH_2COOH
d:R_1=Cl, R_2=R_3=H
e:R_1= Cl, R_2= H, R_3= C_6H_5
f: R_1=R_2= Cl, R_3= H
g:R_1= Br, R_2=R_3= H
h:R_1=R_2= Br, R_3= H

Scheme

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The ^{1}H NMR spectra were determined using a Varian Unity 300 spectrometer and the chemical shifts (δ) refer to tetramethylsilane. The FTIR spectra were recorded on a Perkin Elmer 2000 spectrophotometer on NaCl mulls. Elemental analyses were carried out on a Carlo Erba 106 Elemental analyzer. MS spectra were taken with a QMD 1000 instrument (Fisons Instruments) at 70 eV using a direct inlet system. All compounds were purchased from Aldrich Chemical Co. and the solvents were dried rigorously before use according to standard methods.

The carbon suboxide was prepared from pyrolysis of di-*O*-acetyltartaric anhydride.[7]

General procedure for the synthesis of **3a-h** and **4a-h**.

Carbon suboxide (**2**) (1.10 g, 16.0 mmol) was slowly added at -70 °C to stirred solutions of **1a-h** (14.0 mmol) in 500 mL of anhydrous acetone. When the addition was completed, the mixture was kept under stirring at 0 °C for 4 h and at rt for 48 h.. At completion of the reaction, the solution was evaporated under reduced pressure and the crude residue was crystallized from petroleum ether (30 - 60°) and ether to give **3a-h**. Following the same route, but using 200 mL of the previously mentioned solvent, a crude residue was obtained. It was flash chromatographed (silica gel -0.04 mm : 230 mesh ;flow 20 mL/min, n-hexane:ethyl acetate 1:3 as eluants) to give **4a-h** as first eluate. The analytical and spectral data for **3a-h** are shown in Table 1.

Table 1. Analytical and spectral data for compounds (**3a-h**)

Compd	Yield (%)	mp (°C)	IR (nujol) ν_{max} (cm^{-1})	^{1}H NMR δ (ppm)	Elemental Analysis Calcd (%) (Found) C	H	N	Molecular Formula M^+ (*m/z*)
3a	70	119-120	3390, 3350, 1730, 1680, 1620	($CDCl_3$): 12.00 (s, 2H, NH_2, D_2O exch), 7.92 (s, 1H, CH), 7.54-6.84 (m, 4H, arom)	58.54 3.44 6.83	(58.62) (3.45) (6.80)		$C_{10}H_7NO_4$ 205
3b	74	99-100	3290, 1730, 1620, 1585	($CDCl_3$): 11.93 (s, 1H, NH, D_2O exch), 7.85 (s, 1H, CH), 7.51-6.87 (m, 9H, arom)	68.32 3.94 4.98	(68.20) (3.91) (5.00)		$C_{16}H_{11}NO_4$ 281
3c	68	158-160	3390, 3340, 1720, 1680, 1620, 1605	(DMSO-d_6): 12.69 (s, 1H, OH, D_2O exch), 12.18 (s, 1H, NH, D_2O exch), 8.09 (s, 1H,	54.76 3.45 5.32	(54.87) (3.42) (5.35)		$C_{12}H_9NO_6$ 263

				CH), 7.64-6.87 (m, 4H, arom), 3.95 (d, J= 5.37 Hz, 2H, CH_2)			
3d	80	130-132	3420, 1710, 1680, 1600	($CDCl_3$): 13.00 (s, 2H, NH_2, D_2O exch), 8.21 (s, 1H, CH), 8.03 (s, 1H, OH, D_2O exch), 7.93-6.87 (m, 3H, arom)	50.12 2.52 5.84	(50.14) (2.50) (5.87)	$C_{10}H_6NO_4Cl$ 239
3e	73	189-190	3350, 1720, 1680, 1650, 1640	($CDCl_3$): 11.82 (s, 1H, NH, D_2O exch), 8.11 (s, 1H, CH), 7.88 (s, 1H, OH, D_2O exch), 7.78-6.90 (m, 8H, arom)	60.86 3.19 4.43	(60.74) (3.20) (4.45)	$C_{16}H_{10}NO_4Cl$ 315
3f	69	162-163	3400, 1720, 1680, 1620	(DMSO-d_6): 12.12 (s, 2H, NH_2, D_2O exch), 8.13 (s, 1H, CH), 8.00 (s, 1H, OH, D_2O exch), 7.95 (s, 1H, arom), 7.70 (s, 1H, arom)	43.82 1.83 5.11	(43.75) (1.81) (5.14)	$C_{10}H_5NO_4Cl_2$ 274
3g	78	150-151	3410, 1720, 1680, 1620	(DMSO-d_6): 12.45 (s, 2H, NH_2, D_2O exch), 8.29 (s, 1H, CH), 8.10 (s, 1H, OH, D_2O exch), 7.95-7.20 (m, 3H, arom)	42.27 2.12 4.93	(42.36) (2.15) (4.90)	$C_{10}H_6NO_4Br$ 284
3h	82	144-145	3390, 1720, 1680, 1620	(DMSO-d_6): 12.29 (s, 2H, NH_2, D_2O exch), 8.30 (s, 1H, OH, D_2O exch), 8.13 (s, 1H, CH), 7.96 (s, 1H, arom), 7.94 (s, 1H, arom)	33.08 1.38 3.86	(33.19) (1.38) (3.90)	$C_{10}H_5NO_4Br_2$ 363

General procedure for the synthesis of **5a-h**.

Carbon suboxide (**2**) (1.10 g, 16.0 mmol) was added during one hour at -70°C to a stirred solution of **1a-h** (5.3 mmol) in dry acetone (500 mL). When the addition was completed, the mixture was kept under stirring at 0°C for 5 h and at rt for 48 h. At completion of the reaction, the solution was filtered and evaporated under reduced pressure. The residue was flash chromatographed (silica gel - 0.04 mm : 230

mesh, flow 20 mL/min, n-hexane:ethyl acetate 1:1 and then methyl alcohol as eluents) to give **5a-h**, as last eluate. The analytical and spectral data for **5a-h** are shown in Table 2.

Table 2. Analytical and spectral data for compounds (**5a-h**)

Compd	Yield (%)	mp (°C)	IR (nujol) ν_{max} (cm^{-1})	^1H NMR (DMSO-d_6) δ (ppm)	Elemental Analysis Calcd (%) (Found) C	H	N
5a	65	239-240	3450, 3140, 1730, 1670	12.10 (s, 2H, NH_2, D_2O exch), 8.05 (s, 1H, OH, D_2O exch), 7.50 - 6.90 (m, 4H, arom)	57.15 (57.00)	2.58 (2.60)	5.13 (5.13)
5b	55	253-254	3400, 3140, 1740, 1670	11.90 (s, 1H, NH, D_2O exch), 8.10 (s, 1H, OH, D_2O exch), 7.75 - 6.75 (m, 9H, arom)	65.33 (65.22)	3.17 (3.14)	4.01 (4.00)
5c	70	273-274	3420, 3310, 1740, 1670, 1630	13.00 (s, 1H, OH, D_2O exch), 12.20 (s, 1H, NH, D_2O exch), 8.00 (s, 1H, OH, D_2O exch), 7.80 - 6.87 (m, 4H, arom), 4.04 (d, 2H, CH_2)	54.39 (54.51)	2.74 (2.74)	4.23 (4.19)
5d	55	237-238	3430, 3130, 1720, 1680, 1650	12.45 (s, 1H, NH_2, D_2O exch), 8.13 (s, 1H, OH, D_2O exch), 7.95 - 6.95 (m, 3H, arom)	50.76 (50.60)	1.95 (1.90)	4.55 (4.50)
5e	60	259-260	3400, 3130, 1720, 1680, 1640	11.75 (s, 1H, NH, D_2O exch), 8.00 (s, 1H, OH, D_2O exch), 7.80 - 6.85 (m, 8H, arom)	59.48 (59.60)	2.60 (2.65)	3.65 (3.61)
5f	60	230	3410, 3170, 1710, 1670, 1610	12.10 (s, 2H, NH_2, D_2O exch), 8.10 (s, 1H, OH, D_2O exch), 7.90 (s, 1H, arom), 7.70 (s, 1H, arom)	45.65 (45.62)	1.46 (1.47)	4.09 (4.00)
5g	67	230	3410, 3120, 1720, 1670, 1620	12.70 (s, 2H, NH_2, D_2O exch), 8.10 (s, 1H, OH, D_2O exch), 7.80-7.60 (m, 3H, arom)	44.35 (44.50)	1.70 (1.70)	3.98 (4.00)
5h	70	230	3420, 3200, 1710, 1660, 1600	12.00 (s, 2H, NH_2, D_2O exch), 8.35 (s, 1H, OH, D_2O exch), 8.15 (s, 1H, arom), 7.95 (s, 1H, arom)	36.23 (36.20)	1.16 (1.20)	3.25 (3.28)

Table 3. MS spectra (*m/z*) for compounds (**5a-h**)

Ionic Species	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**
$M^{+\cdot}$	273	349	331	307	383	342	352	431
$[M - CO]^{+\cdot}$	245	321	303	279	355	314	324	403
$[M - CO_2]^{+\cdot}$	229	305	287	263	339	298	308	387
$[M - OH]^{+}$	256	332	314	290	366	325	335	414
$[M - (NHR_3)]^{+}$	257	257	257	291	291	326	336	415
$[M - (CONHR_3)]$	229	229	229	263	263	298	308	387

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