

## Structural Reassignment of the Dehydration Product of 2'-Hydroxywarfarin

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Received November 1, 1976

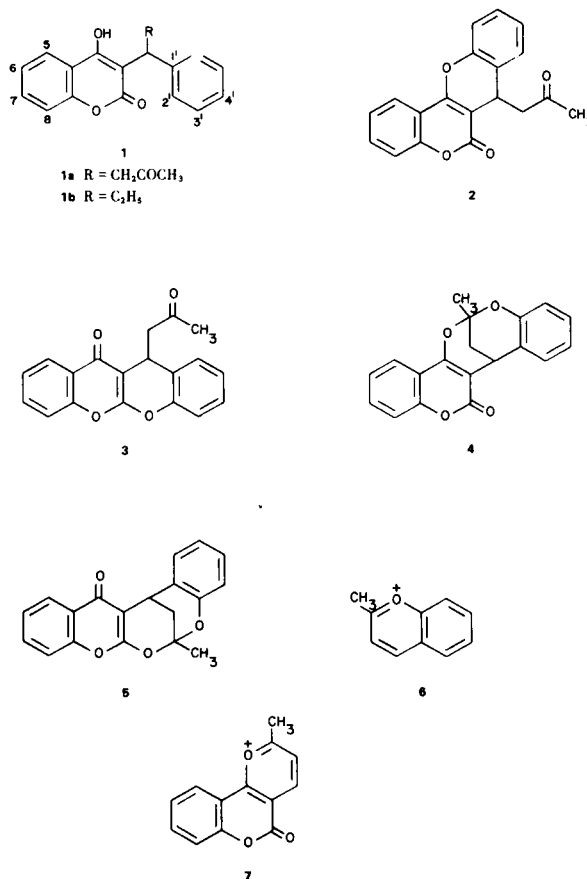
The base catalyzed condensation reaction between 4-hydroxycoumarin and *o*-hydroxybenzaldehyde yields 6-methyl-6,12-methano-6*H*,12*H*,13*H*-[1]benzopyran[4,3-*d*][1,3]benzodioxocin-13-one as the product rather than 6-oxo-7-(2-oxopropyl)-6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]benzopyran as had been previously postulated.

*J. Heterocyclic Chem.*, **14**, 319 (1977).

Most of the aromatic monohydroxylated metabolites of the anticoagulant warfarin (3- $\alpha$ -acetylbenzyl-4-hydroxycoumarin), (**1a**), can be obtained from the condensation of an appropriately substituted 4-hydroxycoumarin with an appropriately substituted benzaldehyde. The synthesis of 2'-hydroxywarfarin (2'-OH-**1a**) fails when this procedure is utilized and instead yields a substance which upon acid work up is converted to a high melting compound which is insoluble in dilute alkali (1). This material has been assigned structure **2** by early investigators (1,2) and presumably arose by the thermal or acid catalyzed cyclization of the desired product. We have reinvestigated the synthesis of 2'-OH-**1a** and have found that an alternate structure to that proposed better accounts for the observed physical and chemical properties of the product obtained.

A series of 3-(*o*-hydroxybenzyl)-4-hydroxycoumarins (**3**) were found to be stable under conditions that should lead to cyclization based on structure **2**. Similarly 2'-hydroxyphenprocoumon (**4**) (4-hydroxy-2-(*o*-hydroxyphenylpropyl)-2*H*-1-benzopyran-2-one), (2'-OH-**1b**), is stable to the conditions of the dehydration of 2'-OH-**1a** and is recovered unchanged after refluxing in benzene for 15 hours (5). These results are clearly inconsistent with structure **2**.

The insolubility of the condensation product in dilute alkali strongly suggests that the 4-hydroxy group ( $pK_a \sim 5$ ) must have been modified during the course of the reaction while its molecular ion,  $m/e$  306,  $C_{19}H_{14}O_4$  establishes that it is isomeric with structure **2**. Thus, three alternate structures must be considered. There are the chromone ether, **3**, and the intramolecular coumarin and chromone ketals **4** and **5**, respectively. Structure **3** can be discounted by the same evidence that was used to discount **2**. In addition **2** and **3** can be eliminated on the basis of mass



spectral and nmr data. The acetyl group in structures **2** and **3** should give rise to an intense ion in the mass spectrum (**6**) at  $m/e$  43, but does not. Indeed the mass spectrum contains three equally intense base peak ions attributable to the molecular ion,  $M^+$ -methyl and an ion at  $m/e$  145,  $C_{10}H_9O$ , consistent with structure **6**. The next

most important ion in the spectrum (27%) is found at  $m/e$  213,  $C_{13}H_9O_3$  and accounts for the remaining half of the molecule, structure **7**. These data are consistent with structures **4** and **5** but not with either **2** or **3**. In the nmr the methyl and methylene protons for structures **2** and **3** are expected to have chemical shifts of 2.1-2.3  $\delta$  respectively and vicinal coupling constants between the benzylic proton and the methylene protons of 6-8 Hz (7). These expectations are derived by analogy to the chemical shifts and coupling constants of the corresponding protons in warfarin-4-methyl ether (7), a similar compound, known to have a conformationally nonrestricted side chain (7). Experimentally these signals are observed at 1.98  $\delta$  (methyl) and 2.23  $\delta$  (methylene) while the vicinal coupling is 3 Hz. The chemical shift positions are similar to those found for the corresponding protons in cyclocoumarol (7) a compound which of the four possible structures most closely approximates **4**. The magnitude of the observed vicinal coupling is also consistent with structure **4** since both methano protons are constrained to be gauche to the benzylic proton.

Finally, structure **4** can be unambiguously differentiated from **5** on the basis of ir. Coumarin carbonyls are expected to absorb at approximately  $1720\text{ cm}^{-1}$  while chromone carbonyls are expected (8) at approximately  $1650\text{ cm}^{-1}$ . The observed carbonyl stretch is found at  $1705\text{ cm}^{-1}$  and therefore all the data strongly suggest that 6-methyl-6,12-methano-6*H*,12*H*,13*H*-[1]benzopyrano[4,3-*d*][1,3]benzodioxocin-13-one, (**4**), is the correct structure of the product.

#### EXPERIMENTAL

Melting points were determined by the capillary method and are uncorrected. Ir spectra were recorded on a Beckman IR-5 spectrophotometer. Nmr spectra were determined at ambient temperature on a Varian T-60 spectrometer, using TMS as the internal standard. High resolution electron impact mass spectra were obtained on an AEI MS9 double focussing high resolution mass spectrometer on line to a PDP-12 computer at a resolution of 10,000 (10% valley definition).

6-Methyl-6,12-methano-6*H*,12*H*,13*H*-[1]benzopyrano[4,3-*d*][1,3]benzodioxocin-13-one (**4**).

A solution of salicylaldehyde (50 g., 0.38 mole) in acetone (100 ml.) and 10% sodium hydroxide (340 ml.) was diluted with water to a final volume of 1.5 l. and stirred at room temperature for 4 days. The pH was adjusted to 13.0 with phosphoric acid, the solution extracted with chloroform (400 ml.), suction filtered and the phases separated. The stirred aqueous phase was carefully acidified to pH 6 with 5*N* hydrochloric acid. The yellow precipitate was filtered, washed with water and air dried (56 g., 73%), m.p.  $138-139^\circ$  (lit. (9) m.p.  $139^\circ$ ). To salicylidene acetone (2.0 g., 0.123 mole) dissolved in anhydrous pyridine (25 ml.) was added 4-hydroxycoumarin (2.0 g., 0.123 mole). The solution was refluxed for 1 hour, cooled and poured into water (200 ml.). After acidifying to pH 1 with 5*N* hydrochloric acid the mixture was stirred for 30 minutes. The precipitate was collected by suction filtration, washed with 70% ethanol (10 ml.) followed by 95% ethanol (10 ml.), then dried at  $110^\circ$  for 30 minutes (2.99 g., 75%), m.p.  $258^\circ$  dec. (lit. (1)  $263^\circ$  dec.); nmr (deuteriochloroform):  $\delta$  7.8-6.7 (m, 8H, aromatic CH), 4.25 (t, 1H, benzylic CH,  $J = 3$  Hz), 2.23 (d, 2H, methano  $CH_2$ ,  $J = 3$  Hz), 1.98 (s, 3H,  $CH_3$ ); ir (potassium bromide): 3010, 1705, 1630, 1475, 1445, 1385, 1220, 1137, 1100, 1075, 1040, 990, 950, 883, 865, 800, 760, 733, 700, 670; high resolution mass spectrum: (70 eV) found for  $C_{19}H_{14}O_4$ , 306.0836; Calcd., 306.0888.

Acknowledgment.

Support for this research was provided by the American Foundation for Pharmaceutical Education (W.R.P.). We wish to thank Mr. Edward Valente for helpful discussions.

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