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Synthesis and Reactions of New 4-Oxo-4H-benzopyran-3-carboxaldehydes Containing Hydroxy Groups or 2-Oxopyran Cycles

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Abstract: The synthesis of eight hydroxy- and 2-oxopyranochromone-3-carboxaldehydes **3**, **5** and their reactions with 2-hydroxyaniline, 2,4-dinitrophenylhydrazine and 2-benzothiazolylhydrazine were investigated. Products were confirmed by IR, NMR spectral and elemental analysis data. The semi-empirical AM1 quantum-chemical method has been used to study optimal geometries and heats of formation of synthesized 3-formylchromones

Keywords: 3-Formylchromones, Vilsmeier - Haack reaction, 2-oxobenzopyrane, imines, enamines, AM1 calculations

Introduction

This work was done in connection with our study of synthetic, theoretical, spectral [1 - 5] and biological [6, 7] properties of 3-formylchromone derivatives. In the course of biological investigation of 3-formylchromone derivatives we found a hereditary bleaching effect on the plastid system of *Euglena gracilis* [7] and antimycobacterial activity similar to effect of isonicotin acid hydrazide (INH) [5, 7]. Due to their biological activity are chromone derivatives are a subject of considerable pharmaceutical and chemical interest. The natural chromones of the abundant flavonoid family contain prevailingly one or several hydroxyl groups which can be free or protected. 3-Formylchromones are also attractive syntons for preparative organic chemistry due to a behaviour similar to α,β-unsaturated aldehydes [8, 9]. Therefore our attention was aimed at the investigation of favourable conditions for the preparation of two biologically interesting groups of aldehydes e.g. 3-formylchromones containing the condensed 2-oxopyran

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ring **5a** - **5e** and difficultly accessible aldehydes with non - protected hydroxy groups at the benzene ring **3a** - **3c**.

Results and Discussion

In the first part of the work the preparation of 7-hydroxy-, 6-n-hexyl-7-hydroxy- and 7, 8-dihydroxy-3-formylchromones **3a** - **3e** was studied. It has been found that their preparation using the Vilsmeier-Haack formylation of appropriate o-hydroxyacetphenones afforded very low yields (20 - 30 %). Our efforts to prepare 5,7-dihydroxy-3-formylchromones by direct formylation of 2, 4, 6-trihydroxyacetphenone **1d** were unsuccesfull. The reaction resulted in polymeric products in all experiments. It can be assumed that the hydroxy groups of compounds **1a** - **1d** caused the lowering of the acetyl group acidity and preferably enables the formylation of the benzene ring and polycondensation of intermediates. The new 2, 4-dihydroxy-5-hexylacetophenone **1c** was prepared by acetylation in acetic acid and $ZnCl_2$ at reflux in 56% yield.

In the second part of this work we developed the method of synthesis of a 3-formyl- chromone having a condensed 2-oxopyrane ring. The synthetic strategy of 3-formylchromones **5a - 5e** had to be based on building up the 2-benzopyrone skeleton. The key - step in this synthesis was the preparation of a suitable acetyl derivative **4a** - **4d**, from which the requested 3-formylchromones were obtained by Vilsmeier-Haack double formylation in 80 - 90 % yields. The synthesis of **5a** - **5e** is shown in Scheme 2.

The Vilsmeier-Haack formylation was used to afford two different aldehydes **5d** and $\mathbf{5d_1}$ from 2-oxo-2H-6-acetyl-5,7-dihydroxy-4-methylbenzopyran **4d**. However, only one product was isolated from the reaction mixture. The ^{1}H NMR spectra confirmed the structure of **5d**. The signal of the proton of the hydroxy group was a singlet and a coupled constant ^{4}J for a hydroxy group was absent.

8-Acetyl-7-hydroxy-4-methylcoumarin **4a** was prepared from 1,3-dihydroxybenzene in three reaction steps, namely by the Pechmann reaction, acetylation, and then by Fries rearrangement. All three reaction steps proceeded in high yields (84 - 90 %). After recrystallisation of the Fries rearrangement product another isomer **4b** (6 %) was isolated from the mother liquor. The product **4b** (6-acetyl-7-hydroxycoumarin) was obtained directly as the main product from 2, 4-dihydroxyacetophenone **1a** by the Pechmann reaction in the presence of $POCl_3$.

6-Acetyl-5-hydroxy-4-methyl coumarin **4c** was also prepared from compound **1a** by Pechmann reaction in the presence of $AlCl_3$. 2, 4, 6-Trihydroxyacetophenone **1d** yielded a mixture of both isomers **4d** and **4e** by Pechmann reaction in a ratio 1 : 1. The pure products **4d** were isolated by recrystallization from ethanol. Product **4e** was soluble and was isolated after evaporation of the mother liquor. The preparation of compounds **5d** and **5e** from the parent phenol involved three steps. Two steps of the synthesis yielded about 80 - 90 % of products. Only the second step, the product of the Pechmann reaction gave 40 - 50 % yield. The elemental analysis data of the prepared compounds is listed in Table 1.

The assumed structures of the aldehydes **3**, **5** and the compounds **4** were proved by infrared and ^{1}H NMR spectra. The infrared spectra of 3-formylchromones **3** showed two strong absorption bands of the C=O stretching vibrations belonging to the carbonyl group of γ-pyrone at 1620 cm^{-1} and to the aldehyde carbonyl group at 1695 cm^{-1}.

The C=O stretching vibrations of the carbonyl groups of **5** exhibited strong absorption bands in three very well distinguished regions: 1655 - 1637 cm^{-1}, 1704 - 1694 cm^{-1} and 1760 - 1724 cm^{-1} belonging to the ν(C=O) of the γ-pyrone ring, the aldehyde groups and the α-pyrone ring, respectively (Table 2).

The structure of the prepared compounds was also confirmed by ^{1}H NMR spectra. The resonance signals and their multiplicity are given in Table 3. In this table also included are the chemical shifts for the acetyl derivatives **4a** - **4c,** because these compounds were previously reported without ^{1}H NMR spectral data.

The condensation reactions of the aldehydes **3a** - **3c** and **5a** - **5e** were carried out with 2-hydroxyaniline, 2,4-dinitrophenylhydrazine, 2-benzothiazolylhydrazine and ethyl acetoacetate. 2,4-Dinitrophenylhydrazones and 2-benzothiazolylhydrazones **7a** - **7k** were formed by refluxing the starting mixture in ethanol. The products appeared as coloured and slightly soluble compounds decomposing near their melting points. The reaction of 2-hydroxyaniline with 3-formylchromones gives chromanones **8** or **9** using different reaction media (Scheme 3). In ethanol the adducts **8** were obtained, in diethylether the compounds **9** were formed with two molecules of 2-hydroxyaniline. The aldol condensation product **6** was obtained by heating the aldehyde **3a**, and ethyl acetatoacetate with CH_3COOK as catalyst.

The starting compounds **1,** and 3-formylchromone derivatives **3a** - **3c**, **5a** - **5e** were studied by the semi-empirical quantum chemical AM1 method [10]. The full optimisation of the geometry of every structural parameter for several conformers was performed. Heats of formation were calculated for all s-cis and s-trans conformations. The s-cis conformations appeared to be energetically more favourable then the s-trans ones. The difference in the heats of formation is about 20 kJ mol^{-1} for acetophenones **1** and 22 - 26 kJ mol^{-1} for 3-formylchromones **3**, **5** . In accordance with the ^{1}H NMR spectra, the results of theoretical calculation of both isomers of aldehydes **5d** and $\mathbf{5d_1}$ (Scheme 2) shows that the isomer **5d** is about 4.5 kJ/mol more stable than the isomer $\mathbf{5d_1}$.

Table 1. Elemental analysis data of prepared compounds.

Compound	Formula M_r	W_i (calc.) % W_i (found) % C	H	N	M.p. (^oC)
1c	$C_{14}H_{20}O_3$	71.18	8.51		75-77
	236.2	71.13	8.47		
3a	$C_{10}H_6O_4$	63.14	3.17		268-270
	190.2	63.31	3.10		
3b	$C_{10}H_6O_5$	58.30	2.91		264-266
	206.2	58.26	2.98		
3c	$C_{16}H_{18}$	70.07	6.57		233-234
	274.2	70.01	6.60		
5a	$C_{14}H_8O_5$	65.62	3.13		310-312
	256.2	65.33	3.12		
5b	$C_{14}H_8O_5$	65.62	3.13		255-260
	256.2	65.48	3.01		
5c	$C_{14}H_8O$	65.62	6.57		233-234
	256.2	65.32	3.07		
5d	$C_{14}H_8O_6$	61.79	2.94		273-274
	272.2	61.62	2.99		
5e	$C_{14}H_8O_6$	61.79	2.94		291-293
	272.2	61.77	2.92		
7a	$C_{17}H_{11}N_3O_3S$	60.53	3.26	12.46	248-250
	337.3	60.37	3.25	12.27	
7b	$C_{23}H_{23}N_3O_3S$	65.60	5.46	9.97	219-220
	421.4	65.35	5.33	9.54	
7c	$C_{17}H_{11}N_3O_4S$	57.79	3.12	11.90	259-261
	403.3	57.48	3.11	11.76	
7d	$C_{21}H_{13}N_3O_4S$	62.50	3.24	10.41	253-255
	403.3	62.37	3.23	10.29	

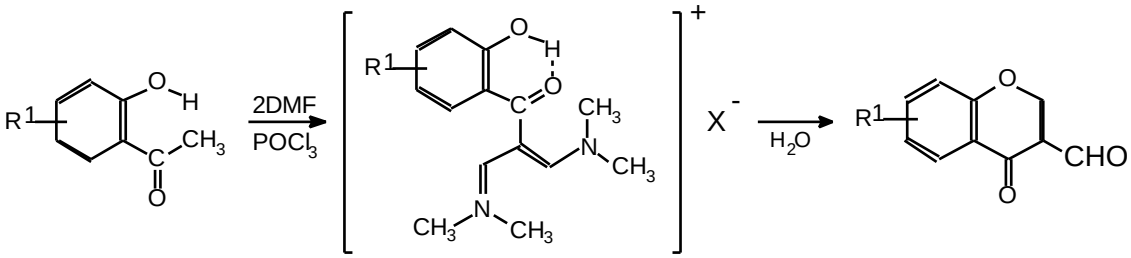
Table 1. *Continued.*

Compound	Formula M_r	W_i (calc.) % W_i (found) % C	H	N	M.p. (^oC)
7e	$C_{21}H_{13}N_3O_5S$	60.13	3.12	10.01	325-8
	419.3	60.22	3.19	9.71	
7f	$C_{21}H_{13}N_3O_4S$	62.50	3.24	10.41	240-242
	403.3	62.38	3.20	10.39	
7g	$C_{16}H_{10}O_7N_4$	51.90	2.72	15.13	297-9
	378.3	51.62	2.76	14.89	decomp.
7h	$C_{22}H_{22}O_7N_4$	58.15	4.88	12.33	296-8
	454.4	57.86	4.84	12.09	decomp.
7i	$C_{16}H_{10}O_8N_4$	49.75	2.61	14.50	173-6
	386.3	49.36	2.66	14.28	decomp.
7j	$C_{20}H_{12}O_8N_4$	55.05	2.77	12.84	289-94
	436.3	54.89	2.77	12.75	
7k	$C_{20}H_{12}O_9N_4$	53.11	2.67	12.38	300-2
	452.3	52.84	2.80	12.06	decomp.
8a	$C_{22}H_{19}NO_6$	67.18	4.83	3.56	275-6
	393.4	66.89	4.59	3.12	
8b	$C_{22}H_{19}NO_7$	64.55	4.65	3.42	259-60
	409.4	64.36	4.00	3.30	
9a	$C_{26}H_{20}N_2O_6$	68.42	4.39	6.13	180-5
	456.4	68.22	4.51	6.02	
9b	$C_{26}H_{20}N_2O_6$	66.10	4.24	5.92	158-62
	472.4	66.05	4.24	5.74	
9c	$C_{26}H_{20}N_2O_6$	68.42	4.39	6.13	188-90
	456.4	68.51	4.37	6.19	

Table 2. IR - spectral data (in cm^{-1}).

Compound	$C^4=O^a$	CH=O	$C^8=O^a$	$\nu_s(NO_2)$	$\nu_{as}(NO_2)$
3a	1620	1695	-	-	-
3b	1630	1682	-	-	-
3c	1630	1696	-	-	-
5a	1657	1700	1726	-	-
5b	1655	1693	1748	-	-
5c	1637	1693	1700	-	-
5d	1640	1702	1734	-	-
5e	1640	1704	1724	-	-
7a	1634	-	-	-	-
7b	1630	-	-	-	-
7d	1630	-	1720	-	-
7g	1640	-	-	1318	1580
7h	1612	-	-	1350	1580
7i	1610	-	-	1345	1580
7j	1640	-	1722	1345	1580
7k	1606	-	1748	1310	1580
8a	1642	-	1718	-	-
8b	1642	-	1708	-	-
9a	1648	-	1700	-	-

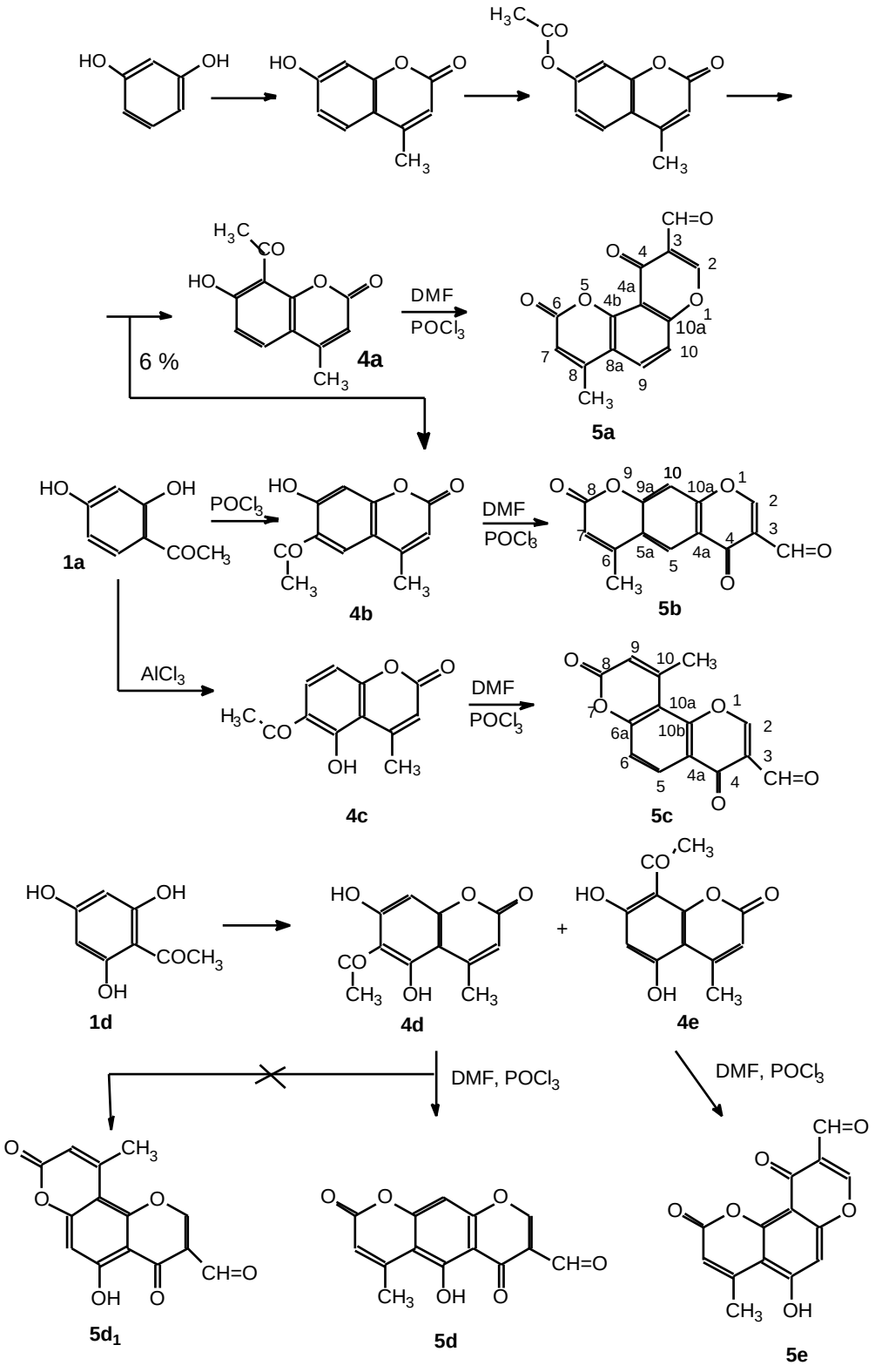
[a] For numbering of carbon atoms see Scheme 2.



1 **2** **3**

	R^1		R^1
1a	4-OH	**3a**	7-OH
1b	3,4-$(OH)_2$	**3b**	7,8-$(OH)_2$
1c	4-OH - 5-n-C_6H_{13}	**3c**	6-n-C_6H_{13}, 7-OH
1d	4,6-$(OH)_2$		

Scheme 1.

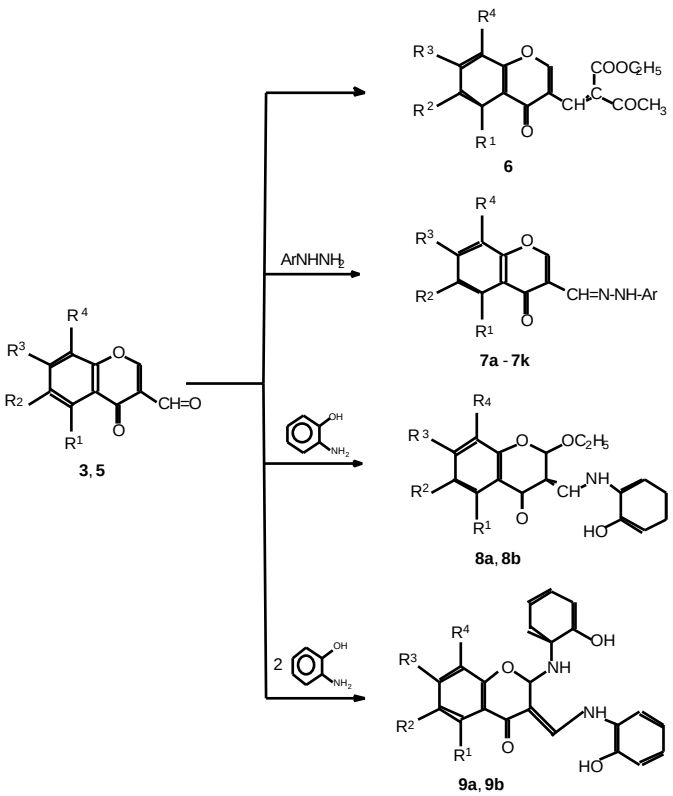


Scheme 2.

Table 3. ^{1}H NMR - spectral data.

compound	solvent	spectra δ (ppm)
1a	$CDCl_3$	12.52 (1H,s,OH), 7.42 (1H,s,H-6), 6.34 (1H,s,H-3), 1.65-0.87 (13Hm)
3a	DMSO	10.11 (1H,s,CHO), 8.78 (1H,s,H-2), 7.99 (1H,d,H-5), 7.04-6.94 (2H,t,H-6,8)
3b	DMSO	10.12 (1H,s,CHO), 8.77 (1H,s,H-2), 7.48 (1H,d,H-5), 7.00 (1H,d,H-6)
3c	DMSO	10.12 (1H,s.CHO), 8.73 (1H,s,H-2), 7.79 (1H,s,H-5), 6.93 (1H,s,H-8), 2.9 (2H,t), 1.30 (8H,m), 0.86 (3H,t)
4a	$CDCl_3$	7.68 (1H,d,H-5), 6.90 (1H,d,H-6), 6.12 (1H,s,H-3), 2.95 (3H,s,CH CO), 2.41 (3H,s,CH), 13.54 (1H,s,OH)
4b	$CDCl_3$	7.96 (1H,s,H-5), 6.84 (1H,s,H-8), 6.17 (1H,s,H-3), 2.70 (3H,s,CH CO), 2.44 (3H,s,CH), 12.61 (1H,s,OH)
4c	$CDCl_3$	7.85 (1H,d,H-7), 6.83 (1H,d,H-8), 6.13 (1H,s,H-3), 2.66 (6H,s,CHCO), 14.07 (1H,s,OH)
4d	$CDCl_3$	6.26 (1H,s,H-3), 5.99 (1H,d,H-8), 2.68 (3H,s,CH CO), 2.51 (3H,s,CH)
4e	$CDCl_3$	6.37 (1H,s,H-3), 5.94 (1H,s,H-6), 2.68 (3H,s,CH CO), 2.51 (3H,s,CH)
5a[a]	DMSO	10.12 (1H,s,CHO), 8.86 (1H,s,H-2), 8.18 (1H,d,H-10), 7.67 (1H,d,H-9), 6.53 (1H,s,H-7)
5b[a]	DMSO	10.12 (1H,s,CHO), 8.97 (1H,s,H-2), 8.39 (1H,s,H-5), 7.87 (1H,s,H-10), 6.56 (1H,s,H-7), 2.54 (3H,s,CH)
5c[a]	DMSO	10.14 (1H,s,CHO), 9.02 (1H,s,H-2), 8.31 (1H,d,H-5), 7.58 (1H,d,H-6), 6.57 (1H,s,H-9), 2.74 (3H,s,CH)
5d[a]	DMSO	10.05 (1H,s,CHO), 8.63 (1H,s,h-2), 8.12 (1H,s,H-10), 6.78 (1H,s,H-7), 6.26 (1H,s,OH), 2.54 (3H,s,CH)
5e	DMSO	10.07 (1H,s,CHO), 9.06 (1H,s,H-2), 7.30 (1H,s,H-10), 6.31 (1H,s,H-7), 2.62 (3H,s,CH)
6	$CDCl_3$	8.26 (2H,t,H-2,CH), 7.10-7.56 (3H,m,arom), 4.31 (2H,q,CH), 2.47 (3H,s,CH COO), 2.35 (3H,s,CH CO), 1.35 (3H,t,CH)

[a] spectra were recorded on a Bruker AM 300



	R^1	R^2	R^3	R^4
7a	H	H	OH	H
7b	H	n-C_6H_{13}	OH	H
7c	H	H	OH	OH
7d	-O-(CO)CH=C(CH_3)-		H	H
7e	-O-(CO)CH=C(CH_3)-		OH	H
7f	H	H	-O-(CO)CH=C(CH_3)-	
7g	H	H	OH	H
7h	H	n-C_6H_{13}	OH	H
7i	H	H	OH	OH
7j	-O-(CO)CH=C(CH_3)-		H	H
7k	-O-(CO)CH=C(CH_3)-		OH	H
8a	-O-(CO)CH=C(CH_3)-		H	H
8b	-O-(CO)CH=C(CH_3)-		OH	H
9a	-O-(CO)CH=C(CH_3)-		H	H
9b	-O-(CO)CH=C(CH_3)-		OH	H
9c	H	H	-O-(CO)CH=C(CH_3)-	

7a - 7f Ar =

7g - 7k Ar = 2,4-$(NO_2)_2C_6H_3$

Scheme 3.

Experimental Section

General details

The synthesized compounds were characterized by melting points, elemental analysis, IR and ^{1}H NMR spectra.

The melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra were taken on a Specord M-80 (Zeiss) spectrophotometer in a nujol suspension.

The NMR spectra were measured on a Tesla BS 487 (80 MHz) and Bruker AM 300 (300.13 MHz) spectrometers in deuterated DMSO and $CHCl_3$.

The synthesis of acetophenones **1a**, **1b**, **1d** is described in papers [11 - 13] and the preparation of compounds **4a** - **4e** in papers [14 - 16].

*2, 4-Dihydroxy-5-n-hexylacetophenone **1c***

4-n-Hexyl-1, 3-dihydroxybenzene (30 g, 0.15 mol) was gradually added to a stirred and hot mixture (120 ^{o}C) of glacial acetic acid (45 ml) and anhydrous $ZnCl_2$ (44.6 g, 0.32 mol). The mixture was refluxed for 10 minutes. After cooling the mixture was diluted with HCl (120 ml, diluted 1 : 1) and was kept in refrigerator (12 hrs). The crystals were filtered off, washed with diluted HCl (1 : 3) and recrystallized from methanol. Yield 25 g (72 %)

*3-Formylchromones **3**, **5**. General procedure*

To the dry dimethylformamide (121 ml) in a three necked flask, $POCl_3$ (0.49 mol) was added slowly with intensive stirring at 50 ^{o}C. Heating and stirring was continued for 2 hrs at 45 - 55 ^{o}C. The solution of 2-hydroxyacetophenone (0.12 mol) in DMF (25 ml) was then slowly added under stirring at 50 ^{o}C. The stirring was continued for 2 hrs at 55 - 60 ^{o}C. After cooling the mixture was kept over night at room temperature and diluted slowly by adding crushed ice (500 g) and stirred again for

6 hrs. The crystals were filtered off and recrystallized from alcohol. Yields of compounds **3** are 20 - 30 %, of **5** are 80 - 90 %

*3-(4-Oxo-7-acetoxy-4H-1-benzopyran-3-yl)-2-(1-oxoethyl)-2-ethylpropenoate **6***

A mixture of 7-hydroxy-3-formylchromone **3a** (1 g, 5.3 mmol), ethyl acetoacetate (0.82 g, 6.3 mmol), acetic anhydride (4.32 g, 42 mmol) and K_2CO_3 (0.07 g, 0.53 mmol) was heated for 1 hr. After cooling, 30 ml diethylether was added and the ester was allowed to crystallize over 12 hours at room temperature. A yellow solid product was filtered off and recrystalized from ethanol. Yield 56 %.

*2-Benzothiazolylhydrazone-3-formylchromone **7a** - **7f**, 2, 4-dinitrophenylhydrazone-3-formylchromone **7g** - **7k** and 2-ethoxy-3-(2-hydroxyphenylaminomethylene)chroman-4-ones **8a**, **8b***

Ethanolic solutions of 3-formylchromone derivatives (1 mmol), and 2-benzotiazolhydrazine (or 2, 4-dinitrophenylhydrazine, or 2-hydroxyaniline) (1 mmol) and one crystral of p-toluenesulfonic acid were mixed together and stirred for 1 h, at 30 - 35 ^{o}C. The reaction mixture was then cooled to 10 ^{o}C. The yellow precipitate was filtered off and recrystallized from ethanol or a mixture DMSO - ethanol. Yields about 70 - 75 %.

*2-(2-hydroxyphenylamino)-3-(2-hydroxyphenylaminometylene)chroman-4-ones **9a** - **9c***

The anhydrous chloroform solution (15 ml) of 3-formylchromone (1 mmol) and 2-hydroxyaniline (2 mmol) was stirred for 30 minutes at 50 ^{o}C. After cooling the mixture petroleum ether was added to form a precipitate. The product was filtered off. Toluene was used for recrystalization. Yields 50 - 58 %.

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Samples Availability: Samples are available from MDPI and the authors.