HETEROCYCLES. XIX.[1] REACTION OF 2'-HYDROXYCHALCONES WITH ALKALINE HYDROGEN PEROXIDE

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Abstract —— Reaction of 2'-hydroxychalcones, which contain the hydroxyl and/or the methoxyl group at the 4- and 6'-positions, with alkaline hydrogen peroxide has been examined. It is observed that these substituents intricately influence the formation of the products.

It is well known that the oxidation of 2'-hydroxychalcones with alkaline hydrogen peroxide affords flavanonols and flavonols in arbitary ratios via chalcone epoxides, provided the 6'-position contains no substituent, and that the latter compounds are formed by the autoxidation of the former compounds in the alkaline solution.[2] Later, Geissman and Fukushima[3] reported that 2'-hydroxy-6'-methoxychalcones give aurones, when the 2- or 4-position does not contain a hydroxyl group. Along this view, Patil and Deshpande[4] have recently reported the following oxidative cyclization of 2'-hydroxychalcones. The chalcones 1 and 2 gave the flavonol 3 (52%) and the aurone 4 (80%), respectively, under condition-1 (H_2O_2/NaOH/EtOH/0°C/24 h). Alternatively, the chalcone 5 furnished the flavanonol 6 (88%) under condition-2 (H_2O_2/NaOH/acetone/room temperature/5 min). In connection of our studies on flavonoid synthesis, we re-investigated the effect of 4- and 6'-substituents in 2'-hydroxychalcones on the formation of product in the foregoing reactions.

Under Condition-1

The chalcones 1 and 7 gave the flavanones 8 (29%) and 9 (16%), respectively, due to direct cyclization of the starting materials.[5] In the case of 1, unidentified compounds were additionally obtained, and the formation of 3 was not observed.

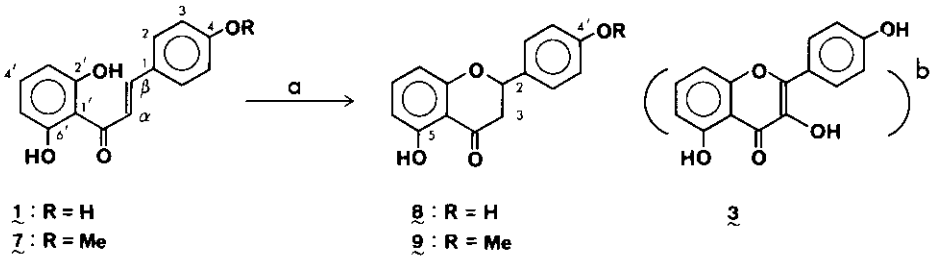
The characterization of 8 and 9 was based on ^{1}H-NMR spectroscopy (8; $J_{2,3}$ 12.5 and 3.5 Hz. 9; $J_{2,3}$ 9.5 and 4 Hz). The chalcone 2 afforded the flavanonol 10 (14%) and the flavanone 11 (19%) along with anisaldehyde (12) (20%) resulted from fragmentation of 2 (10; $J_{2,3}$ 12.5 Hz. 11; $J_{2,3}$ 12.5 and 4 Hz). The formation of 4 was not observed. The chalcones 5 and 13 furnished the flavanonols 6 (17%) and 14 (16%), respectively, due to epoxidation followed by cyclization of the resulting chalcone epoxides (6; $J_{2,3}$ 12.5 Hz. 14; $J_{2,3}$ 12.5 Hz). In the case of 5, two fragments, 4-hydroxybenzoic acid (15) (22%) and 6-benzyloxysalicylic acid (16) (45%), were additionally obtained.

Under Condition-2

The chalcone 5 afforded no product, but application of a prolonged reaction time (20 h) provided 6 (45%) and the flavonol 17 (10%), which is considered to be formed by autoxidation of 6. The structure of 17 was confirmed by comparison of its ^{1}H-NMR spectrum with that of 6. The chalcone 2 gave 10 (10%) and 12 (13%).

Thus, although we repeatedly followed the procedure described by Patil and Deshpande,[4] the obtained compounds were different and the yields were low, being tremendously in contrast to their results.

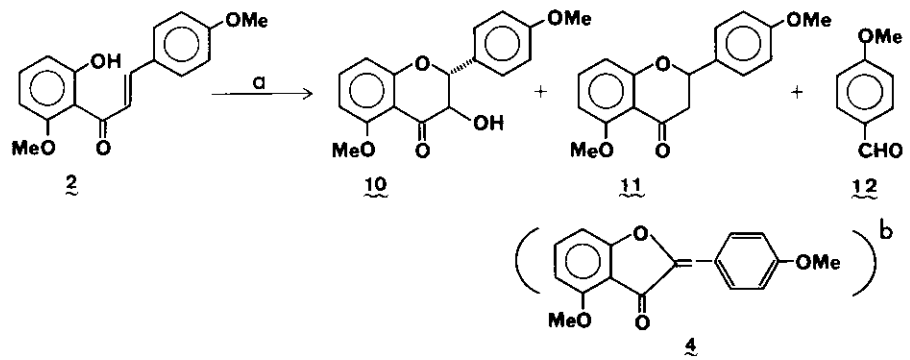
Since the direct cyclization of the chalcones, the epoxidation followed by cyclization of the resulting chalcone epoxides, the fragmentation of the chalcones and the autoxidation of the flavanonols competitively occur under these reaction conditions, it seems likely that the substituent, the solvent, the reaction temperature and the reaction time affect each reaction in a different manner, and these factors as a whole intricately influence the formation of the products. This is a reason why the foregoing scattered results were obtained. However, if the consideration is confined to the cyclized products obtained under condition-1, our results are summarized as follows: (1) The 6'-hydroxyl group prompts the direct cyclization regardless of the 4-substituent (1 ⟶ 8 and 7 ⟶ 9). (2) The 6'-ether functions enhance the epoxidation followed by cyclization, provided a hydroxyl group is present at the 4-position (5 ⟶ 6 and 13 ⟶ 14). (3) The 4- and 6'-methoxyl groups competitively stimulate the foregoing reactions (2 ⟶ 10 and 11).



1 : R = H
7 : R = Me

8 : R = H
9 : R = Me

3



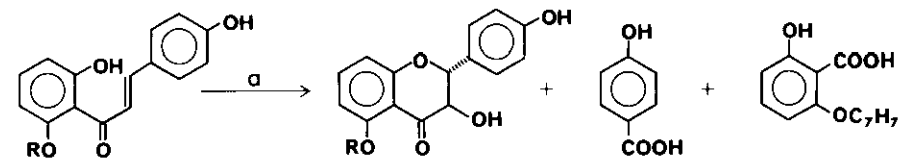
2

10

11

12

4

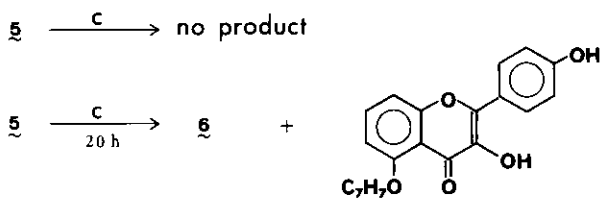


5 : R = C_7H_7
13 : R = Me

6 : R = C_7H_7
14 : R = Me

15

16



5 —c→ no product

5 —c, 20 h→ 6 + 17

2 —c→ 10 + 12

a) Condition-1; b) These compounds were reported to be formed as a sole product;[4] c) Condition-2

Chart 1

EXPERIMENTAL

Melting points are uncorrected. Preparative (prep) TLC was carried out on silica gel plates using acetone (A)/benzene (B) (v/v) as the solvents. Spectral data were recorded on the following spectrometers: IR, Hitachi 260-30; ^{1}H-NMR, Varian EM-390 (90 MHz); MS, JEOL LMS DX-300.

4,2',6'-Trihydroxychalcone (1)

a) A solution of 4,2',6'-tris(methoxymethoxy)chalcone[6] (56.2 mg) in 12% methanolic HCl (0.4 ml) was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with ethyl acetate. The organic phase was washed with 5% aq Na_2CO_3 and dried over Na_2SO_4. Removal of the solvent *in vacuo* and purification of the residue by prep TLC (A/B=1/5) gave 1 (12.1 mg, 33%) as orange needles of mp 215-216°C (acetone) (lit.,[4] mp 202-204°C), Rf 0.42, and the flavanone 8 (*vide infra*) (24.2 mg, 65%), Rf 0.64. IR (KBr): 3252 (OH), 1630 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 8.12 (1H, d, J 15.5 Hz, β-H), 7.78 (1H, d, J 15.5 Hz, α-H), 7.57 (2H, d, J 8.5 Hz, 2-, 6-H's), 7.25 (1H, t, J 8 Hz, 4'-H), 6.92 (2H, d, J 8.5 Hz, 3-, 5-H's), 6.43 (2H, d, J 8 Hz, 3'-, 5'-H's). MS Calcd for $C_{15}H_{12}O_4$: M, 256.074. Found m/z: M^+, 256.073.

b) Application of the procedure described in the literature[4] afforded 1 in 8.5% yield (lit.,[4] 81%), and 2,6-dihydroxyacetophenone (73%) and 4-hydroxybenzaldehyde (46%) were recovered.

4,6'-Dimethoxy-2-hydroxychalcone (2)

A mixture of 2-hydroxy-6-methoxyacetophenone[7] (350.6 mg), anisaldehyde (290.2 mg) and KOH (407.2 mg) in anhyd ethanol (8 ml) was stirred at room temperature for 28 h. The reaction mixture was poured into ice-water and acidified with dil HCl. The precipitate was collected and recrystallized from ethanol to yield 2 (543.5 mg, 91%) as orange needles of mp 113-115°C. IR ($CHCl_3$): 3540 (OH), 1628 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 13.21 (1H, s, 2'-OH),[8] 7.76 (2H, s, α-, β-H's), 7.55 (2H, d, J 9 Hz, 2-, 6-H's), 7.34 (1H, t, J 8.5 Hz, 4'-H), 6.91 (2H, d, J 9 Hz, 3-, 5-H's), 6.59, 6.41 (each 1H, dd, J 8.5, 1 Hz, 3'-, 5'-H's), 3.92, 3.84 (each 3H, s, 4-, 6'-OMe's). MS Calcd for $C_{17}H_{16}O_4$: M, 284.105. Found m/z: M^+, 284.105.

6'-Benzyloxy-4,2'-dihydroxychalcone (5)

This compound was prepared in 89% yield by the same procedure as described in the

literature.[4] Orange needles of mp 186–187°C (MeOH) (lit.,[4] mp 189°C). IR (KBr): 3312 (OH), 1624 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 13.52 (1H, s, 2'-OH),[8] 8.87 (1H, s, 4-OH),[8] 7.78–7.33 (8H, m, aromatic, α-, β-H's), 7.13 (2H, d, J 8.5 Hz, 2-, 6-H's), 6.68, 6.55 (each 1H, dd, J 8.5, 1 Hz, 3'-, 5'-H's), 6.75 (2H, d, J 8.5 Hz, 3-, 5-H's), 5.22 (2H, s, 6'-OC$\underline{H}_2$Ph). MS Calcd for $C_{22}H_{18}O_4$: M, 346.121. Found m/z: M^+, 346.121.

2',6'-Dihydroxy-4-methoxychalcone (7)

A mixture of 2,6-bis(methoxymethoxy)acetophenone[6] (340.7 mg), anisaldehyde (190.5 mg) and KOH (145.6 mg) in anhyd ethanol (8 ml) was stirred at room temperature for 27 h. Work-up of the reaction mixture and purification of the product by prep TLC (A/B=1/10) gave 2',6'-bis(methoxymethoxy)-4-methoxychalcone (446.4 mg, 88%) as an orange oil, Rf 0.60.

A solution of the above chalcone (102.7 mg) in 12% methanolic HCl (0.5 ml) was stirred at room temperature for 3 h. Work-up of the reaction mixture and recrystallization of the product from ethanol to yield 7 (71.7 mg, 88%) as orange needles of mp 131–133°C. IR ($CHCl_3$): 3576, 3240 (OH), 1626 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 9.25 (2H, s, 2'-, 6'-OH's),[8] 7.86 (2H, s, α-, β-H's), 7.56 (2H, d, J 8.5 Hz, 2-, 6-H's), 7.23 (1H, t, J 8 Hz, 4'-H), 6.87 (2H, d, J 8.5 Hz, 3-, 5-H's), 6.38 (2H, d, J 8 Hz, 3'-, 5'-H's), 3.83 (3H, s, 4-OMe). MS Calcd for $C_{16}H_{14}O_4$: M, 270.089. Found m/z: M^+, 270.089.

4,2'-Dihydroxy-6'-methoxychalcone (13)

A mixture of 2,6-dihydroxyacetophenone (1.2 g), methyl iodide (1.2 g) and K_2CO_3 (5.2 g) in anhyd acetone (40 ml) was refluxed for 5 h. The reaction mixture was filtered and concentrated *in vacuo*, and the residue was extracted with chloroform. Removal of the solvent *in vacuo* and purification of the residue by chromatography (silica gel, 50 g) using benzene as an eluent afforded 2-hydroxy-6'-methoxyacetophenone (946.3 mg, 72%) as colorless crystals of mp 57–59°C (EtOH) (IR ($CHCl_3$): 3520 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s, 6-OMe). MS m/z: M^+, 166.063 (M, 166.063 for $C_9H_{10}O_3$)).

A mixture of the above acetophenone (201.9 mg), 4-methoxymethoxybenzaldehyde[6] (199.0 mg) and KOH (400.0 mg) in anhyd ethanol (6 ml) was stirred at room temperature for 18 h. Work-up of the reaction mixture and purification of the product by prep TLC (A/B=1/20) gave 2'-hydroxy-6'-methoxy-4-methoxymethoxychalcone

(303.7 mg, 80%) as a yellow oil, Rf 0.70 (^{1}H-NMR ($CDCl_3$) δ: 7.79 (2H, s, α-, β-H's). MS m/z: M^+, 314.115 (M, 314.115 for $C_{18}H_{18}O_5$)).

A solution of the above chalcone (234.1 mg) in 10% HCl/dioxane (1.5 ml) was stirred at room temperature for 25 min. Work-up of the reaction mixture and purification of the product by prep TLC (A/B=1/20) gave 13 (174.7 mg, 87%) as orange needles of mp 154–155°C (MeOH), Rf 0.37. IR (KBr): 3540 (OH), 1630 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 13.10 (1H, s, 2'-OH),[8] 8.92 (1H, s, 4-OH),[8] 7.80 (2H, s, α-, β-H's), 7.61 (2H, d, J 9 Hz, 2-, 6-H's), 7.37 (1H, t, J 8.5 Hz, 4'-H), 6.90 (2H, d, J 9 Hz, 3-, 5-H's), 6.57, 6.48 (each 1H, dd, J 8.5, 1 Hz, 3'-, 5'-H's), 3.98 (3H, s, 6'-OMe). MS Calcd for $C_{16}H_{14}O_4$: M, 270.089. Found m/z: M^+, 270.089.

Reaction of 1

A mixture of 8% H_2O_2 (0.03 ml) and 2N NaOH (0.06 ml) was added to a solution of 1 (14.0 mg) in ethanol (0.3 ml), and the whole was stirred at 0°C for 24 h. The reaction mixture was concentrated in vacuo. The residue was acidified with dil HCl and extracted with ethyl acetate. The organic phase was successively washed with 5% aq $NaHCO_3$, 10% aq KI, 10% aq $Na_2S_2O_3$ and water, and then dried over Na_2SO_4. Removal of the solvent in vacuo and purification of the residue by prep TLC (A/B=1/5) gave (±)-5,4'-dihydroxyflavanone (8) (4.0 mg, 29%) as colorless needles of mp 205–206°C (MeOH) (lit.,[4] mp 202–204°C), Rf 0.67. IR (KBr): 3260 (OH), 1628 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 11.81 (1H, s, 5-OH),[8] 8.42 (1H, s, 4'-OH),[8] 7.43 (1H, t, J 8.5 Hz, 7-H), 7.37 (2H, d, J 8.5 Hz, 2'-, 6'-H's), 6.88 (2H, d, J 8.5 Hz, 3'-, 5'-H's), 6.45 (2H, d, J 8.5 Hz, 6-, 8-H's), 5.48 (1H, dd, J 12.5, 3.5 Hz, 2-H), 3.27 (1H, dd, J 17, 12.5 Hz, 3-H), 2.82 (1H, dd, J 17, 3.5 Hz, 3-H). MS Calcd for $C_{15}H_{12}O_4$: M, 256.074. Found m/z: M^+, 256.074.

Reaction of 2

a) A mixture of 8% H_2O_2 (0.2 ml) and 2N NaOH (0.2 ml) was added to a solution of 2 (78.2 mg) in ethanol (30 ml), and the whole was stirred at 0°C for 24 h. Work-up of the reaction mixture and purification of the products by prep TLC (A/B=1/10) afforded the following compounds.

(2R*,3R*)-5,4'-Dimethoxyflavanonol (10): Colorless needles of mp 144–146°C (MeOH), Rf 0.60. Yield, 11.6 mg (14%). This compound was identified with an authentic sample[6] by direct comparison.

(±)-5,4'-Dimethoxyflavanone (11): Colorless needles of mp 156–160°C (EtOH), Rf 0.65. Yield, 14.5 mg (19%). IR ($CHCl_3$): 1674 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.37 (1H, t, J 8.5 Hz, 7-H), 7.34 (2H, d, J 8.5 Hz, 2'-, 6'-H's), 6.92 (2H, d, J 8.5 Hz, 3'-, 5'-H's), 6.65, 6.61 (each 1H, dd, J 8.5, 1 Hz, 6-, 8-H's), 5.35 (1H, dd, J 12.5, 4 Hz, 2-H), 3.91, 3.79 (each 3H, s, 5-, 4'-OMe's), 3.07 (1H, dd, J 16, 12.5 Hz, 3-H), 2.76 (1H, dd, J 16, 4 Hz, 3-H). MS Calcd for $C_{17}H_{16}O_4$: M, 284.105. Found m/z: M^+, 284.104.

Anisaldehyde (12): A light yellow oil, Rf 0.07. Yield, 7.4 mg (20%). This compound was identified with a commercially available sample by direct comparison. In addition, unreacted 2 (31.7 mg, 41%) was recovered.

b) A mixture of 10% H_2O_2 (0.1 ml) and 2N NaOH (0.08 ml) was added to a solution of 2 (50.6 mg) in acetone (0.4 ml), and the whole was stirred at room temperature for 5 min. Work-up as above furnished 10 (5.4 mg, 10%) and 12 (3.2 mg, 13%) together with unreacted 2 (20.2 mg, 40%).

Reaction of 5

a) A mixture of 8% H_2O_2 (0.3 ml) and 2N NaOH (0.15 ml) was added to a solution of 5 (44.3 mg) in ethanol (5 ml), and the whole was stirred at 0°C for 24 h. Work-up of the reaction mixture and purification of the products by prep TLC (A/B=1/10) afforded the following compounds.

(2R*,3R*)-5-Benzyloxy-4'-hydroxyflavanonol (6): Colorless needles of mp 176–178°C (MeOH) (lit.,[4] mp 114–115°C), Rf 0.34. Yield, 7.9 mg (17%). IR (KBr): 3312 (OH), 1686 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 7.68–7.26 (6H, m, aromatic H's), 7.42 (2H, d, J 8.5 Hz, 2'-, 6'-H's), 6.86 (2H, d, J 8.5 Hz, 3'-, 5'-H's), 6.75, 6.56 (each 1H, dd, J 8.5, 1 Hz, 6-, 8-H's), 5.22 (2H, s, 5-OC$\underline{H}_2$Ph), 5.02 (1H, d, J 12.5 Hz, 2-H), 4.50 (1H, dd, J 12.5, 3 Hz, 3-H),[9] 4.25 (1H, d, J 3 Hz, 3-OH).[8] MS Calcd for $C_{22}H_{18}O_5$: M, 362.115. Found m/z: M^+, 362.115.

4-Hydroxybenzoic Acid (15): Colorless needles of mp 215–217°C (H_2O), Rf 0.10. Yield, 3.5 mg (22%). This compound was identified with a commercially available sample by direct comparison.

6-Benzyloxysalicylic Acid (16): Colorless needles of mp 124–125°C (MeOH), Rf 0.45. Yield, 14.0 mg (45%). IR ($CHCl_3$): 3548, 3248 (C$\underline{OOH}$, OH), 1690 cm^{-1} (C$\underline{O}$OH). ^{1}H-NMR ($CDCl_3$) δ: 12.21, 11.43 (each 1H, s, 1-COOH, 2-OH),[8] 7.39 (1H, t, J 8.5 Hz, 4-H), 6.70, 6.54 (each 1H, dd, J 8.5, 1 Hz, 3-, 5-H's), 5.22 (2H, s, 6-OC$\underline{H}_2$Ph). MS Calcd for $C_{14}H_{12}O_4$: M, 244.073. Found m/z: M^+, 244.073.

b) A mixture of 15% H_2O_2 (0.9 ml) and 2N NaOH (0.5 ml) was added to a solution of 5 (151.1 mg) in acetone (4.5 ml), and the whole was stirred at room temperature for 20 h. Work-up as above gave 6 (71.9 mg, 45%) and 5-benzyloxy-4'-hydroxyflavonol (17) (16.1 mg, 10%) as yellow needles of mp 222–223°C (MeOH), Rf 0.38. IR (KBr): 3336, 3240 (OH), 1644 cm^{-1} (C=O). ^{1}H-NMR (DMSO-d_6) δ: 9.86, 8.85 (each 1H, s, 3-, 4'-OH's),[8] 8.08 (2H, d, J 9 Hz, 2'-, 6'-H's), 7.76–6.90 (8H, m, aromatic H's), 6.92 (2H, d, J 9 Hz, 3'-, 5'-H's), 5.26 (2H, s, 5-O$\underline{CH_2}$Ph). MS Calcd for $C_{22}H_{16}O_5$: M, 360.100. Found m/z: M^+, 360.100.
In addition, unreacted 5 (17.1 mg, 12%) was recovered.

Reaction of 7

A mixture of 10% H_2O_2 (0.2 ml) and 2N NaOH (0.2 ml) was added to a solution of 7 (45.2 mg) in ethanol (5 ml), and the whole was stirred at 0°C for 24 h. Work-up of the reaction mixture and purification of the product by prep TLC (A/B=1/5) gave (±)-5-hydroxy-4'-methoxyflavanone (9) (7.3 mg, 16%) as yellow needles of mp 142–144°C ($CHCl_3$/MeOH), Rf 0.54, together with unreacted 7 (35.1 mg, 78%). IR ($CHCl_3$): 3548, 3364 (OH), 1704 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 7.38 (2H, d, J 9 Hz, 2'-, 6'-H's), 6.88 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.44–6.10 (3H, m, aromatic H's), 5.38 (1H, dd, J 9.5, 4 Hz, 2-H), 3.76 (3H, s, 4'-OMe), 3.12 (1H, dd, J 11, 9.5 Hz, 3-H), 2.73 (1H, dd, J 11, 4 Hz, 3-H). MS Calcd for $C_{16}H_{14}O_4$: M, 270.089. Found m/z: M^+, 270.090.

Reaction of 13

A mixture of 8% H_2O_2 (0.1 ml) and 2N NaOH (0.1 ml) was added to a solution of 13 (30.2 mg) in ethanol (5 ml), and the whole was stirred at 0°C for 24 h. Work-up of the reaction mixture and purification of the product by prep TLC (A/B=1/10) gave (2R*,3R*)-4'-hydroxy-5-methoxyflavanonol (14) (5.2 mg, 16%) as colorless needles of mp 203–205°C (acetone), Rf 0.49, along with unreacted 13 (21.7 mg, 72%). IR (KBr): 3352 (OH), 1660 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 8.41 (1H, s, 4'-OH),[8] 7.48 (1H, t, J 8.5 Hz, 7-H), 7.45 (2H, d, J 8.5 Hz, 2'-, 6'-H's), 6.90 (2H, d, J 8.5 Hz, 3'-, 5'-H's), 6.72, 6.58 (each 1H, dd, J 8.5, 1 Hz, 6-, 8-H's), 5.03 (1H, d, J 12.5 Hz, 2-H), 4.51 (1H, dd, J 12.5, 3 Hz, 3-H),[9] 4.25 (1H, d, J 3 Hz, 3-OH),[8] 3.90 (3H, s, 5-OMe). MS Calcd for $C_{16}H_{14}O_5$: M, 286.084. Found m/z: M^+, 286.085.

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8. On addition of deuterium oxide, these signals disappeared.
9. On addition of deuterium oxide, these splittings changed to doublets due to the disappearance of the corresponding hydroxyl protons.

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