Formation of Flavans in Reactions of 4-Hydroxycoumarin with Flavylium Salts

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4'-Hydroxyflavylium salts react with 4-hydroxycoumarin to form novel flavan derivatives of type **6**.

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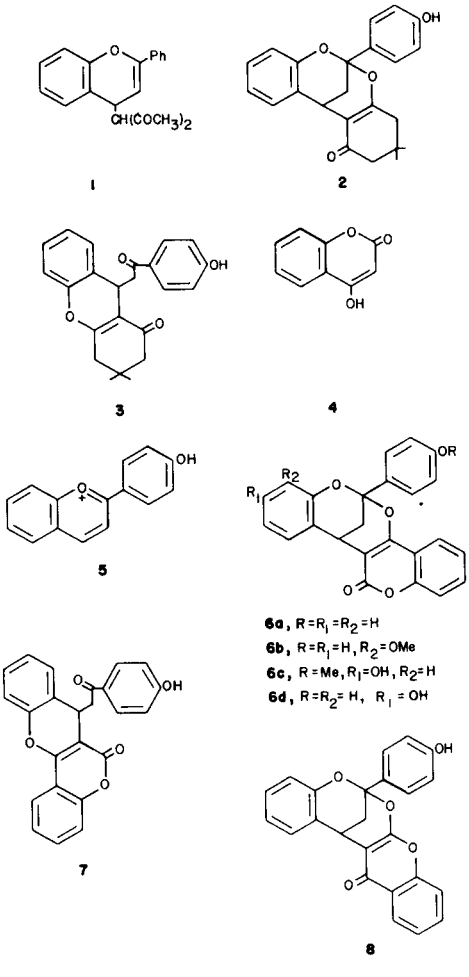
Flavylium salts and 2,4-pentanedione react to give 4-substituted flav-2-enes of type **1** (1). However, with the cyclic β-diketone, 5,5-dimethyl-1,3-cyclohexanedione, 4'-hydroxyflavylium salts form novel flavan derivatives of the type **2** in aqueous alcoholic reaction solutions (2) and phenacylxanthene derivatives of type **3** in acidic reaction solutions (3). The flavans **2** are unstable in both acid and alkaline solutions, and in these media they undergo ring opening and isomerization to the corresponding xanthene derivatives **3**. It has now been determined that, in contrast to 5,5-dimethyl-1,3-cyclohexanedione, 4-hydroxycoumarin **4** reacts with flavylium salts in both aqueous alcoholic and in acidic media to yield stable flavans. The formation of xanthene derivatives related to **3** has not been detected in any of the reactions with 4-hydroxycoumarin.

Thus, 4'-hydroxyflavylium chloride **5** reacts with **4** in acetic acid-aqueous hydrochloric acid solutions to yield a colorless, monohydroxy compound, $C_{24}H_{16}O_5$. The same product is formed by reaction in aqueous methanol, and on the basis of the ^1H and ^{13}C nmr spectra of its mono-*O*-methyl- and *O*-acetyl derivatives, it has been identified as the flavan derivative **6a**. In accordance with this structure, the ^1H nmr spectrum of the *O*-methyl derivative shows the presence of a methylene group as a doublet at δ 2.40, coupled to a benzylic methine proton at δ 4.37. These chemical shifts closely agree (4) with those of the corresponding methylene and methine protons of **2**. In addition, a phenacylxanthene derived structure, *e.g.*, **7**, can be unequivocally excluded on the basis of the ^{13}C nmr spectrum of the *O*-methyl derivative, which shows the presence of only a single carbonyl group (δ 161.4). In the ^{13}C nmr spectrum of 4-methoxycoumarin (and other 2-pyrone derivatives), the lactone carbonyl carbon has a chemical shift of 161.3 ppm (5); for isoflavones, rotenoids and other 4-pyrone derivatives (6), on the other hand, the carbonyl carbon signal appears well downfield at 175-190 ppm. The chemical shift (161.4) of the carbonyl carbon of the *O*-methyl derivative, therefore, clearly favors the 2-pyrone structure **6** for this flavan, rather than the isomeric 4-pyrone structure **8**. Flavan derivatives of type **6** were also formed by reaction of 8-methoxy-4'-hydroxy-, 7-hydroxy-4'-methoxy-, and 4',7-dihydroxy- flavylium salts with 4-hydroxycoumarin.



EXPERIMENTAL

Melting points are uncorrected. Ir spectra were determined in mineral oil. Nmr spectra, unless otherwise stated, were determined in deuteriochloroform with TMS as internal standard on a modified Varian HA-100 instrument.

Reaction of 4'-Hydroxyflavylium Chloride with 4-Hydroxycoumarin. (a).

A solution of 4'-hydroxyflavylium chloride (1.0 g.) and **4** (2.0 g.) in warm acetic acid (10 ml.) and 2% aqueous hydrochloric acid (10 ml.) was heated on a steam bath for 5 minutes and allowed to cool. Slightly yellow crystals separated. These were collected and recrystallized from acetone-methanol to give **6a** as cream-colored, glistening prisms, m.p. 262-264°

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dec. (1.02 g.); ir: ν max 3250, 1680, 1630 cm^{-1}; ^1H nmr (pyridine-d_5): δ 2.42 (3H, d, J = 3 Hz), 4.38 (1H, t, J = 3 Hz), 6.80-7.90 (12H, m), 11.80 (1H, br s).

Anal. Calcd. for $C_{24}H_{16}O_5$: C, 75.0; H, 4.20. Found: C, 75.1; H, 4.20.

A solution of the above product (0.5 g.) in acetic anhydride (5 ml.) and pyridine (2 ml.) was warmed on a steam bath for 10 minutes and diluted with water. The solid product crystallized from acetone-methanol to give the acetate of **6a** as colorless, felted needles, m.p. 225-226° (0.58 g.); ir: ν max 1755, 1715, 1640 cm^{-1}; ^1H nmr: δ 2.30 (3H, s), 2.39 (2H, d, J = 3 Hz), 4.36 (1H, s), 6.90-7.90 (12H, m).

Anal. Calcd. for $C_{26}H_{18}O_6$: C, 73.2; H, 4.26; CH_3CO-, 10.1. Found: C, 73.2; H, 4.22; CH_3CO-, 9.94.

The above product (1.0 g.) was heated under reflux in dimethyl sulfate (2.5 ml.), potassium carbonate (4 g.) and dry acetone (60 ml.) for 2 hours, concentrated and diluted with water. The solid product crystallized from methanol to give the methyl ether of **6a** as colorless brittle needles, m.p. 201-202° (0.71 g.); ir: ν max 1715, 1695, 1635 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (2H, d, J = 3 Hz), 3.84 (3H, s), 4.37 (1H, t, J = 3 Hz), 6.90-7.90 (12H, m).

Anal. Calcd. for $C_{25}H_{18}O_5$: C, 75.4; H, 4.55. Found: C, 75.3; H, 4.55.

(b).

A solution of 4'-hydroxyflavylium chloride (1.0 g.) and 4-hydroxycoumarin (2 g.) in methanol (15 ml.) and water (10 ml.) was heated on a steam bath for 10 minutes. Colorless crystals separated. Recrystallized from acetone-methanol, **6a** was obtained as cream-colored prisms, m.p. 262-264°, identical (mixed m.p., ^1H nmr, acetate) with the above product.

Reaction of 8-Methoxy-4'-hydroxyflavylium Chloride with **4**.

A solution of 8-methoxy-4'-hydroxyflavylium chloride (10 g.) and 4-hydroxycoumarin (20 g.) in methanol (500 ml.) and water (250 ml.) was boiled under reflux for 15 minutes. The crystalline product which separated was collected and recrystallized from tetrahydrofuran-methanol to give **6b** as colorless needles, m.p. 263-265° dec. (9.0 g.); ir: ν max 3350, 1690, 1630 cm^{-1}; ^1H nmr (pyridine-d_5): δ 2.44 (2H, d, J = 3 Hz), 3.71 (3H, s), 4.44 (1H, s), 6.80-8.02 (11H, m), 11.90 (1H, br s).

Anal. Calcd. for $C_{25}H_{18}O_6$: C, 72.5; H, 4.37; MeO-, 7.49. Found: C, 72.5; H, 4.44; MeO-, 7.74.

With acetic anhydride and pyridine, the above product formed a monoacetate, colorless, glistening prism from acetone-methanol, m.p. 221°; ir: ν max 1765, 1720, 1635 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27 (3H, s), 2.39 (2H, d, J = 3 Hz), 3.82 (3H, s), 4.37 (1H, t, J = 3 Hz), 6.68-7.90 (11H, m).

Anal. Calcd. for $C_{27}H_{20}O_7$: C, 71.0; H, 4.42; CH_3CO-, 9.42. Found: C, 71.1; H, 4.46; CH_3CO-, 9.38.

Methylation of **6b** as described above gave the *O*-methyl derivative which crystallized from acetone-methanol as colorless prisms, m.p. 224-225°; ir: ν max 1690, 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.38 (2H, d, J = 3 Hz), 3.84 (6H, s), 4.37 (1H, t, J = 3 Hz), 6.80-7.80 (11H, m).

Anal. Calcd. for $C_{26}H_{20}O_6$: C, 72.9; H, 4.71; MeO-, 14.5. Found: C, 72.9; H, 4.76; MeO-, 14.6.

Reaction of 7-Hydroxy-4$_9$-methoxyflavylium Chloride with **4**.

A solution of 7-hydroxy-4'-methoxyflavylium chloride (1 g.) and 4-hydroxycoumarin (1 g.) in methanol (20 ml.) and water (10 ml.) was heated for 10 minutes. The crystals which separated were collected and recrystallized from tetrahydrofuran-methanol to give **6c** as slightly pink colored prisms, m.p. 293-294° (0.95 g.).

Anal. Calcd. for $C_{25}H_{18}O_6$: C, 72.5; H, 4.38. Found: C, 72.6; H, 4.42.

Heated with acetic anhydride and a drop of pyridine, **6c** formed a monoacetate, which crystallized from acetone-methanol as glistening, flat needles, m.p. 171°. ^1H nmr (deuteriochloroform): δ 2.25 (3H, s), 2.41 (2H, d, J = 3 Hz), 3.84 (3H, s), 4.36 (1H, t, J = 3 Hz), 6.64-7.86 (11H, m).

Reaction of 4',7-Dihydroxyflavylium Perchloride with 4-Hydroxycoumarin.

A solution of 4',7-dihydroxyflavylium perchloride (3.38 g.) and 4-hydroxycoumarin (1.62 g.) in methanol (20 ml.) and water (40 ml.) was refluxed for 30 minutes and cooled. The solid product (3.30 g.) was crystallized from acetone-methanol to give **6d** as almost colorless prisms, which darken at 240-245° but do not melt below 325° (2.30 g.); ir: ν max 3375, 3200, 1665, 1630 cm^{-1}; ^1H nmr (pyridine-d_5): δ 2.46 (2H, d, J = 3 Hz), 4.39 (1H, t, J = 3 Hz), 6.75-7.94 (11H, m), 11.0 (2H, br s).

Anal. Calcd. for $C_{24}H_{16}O_6$: C, 72.0; H, 4.03. Found: C, 72.0; H, 4.04.

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