139. The Chemistry of Coumarin Derivatives

Part 3[1])

Synthesis of 3-Alkyl-4-hydroxycoumarins by Reductive Fragmentation of 3,3′-Alkylidene-4,4′-dihydroxybis[coumarins]

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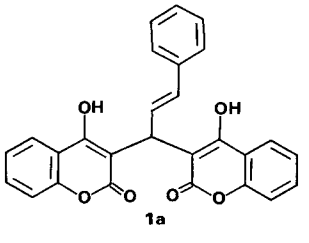
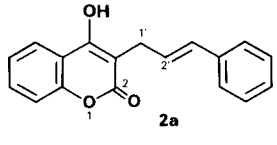
Treatment of 3,3′-alkylidene-4,4′-dihydroxybis[coumarins] **1** with $NaBH_3CN$ in refluxing MeOH affords 3-alkyl-4-hydroxycoumarins **2** and 4-hydroxycoumarin (**3**; *Scheme 1*). The reaction might take place *via* hydride trapping of alkylidenechromandiones **C** formed from **1** in a *retro-Michael* reaction. Such a *retro-Michael* reaction of **1** might be biologically relevant. The presence of **C** during the reductive fragmentation **1** → **2** is suggested by *Diels-Alder* and nucleophilic trapping of the alkylidenechromandiones **C** as well as from cross-over experiments with coumarins other than **3** (see *Scheme 2*). The reductive fragmentation of **1** allows the chemo- and regioselective synthesis of a variety of 3-alkyl-4-hydroxycoumarins **2** (see *Table*).

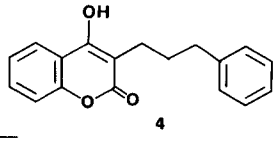
Introduction. – In the course of studies on the reaction of 4-hydroxycoumarin (= 4-hydroxy-2*H*-1-benzopyran-2-one) and enals [1], we serendipitously discovered that treatment of 3,3′-alkylidene-4,4′-dihydroxybis[coumarin] **1a** with an excess of $NaBH_4$ in EtOH gave 3-alkyl-4-hydroxycoumarin **2a**. Whereas the synthesis of 3-alkyl-4-hydroxycoumarins by direct alkylation of 4-hydroxycoumarin (**3**) is notoriously hampered by



1a



2a



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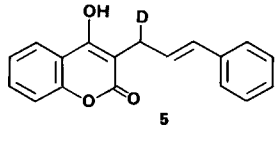

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[1]) Part 2, see [1].

regioselectivity and polyalkylation problems [2], the reaction of **3** with aldehydes is instead fully regio- and chemoselective, affording 3,3′-alkylidene-4,4′-dihydroxybis[coumarins] in high yield [3] (see below, *Scheme 1*). The formation of these adducts coupled to their reductive cleavage might thus represent a general procedure for the regioselective alkylation of **3**, allowing an easy entry into 3-alkyl-4-hydroxycoumarins. These belong to an important class of biologically active compounds for which no general direct synthesis from 4-hydroxycoumarin (**3**) is available [4]. The synthetic potential of the reductive fragmentation of 3,3′-alkylidene-4,4′-dihydroxybis[coumarins] **1** was thus investigated.

Results and Discussion. – Attempts to extend the reductive fragmentation to 3,3′-alkylidenebis[coumarins] different from **1a** met with very limited success, since most of the tested compounds either did not react or gave a reaction too slow to be of practical applicability. On the other hand, treatment of **1a** with stronger hydride reagents ($LiBH_4$, $LiAlH_4$, diisobutylaluminum hydride(DIBAH)) or under other reduction conditions (catalytic, $Na(Li)/NH_3$)) proved completely uneffective, whereas the reduction of **1a** with Zn/AcOH gave in low yield 4-hydroxy-3-(3-phenylpropyl)coumarin (**4**).

Much to our surprise, the mild reducing agent $NaBH_3CN$ turned out to be the reagent of choice. It allowed the smooth reduction, often in almost quantitative yields, of all 3,3′-alkylidenebis[coumarins] **1** investigated to give the 3-alkyl-4-hydroxycoumarins **2** (*Scheme 1, Table*). Although the reaction was feasible at room temperature in EtOH, the use of MeOH at its boiling temperature allowed to overcome the problems posed by the very limited solubility of most bis[coumarins] in the common organic solvents [3]. In all cases, the conversion was complete (TLC monitoring). The relatively poor yield of the *para*- and *ortho*-isomers **2m,n** of 4-hydroxy-3-(nitrobenzyl)coumarin (*Table*) reflects their high insolubility and polarity, leading to considerable loss of material on purification.

Scheme 1

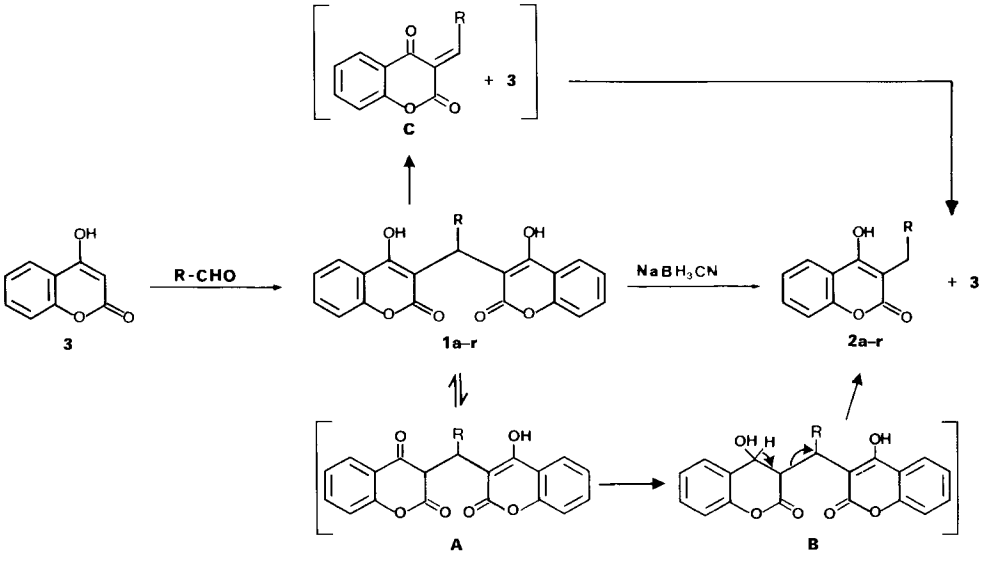


Table. *Synthesis of 3,3′-Alkylidene-4,4′-dihydroxybis[coumarins]* **1** *and Reductive Fragmentation to 3-Alkyl-4-hydroxycoumarins* **2**

	R	Yield [%] of **1**	Yield [%] of **2**	Reduction time [h]
a	(*E*)-PhCH=CH	89	95	5
b	H	62	90	40
c	Me	75	80	80
d	$Me(CH_2)_5$	56	99	80
e	$Me(CH_2)_8$	38	70	70
f	$4\text{-}(Me_2N)C_6H_4$	83	70	3
g	$4\text{-}(MeO)C_6H_4$	85	77	10
h	$2\text{-}(MeO)C_6H_4$	89	90	16
i	1,3-benzodioxol-5-yl	96	94	13
j	$4\text{-}MeC_6H_4$	93	96	25
k	Ph	90	88	42
l	$4\text{-}ClC_6H_4$	88	81	48
m	$4\text{-}(NO_2)C_6H_4$	85	32	98
n	$2\text{-}(NO_2)C_6H_4$	73	37	125
o	furan-2-yl	90	73	2
p	furan-3-yl	81	83	4
q	cyclohexyl	51	85	72
r	$(E)\text{-}4\text{-}(NO_2)C_6H_4\text{–}CH{=}CH$	79	62	24

Regioselective syntheses of 3-alkyl-4-hydroxycoumarins have been accomplished starting from *ortho*-hydroxybenzophenones [5], acylated methyl salicylates [6], substituted malonates and phenols [7], or 3-acyl-4-hydroxycoumarins [8]. Their preparation from 3,3′-alkylidene-4,4′-dihydroxybis[coumarins] **1** represents a new alternative to these procedures, especially valuable in terms of availability of the precursors, mildness of the conditions, and yields. The procedure is not suitable for the introduction of allylic residues different from cinnamyl, since enals different from cinnamaldehyde (= 3-phenylprop-2-enal) and its derivatives do not give compounds **1** upon reaction with 4-hydroxycoumarin [1]. Another drawback is that in some cases (**2b**, **c**, **l**), the separation of the 3-alkyl-4-hydroxycoumarin **2** from 4-hydroxycoumarin (**3**) is tedious and requires careful column chromatography.

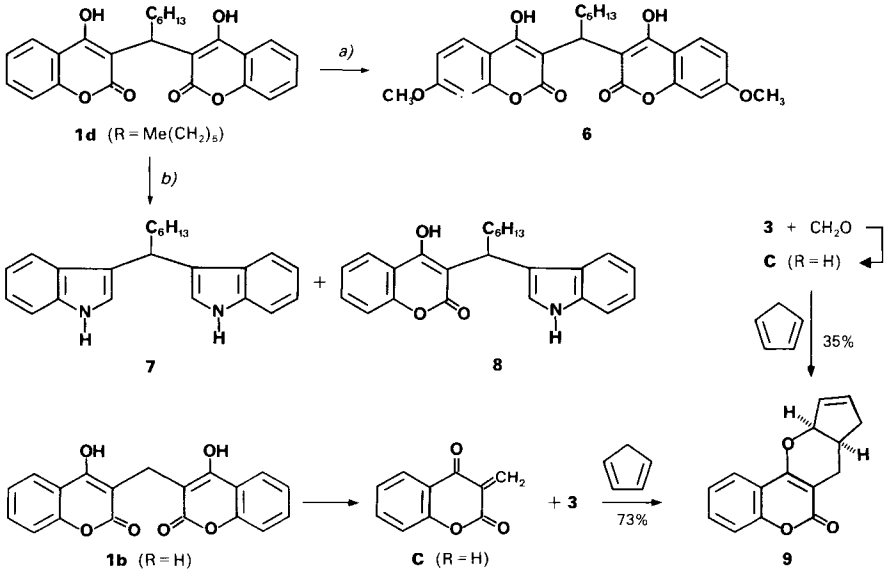
As to the mechanism, the analogy of the reaction with the known reductive fragmentation of cyclic α-nitroketones [9] makes the addition-elimination mechanism *via* **A** and **B** plausible (see *Scheme 1*). However, a series of data are inconsistent with a mechanism of this type: *i*) With the *para*-substituted 3,3′-benzylidene-4,4′-dihydroxybis[coumarins] **1f**,**g**,**i**,**j**,**l**,**m**, the reduction was very sensitive to the electronic effects: electron-donating groups in *para*-position accelerated the reaction, whereas electron-withdrawing groups slowed it down. The observed rate-order ($4\text{-}Me_2N > 4\text{-}MeO > 4\text{-}Me > H > 4\text{-}Cl \gg 4\text{-}NO_2$) was opposite to that expected if the coumarin-substituted benzyl group were to be lost as an anion (see **B**). *ii*) The reduction of **1a** with $NaBH_4$ in EtOD did not lead to incorporation of the D-atom at C(1′) of **2a**. Conversely, the 1′-deuterated **2a** was obtained with $NaBD_4$ in EtOH. These data could be explained by a *retro-Michael* reaction of **1** giving a 1:1 mixture of an alkylidenechromandione **C** and **3** (see *Scheme 1*)[2]. The

[2] A related reaction has been postulated for some alkylidene derivatives of dimedone [10] and *Meldrum*'s acid [11].

reductive cleavage could thus take place *via* hydride trapping of highly reactive electrophilic chromandiones which would be in accordance with *i* and *ii*. The order of reactivity in 3,3′-benzylidene-4,4′-dihydroxybis[coumarins] **1f,g,i,j,l,m** parallels in fact the order of stability, and, therefore, the facility of formation, of the corresponding benzylidenechromandiones [1]. The mechanism *via* **C** could also explain the observation that methylation or acetylation of **1** suppressed completely the reaction.

No spectroscopic evidence for the intermediacy of alkylidenechromandione **C** could be obtained (NMR, IR, UV), presumably because of its very low concentration. The presence of **C** during the reductive fragmentation is, however, suggested by cross-over experiments with coumarins different from 4-hydroxycoumarin (**3**) and by trapping of the chromandiones with nucleophiles or cyclopentadiene, the latter being a powerful dienophile in the inverse electron demand hetero-*Diels-Alder* reaction of alkylidenechromandiones [12]. Thus, treatment of bis[coumarin] **1d** (R = $Me(CH_2)_5$)[3]) in EtOH at reflux temperature with an excess of 4-hydroxy-7-methoxycoumarin (= 4-hydroxy-7-methoxy-2*H*-1-benzopyran-2-one) led to the formation of 4,4′-dihydroxy-7,7′-dimethoxybis[coumarin] **6**, whereas treatment of **1b** (R = H) with cyclopentadiene in refluxing dioxane gave adduct **9** which was identical to the product obtained from the three-component condensation of 4-hydroxycoumarin (**3**), formaldehyde, and cyclopentadiene [12] (*Scheme 2*). The alkylidenechromandione **C** could also be trapped with C-nucleophiles other than 4-hydroxycoumarins: treatment of **1d** in EtOH with an excess of indole [13]

Scheme 2. *Trapping by Nucleophiles or Cyclopentadiene of Alkylidenechromandiones* **C** *Produced from 3,3′-Alkylidene-4,4′-dihydroxybis[coumarins]* **1**

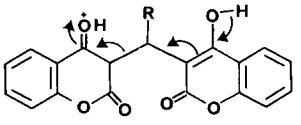


a) 4-Hydroxy-7-methoxycoumarin, EtOH, reflux (77%). *b)* 1*H*-Indole, EtOH; at reflux, 71% of **7** and 7.8% of **8**; at r.t., 31% of **7** and 5.6% of **8**.

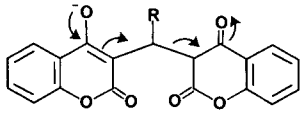
[3]) The extremely low solubility of **1b** (R=H) in the solvents used for the cross-over experiments made us use the more soluble **1d** for these reactions.

gave bis[indole] **7** and [(indolyl)heptyl]coumarin **8**. However, trapping with heteronucleophiles (piperidine, trimethyl phosphite, thiophenol) gave product mixtures that could not be characterized; attempts to trap with these nucleophiles the chromandiones generated by reaction of 4-hydroxycoumarin (**3**) and saturated aldehydes also failed. In the case of α,β-unsaturated aldehydes, the corresponding adducts could instead be isolated and fully characterized [1].

The reasons for the superior properties of $NaBH_3CN$ compared to more powerful reducing agents are not clear. The *retro-Michael* reaction of the bis[coumarins] **1** is subjected to acid and base catalysis and could readily take place on both the monoprotonated form **D** and the monodeprotonated form **E**; no possibility exists instead for the formation of a dianion or dication. Strongly basic reducing agents might convert **1** to their dienolates much faster than they add to the chromandiones, thus preventing the *retro-Michael* reaction and, therefore, the reductive cleavage to take place.



D



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The suggested *retro-Michael* reaction of the 3,3′-alkylidene-4,4′-dihydroxybis[coumarins] **1** to alkylidenechromandiones **C** is biologically relevant, since electrophilic quinone methides are the active form of some known inhibitors of vitamin K epoxide reductase [14], the target enzyme of haemorrhagic alkylidene-4,4′-dihydroxybis[coumarins] [15]. It has also been suggested that the inhibition of this enzyme by haemorrhagic 4-hydroxycoumarins involves the electrophilic trapping of a critical thiol group [15a]. This raises the intriguing question of whether 4,4′-dihydroxy-3,3′-methylenebis[coumarin] (**1b**) and related compounds act at molecular level as the alkylidene-linked bis-compounds (*cf.* **1**) or as their corresponding highly electrophilic alkylidenechromandiones (*cf.* **C**).

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Experimental Part

General. All aldehydes used in this work are commercially available and used as such. Column chromatography (CC): silica gel *60* (*Merck*, 70–230 mesh). TLC: Pre-coated silica gel *60* F_{254} plates (*Merck*); detection with UV light or 5% H_2SO_4 soln. and heating. M.p.: *Büchi-SMP-20* apparatus (uncorrected). UV (λ_{max} in nm): *Beckman-DB-GT* spectrophotometer; in EtOH. IR (in cm^{-1}): *Perkin-Elmer-237* grating spectrometer. ^1H- and ^{13}C-NMR spectra: *Jeol-GX270/89* apparatus (270 and 67.5 MHz, resp.); chemical shifts in ppm downfield from TMS (= 0 ppm); $CDCl_3$/(D_6)DMSO means that (D_6)DMSO is added dropwise to a suspension of the compound in $CDCl_3$ until a clear soln. is obtained. EI-MS: *Varian-MAT-CH7A* spectrometer (70 eV). Microanalyses (C and H) of all new compounds agree with theoretical values (±0.3%).

1. *3,3′-Alkylidene-4,4′-dihydroxybis[2H-1-benzopyran-2-ones]* **1**, *General Procedure* (see *Table*). The aldehydes are treated at r.t. with 2.4 mol-equiv. of 4-hydroxycoumarin (**3**) and 0.05 mol-equiv. of ethylenediammonium diacetate [16] in EtOH. After stirring at r.t. for 4 days, the precipitate is filtered off, washed with cold EtOH, and dried. All adducts are used for the next step without further purification. In the case of **1d** and **1e**, no precipitate is

formed, and the adducts are obtained as follows: the reaction mixture is evaporated, the residue dissolved in CH_2Cl_2, the mixture filtered to remove unreacted **3**, and the product purified by CC (hexane/AcOEt 6:4).

2. *Reductive Fragmentation of* **1** *with* $NaBH_3CN$ *to 3-Alkyl-4-hydroxy-2*H*-1-benzopyran-2-ones* **2**, *General Procedure* (see *Table*). *Warning:* the reaction must be carried out in a well-vented hood. To a suspension of **1** (1–5 g) in MeOH (*ca.* 20 ml/mmol), an excess of $NaBH_3CN$ (2 mol/mol of **1**) is added. The suspension is refluxed up to the complete disappearance of **1** (see *Table*; TLC control (hexane/AcOEt 1:9 or toluene/Et_2O 1:1 sat. with 10% AcOH in H_2O)). The solvent is then removed on a steam-bath (*hood*!), and sat. NH_4Cl soln. is added to the residue. The mixture is extracted 4 times with AcOEt and the org. phase washed 3 times with sat. $NaHCO_3$ soln. to remove **3** (no such washing in the case of **2b** and **2c** which are partly soluble in aq. $NaHCO_3$ soln.). After washing with brine and drying ($MgSO_4$), the solvent is removed and the residue mixed with silica gel *40* (35–70 mesh) and purified by CC (hexane/AcOEt 7:3 for **2d,e,o,p,q**, 8:2 for **2g–l,a** and 1:9 for **2b,c,f,m,n,r**). CC has to be repeated for **2b,c,l,m**. Coumarin **2r** is insoluble in hot MeOH and thus obtained by simple filtration of the reaction mixture and repeated washings of the precipitate with MeOH. *3-Methyl-*(**2b**), *3-ethyl-*(**2c**), *3-benzyl-*(**2k**) [6], *3-cinnamyl-*(**2a**) [1], and *3-decyl-4-hydroxy-2*H*-1-benzopyran-2-one* (**2e**) [17] are known. The remaining **2**'s are new.

*3-Heptyl-4-hydroxy-2*H*-1-benzopyran-2-one* (**2d**). M.p. 126° (hexane/AcOEt). UV (EtOH): 320, 307, 282, 272. IR (KBr): 3170, 1670, 1605, 1565, 1500, 1200, 1100, 1050, 910, 752, 662. ^{1}H-NMR (270 MHz, $CDCl_3$/(D_6)DMSO): 7.92 (br. *s*, OH); 7.90 (*d*, *J* = 7.8, 1 H); 7.51 (*t*, *J* = 7.7, 1 H); 7.32–7.27 (overlapped signals, 2 H); 2.63 (*t*, *J* = 7.7, 1 H); 1.56 (*m*, 2 H); 1.35–1.24 (overlapped signals, 8 H); 0.82 (*t*, *J* = 6.6, 3 H).

*3-{[4-(Dimethylamino)phenyl]methyl}-4-hydroxy-2*H*-1-benzopyran-2-one* (**2f**). M.p. 162° (heptane/AcOEt). UV (EtOH): 320, 307, 282, 253. IR (KBr): 3180, 1660, 1635, 1615, 1520, 1395, 1350, 1180, 1070, 950, 760. ^{1}H-NMR (270 MHz, $CDCl_3$/(D_6)DMSO): 7.93 (*d*, *J* = 7.9, 1 H); 7.45 (*t*, *J* = 7.8, 1 H); 7.38–7.22 (overlapped signals, 2 H); 7.19 (*d*, *J* = 8.5, 2 H); 6.61 (*d*, *J* = 8.5, 2 H); 3.87 (*s*, 2 H); 2.84 (*s*, 6 H).

*4-Hydroxy-3-[(4-methoxyphenyl)methyl]-2*H*-1-benzopyran-2-one* (**2g**). M.p. 179–183° (hexane/AcOEt). UV (EtOH): 312, 292, 240, 218. IR (KBr): 3060, 1650, 1625, 1510, 1395, 1250, 1200, 1040, 965, 760. ^{1}H-NMR (270 MHz, $CDCl_3$/(D_6)DMSO): 10.50 (br. *s*, OH); 7.71 (*d*, *J* = 8.2, 1 H); 7.26 (*t*, *J* = 7.6, 1 H); 7.01 (br. *s*, 4 H); 6.51 (*d*, *J* = 8.2, 2 H); 3.66 (*s*, 2 H); 3.48 (*s*, 3 H).

*4-Hydroxy-3-[(2-methoxyphenyl)methyl]-2*H*-1-benzopyran-2-one* (**2h**). M.p. 124–126° (AcOEt). UV (EtOH): 310, 280, 239, 219. IR (KBr): 3200, 1690, 1630, 1495, 1310, 1240, 1150, 1110, 1025, 910, 760. ^{1}H-NMR (270 MHz, $CDCl_3$/(D_6)DMSO): 9.39 (br. *s*, OH); 7.73 (*d*, *J* = 8.2, 1 H); 7.40 (*t*, *J* = 8.4, 1 H); 7.37–7.09 (overlapped signals, 4 H); 6.87–6.81 (overlapped signals, 2 H); 3.91 (*s*, 3 H); 3.81 (*s*, 2 H).

*3-[(1,3-Benzodioxol-5-yl)methyl]-4-hydroxy-2*H*-1-benzopyran-2-one* (**2i**). M.p. 211–214° (AcOEt). UV (EtOH): 310, 280, 239, 219. IR (KBr): 3150, 1660, 1630, 1490, 1400, 1250, 1170, 1040, 940, 760. ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 7.91 (*d*, *J* = 8.2, 1 H); 7.44 (*t*, *J* = 8.4, 1 H); 7.24–7.19 (overlapped signals, 2 H); 6.80 (*s*, 1 H); 6.76 (*d*, *J* = 7.9, 1 H); 6.62 (*d*, *J* = 7.9, 1 H); 5.81 (*s*, 2 H); 3.84 (*s*, 2 H).

*4-Hydroxy-3-[(4-methylphenyl)methyl]-2*H*-1-benzopyran-2-one* (**2j**). M.p. 176–180° (AcOEt). UV (EtOH): 312, 293, 240, 219. IR (KBr): 3200, 1670, 1630, 1500, 1450, 1400, 1260, 1175, 1110, 1070, 950, 760. ^{1}H-NMR (270 MHz, $CDCl_3$/(D_6)DMSO): 10.50 (br. *s*, OH); 7.78 (*d*, *J* = 6.4, 1 H); 7.30 (*t*, *J* = 8.2, 1 H); 7.01–6.87 (overlapped signals, 6 H); 3.77 (*s*, 2 H); 2.09 (*s*, 3 H).

*3-[(4-Chlorophenyl)methyl]-4-hydroxy-2*H*-1-benzopyran-2-one* (**2l**). M.p. 238–240° (AcOEt). UV (EtOH): 311, 290, 240, 220. IR (KBr): 3220, 1660, 1630, 1495, 1455, 1400, 1160, 1150, 960, 760, 640. ^{1}H-NMR (270 MHz, (D_6)DMSO): 11.77 (br. *s*, OH); 8.00 (*d*, *J* = 7.0, 1 H); 7.63 (*t*, *J* = 7.0, 1 H); 7.41–7.26 (overlapped signals, 6 H); 3.89 (*s*, 2 H).

*4-Hydroxy-3-[(4-nitrophenyl)methyl]-2*H*-1-benzopyran-2-one* (**2m**). M.p. 260° (AcOEt). UV (EtOH): 290, 240, 208. IR (KBr): 3190, 1660, 1630, 1515, 1460, 1400, 1350, 1190, 1110, 950, 760. ^{1}H-NMR (270 MHz, (D_6)DMSO): 8.16 (*d*, *J* = 8.0, 2 H); 8.02 (*d*, *J* = 7.9, 1 H); 7.65 (*t*, *J* = 7.9, 1 H); 7.53 (*d*, *J* = 8.0, 2 H); 7.42–7.37 (overlapped signals, 2 H); 4.03 (*s*, 2 H).

*4-Hydroxy-3-[(2-nitrophenyl)methyl]-2*H*-1-benzopyran-2-one* (**2n**). M.p. 245–247° (AcOEt). UV (EtOH): 290, 240. IR (KBr): 3170, 1670, 1630, 1570, 1530, 1500, 1400, 1350, 1200, 1160, 965, 760, 730. ^{1}H-NMR (270 MHz, (D_6)DMSO): 10.88 (br. *s*, OH); 7.70–7.67 (overlapped signals, 2 H); 7.27–7.19 (overlapped signals, 2 H); 7.16–7.00 (overlapped signals, 4 H); 4.02 (*s*, 2 H).

*3-[(2-Furyl)methyl]-4-hydroxy-2*H*-1-benzopyran-2-one* (**2o**). M.p. 158–161° (hexane/AcOEt). UV (EtOH): 310, 291, 240, 218. IR (KBr): 3200, 1670, 1620, 1570, 1495, 1190, 1060, 1010, 910, 760. ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 7.83 (*d*, *J* = 7.9, 1 H); 7.51 (*t*, *J* = 6.8, 1 H); 7.34–7.24 (overlapped signals, 3 H); 6.32 (br. *s*, 1 H); 6.25 (br. *s*, 1 H); 4.03 (*s*, 2 H).

*3-[(3-Furyl)methyl]-4-hydroxy-2*H*-1-benzopyran-2-one* (**2p**). M.p. 175–179° (dec.; hexane/AcOEt). UV (EtOH): 310, 291, 240, 217. IR (KBr): 3190, 1675, 1610, 1570, 1500, 1200, 1070, 1020, 880, 760. ^{1}H-NMR (270 MHz, $CDCl_3$): 10.81 (br. *s*, OH); 7.89 (*d*, *J* = 8.3, 1 H); 7.45 (*t*, *J* = 3.2, 1 H); 7.27–7.19 (overlapped signals, 4 H); 6.34 (br. *s*, 1 H); 3.68 (br. *s*, 2 H).

*3-(Cyclohexylmethyl)-4-hydroxy-2*H*-1-benzopyran-2-one* (**2q**). M.p. 182–184° (hexane/AcOEt). UV (EtOH): 320, 307, 282, 272. IR (KBr): 3200, 1670, 1620, 1570, 1500, 1210, 1090, 1040, 915, 760. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.68 (*d*, *J* = 7.9, 1 H); 7.54 (*t*, *J* = 8.0, 1 H); 7.34–7.29 (overlapped signals, 2 H); 6.51 (br. *s*, OH); 2.49 (*d*, *J* = 7.4, 2 H); 1.80–1.65 (overlapped signals, 5 H); 1.26–1.00 (overlapped signals, 6 H). ^{13}C-NMR (67.5 MHz, $CDCl_3$): 163.76 (*s*); 150.42 (*s*); 152.28 (*s*); 131.59 (*d*); 123.85 (*d*); 122.84 (*d*); 116.44 (*d*); 115.29 (*s*); 104.21 (*s*); 37.13 (*d*); 33.34 (2*t*); 31.64 (*t*); 26.25 (*t*); 26.11 (2*t*).

*(E)-4-Hydroxy-3-[3-(4-nitrophenyl)prop-2-enyl]-2*H*-1-benzopyran-2-one* (**2r**). M.p. 255–259°. UV (EtOH): 314, 290, 240. IR (KBr): 3150, 1660, 1630, 1515, 1400, 1340, 1150, 1110, 940, 850, 760. ^{1}H-NMR (270 MHz, (D_6)DMSO): 8.14 (*d*, *J* = 8.5, 2 H); 7.98 (*d*, *J* = 7.3, 1 H); 7.67 (*d*, *J* = 8.5, 2 H); 7.63 (*t*, *J* = 7.8, 1 H); 7.41–7.35 (overlapped signals, 2 H); 6.60 (br. *s*, 2 H); 3.52 (*d*, *J* = 4.3, 2 H). EI-MS: 323 (10, M^+, $C_{18}H_{13}NO_4^+$), 306 (10), 187 (100), 128 (13), 121 (64), 120 (14).

3. *Reductive Fragmentation of 4,4'-Dihydroxy-3,3'-(3-phenylprop-2-enylidene)bis[2*H*-1-benzopyran-2-one]* (**1a**) *with Zn/HOAc.* To a suspension of 188 mg (0.43 mmol) of **1a** in 10 ml of AcOH, an excess of activated Zn powder is added. The mixture is refluxed for 8 h, then solid $NaHCO_3$ is added to neutralize the acid, followed by H_2O and CH_2Cl_2. The org. phase is washed with brine, dried, and evaporated and the residue purified by CC (15 g, hexane/AcOEt 8:2): 42 mg (35%) *4-hydroxy-3-(3-phenylpropyl)-2*H*-1-benzopyran-2-one* (**4**), identical to a sample prepared by catalytic hydrogenation of **2a** (H_2, Pd/C, 97% yield). M.p. 137°. UV (EtOH): 320, 307, 283, 272, 204. IR (KBr): 3200, 1670, 1610, 1570, 1495, 1230, 1210, 1180, 750. ^{1}H-NMR (270 MHz, (D_6)DMSO): 8.03 (br. *d*, *J* = 8.6, 1 H); 7.68 (br. *t*, *J* = 7.9, 1 H); 7.47–7.24 (overlapped signals, 7 H); 2.77–2.59 (overlapped signals, 4 H); 1.85 (br. *quint.*, *J* = 7.9, 2 H). ^{13}C-NMR (67.5 MHz, (D_6)DMSO): 162.98 (*s*); 159.94 (*s*); 151.95 (*s*); 142.21 (*s*); 131.61 (*d*); 129.00 (*d*); 128.32 (*d*); 125.72 (*d*); 123.87 (*d*); 123.25 (*d*); 116.42 (*s*); 116.18 (*d*); 105.05 (*s*); 35.23 (*t*); 29.86 (*t*); 23.73 (*t*).

4. *Reductive Fragmentation of* **12** *with $NaBD_4$ in EtOH.* To a suspension of **1** (100 mg, 0.23 mmol) in EtOH (4 ml), an excess of $NaBD_4$ (40 mg, 0.91 mmol) is added and stirred at r.t. for 3 days. After addition of sat. NH_4Cl soln. and extraction with AcOH, the org. phase is dried ($MgSO_4$) and evaporated and the residue purified by prep. TLC (hexane/AcOEt 5:5): 28 mg (44%) of *4-hydroxy-3-[3-phenyl(1-$^2H_1$)prop-2-enylidene]bis[2*H*-1-benzopyran-2-one]* (**5**). Colourless powder. M.p. 132–134°. UV (EtOH): 307, 252, 206. IR (KBr): 3200, 1670, 1630, 1495, 1395, 1170, 1110, 970, 910, 760. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.99 (br. *d*, *J* = 7.7, 1 H); 7.49 (br. *t*, *J* = 8.6, 1 H); 7.42–7.14 (overlapped signals, 7 H); 6.51 (*d*, *J* = 15.9, 1 H); 6.34 (*dd*, *J* = 15.9, 6.2, 1 H); 3.52 (br. *d*, *J* = 6.2, 1 H). EI-MS: 279 (56, M^+, $C_{18}H_{13}DO_3$), 188 (100).

5. *Condensation of* **3**, *Formaldehyde, and Cyclopentadiene.* To a suspension of **3** (1.00 g, 6.17 mmol) in dry dioxane (50 ml), paraformaldehyde (0.3 g, *ca.* 9.4 mmol, *ca.* 1,5 mol-equiv.) and freshly distilled cyclopentadiene (1.02 ml, 814 mg, 12.34 mmol, 2 mol-equiv.) are added. After refluxing for 4 h, the solvent is evaporated and the residue suspended in CH_2Cl_2 and washed with sat. $NaHCO_3$ soln. and brine. The CH_2Cl_2-soluble material is mixed with silica gel *40* and charged at the top of a short column (10 g of silica gel *60*, packed with hexane). Elution with hexane removed dicyclopentadiene, and elution with hexane/AcOEt 8:2 gave 1.08g (73%) of *7,7a,8,10a-tetrahydro-6*H*-cis-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one* (**9**). Crystals (hexane). M.p. 99°. UV (EtOH): 320, 304, 282, 270. IR (KBr): 1690, 1630, 1495, 1410, 1280, 1180, 1120, 1050, 1010, 890, 750. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.77 (br. *d*, *J* = 7.9, 1 H); 7.49 (br. *t*, *J* = 8.5, 1 H); 7.31–7.22 (overlapped signals, 2 H); 6.14 (*m*, 1 H); 6.04 (*m*, 1 H); 5.27 (*d*, *J* = 5.3, 1 H); 2.86–2.24 (overlapped signals, 5 H). ^{13}C-NMR (67.5 MHz, $CDCl_3$): 162.95 (*s*); 160.45 (*s*); 151.87 (*s*); 137.04 (*d*); 130.98 (*d*); 130.52 (*d*); 123.41 (*d*); 122.24 (*d*); 116.16 (*d*); 115.67 (*s*); 98.75 (*s*); 83.07 (*d*); 37.47 (*t*); 34.45 (*d*); 20.30 (*t*). EI-MS: 240 (40, M^+, $C_{15}H_{12}O_3^+$), 175 (80), 121 (25), 92 (33), 66 (100).

6. *Reaction of 4,4'-Dihydroxy-3,3'-methylenebis[2*H*-1-benzopyran-2-one]* (**1b**) *and Cyclopentadiene.* To a suspension of **1b** (225 mg, 0.67 mmol) in 25 ml of dry dioxane, an excess of freshly distilled cyclopentadiene (1.00 ml, 802 mg, 12.1 mmol) is added. After 8 h refluxing, the solvent is evaporated and the residue worked up and purified as described above: 56 mg (35%) of **9**, identical (IR, ^{1}H-NMR) to the product obtained from the condensation of **3**, paraformaldehyde, and cyclopentadiene.

7. *Reaction of 3,3'-Heptylidene-4,4'-dihydroxybis[2*H*-1-benzopyran-2-one]* (**1d**) *and 4-Hydroxy-7-methoxy-2*H*-1-benzopyran-2-one.* To a soln. of **1d** (100 mg, 0.23 mmol) in EtOH (20 ml), an excess of 4-hydroxy-7-methoxy-2*H*-1-benzopyran-2-one (300 mg, 1.56 mmol, 6.8 mol-equiv.) is added and refluxed overnight. After evaporation

the residue is dissolved in CH_2Cl_2 and washed several times with sat. $NaHCO_3$ soln. and then with brine. The oily residue is purified by CC (10 g of silica gel, hexane/AcOEt 3:7): 85 mg (77%) of *3,3'-heptylidene-4,4'-dihydroxy-7,7'-dimethoxybis[2H-1-benzopyran-2-one]* (**6**), identical to a sample prepared by condensation of heptanal and 4-hydroxy-7-methoxy-2*H*-1-benzopyran-2-one. Oil. UV (EtOH): 320, 306, 283, 210. IR (liq.): 1660, 1610, 1560, 1290, 1250, 1160, 800. ^{1}H-NMR (270 MHz, $CDCl_3$): 11.92 (br. *s*, 2 OH); 7.86 (br. *d*, *J* = 8.8, 2 H); 6.88 (br. *d*, *J* = 9.2, 2 H); 6.80 (br. *s*, 2 H); 4.39 (*t*, *J* = 7.6, 1 H); 3.86 (*s*, 2 MeO); 2.32 (br. *q*, *J* = 7.6, 2 H); 1.27–1.20 (overlapped signals, 8 H); 0.82 (*t*, *J* = 6.2, 3 H).

8. *Reaction of* **1d** *and 1H-Indole*. 8.1. *In Refluxing EtOH*. A soln. of **1d** (500 mg, 1.19 mmol) and 1*H*-indole (1.39 g, 11.9 mmol, 10 mol-equiv.) in 40 ml of EtOH is refluxed overnight. After addition of CH_2Cl_2, the soln. is washed 3 times with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated. The oily residue is purified by CC (20 g of silica gel, hexane/AcOEt 8:2): 278 mg (71%) of **7** and 35 mg (7.8%) of **8**.

8.2. *In EtOH at r.t.* A soln. of **1d** (10 mg, 0.24 mmol) and 1*H*-indole (278 mg, 2.4 mmol, 10 mol-equiv.) is stirred at r.t. for 70 h. Workup as described in *8.1:* 25 mg (31%) of **7** and 5 mg (5.6%) of **8**.

3,3'-Heptylidenebis[1H-indole] (**7**): Oil. UV (EtOH): 290, 283, 224. IR (liq.): 3400, 1710, 1615, 1450, 1415, 1335, 1220, 1090, 1010, 740. ^{1}H-NMR (270 MHz, $CDCl_3$): 7.87 (br. *s*, =NH); 7.59 (br. *d*, *J* = 7.8, 2 H); 7.32 (br. *d*, *J* = 7.9, 2 H); 7.14 (br. *t*, *J* = 7.8, 2 H); 7.05 (br. *t*, *J* = 7.9, 2 H); 6.98 (br. *s*, =NH); 4.47 (*t*, *J* = 7.6, 1 H); 2.20 (*q*, *J* = 7.6, 2 H); 1.54–1.23 (overlapped signals, 8 H); 0.84 (*t*, *J* = 6.5, 3 H). ^{13}C-NMR (67.5 MHz, $CDCl_3$): 136.48 (*s*); 127.06 (*s*); 121.59 (*d*); 121.30 (*d*); 120.61 (*s*); 119.74 (*d*); 118.87 (*d*); 110.97 (*d*); 35.79 (*d*); 33.90 (*t*); 31.78 (*t*); 29.38 (*t*); 28.23 (*t*); 22.62 (*t*); 14.03 (*q*). EI-MS: 330 (25, M^+, $C_{23}H_{26}N_2^+$), 245 (100), 214 (42).

4-Hydroxy-3-[1-(1H-indol-3-yl)heptyl]-2H-1-benzopyran-2-one (**8**): Oil. UV (EtOH): 310, 290, 283, 223. IR (liq.): 3480, 3020, 1690, 1630, 1220, 760. ^{1}H-NMR (270 MHz, $CDCl_3$): 8.34 (br. *s*, D_2O-exchangeable, 1 H); 7.51–6.93 (overlapped signals, 9 H); 4.71 (*t*, *J* = 7.6, 1 H); 2.02 (*q*, *J* = 7.6, 2 H); 1.54–1.13 (overlapped signals, 8 H); 0.78 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (67.5 MHz, $CDCl_3$): 163.68 (*s*); 160.99 (*s*); 152.52 (*s*); 137.09 (*s*); 131.11 (*d*); 126.62 (*s*); 123.57 (*d*); 122.73 (*d*); 120.62 (*d*); 120.26 (*d*); 119.75 (*s*); 119.03 (*s*); 117.03 (*d*); 116.22 (*d*); 116.00 (*d*); 111.33 (*d*); 107.44 (*s*); 32.69 (*d*); 32.07 (*t*); 31.66 (*t*); 29.48 (*t*); 27.45 (*t*); 22.57 (*t*); 13.98 (*q*).

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