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The Reaction of 3-Hydroxyflavones with Metal Salts

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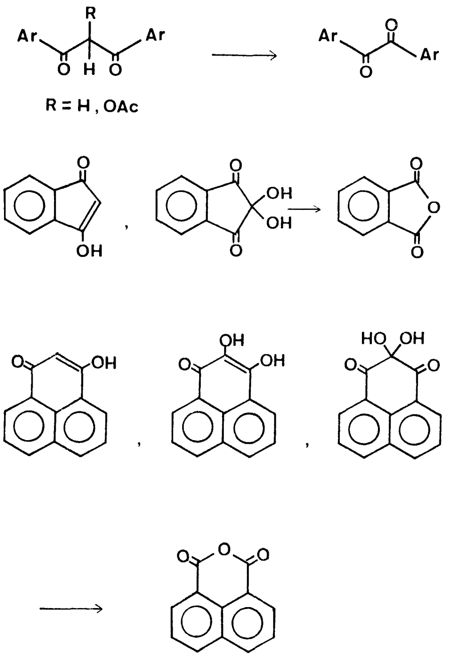
The reaction of 3-hydroxyflavones (**1a**—**d**) with lead(IV) acetate gave 1,2-diphenylethanediones (**2a**—**d**), 1,2-diphenyl-2-hydroxyethanones, 2-hydroxybenzoic acids (**7** and **9**), and benzoic acids (**8** and **10**), and the reaction with manganese(III) acetate yielded **2**, **7**, **8**, **9**, and **10**. In addition to **2**, **7**, and **10**, 6-methoxy-2-(4-methoxybenzoyloxy)-3(2*H*)-benzofuranone and 2-hydroxy-4-methoxybenzaldehyde were obtained in the reaction of **1c** with manganese(III) acetate. It has been established by the studies of ^{14}C-labelled compounds that the $C_{(3)}$ in the 3-hydroxyflavone was lost during the reaction.

In previous papers,[1,2] the decarbonylation reactions of 1,3-diphenyl-1,3-propanediones and 1,3-indandiones with lead(IV) acetate have been reported. The reaction of ^{14}C-labelled compounds showed that the $C_{(2)}$ was lost completely in the case of 2-acetoxy-1,3-diphenyl-1,3-propanedione, but that 53 percent of the $C_{(\alpha)}$ was retained in the case of β-hydroxychalcone (1,3-diphenyl-1,3-propanedione), suggesting that there may be binary reaction pathways. Similar results were obtained in the reaction of ^{14}C-labelled 1,3-indandiones and 1*H*-phenalene-1,3(2*H*)-dione with lead(IV) acetate[2] (Scheme 1). In order to obtain further information about the nature of the decarbonylation reaction, we studied the reaction of 3-hydroxyflavones with lead(IV) acetate under various reaction conditions.

When 4′,7-dimethoxy-3-hydroxyflavone (**1c**) was heated in acetic acid with lead(IV) acetate, five compounds (**2c**, **3c**, **4c**, **7**, and **10**) were obtained. The NMR spectrum of **2c** indicated the presence of a para-substituted benzoyl group [δ=7.92 (2H, m) and 6.96 (2H, m)], a 2,4-disubstituted benzyol group [δ=7.4 (1H, d, J=9 Hz) and 6.25—6.5 (2H, m)], a hydrogen-bonded hydroxyl group [δ=11.9 (1H, s)] which disappeared on deutration, and two methoxyl groups [δ=3.82 (3H, s) and 3.85 (3H, s)]. Two carbonyl functions, one of which was hydrogen-bonded, were characterized by IR absorption at 1685 and 1630 cm^{-1}. The mass spectrum of **2c** showed four prominent ions, at *m*/*e* 151, 135, 123, and 107, due to the α-cleavages to the carbonyls that are shown in Fig. 1. This spectroscopic evidence clearly showed that this compound was 1-(2-hydroxy-4-methyoxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2c**). The structure was confirmed by an unambiguous synthesis of **2c**: the reaction of 2′-benzyloxy-4,4′-dimethoxychalocone with thallium(III) nitrate[3] gave 1-(2-benzyloxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2e**), which was then debenzylated to give the identical **2c**.



Scheme 1. Reactions of 1,3-diaryl-1,3-propanediones, 1,3-indandiones, and 1*H*-phenalene-1,3(2*H*)-dione with lead(IV) acetate.

The NMR spectrum of **3c** showed that presence of a para-substituted phenyl group [δ=7.28 (2H, m) and 6.85 (2H, m)], three atomatic protons [δ=7.15 (1H, d, J=8 Hz) and 6.3—6.45 (2H, m)], two methoxyl groups [δ=3.76 (3H, S) and 3.75 (3H, s)], two hydroxyl groups [δ=12.1 (1H, s) and 4.25 (1H, broad s)], and a broad singlet [5.8 (1H)]. The latter singlet became sharp and the hydroxyl groups disappeared when shaken with deuterium oxide. The IR spectrum of this compound indicated the presence of hydroxyl groups (3460 and 2500—3300 cm^{-1}) and a hydrogen-bonded carbonyl group (1640 cm^{-1}). Thus, the structure of **3c** is shown as 2-hydroxyl-1-(2-hydroxy-4-methoxyphenyl)-2-(4-meth-

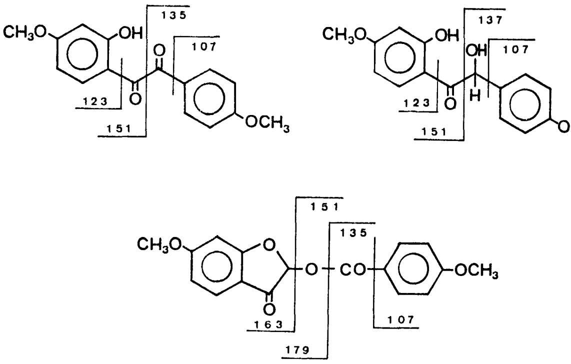


Fig. 1. The mass spectral data of 1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2c**), 2-hydroxy-1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanone (**3c**), and 6-methoxy-2-(4-methoxybenzoyloxy)-3(2*H*)-benzofuranone (**5**).

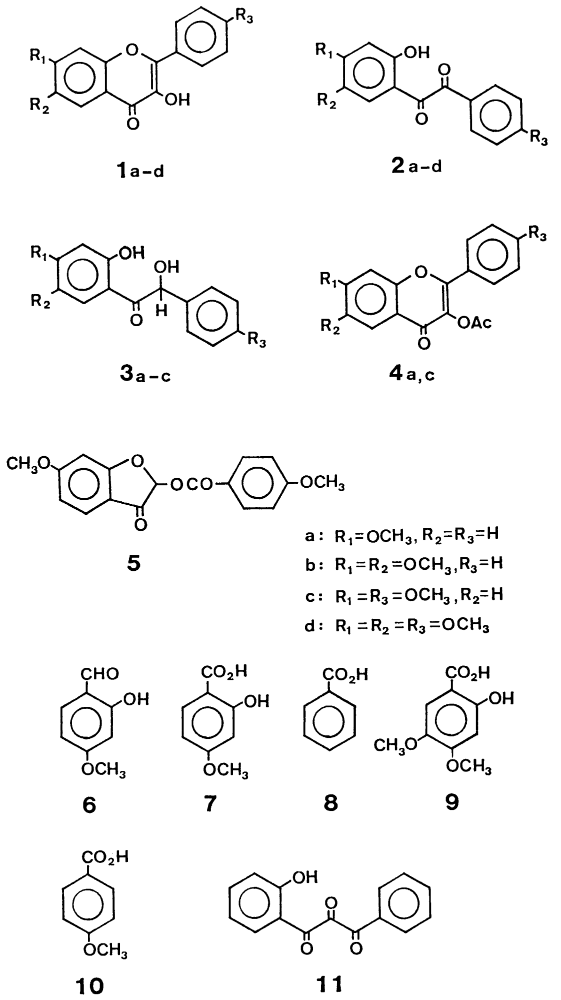
oxyphenyl)ethanone. This was further confirmed by the mass spectrum of **3c**, which showed prominent ions at *m/e* 151 and 123 due to α-cleavages to the carbonyl group, and at 137 and 107 due to α-cleavages to the alcoholic hydroxyl group (Fig. 1).

The third compound was found to be 3-acetoxy-4′,7-dimethoxyflavone (**4c**), which was identified with an authentic sample by a comparison of their IR spectra. The two carboxylic acids (**7** and **10**), as a mixture, were compared with the mixture of authentic samples on NMR, and then the methyl-esterified mixture was identified by a comparison of its GC retention time with that of the authentic specimen. When the reaction was conducted in a benzene solution, the yields of these products (**2c** and **3c**) were poor so that all the reactions hereafter were carried out in acetic acid.

When **1c** was oxidized with manganese(III) acetate, five products (**2c**, **5**, **6**, **7**, and **10**) were obtained. **6** was found to be 2-hydroxy-4-methoxybenzaldehyde. The NMR spectrum of **5** indicated the presence of a para-substituted benzoyl group [$\delta=8.09$ (2H, m) and 6.95 (2H, m)], three aromatic protons [$\delta=7.69$ (1H, d, $J=10$ Hz) and 6.53—6.84 (2H, m)], and a singlet [$\delta=6.50$ (1H)]. The mass spectrum of **5** showed prominent ions due to all the possible cleavages shown in Fig. 1. The IR spectrum of **5** showed a carbonyl absorption at 1745 $\mathrm{cm^{-1}}$. These spectral data are consistent with the structure of **5** shown in Scheme 2.

Three other 3-hydroxyflavones (**1a**, **1b**, and **1d**) were also oxidized with lead(IV) acetate to give 1-(2-hydroxyphenyl)-2-phenylethanediones (**2a**, **2b**, and **2d**), 2-hydroxy-1-(2-hydroxyphenyl)-2-phenylethanones (**3a** and **3b**), 3-acetoxy-7-methoxyflavone (**4a**), 2-hydroxybenzoic acids (**7** and **9**), and benzoic acids (**8** and **10**). The oxidations of **1a**, **1b**, and **1d** with manganese(III) acetate again gave 1-(2-hydroxyphenyl)-2-phenylethanediones (**2a**, **2b**, and **2d**).

In order to establish the nature of the decarbonylation reaction, the reaction was carried out using ^{14}C-labelled 3-hydroxyflavone. When 3-hydroxy-4′,6,7-trimethoxyflavone-3-^{14}C was oxidized with lead(IV) acetate, an inactive **2d** and an active carbon dioxide were obtained (Scheme 3), indicating that the $C_{(3)}$ was lost during the oxidation. That the 2-hydroxy-1-(2-hydroxyphenyl)-2-phenylethanones (**3a**—**c**) and the aldehyde (**6**) were isolated in the reactions seems to show the complex features of the reaction. It is well known that 1,2-diphenyl-2-hydroxyethanone is oxidized to give 1,2-diphenylethanedione, benzaldehyde, and benzoic acid by lead(IV) acetate.[4] Thus, this suggests that, *via* an unknown process, 3-hydroxyflavone

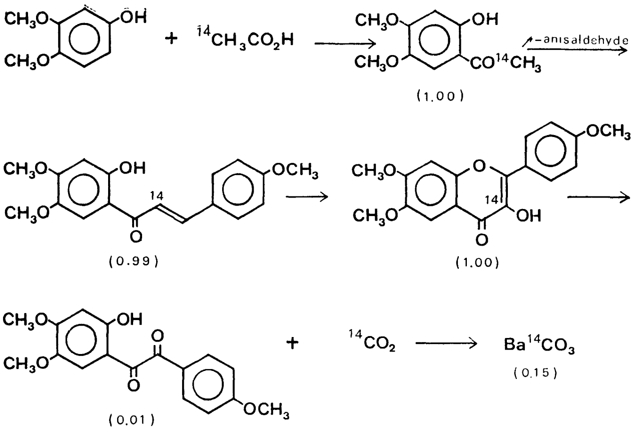


Scheme 2. 3-Hydroxyflavones and products in the oxidations of 3-hydroxyflavones with lead(IV) acetate and manganese(III) acetate.

Table 1. The reactions of 3-hydroxyflavones with lead(IV) acetate and manganese(III) acetate[a)]

Substrate	Oxidant	Products (yield/%[b)])								
		2	3	4	5	6	7	8	9	10
1a	$Pb(OAc)_4$	2	6	2			78	56		
1b	$Pb(OAc)_4$	13	1					17	56	
1c	$Pb(OAc)_4$	7	8	3			59			59
1d	$Pb(OAc)_4$	16							47	19
1a	$Mn(OAc)_3$	4					42	21		
1b	$Mn(OAc)_3$	1						29	14	
1c	$Mn(OAc)_3$	8			4	3	16			34
1d	$Mn(OAc)_3$	2							44	25

a) The reactions were carried out in acetic acid at the reflux temperature. b) Yields are based on the amount of 3-hydroxyflavone consumed. c) The yields of carboxylic acids (**7**, **8**, **9**, and **10**) are estimated from the NMR spectra.



Scheme 3. Synthesis and the oxidation of 3-hydroxy-4′,6,7-trimethoxyflavone-3-^{14}C (the figures under the formulae refer to the specific radioactivities of the compounds relative to the acetophenone).

is transformed into 1,2-diphenyl-2-hydroxyethanone, with is then oxidized to 1,2-dipehnylethanedione. However, it is still possible to assume another reaction pathway in which an open-chain triketone (**11**), formed from 3-hydroxyflavone by the oxidation, could give rise to 1,2-diphenylethanedione by decarbonylation.[5]

Experimental

All the ^1H NMR spectra were recorded for the deuteriochloroform solution with a Hitachi-Perkin-Elmer R 24 NMR spectrometer, with tetramethylsilane as the internal reference. The IR spectra were recorded for the chloroform solution with a JASCO IRA-1 grating spectrometer, while the mass spectra were measured with a Hitachi RMU-6M mass spectrometer. The melting points were determined with a Yanagimoto hot-stage apparatus and were not corrected. The radioactivities were recorded, for samples crystallized to a constant specific radioactivity, with an Aloka liquid scintillation spectrometer. The scintillator consisted of 0.4% DPO and 0.01% POPOP (Dojin Laboratories, Kumamoto) dissolved in toluene. Barium carbonate samples were suspended in a gel made up with 4% w/v CAB-O-SIL (Beckmann Instruments, Inc., U.S.A.). Sample counts were repeated twice; the maximum observed error was within 0.5%.

3-Hydroxyflavones. The 3-hydroxyflavones (**1a**—**d**) were prepared by the literature methods.[6,7]

Oxidation of 3-Hydroxyflavones with Lead(IV) Acetate. A typical procedure for the oxidation of 3-hydroxyflavones was as follows. To a 3-hydroxyflavone (500 mg) dissolved in boiling acetic acid (30 ml), lead(IV) acetate (2.0 equivalents) was added. After the removal of the acetic acid *in vacuo*, the residue was treated with 2 M hydrochloric acid (60 ml) and extracted with chloroform (100 ml). The chloroform solution was washed with an aqueous sodium hydrogencarbonate solution (100 ml) three times and then evaporated. The aqueous sodium hydrogencarbonate solution was acidified, and subsequent extraction with chloroform gave acidic products. The neutral products were separated on TLC, with chloroform as the developing solvent. The acidic products were identified by a comparison of their retention times as methyl esters and their NMR spectra with those of the authentic samples.

*Oxidation Products of 3-Hydroxy-7-methoxyflavone (**1a**).* *1-(2-Hydroxy-4-methoxyphenyl)-2-phenylethanedione (**2a**)*: Mp 82—83 °C (ethanol) (Found: C, 70.18; H, 4.73%. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72%); IR 1695 and 1635 cm^{-1}; NMR $\delta=11.82$ (1H, s, OH), 7.9—8.1 (2H, m), 7.3—7.7 (4H, m), 6.3—6.6 (2H, m), and 3.85 (3H, s, OCH_3); MS *m/e*=151, 123, 105, and 77.

*2-Hydroxy-1-(2-hydroxy-4-methoxyphenyl)-2-phenylethanone (**3a**)*: Mp 75—76 °C (ligroin) (Found: C, 69.56; H, 5.44%. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46%); IR 1640 and 3460 cm^{-1}; NMR $\delta=12.05$ (1H, s, OH), 7.50 (1H, d, $J=8$ Hz), 7.31 (5H, s, Ph), 6.15—6.5 (2H, m), 5.85 (1H, s), 4.3 (1H, broad s), and 3.75 (3H, s, OCH_3); MS *m/e*=151, 123, 107, and 77.

*3-Acetoxy-7-methoxyflavone (**4a**)*: Mp 172—174 °C (ethanol) (lit,[5] mp 176 °C).

*2-Hydroxy-4-methoxybenzoic Acid (**7**) and Benzoic Acid (**8**). Oxidation Products of 6,7-Dimethoxy-3-hydroxyflavone (**1b**).* *1-(4,5-Dimethoxy-2-hydroxyphenyl)-2-phenylethanedione (**2b**)*: Mp 171.5—172 °C (ethanol) (Found: C, 66.97; H, 5.04%. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93%); IR 1690 and 1630 cm^{-1}; NMR $\delta=11.83$ (1H, s, OH), 7.9—8.15 (2H, m), 7.3—7.7 (3H, m), 6.82 (1H, s), 6.56 (1H, s), 3.97 (3H, s, OCH_3), and 3.70 (3H, s, OCH_3); MS *m/e*=181, 153, 105, and 77.

*1-(4,5-Dimethoxy-2-hydroxyphenyl)-2-hydroxy-2-phenylethanone (**3b**)*: Mp 133—135 °C (ligroin); IR 1630 and 3440 cm^{-1}; NMR $\delta=11.94$ (1H, s, OH), 7.35 (5H, s, Ph), 6.79 (1H, s), 6.4 (1H, s), 5.8 (1H, s), 4.45 (1H, broad s), 3.87 (3H, s, OCH_3), and 3.65 (3H, s, OCH_3).

*4,5-Dimethoxy-2-hydroxybenzoic Acid (**9**) and Benzoic Acid (**8**). Oxidation Products of 4′,7-Dimethoxy-3-hydroxyflavone (**1c**).* *1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2c**)*: Mp 99—101 °C (ethanol) (Found: C, 66.92; H, 4.90%. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93%).

*2-Hydroxy-1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanone (**3c**)*: Mp 111—113 °C (ligroin) (Found: C, 66.41; H, 5.51%. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59%).

*3-Acetoxy-4′,7-dimethoxyflavone (**4c**)*: Mp 188—190 °C (lit,[7] mp 190 °C) (ethanol).

p-*Anisic Acid (**10**) and 2-Hydroxy-4-methoxybenzoic Acid (**7**). Oxidation Products of 3-Hydroxy-4′,6,7-trimethoxyflavone (**1d**).* *1-(4,5-Dimethoxy-2-hydroxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2d**)*: Mp 129—131 °C (ethanol) (Found: C, 64.35; H, 5.15%. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10%); IR 1680 and 1630 cm^{-1}; NMR $\delta=11.85$ (1H, s, OH), 7.96 (2H, m), 6.98 (2H, m), 6.86 (1H, s), 6.53 (1H, s), 3.92 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), and 3.70 (3H, s, OCH_3).

*3,4-Dimethoxy-2-hydroxybenzoic Acid (**9**) and* p-*Anisic Acid (**10**)*: Mp 185 °C.

Oxidation of 3-Hydroxyflavones with Manganese(III) Acetate. A typical procedure for the oxidation of 3-hydroxyflavones with manganese(III) acetate was as follows. A mixture of a 3-hydroxyflavone (500 mg), manganese(III) acetate[8] (3.8 equivalents), and acetic acid (30 ml) was heated under reflux for several minutes. After the subsequent removal of the acetic acid *in vacuo*, the residue was extracted with chloroform and separated in the manner described previously. **1a** gave **2a**, **7**, and **8**. **1b** yielded **2b**, **8**, and **9**. **1c** gave **2c**, 6-methoxy-2-(4-methoxybenzoyloxy)-3(2*H*)-benzofuranone (**5**); mp 163—164.5 °C (ethanol) (Found: C, 64.91; H, 4.60%. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49%); IR 1745 cm^{-1}; NMR $\delta=8.09$ (2H, m), 7.69 (1H, d), 6.95 (2H, m), 6.53—6.84 (2H, m), 6.50 (1H, s), 3.94 (3H, s, OCH_3), and 3.92 (3H, s, OCH_3); MS *m/e*=285, 179, 163, 151, 135, and 107, 2-hydroxy-4-methoxybenzaldehyde (**6**), mp 41 °C, **7**, and **10**. **1d** yielded **2d**, **9**, and **10**.

*1-(2-Benzyloxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2e**).* A mixture of 2′-benzyloxy-4,4′-dimethoxychalcone[9] (1 g), thallium(III) nitrate (3.2 g), methanol (6 ml), and 35% perchloric acid (3 ml) was stirred at room temperature for 2 h. Water (150 ml) was added to the reaction mixture, and then the mixture was extracted with chloroform (30 ml). After the removal of the chloroform, the resulting substance was purified by TLC, with chloroform as the developing solvent, to give **2e**; mp 114—119 °C (ethanol) (360 mg, 36%) (Found: C, 73.14; H, 5.30%. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36%); IR 1680 cm^{-1}; NMR δ=8.02 (1H, d, J=9 Hz), 7.62 (2H, m), 6.77 (2H, m), 6.9—7.2 (5H, m), 6.4—6.73 (2H, m), 4.85 (2H, s, $-CH_2-$), and 3.80 (6H, s, $2\times OCH_3$).

Debenzylation of 2e. **2e** (50 mg) was added to a mixture of 35% perchloric acid (10 ml) and methanol (16 ml), and the mixture was heated under reflux for 2.5 h. After the removal of the methanol *in vacuo*, the residue was extracted with chloroform (60 ml) and purified on TLC to give **2c**; mp 99—101 °C (ethanol) (34 mg, 89%).

4′,5′-Dimethoxy-2′-hydroxyacetophenone-2-^{14}C. A mixture of 3,4-dimethoxyphenol (10.6 g), a boron trifluoride–acetic acid complex (13 g), and sodium acetate-2-^{14}*C* (250 μCi, Radiochemical Center, Amersham, England) was heated at 100 °C for 25 min. The reaction mixture was then poured into 2 M hydrochloric acid (150 ml). The insoluble materials were dissolved in methanol, and the methanol solution was then added to the acid solution. After the removal of the methanol, the residue was extracted with benzene and the benzene solution was purified by means of a silica column yielding 4′,5′-dimethoxy-2′-hydroxyacetophenone-2-^{14}*C*; mp 112—113 °C (6.85 g; 54%; specific radioactivity, 1.50 μCi/mmol).

2′-Hydroxy-4,4′,5′-trimethoxychalcone-α-^{14}C. A mixture of 4′,5′-dimethoxy-2′-hydroxyacetophenone-2-^{14}*C* (6.3 g), *p*-anisaldehyde (5.0 g), 40% aqueous potassium hydroxide (50 ml), and ethanol (50 ml) was stirred at room temperature for 2 h. The reaction mixture was then poured into cold hydrochloric acid, and the precipitates were collected. These precipitates gave 2′-hydroxy-4,4′,5′-trimethoxychalcone-α-^{14}*C*; mp 133—135 °C (ethanol) (1.64 g; 14.3%; specific radioactivity, 1.48 μCi/mmol).

3-Hydroxy-4′,6,7-trimethoxyflavone-3-^{14}C. To a mixture of 2′-hydroxy-4,4′,5′-trimethoxychalcone-α-^{14}*C* (1.54 g), 22% aqueous potassium hydroxide (30 ml), and ethanol (90 ml), we added cold 15% hydrogen peroxide (20 ml). The reaction mixture was allowed to react for two days and then poured into 2 M hydrochloric acid. The precipitates were collected and recrystallized, giving 3-hydroxy-4′,6,7-trimethoxyflavone-3-^{14}*C*, mp 229.5—230 °C (ethanol) (740 mg; 47%; specific radioacitivity, 1.49 μCi/mmol).

Oxidation of 3-Hydroxy-4′,6,7-trimethoxyflavone-3-^{14}C *with Lead(IV) Acetate.* To 3-hydroxy-4′,6,7-trimethoxyflavone-3-^{14}*C* (250 mg) dissolved in boiling acetic acid (30 ml), lead(IV) acetate (676 mg) was added under a nitrogen stream, after which the reaction mixture was worked-up in a manner described previously, giving 1-(4,5-dimethoxy-2-hydroxyphenyl)-2-(4-methoxyphenyl)ethanedione (**2d**) (mp 128—130 °C (ethanol) (10 mg; 4.2%; specific radioactivity, 0.02 μCi/mmol)), carbon dioxide, which was later converted to barium carbonate (142 mg; 95%; specific radioactivity, 0.23 μCi/mmol), and *p*-anisic acid (**10**) (mp 185 °C (water) (40 mg; 28%; specific radioactivity, 0.01 μCi/mmol)).

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