68. The Chemistry of Coumarin Derivatives

Part 5[1])

Unusual Course of the Reaction of 4-Hydroxycoumarin and Aliphatic Aldehydes

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(6.I.93)

The reaction of 4-hydroxycoumarin and certain aliphatic aldehydes affords 1:1 or complex 2:2 adducts besides (or in place) of the expected 2:1 bis(coumarin) adducts. Reaction with heptanal, cyclohexanecarbaldehyde, and pivalaldehyde are reported as representative. The structure of the reaction products was established by spectroscopical techniques, including X-ray analysis, and their formation was mechanistically rationalized. Some of the 1:1 adducts are synthetically useful for the preparation of 3-alkyl-4-hydroxycoumarins.

Introduction. – The formation of alkylidenebis(4-hydroxycoumarins) (= 3,3′-alkylidene-4,4′-dihydroxybis(coumarins)) by condensation of 4-hydroxycoumarin (= 4-hydroxy-2*H*-1-benzopyran-2-one) and aldehydes was first described by *Anschütz* at the beginning of the century [2] and thoroughly investigated by *Link* and coworkers in the course of studies on the haemorrhagic agent of fermented sweet clover [3]. We became interested in this reaction after discovering that alkylidenebis(4-hydroxycoumarins) can be reductively fragmented to 3-alkyl-4-hyroxycoumarins by $NaBH_3CN$ [4]. This led to the development of a two-step procedure (reaction with aldehydes followed by reductive cleavage) for the alkylation of 4-hydroxycoumarin, an ambident nucleophile whose reaction with halides is of limited utility on account of regioselectivity and polyalkylation problems [4]. When this protocol was applied to the preparation of some long-chain 3-alkyl-4-hydroxycoumarins, we noticed that the condensation of 4-hydroxycoumarin and aliphatic aldehydes gave consistently lower yields with increasing length of the alkyl chain. A similar trend had already been observed by *Link* [3] and others [5]. The condensation is routinely carried out stirring an ethanolic solution of 4-hydroxycoumarin and the aldehyde at room [4] or at refluxing temperature [3], and the product is obtained by filtration of the reaction mixture. Lower yields might, thus, simply reflect a higher solubility of the bis(coumarin) adducts. However, when the mother liquors were inspected, some new compounds could also be detected.

[1]) Part 4: [1].

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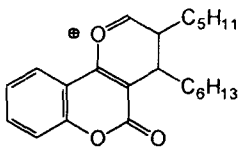
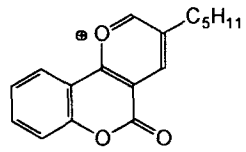
Results and Discussion. – For the isolation and characterization of these additional products, the condensation of heptanal and 4-hydroxycoumarin was investigated as representative. After separation of the bis(coumarin) adduct **1** (28%), the mother liquors were chromatographed to give, besides further amounts of **1** (final yield 52%), two additional products **2** and **3** in 16 and 9% yield, respectively (*Scheme 1*). Mass spectroscopy suggested that these compounds are 'tetrameric', and NMR analysis showed indeed the presence of two non-isochronous coumarin and alkyl moieties. Extensive NMR experiments allowed to assign a pyrano[3,2-*c*]coumarin structure to **2** and a furano[3,2-*c*]coumarin structure to **3**.

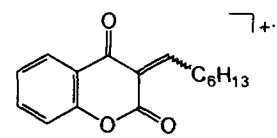
High-resolution (HR) MS showed the molecular formula $C_{32}H_{36}O_6$ for **2**, corresponding to two heptylidenechromandione units **A** (see *Scheme 1*). Other relevant ions were observed at *m/z* 354 (22%, *a*), 269 (85%, *b*), 258 (71%, *c*), 187 (65%, *d*), 175 (98%, *e*), and 121 (100%, *f*). The fragmentation patterns $M^{+\cdot} \rightarrow 354$ (*McLafferty* rearrangement) $354 \rightarrow 269$ ($-C_6H_{13}$; β-fission) and $M^{+\cdot} \rightarrow 258$ (*retro-Diels-Alder* fragmentation) were ascertained by linked-scan spectra at constant *B*/*E*. The $M^{+\cdot} \rightarrow 258$ fragmentation indicated that **2** can be regarded as the cyclocondensation product of units **A** and **B** [6].



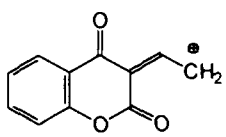
a, m/z 354



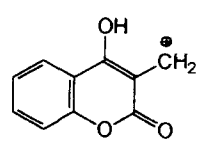
b, m/z 269



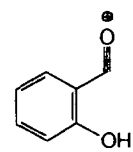
c, m/z 258



d, m/z 187



e, m/z 175



f, m/z 121

In addition to two sets (4 H each) of aromatic protons, the ^{1}H-NMR spectrum (*Table 1*) of **2** contained as relevant signals 1 exchangeable H (br. *s* at 8.66 ppm), 3 CH (5.70 (*d*, J = 2 Hz), 2.83 (*dd*, J = 9 and 2 Hz), 2.4 ppm (*d*, J = 9 Hz)) and 2*d* in the high-field region (0.90 and 0.76 ppm), corresponding to 2 different Me's at the end of alkyl chains. The ^{13}C-NMR spectrum showed only 28 signals for the 32 C-atoms, since some signals (2 aliphatic CH_2, 1 aromatic CH, and 1 quaternary C) turned out to be isochronous with signals of different C-atoms of the same multiplicity (*Table 1*). The procedure for the assignment of the NMR spectra involved: *i*) assignment of the ^{1}H-NMR using homonuclear *Hartmann-Hann* (HOHAHA) [7], COSY, and NOESY [8] methods, *ii*) correlation *via* ^1J(C,H) using ^{1}H-detected heteronuclear multiple-quantum coherence (HMQC) [9] to provide the ^{13}C-assignment of the protonated C-atoms, and *iii*) correlation *via* ^2J(C,H) and ^3J(C,H) using heteronuclear multiple-bond correlation (HMBC) [10] to assign non-protonated C-atoms and verify the consistency of the ^{1}H- and ^{13}C-assignments made by the above mentioned techniques. The ^{1}H- and ^{13}C-NMR data as well as the diagnostic correlations

Scheme 1. *Condensation of 4-Hydroxycoumarin and Heptanal*

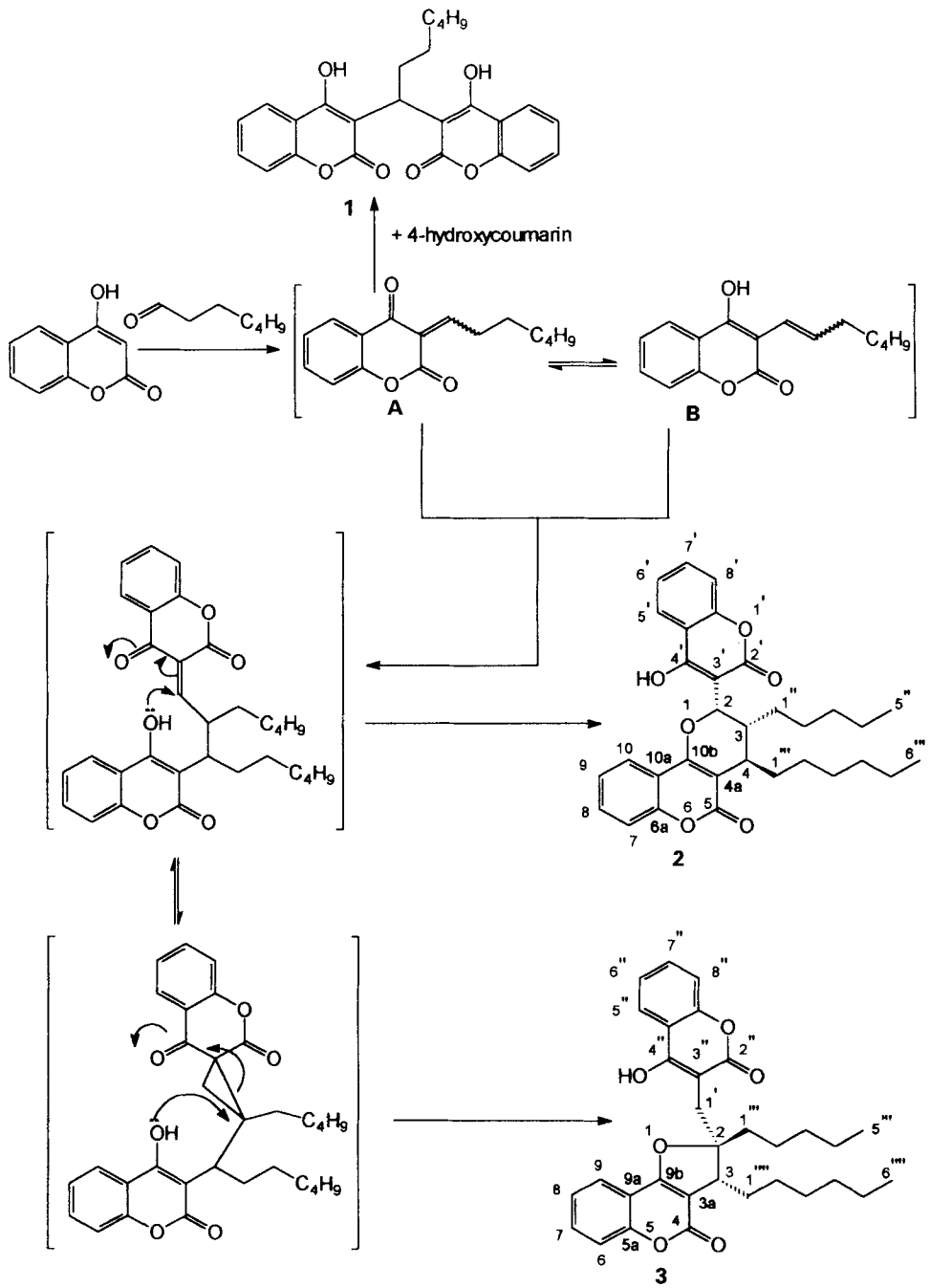


Table 1. *^{13}C- and ^{1}H-NMR Data of* **2**

	$\delta(^{13}C)$ [ppm][a]	$\delta(^{1}H)$ [ppm][b]	CH Long-range correlation (HMBC)
H–C(2)	78.8 (*d*)	5.70 (*d*, *J* = 2)	*H*–C(4)
H–C(3)	36.5 (*d*)	2.40 (*d*, *J* = 9)	–
H–C(4)	34.4 (*d*)	2.83 (*dd*, *J* = 9, 2)	–
H–C(4a)	107.0 (*s*)	–	*H*–C(3), *H*–C(4)
H–C(5)	162.3 (*s*)	–	–
H–C(6a)	152.2 (*s*)	–	*H*–C(8), *H*–C(10)
H–C(7)	117.0 (*d*)	7.36 (*dd*, *J* = 8, 1.5)	*H*–C(9)
H–C(8)	132.0 (*d*)	7.56 (*dt*, *J* = 8, 1.5)	*H*–C(10)
H–C(9), H–C(6′)	124.3 (*d*)	7.33 (*dt*, *J* = 8, 1.5)	*H*–C(7), *H*–C(8′)
H–C(10)	121.3 (*d*)	7.66 (*dd*, *J* = 8, 1.5)	*H*–C(8), *H*–C(9)
H–C(10a)	115.4 (*s*)	–	*H*–C(7)
H–C(10b)	156.9 (*s*)	–	*H*–C(10)
H–C(2′)	161.0 (*s*)	–	*H*–C(2)
H–C(3′)	99.8 (*s*)	–	*H*–C(2), OH
H–C(4′)	162.3 (*s*)	–	*H*–C(5′), *H*–C(2)
H–C(4′a)	114.6 (*s*)	–	*H*–C(8′), *H*–C(6′)
H–C(5′)	123.4 (*d*)	7.95 (*dd*, *J* = 8, 1.5)	–
H–C(7′)	132.7 (*d*)	7.61 (*dt*, *J* = 8, 1.5)	*H*–C(5′)
H–C(8′)	116.6 (*d*)	7.36 (*dd*, *J* = 8, 1.5)	–
H–C(8′a)	153.0 (*s*)	–	*H*–C(5′), *H*–C(7′)
CH_2(1″)	26.5 (*t*)	1.16 (*m*), 1.40 (*m*)	*H*–C(2)
CH_2(2″)	27.1 (*t*)	1.16 (*m*)	*H*–C(1″), *H*–C(3″)
CH_2(3″)	31.7 (*t*)	1.13 (*m*)	*H*–C(2″), *H*–C(4″)
CH_2(4″)	22.5 (*t*)	1.13 (*m*)	*H*–C(5″)
CH_3(5″)	13.9 (*q*)	0.76 (*t*, *J* = 6.9)	*H*–C(4″)
CH_2(1‴)	34.1 (*t*)	1.53 (*m*), 2.00 (*m*)	–
CH_2(2‴)	27.1 (*t*)	1.50 (*m*)	*H*–C(3‴)
CH_2(3‴)	29.0 (*t*)	1.43 (*m*)	–
CH_2(4‴)	31.7 (*t*)	1.43 (*m*)	–
CH_2(5‴)	22.6 (*t*)	1.40 (*m*)	*H*–C(6‴)
CH_3(6‴)	14.1 (*q*)	0.90 (*t*, *J* = 6.9)	*H*–C(5‴)

[a]) In $CDCl_3$ at 75.47 MHz.
[b]) In $CDCl_3$ at 300 MHz.

observed in the 2D-NMR experiments are collected in *Table 1*. *H*–C(2) could be easily recognized by its chemical shift and the correlation to the oxygenated C-atom at 78.8 ppm, and this assignment provided the starting point for the identification of the two other aliphatic CH groups. In the HMBC experiment, the signals of *H*–C(3) and *H*–C(4) were both coupled to C(4a); *H*–C(2) showed long-range couplings with two C-signals (C(2′) and C(3′)) and *H*–C(4) correlated with C(2). This established the presence of a pyranocoumarin structure with an additional coumarin moiety bound at C(2). The connectivity networks for the two side chains were observed in the HOHAHA spectrum and confirmed by long-range ^{1}H,^{13}C correlations. The relative configuration at the three contiguous stereocenters (C(2), C(3), C(4)) was established taking into account the coupling constant of the corresponding H-atoms and the results of NOESY experiments (NOE between H–C(2) and *H*–C(3)/H_b–C(1‴), between *H*–C(3) and *H*–C(2)/*H*–C(4) but not between *H*–C(2) and *H*–C(4)). The preferred conformation of dihydropyran derivatives is generally the half-chair, with bulky substituents on C(α) in pseudoequatorial orientation [11]. The NOESY spectrum showed that in **2**, H–C(2) and H–C(3) are *cis*, and thus in pseudoaxial and pseudoequatorial orientation, respectively. The NOE cross-peaks H–C(2)/H_b–C(1‴) and the presence of a ^{3}J(C,H) between C(2) and *H*–C(4) suggested a pseudoequatorial orientation for *H*–C(4) and thus a pseudoaxial orientation (*cis* to *H*–C(2)) for the alkyl chain at C(4). In a similar way, the pseudoaxial orientation for the alkyl chain at C(3) was cleary indicated by NOE correlations (*H*–C(2)/*H*–C(3) and *H*–C(4)/H_a–C(1″)) and the presence of a ^{3}J(C,H) between C(1″) and *H*–C(2)

Table 2. *^{13}C- and ^{1}H-NMR Data of* **3**

	$\delta(^{13}C)$ [ppm][a]	$\delta(^{1}H)$ [ppm][b]	C,H Long-range correlation (HMBC)
H–C(2)	102.3 (*s*)	–	$H_{a,b}$–C(1′), H–C(1‴), $H_{a,b}$–C(1⁗)
H–C(3)	46.3 (*d*)	3.48 (*dd*, *J* = 8, 4.8)	H–C(1‴), $H_{a,b}$–C(1⁗)
H–C(3a)	107.2 (*s*)	–	H–C(3), H–C(1⁗)
H–C(4)	162.2 (*s*)	–	–
H–C(5a)	154.7 (*s*)	–	H–C(6), H–C(7), H–C(9)
H–C(6)	117.2 (*d*)	7.41 (*dd*, *J* = 8, 1.5)	H–C(8)
H–C(7)	132.7 (*d*)[c]	7.62 (*dt*, *J* = 8, 1.5)	H–C(9)
H–C(8)	124.3 (*d*)[d]	7.35 (*dt*, *J* = 8, 1.5)	H–C(6)
H–C(9)	121.9 (*d*)	7.57 (*dd*, *J* = 8, 1.5)	H–C(7), H–C(8)
H–C(9a)	112.1 (*s*)	–	H–C(8)
H–C(9b)	160.2 (*s*)	–	H–C(9)
CH_2(1′)	30.1 (*t*)	3.06 (*d*, *J* = 15.5), 3.67 (*d*, *J* = 15.5)	H–C(1‴)
H–C(2″)	162.7 (*s*)	–	H_b–C(1′)
H–C(3″)	100.4 (*s*)	–	$H_{a,b}$–C(1′)
H–C(4″)	164.3 (*s*)	–	H–C(5″), $H_{a,b}$–C(1′)
H–C(4″a)	115.8 (*s*)	–	H–C(6″), H–C(8)
H–C(5″)	123.5 (*d*)	7.99 (*dd*, *J* = 8, 1.5)	H–C(6″), H–C(7″)
H–C(6″)	124.1 (*d*)[d]	7.37 (*dt*, *J* = 8, 1.5)	H–C(8″)
H–C(7″)	132.4 (*d*)[c]	7.60 (*dt*, *J* = 8, 1.5)	H–C(5″)
H–C(8″)	116.5 (*d*)	7.35 (*dd*, *J* = 8, 1.5)	H–C(6″)
H–C(8″a)	152.6 (*s*)	–	H–C(5″), H–C(7″), H–C(8″)
CH_2(1‴)	37.5 (*t*)	1.75 (*t*, *J* = 6.9)	H–C(3), H_a–C(1′)
CH_2(2‴)	22.6 (*t*)	1.53 (*m*)	$H_{a,b}$–C(1‴)
CH_2(3‴)	31.6 (*t*)	1.23 (*m*)	–
CH_2(4‴)	22.3 (*t*)	1.23 (*m*)	H–C(5‴)
CH_3(5‴)	13.9 (*q*)	0.79 (*t*, *J* = 6.9)	–
CH_2(1⁗)	28.8 (*t*)	a) 1.87 (*m*)	H–C(3), H–C(2⁗)
		b) 3.05 (*m*)	H–C(3), H–C(2⁗)
CH_2(2⁗)	28.3 (*t*)	1.58 (*m*)	$H_{a,b}$–C(1⁗)
CH_2(3⁗)	29.6 (*t*)	1.40 (*m*)	H–C(2⁗), H–C(4⁗)
CH_2(4⁗)	31.9 (*t*)	1.33 (*m*)	H–C(3⁗)
CH_2(5⁗)	22.6 (*t*)	1.33 (*m*)	H–C(6⁗)
CH_3(6⁗)	14.0 (*q*)	0.87 (*t*, *J* = 6.9)	H–C(5⁗)

[a]) In $CDCl_3$ at 75.47 MHz.
[b]) In $CDCl_3$ at 300 MHz.
[c])[d]) These assignments can be interchanged.

The HR-EI-MS of **3** showed a molecular ion corresponding to the formula $C_{32}H_{36}O_6$. The ^{13}C-NMR spectrum exhibited 11 sp^2 quaternary C-atoms, 8 sp^2 and 1 sp^3 CH, 9 sp^2 CH_2 (corresponding to 10-CH_2–), and 2 Me (*Table 2*). The ^{13}C-NMR spectrum was similar to that of **2**, the major differences being the presence of a CH_2 at 30.1 ppm and a quaternary C-atom at 102.3 ppm in place of 2 CH at 78.8 and 36.5 ppm. As to the ^{1}H-NMR spectra, the most striking difference between **2** and **3** was the presence in the latter of an *AB* system (3.67 and 3.06 ppm, ^{2}J = 15.5 Hz). Further information on the structural framework was obtained through a series of HMBC spectra (*Table 2*). The presence of long-range correlations between $H_{a,b}$–C(1′) and C(3″) and C(4″) of the 4-hydroxycoumarin subunit as well as with C(2) and C(1‴) of the dihydrofuran moiety connected these fragments together. The relative configuration was assessed by NOE data. In the NOESY spectrum, the correlation of $H_{a,b}$–C(1′) and both $H_{a,b}$–C(1⁗) and $H_{a,b}$–C(2⁗) established that these protons are located on the same side of the dihydrofuran ring, and suggested that the pentyl chain at C(2) and the hexyl chain at C(3) are *trans*-oriented. Further proof of structure **3** was obtained by single-crystal X-ray analysis [12], which fully supported the structure assigned by the NMR studies.

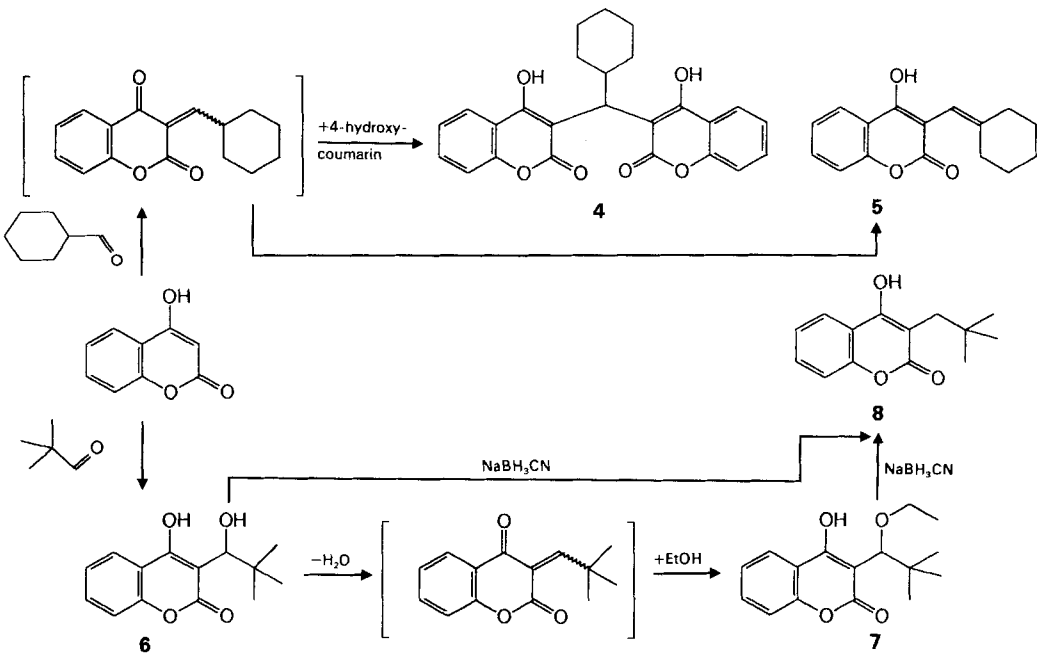
A possible rationalization for the formation of compounds **2** and **3** involves as a key step the tautomerization of the initial alkylidenechromandione 1:1 adduct **A** to a 3-vinyl-4-hydroxycoumarin **B**. This corresponds to a formal 'Umpolung' of the unsaturated system and generates a nucleophilic dienol capable to trap the electrophilic chromandione, thus establishing the basic 'tetrameric' framework of the adducts. Further intramolecular trapping of the newly generated chromandione system by the nucleophilic O-atom of the other coumarin part might eventually afford the polycyclic adducts, directly in the case of **2** or after isomerization to a spiro[chroman-cyclopropane]dione in the case of **3**. Although **2** and **3** bear stereocenters, both compounds were diastereoisomerically homogeneous; their configuration presumably corresponds to the most stable arrangement of the substituents at the dihydropyran or -furan ring. The pyranocoumarin adduct **2** might also be the result of a hetero-*Diels-Alder* reaction between the alkylidenechromandione and the vinylcoumarin intermediates. However, reactions of this type are stereospecific [13], and the configuration found in the adduct requires the presence of a *cis*-configurated 4-hydroxy-3-vinylcoumarin, the sterically more congested (allylic strain) isomer. Since β-substituted enals react with 4-hydroxycoumarin to give 1,2- and not 1,4-adducts [14], 2-pentylnon-2-enal (the crotonization product of heptanal) is most probably not involved in the formation of **2** and **3**.

The tautomerization of 3-alkylidenechroman-2,4-diones to hydroxy-3-vinylcoumarins has so far received little attention. However, a process of this type was successfully exploited in a biomimetic synthesis of the complex coumarin lycoseron [15], and precedents exist in the related system of triacetic acid lactone (= 4-hydroxy-6-methyl-2*H*-pyran-2-one) derivatives [16]. Further proof of this tautomerization came from the isolation of a 4-hydroxy-3-vinylcoumarin from the condensation of cyclohexanecarbaldehyde and 4-hydroxycoumarin (*vide infra*).

The formation of significant amounts of by-products was also observed with α-alkyl-substituted aldehydes, whereas bis(coumarin) adducts could not be obtained at all with α,α-dialkyl-substituted aldehydes. Thus, reaction of 4-hydroxycoumarin and cyclohexanecarbaldehyde afforded, besides the expected 2:1 adduct **4** (51%) also the vinylcoumarin **5** (13%), whereas with pivalaldehyde (= 2,2-dimethylpropanal), the reaction afforded the initial condensation product **6** (8%) and the *Michael* adduct **7** (53%) between its electrophilic dehydration product and ethanol (*Scheme 2*). The side-chain-hetero-substituted hydroxycoumarins **6** and **7** were smoothly reduced by $NaBH_3CN$ to 4-hydroxy-3-neopentylcoumarin (**8**), presumably *via* the same mechanism operating with alkylidenebis(4-hydroxycoumarins) (generation of an alkylidenechromandione and nucleophilic trapping by hydride) [4].

Conclusions. – The reaction of 4-hydroxycoumarin and saturated aldehydes affords reactive alkylidenechromandiones, whose fate depends on the starting aldehyde and the reaction conditions. In EtOH as a solvent, the very low solubility of most alkylidenebis(4-hydroxycoumarins) drives the reaction towards the formation of these intramolecularly H-bonded [17] 2:1 adducts. Increasing length of the alkyl chain leads to a certain solubility of the bis(coumarin) adducts, and alternative pathways involving alkylidenechromandione-vinylcoumarin tautomerization become operative. A similar effect takes also place in solvents where the bis(coumarin) adducts are soluble (DMSO, DMF). Alkyl substitution at C(α) of the aldehyde hinders attack to the intermediate alkyli-

Scheme 2. *Condensation of 4-Hydroxycoumarin with Cyclohexanecarbaldehyde and with Pivalaldehyde*



denechromandione by bulky nucleophiles such as 4-hydroxycoumarin and thus decreases or prevents completely the formation of the bis(coumarin) adducts.

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Experimental Part

General. See [4]. Moreover: ^{1}H- and ^{13}C-NMR: *Bruker-AC300* apparatus (300 and 75.47 MHz resp.). HR-EI-MS and constant-*B*/*E* MS: *VG-7070 EQ* instrument (*R* = 3000).

Condensation of 4-Hydroxycoumarin and Heptanal. To a soln. of 4-hydroxycoumarin (11.37 g, 70.2 mmol, 2 mol-equiv.) in EtOH (110 ml), heptanal (4.70 ml, 4.0 g, 35.1 mmol) was added and the mixture refluxed under N_2 for 5 days, during which a brown paste slowly separated from the soln. After cooling and removal of the liquid, the paste was triturated with hexane/Et_2O 1:1: 4.13 g (28%) of **1**. The combined mother liquors and EtOH soln. were evaporated to give a semisolid residue that was chromatographed (silica gel, hexane/AcOEt). Hexane/AcOEt 7:3 gave 4.7 g of **2**/**3** and hexane/AcOEt 3:7 further 3.54 g of **1** (total yield: 7.67 g, 52%). CC (silica gel, cyclohexane/AcOEt 9:1) of **2**/**3** gave **2** (2.90 g, 16%) and **3** (1.63 g, 9%).

When the reaction was carried out in DMF or DMSO (r.t.), the yield of **1** was low (*ca.* 5%), and several other compounds besides **2** and **3** were formed (TLC control). Purification of **2** and **3** from these complex mixtures was not successful.

(2R,3S*,4S*)-4-Hexyl-3,4-dihydro-2-(4'-hydroxy-2'-oxo-2'*H*-1'-benzopyran-3'-yl)-3-pentyl-2*H*,5*H*-pyrano[3,2-c][1]benzopyran-5-one* (**2**). M.p. 78–80° (Et_2O). UV (EtOH): 320, 302, 286, 270. IR (KBr): 3400, 1700,

1625, 1575, 1490, 1400, 1220, 1170, 1110, 1050, 940. EI-MS: 516 (20, M^+, $C_{32}H_{36}O_6^+$), 354 (22, *a*), 341 (50, *b*), 258 (71, *c*), 187 (65, *d*), 175 (98, *e*), 121 (100, *f*).

*(2*R*,3*R*)-3-Hexyl-2,3-dihydro-2-[(4'-hydroxy-2'-oxo-2'*H*-1'-benzopyran-3'-yl)methyl]-2-pentyl-4*H*-furo-[3,2-c][1]benzopyran-4-one* (**3**). M.p. 96–100° (Et_2O). UV (EtOH): 310, 285. IR (KBr): 3400, 1720, 1670, 1610, 1570, 1500, 1410, 1200, 1050, 910, 750. EI-MS: 516 (10, M^+, $C_{32}H_{36}O_6^+$), 498 (5), 341 (100), 269 (25), 127 (60), 175 (70), 121 (45).

Condensation of 4-Hydroxycoumarin and Cyclohexanecarbaldehyde. To a soln. of 4-hydroxycoumarin (10.0 g, 61.7 mmol, 2 mol-equiv.) in EtOH (100 ml), cylcohexanecarbaldehyde (3.71 ml, 3.46 g, 30.8 mmol) was added and the mixture refluxed for 2 days. After filtration of the bulky precipitate of **4** (6.05 g, 51%), the mother liquors were evaporated and chromatographed (silica gel (40 g), hexane/AcOEt). Hexane/AcOEt 1:1 gave **5** (985 mg, 12.9%) and further **4** (550 mg; overall yield: 6.55 g, 51%).

*3,3'-(Cyclohexylmethylidene)-4,4'-dihydroxybis[2*H*-1-benzopyran-2-one]* (**4**). M.p. 201° (acetone/Et_2O). UV (EtOH): 323, 306, 285, 270. IR (KBr): 3300–2600 (br.), 1660, 1620, 1605, 1570, 1500, 1350, 1325, 810, 760. ^{1}H-NMR ($CDCl_3$): 12.01 (br. *s*, OH); 11.11 (br. *s*, OH); 8.01 (*d*, J = 8.3, 2 H); 7.53 (*t*, J = 7.9, 2 H); 7.37–7.30 (*m*, 4 H); 4.12 (*d*, J = 11.2, 1 H); 2.94 (*m*, 1 H); 1.70–0.82 (*m*, 10 H). EI-MS: no M^+ ($C_{25}H_{22}O_6^+$) at 418, 256 (30), 175 (100), 121 (95), 119 (45).

*3-(Cyclohexylidenemethyl)-4-hydroxy-2*H*-1-benzopyran-2-one* (**5**). M.p. 125° (dec.; acetone/Et_2O). UV (EtOH): 320, 300 (sh), 260 (sh), 220. IR (KBr): 3300–2600 (br.), 1760, 1670, 1600, 1560, 1450, 1290, 1270, 1060, 760. ^{1}H-NMR ($CDCl_3$): 7.85 (*d*, J = 7.6, 1 H); 7.54 (*t*, J = 7.2, 1 H); *ca.* 7.28 (*m*, 2 H); 6.38 (br. *s*, OH); 5.82 (br. *s*, 1 H); 2.36 (*t*, J = 6.1, 2 H); 2.09 (*t*, J = 6.1, 2 H); 1.69–1.58 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 162.3 (*s*); 158.4 (*s*); 152.6 (*s*); 150.8 (*s*); 131.9 (*d*); 123.8 (*d*); 123.3 (*d*); 116.4 (*d*); 114.6 (*s*); 109.7 (*d*); 102.5 (*s*); 36.6 (*t*), 30.6 (*t*); 28.2 (*t*); 27.5 (*t*); 26.1 (*t*). EI-MS: 256 (60, M^+, $C_{16}H_{16}O_3^+$), 175 (100), 162 (30), 121 (88), 81 (38).

Reaction of 4-Hydroxycoumarin and Pivalaldehyde. To a soln. of 4-hydroxycoumarin (5.0 g, 3.08 mmol, 2 mol-equiv.) in EtOH (50 ml), pivalaldehyde (1.70 ml, 1.32 g, 15.4 mmol) was added and the mixture refluxed for 2 days, during which no precipitate was formed. After removal of the solvent, the residue was chromatographed (silica gel (50 g), hexane/AcOEt 1:1): **7** (2.250 g, 53%) and **6** (306 mg, 8.0%).

*4-Hydroxy-3-(1-hydroxy-2,2-dimethylpropyl)-2*H*-1-benzopyran-2-one* (**6**). M.p. 165–170° (dec.; Et_2O). UV (EtOH): 320, 307, 285, 270. IR (KBr): 3500–2600 (br.), 3500, 3250, 1660, 1620, 1610, 1570, 1370, 1315, 950, 770, 755. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.82 (*d*, J = 8.3, 1 H); 7.65 (*t*, J = 8.0, 1 H); 7.40 (*m*, 2 H); 4.70 (*s*, 1 H); 0.94 (*s*, 9 H). ^{13}C-NMR ((D_6)DMSO): 163.4 (*s*); 161.5 (*s*); 152.5 (*s*); 132.3 (*d*); 124.0 (*d*); 122.6 (*d*); 116.1 (*d*); 115.7 (*s*); 102.7 (*s*); 76.4 (*d*); 38.0 (*s*); 25.7 (*q*). EI-MS: no M^+ ($C_{14}H_{16}O_4^+$) at 248, 230 (25), 215 (90), 191 (32), 173 (74), 121 (100).

*3-(1-Ethoxy-2,2-dimethylpropyl)-4-hydroxy-2*H*-1-benzopyran-2-one* (**7**). M.p. 72–74° (hexane/Et_2O). UV (EtOH): 320, 306, 283, 270. IR (KBr): 3300–2700 (br.), 1705, 1635, 1570, 1290, 1060, 945, 760. ^{1}H-NMR ($CDCl_3$): 7.83 (*d*, J = 8.3, 1 H); 7.46 (*t*, J = 8.2, 1 H); 7.28 (*m*, 2 H); 4.49 (*s*, 1 H); 3.62 (*m*, 2 H); 1.23 (*t*, J = 6.2, 3 H); 0.97 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$): 163.5 (*s*); 162.6 (*s*); 153.0 (*s*); 132.0 (*d*); 123.6 (*d*); 122.9 (*d*); 116.2 (*d*); 115.7 (*s*); 100.2 (*s*); 86.2 (*d*); 66.7 (*t*); 38.2 (*s*); 25.8 (*q*); 14.6 (*q*). EI-MS: 276 (2, M^+, $C_{16}H_{20}O_4^+$), 230 (15), 219 (75), 191 (100), 173 (24), 121 (77).

*4-Hydroxy-3-(2,2-dimethylpropyl)-2*H*-1-benzopyran-2-one* (**8**). To a soln. of **7** (513 mg, 1.86 mmol) in MeOH (25 ml), an excess $NaBH_3CN$ (233 mg, 3.71 mmol) was added and the soln. refluxed for 40 min. The solvent was then removed on a steam bath (hood!) and sat. NH_4Cl soln. added to the residue. The mixture was extracted with AcOEt and the org. phase washed with brine, filtered, and evaporated. The yellowish powder obtained in this way was washed with hexane/Et_2O 1:1: **8** (244 mg, 56%). White powder. M.p. 208–211° (EtOH/H_2O). UV (EtOH): 320, 305, 282, 270. IR (KBr): 3300–2700 (br.), 1670, 1610, 1570, 1195, 1075, 920, 765. ^{1}H-NMR ($CDCl_3$): 7.80 (*d*, J = 8.3, 1 H); 7.52 (*t*, J = 8.2, 1 H); 7.28 (*m*, 2 H); 2.54 (*s*, 2 H); 1.03 (*s*, 9 H). EI-MS: 232 (10, M^+, $C_{14}H_{16}O_3^+$), 191 (80), 173 (60), 121 (100).

Starting from **6**, **8** was obtained analogously in 42% yield.

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