Synthesis and Structure of 1-Substituted Benzopyrano-[4',3'-*c*]benzo[3",4"-*f*]-2,8-dioxabicyclo[3.3.1]nonane

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Z. Naturforsch. **61b,** 207 – 212 (2006); received August 17, 2005

The base catalyzed condensation reaction between 4-hydroxycoumarin and 3-acetylcoumarin (3-benzoylcoumarin) in water at reflux led to the formation of 1-methyl (1-phenyl)-benzopyrano[4',3'-*c*]-benzo[3",4"-*f*]-2,8-dioxabicyclo[3.3.1]nonane (**2a, b**) as final products. When 4-hydroxycoumarin and 3-acetylcoumarin reacted in a glacial acetic acid in the presence of potassium acetate the final product was 7-[3-acetyl-2-oxo-3,4-dihydro-2*H*-[1]benzopyran-4-yl]methyl-6*H*,14*H*,14b*H*-bis-([1]benzopyrano)[4,3-*b*:4',3'-*d*]pyran-6,14-dione (**4**). 4-Hydroxycoumarin and 4-(5-bromo-2-hydroxyphenyl)-3-buten-2-one were condensed in water at reflux and 1-methylcoumarino-[4',3'-*c*]-bromobenzo[3",4"-*f*]-2,8-dioxabicyclo[3.3.1]nonane was a final product (**3**).

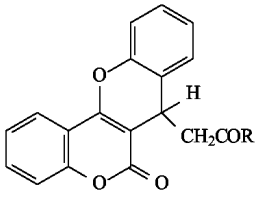
Key words: 4-Hydroxycoumarin, 3-Acetylcoumarin, Dioxabicyclononanes, Benzopyranopyrandione

Introduction

4-Hydroxycoumarin derivatives are of interest because of their anticoagulant [1 – 3], spasmolytic [4, 5], and rodenticidal [6 – 9] activities. Some coumarin derivatives are known for their antifungal and anti-HIV activities [10, 11]. They are also extensively used as analytical reagents [12 – 14]. The most widely used antithrombotic in the USA and Canada is racemic sodium Warfarin. All compounds of this group inhibit vitamin K 2,3-epoxide reductase.

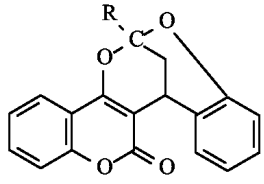
Ikawa *et al.* [15] have established that when α,β-unsaturated ketones derived from salicylaldehyde are condensed with 4-hydroxycoumarin, the Michael condensation products undergo spontaneous dehydration to give products with high melting points, which are insoluble in alkali and have low solubility in ethanol. The products, according to the authors, are 6-oxo-7-substituted-6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]-benzopyrans (**1**).

Porter and Trager [16, 17] have established in 1977 that the base catalyzed condensation reaction between 4-hydroxycoumarin and 2-hydroxybenzylidenacetone yields 6-methyl-6,12-methano-*6H,12H,13H*-[1]benzopyrano[4,3-*d*][1,3]benzodioxocin-13-one (**2a**) as a final product. An analogous structure was described by



1a: R = CH_3

1b: R = Ph



2 a: R = CH_3

2 b: R = Ph

Jurd in 1981 [18]. Later Ruggiero and Valente [19, 20] proved the structure by means of X-ray crystal structure analysis. Abd El-Rahman *et al.* [21] synthesized similar benzodioxocinone derivatives by condensation of salicylidenacetone and hydroxyfurobenzopyran.

We now report a new synthesis for this class of compounds. Instead of 2-hydroxybenzylidenacetone we used 3-acetylcoumarin and 3-benzoylcoumarin and by reaction of Michael addition we synthesized the same benzodioxocinones.

Results and Discussion

Nearly ten years ago we investigated the interaction between 4-hydroxycoumarin and 3-acetylcoumarin or

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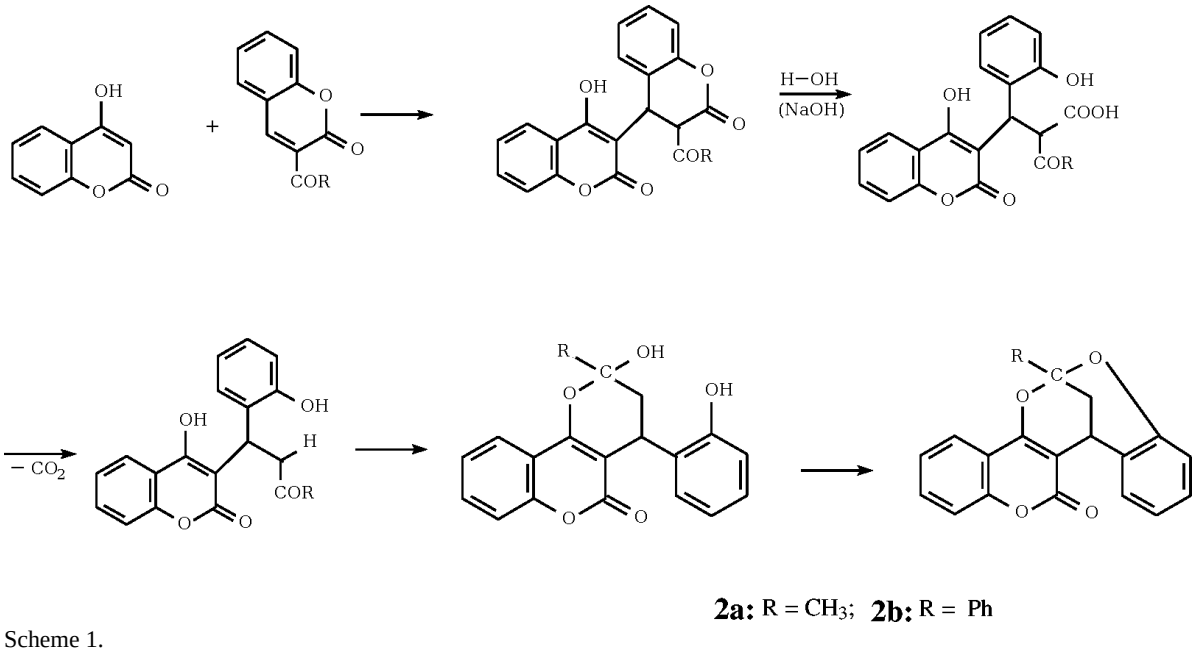


2a: R = CH_3; **2b:** R = Ph

Scheme 1.

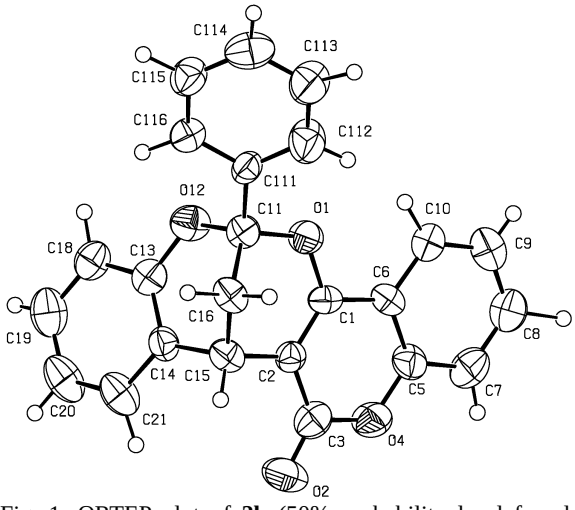


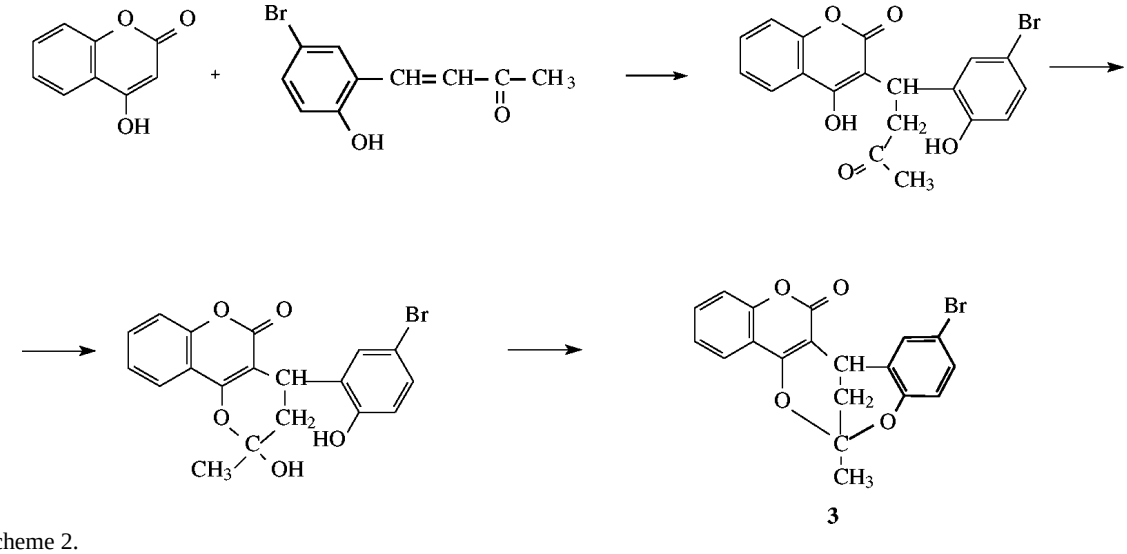
Fig. 1. ORTEP plot of **2b** (50% probability level for ellipsoids of thermal vibration). Bond lengths [pm]: C1–O1 136.6(5), C1–C2 133.8(7), C2–C15 149.8(8), C15–C14 152.4(7), C14–C13 138.3(7), C13–O12 137.6(6), C11–O12 144.9(6).

3-benzoylcoumarin in water and an equimolar quantity of sodium hydroxide at reflux. On the basis of elemental analyses, IR, ^{1}H NMR and mass spectral data we postulated similar to Ikawa *et al*. [15], that the product had the structure of **1a** [22].

This assumption was wrong. In fact only product **2** was formed. An intramolecular interaction between the carbonyl group of the side chain and the hydroxyl group of 4-hydroxycoumarin took place and a semi-ketal was formed. The semi-ketal dehydrated spontaneously and the final product was formed. Products **1** and **2** are isomers (they have the same molecular formula). The data of X-ray crystal structure analyses were a proof that product **2** was formed and not product **1**.

The constitution of the dioxabicyclononanes can be established also on the basis of the IR spectra. Coumarin carbonyls are expected to absorb at approximately 1720 cm^{-1}. The observed carbonyl stretch is found at 1703 cm^{-1} and, therefore, all data strongly suggest that the structure of coumarino-2,8-dioxabicyclo[3.3.1]nonane (**2a, b**) must be assigned to the products [16].

The insolubility of the condensation product in dilute alkali is an indication that the hydroxyl group of the 4-hydroxycoumarin fragments must have been modified during the course of the reaction and that an intramolecular coumarin ketal has been formed (Scheme 1). In the ^{1}H NMR spectrum signals are observed at $\delta = 1.98$ (methyl) and $\delta = 2.23$ (methylene, $^3J = 3$ Hz). The magnitude of the observed vicinal coupling is consistent with structure **2** since both methano protons are constrained to be gauche to the benzylic proton. Similar conclusions have already been made by Porter and Trager [16]. The constitution of **2b** has fi-



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Scheme 2.

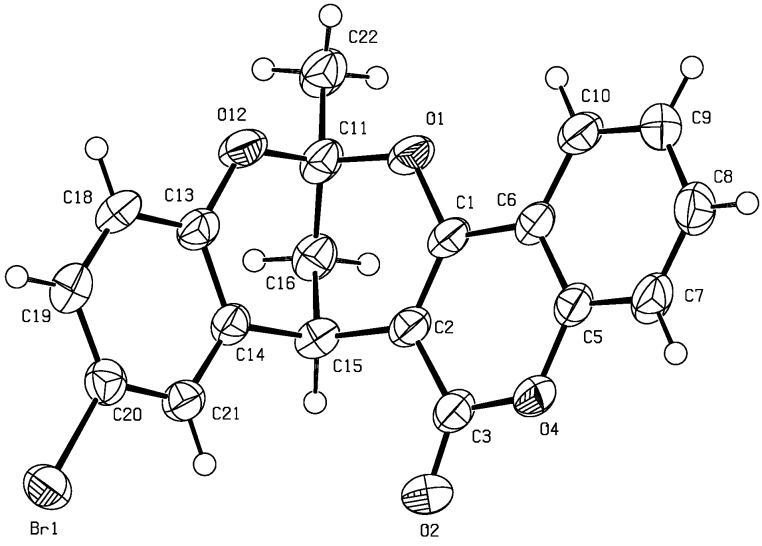


Fig. 2. ORTEP plot of **3** (50% probability level for ellipsoids of thermal vibration). Bond lengths [pm]: C1–O1 134.5(4), C1–C2 134.7(4), C2–C15 151.1(5), C15–C14 151.4(4), C14–C13 139.9(4), C13–O12 138.0(4), C11–O12 142.8(4), C20–Br1 190.5(4).

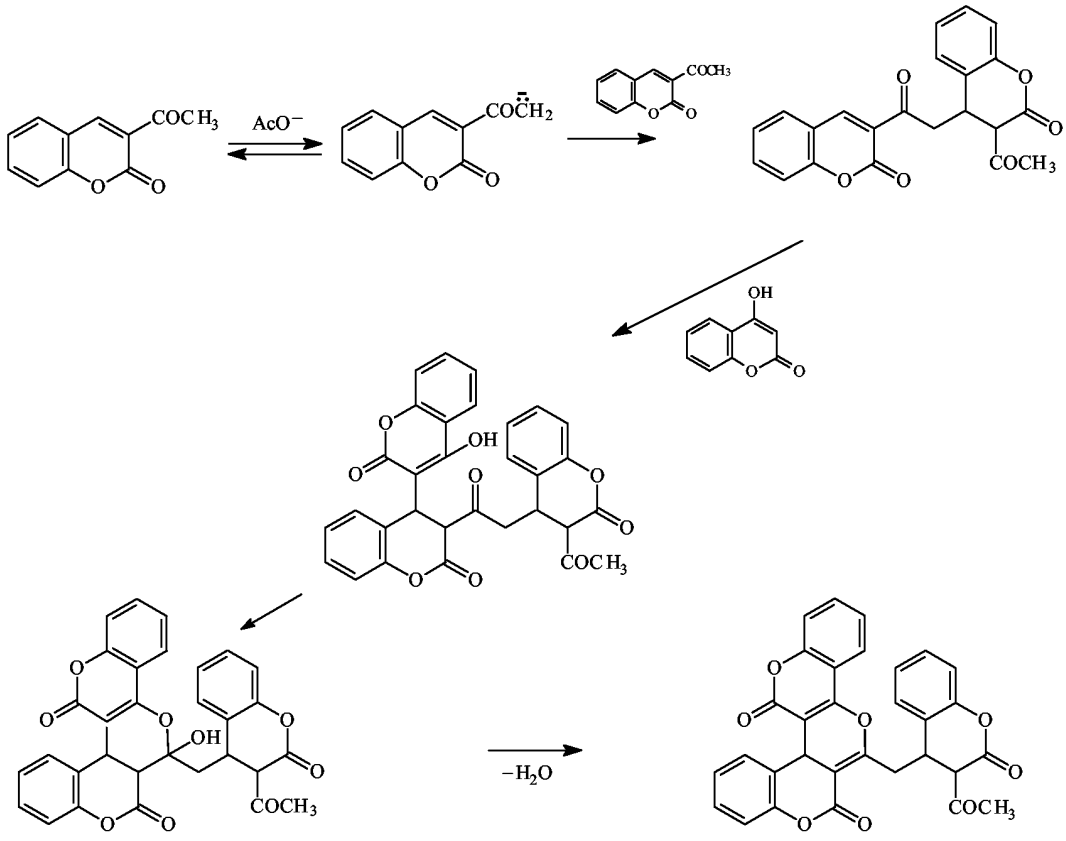
nally been established beyond doubt by an X-ray crystal structure determination (Fig. 1).

The interaction between 4-hydroxycoumarin and 4-(5-bromo-2-hydroxyphenyl)-3-buten-2-one leads to the formation of a new product, 1-methylcoumarino-[4',3'-*c*]bromobenzo[3",4"-*f*]-2 ,8-dioxabicyclo [3.3.1]nonane (**3**) (Scheme 2). The constitution was confirmed by a crystal structure determination (Fig. 2).

When the condensation process between 4-hydroxycoumarin and 3-acetylcoumarin at a molar ratio of 1:1 was carried out in glacial acetic acid and in the presence of potassium acetate (instead of water and an equimolar quantity of sodium hydroxide), the final product was 7-[3-acetyl-2-oxo-3,4-dihydro-2*H*-[1]benzopyran-4-yl]methyl-6*H*,14*H*-14b*H*-bis-[1]benzopyrano-[4,3-*b*:4',3'-*d*]pyran-6,14-dione (**4**) (Scheme 3). The elemental analysis confirmed the molecular formula $C_{31}H_{20}O_8$. IR and ^{1}H NMR data confirmed the structure of the new product.

Crystal Structure

The crystallographic data are presented in Table 1. Compound **2b** crystallized in the orthorhom-



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Scheme 3.

bic space group $Pna2_1$. The molecular structure is shown in Fig. 1. The two dihydropyran rings composed of C1/C2/C15/C16/C11/O1 and C13/C14/C15/C16/C11/O12 are constrained to a diaxial configuration. The dihedral angle between these two hydropyran rings is 69.7° (0.2). Both rings exhibit half-chair conformation. The bond lengths C11-O12 (144.9(6) pm) and C11-O1 (144.1(6) pm) are very similar.

The crystal system of **3** is monoclinic, the space group is $P2_1/c$. The molecular structure is shown in Fig. 2. The structure shows the same characteristics as structure **2b**. All data are in good agreement with the products described by Ruggiero *et al.* [19].

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 284360 (**2b**) and CCDC 284361 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB 1EZ, UK (Fax:(+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)

Experimental Section

Chemicals were reagent grade and were purchased from Fluka. Melting points were measured on a Boetius hot plate microscope (Germany) and are uncorrected. IR spectra (nujol) were recorded on an IR-spectrometer FTIR-8101M Shimadzu. ^{1}H NMR spectra were recorded at ambient temperature on a Bruker 250 WM (250 MHz) spectrometer in [D_6]-acetone. Chemical shifts are given in ppm (σ) relative to TMS used as an internal standard. Mass spectra were recorded on a Jeol JMS D 300 double focusing mass spectrometer coupled to a JMA 2000 data system. The compounds were introduced by direct inlet probe, heated from 50 °C to 400 °C at a rate of 100°/min. The ionization current was 300 mA, the accelerating voltage 3 kV and the chamber temperature 150 °C. TLC was performed on precoated

Table 1. Crystallographic data for **2b** and **3**.

	2b	**3**
Formula	$C_{24}H_{16}O_4$	$C_{19}H_{13}BrO_4$
Molecular mass [g/mol]	368.37	385.20
Temperature [K]	273	213
Radiation	Mo-K_α	Cu-K_α
Crystal system	orthorhombic	monoclinic
Space group	$Pna2_1$	$P2_1/c$
Unit cell dimension [pm, °]	$a = 757.35(14)$	946.26(16)
	$b = 1965.8(4)$	2245.8(3)
	$c = 1208.06(15)$	775.8(9)
	$\beta = 90$	111.47(13)
Volume [10^6pm^3]	1798.5(5)	1534.2(19)
Number of formula units, Z	4	4
Absorption coefficient μ [mm^{-1}]	0.093	3.841
Theta range [°]	3.34 – 30.95	5.02 – 65.04
Largest peak and hole [pm · 10^{-6}]	0.18/ – 0.21	1.13/ – 0.62
Reflections collected	5675	3107
Reflections observed $I > 2(\sigma)$	1445	2235
Parameters	317	218
GOOF	0.893	1.066
Absorption correction	DIFABS	none
Transmission T_{max}/T_{min}	0.604/0.133	
$R_1[I > 2\sigma(I)]$	0.0737	0.0417
R_2 [all data]	0.1084	0.0464

plates Kieselgel 60 F_{254} Merck (Germany) with layer thickness 0.25 mm and UV detection (254 nm). Yields of TLC-homogeneous isolated products are given. The analyses indicated by the symbols of the elements were within ±0.3% of the theoretical values.

*1-Methylcoumarino-[4',3'-c]benzo[3",4"-f]-2,8-dioxabicyclo[3.3.1]nonane (***2a***)*

4-Hydroxycoumarin (1.62 g, 10 mmol) was treated with 3-acetylcoumarin (1.88 g, 10 mmol) and a solution of NaOH (0.4 g, 10 mmol) in 30 ml of water. The reaction mixture was heated at reflux and stirred for 20 h. CO_2 was liberated during the reaction. The reaction was monitored by TLC. The crude product was recrystallized from ethyl acetate. Yield 1.78 g (58%). M. p. 263 °C (dec.), $R_f = 0.74$ (toluene : chloroform : acetone = 8:8:1). – IR (KBr): $\nu = 1703$, 1638, 1615, 1578, 1150 cm^{-1}. – ^{1}H NMR ($CDCl_3$): $\delta = 2.00$ s (3H), 2.28 d (2H), 4.31 t (1 H), 6.8 – 7.9 m (8 H – arom.). – $C_{19}H_{14}O_4$ (306.3): calcd. C 74.51, H 4.58; found C 74.65, H 4.71.

*1-Phenylcoumarino-[4',3'-c]benzo[3",4"-f]-2,8-dioxabicyclo[3.3.1]nonane (***2b***)*

To a solution of 3-benzoylcoumarin (2.5 g, 10 mmol) and NaOH (0.4 g, 10 mmol) in water (30 ml) was added 4-hydroxycoumarin (1.62 g, 10 mmol), and the reaction mixture was boiled at reflux for 15 h. CO_2 was liberated during the reaction. There was a pH change of the reaction medium, so extra NaOH (0.4 g, 10 mmol) was added and as a result the pH remained alkaline. After cooling, the reaction mixture was acidified with diluted sulfuric acid and a brown heavy residue was separated. The aqueous phase was separated and the resin-like residue was dissolved in dioxane. After addition of water to the dioxane solution, white crystals were separated and washed with methanol. Yield 1.51 g (41%). M. p. 240 °C (dec.), $R_f = 0.76$ (toluene : chloroform : acetone = 8:8:1). – IR (KBr): $\nu = 1702$, 1634, 1608, 1483, 1390, 1340, 1275, 1234, 1128, 981, 879, 758, 700. – MS (EI, 70 eV): *m/z* (%) = 368 (100), 351 (6), 291 (4), 275 (11), 263 (7), 207 (27), 194 (38), 178 (13), 121 (11), 92 (6), 77 (7). – $C_{24}H_{16}O_4$ (368.4): calcd. C 78.26, H 4.35; found C 78.39, H 4.27.

*1-Methylcoumarino-[4',3'-c]bromobenzo[3",4"-f]-2,8-dioxabicyclo[3.3.1]nonane (***3***)*

4-Hydroxycoumarin (1.62 g, 10 mmol) and 4-(5-bromo-2-hydroxyphenyl)-3-buten-2-one (2.41 g, 10 mmol) were dissolved in water and the reaction mixture was refluxed for 14 h. After cooling the crude product was separated and recrystallized from ethyl acetate. White crystals, suitable for X-ray crystal structure analyses, were obtained. Yield 2.73 g (71%). M. p. 275 – 277 °C. – MS (EI, 70 eV): *m/z* (%) = 385/387 (32), 384/386 (100), 369/371 (69), 327/329 (13), 305 (52), 213 (38), 144 (18), 121 (20), 92 (8). – ^{1}H NMR ($CDCl_3$): $\delta = 1.99$ s (3H), 2.18 – 2.30 d (2H), 4.24 – 4.26 t (1H), 6.73 – 7.81 m (7H arom). – $C_{19}H_{13}BrO_4$ (385.2): calcd. C 59.22, H 3.38, Br 20.78; found C 59.35, H 3.51, Br 21.07.

*7-[3-Acetyl-2-oxo-3,4-dihydro-2H-(1)benzopyran-4-yl]methyl-6H,14H,14bH-bis-(1)benzopyrano[4,3-b:4',3'-d]pyran-6,14-dione (***4***)*

Anhydrous potassium acetate (30 mmol), 4-hydroxycoumarin (30 mmol) and 3-acetylcoumarin (30 mmol) were dissolved in glacial acetic acid (30 ml). The reaction mixture was refluxed for 7 h. After cooling a yellow-redish precipitate was separated. The precipitate was washed with glacial acetic acid. The filtrate was poured in a large volume of water. The red precipitate was separated. The crude product was recrystallized from acetic acid. Yield 3.40 g (65%). M. p. 305 °C (dec.). $R_f = 0.59$ (toluene : chloroform : acetone 8 : 8 : 1). – IR (chloroform): $\nu = 1780$, 1720, 1630, 1555, 1160, 980, 910 cm^{-1}. – ^{1}H NMR ($CDCl_3$): $\delta = 2.38$ s (3H), 2.50 – 2.80 m (2H, diastereotopic CH_2), 2.96 – 3.33 d,d (two CH), 5.40 s (1H), 7.2 – 8.4 m (12H-arom.). – MS (EI, 70 eV): *m/z* (%) = 520 (13), 505 (7), 375 (54), 332 (27), 188 (100), 162 (11), 120 (74), 92 (83), 77 (19). – $C_{31}H_{20}O_8$ (520.5): calcd. C 71.54, H 3.85; found C 71.77, H 4.04.

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