The Oxidation of 3-(2-Hydroxyphenyl)coumarins with Lead Tetraacetate

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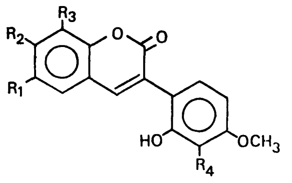
Five 3-(2-hydroxy-4-methoxyphenyl)coumarins (Ia—Ie) were oxidized with lead tetraacetate to the corresponding 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-ones (IIa—IIe) and 3-(1-acetoxy-4-methoxy-2-oxo-3,5-cyclohexadienyl)coumarins (IIIa, IIIb, and IIId). Four 3-(3,4-dimethoxy-2-hydroxy-phenyl)coumarins (If—Ii) gave the corresponding 3-(1-acetoxy-3,4-dimethoxy-2-oxo-3,5-cyclohexadienyl)coumarins (IIIf—IIIi).

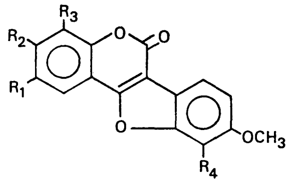
In the lead tetraacetate oxidations of phenolic compounds in which a hydroxyl group and a double bond are located in spatially suitable positions, an oxidative cyclization has often been observed.[1–5] A similar reaction of 3-(2-hydroxyphenyl)coumarin with lead tetraacetate is also expected to give 6*H*-benzofuro-[3,2-*c*][1]benzopyran-6-ones.

The 3-(2-hydroxyphenyl)coumarins (Ia—Ii) were prepared by the Perkin reaction of *o*-hydroxybenzaldehydes and *o*-hydroxyphenylacetic acids; the oxidations of Ia—Ii with lead tetraacetate were also carried out. The structures of the products were determined by examining their spectroscopic properties and by elemental analyses.

When the 3-(2-hydroxy-4-methoxyphenyl)coumarins (Ia—Ie) were oxidized, 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-ones—(IIa)(10%), (IIb)(22%), (IIc)(12%), (IId)(14%), and (IIe)(5%)—were obtained, together with 3-(1-acetoxy-4-methoxy-2-oxo-3,5-cyclohexadienyl)coumarins-(IIIa)(32%), (IIIb)(16%), and (IIId)-(26%). IIc was found to be identical with dimethylcoumestrol[6] by a comparison of their melting points and their spectral data.

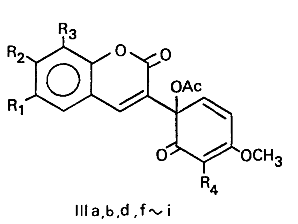


Ia~i



IIa~e

a R$_1$=R$_2$=R$_3$=R$_4$=H
b R$_1$=OCH$_3$, R$_2$=R$_3$=R$_4$=H
c R$_1$=R$_3$=R$_4$=H, R$_2$=OCH$_3$
d R$_1$=R$_2$=R$_4$=H, R$_3$=OCH$_3$
e R$_1$=R$_2$=OCH$_3$, R$_3$=R$_4$=H
f R$_1$=R$_2$=R$_3$=H, R$_4$=OCH$_3$
g R$_1$=R$_4$=OCH$_3$, R$_2$=R$_3$=H
h R$_1$=R$_3$=H, R$_2$=R$_4$=OCH$_3$
i R$_1$=R$_2$=H, R$_3$=R$_4$=OCH$_3$



IIIa,b,d,f~i

When the 3-(3,4-dimethoxy-2-hydroxyphenyl)coumarins (If—Ii) were oxidized, 3-(1-acetoxy-3,4-dimethoxy-2-oxo-3,5-cyclohexadienyl)coumarins—(IIIf)(75%), (IIIg)(82%), (IIIh)(63%), and (IIIi)(84%)—were obtained. In the cases of the oxidation of Ia—Ie, there were considerable amounts of undefined products which could not be purified. It was found that the 6H-benzofuro[3,2-*c*][1]benzopyran-6-ones (IIa—IIe) were best prepared when a 1.5-equivalent of lead tetraacetate was used in boiling benzene.

In contrast to the oxidations of 2′-hydroxychalcones[2,3] and 2-hydroxybenzophenones,[4] which yielded aurones and xanthones respectively in fairly good yields, 3-(2-hydroxyphenyl)coumarins undergo angular acetoxylation in the cyclohexadienone ring rather than ring closure. This could be ascribed to the nature of the phenoxyl radical formed from the 2-hydroxyphenyl group with lead tetraacetate.[7] The phenoxyl radical has an electrophilic character and, therefore, favors an attack on the α-position to one on the carbonyl in the case of 2′-hydroxychalcones, and one on the *p*-position to one on a methoxyl group in the case of 2-hydroxybenzophenones. However, the carbon atom at the 4-position of 3-(2-hydroxyphenyl)coumarin is electron-deficient, as it is an α,β-unsaturated lactone; therefore, the phenoxyl radical is less reactive in this site.

Although several other syntheses of 6*H*-benzofuro-[3,2-*c*][1]benzopyran-6-ones have been reported,[8–10] the oxidative cyclization of 3-(2-hydroxyphenyl)coumarin can be used in the synthesis of 9-oxygenated 6H-benzofuro[3,2-*c*][1]benzopyran-6-ones.

Experimental

All the ^{1}H NMR spectra were recorded for the deuteriochloroform solution, unless otherwise stated, with a Hitachi R 24 NMR spectrometer, with tetramethylsilane as the internal reference. The IR spectra were recorded either for the chloroform solution or for the KBr disk with a JASCO IRA-1 grating spectrometer, while the UV spectra were measured for the methanol solution with a Hitachi EPS-3T spectrophotometer. The melting points were determined with a Yanagimoto hot-stage apparatus and were uncorrected.

Preparations of 3-(2-Hydroxyphenyl)coumarins (Ia—Ii). The general procedure for the preparation of 3-(2-hydroxyphenyl)coumarin was as follows: a mixture of *o*-hydroxybenzaldehyde (10 mmol), *o*-hydroxyphenylacetic acid (10 mmol), acetic anhydride (24 mmol), sodium acetate (50 mmol), and acetic acid (40 ml) was heated under reflux for 24 h. After the removal of the acetic acid, the resulting mixture was triturated with water, and the precipitates were collected by filtration. The crude product was purified by recrystallization.

3-(2-Hydroxy-4-methoxyphenyl)coumarin (Ia); mp 171—172 °C (EtOH), 62%, $\nu_{\max}^{\text{KBr}}$: 3180 (OH) and 1700 cm^{-1} (C=O), δ: 3.82 (s, OCH$_3$), 6.4—6.65 (m, 2H, H$_{(3')}$ and H$_{(5')}$), 7.1—7.7 (m, 5H), 7.82 (s, H$_{(4)}$), and 8.0 (broad s, OH). Found: C, 71.35; H, 4.68%. Calcd for C$_{16}$H$_{12}$O$_4$: C, 71.63; H, 4.51%.

3-(2-Hydroxy-4-methoxyphenyl)-6-methoxycoumarin (Ib); mp 179—180 °C (EtOH), 92%, $\nu_{\max}^{\mathrm{KBr}}$: 3310 (OH) and 1710 cm^{-1} (C=O), δ: 3.80 (s, $\mathrm{OCH_3}$), 3.85 (s, $\mathrm{OCH_3}$), 6.4—6.7 (m, 2H, $\mathrm{H_{(3')}}$ and $\mathrm{H_{(5')}}$), 6.9—7.4 (m, 4H), 7.78 (s, $\mathrm{H_{(4)}}$), and 8.20 (broad s, OH). Found: C, 68.24; H, 4.78%. Calcd for $\mathrm{C_{17}H_{14}O_5}$: C, 68.45; H, 4.73%. 3-(2-Hydroxy-4-methoxyphenyl)-7-methoxycoumarin (Ic); mp 160—161 °C (EtOH), 79%, $\nu_{\max}^{\mathrm{KBr}}$: 3330 (OH) and 1715 cm^{-1} (C=O), δ: 3.80 (s, $\mathrm{OCH_3}$), 3.90 (s, $\mathrm{OCH_3}$), 6.5—7.3 (m, 5H), 7.50 (d, $\mathrm{H_{(5)}}$), 7.80 (s, $\mathrm{H_{(4)}}$), and 8.1 (broad s, OH). Found: C, 68.25; H, 4.78%. Calcd for $\mathrm{C_{17}H_{14}O_5}$: C, 68.45; H, 4.73%.

3-(2-Hydroxy-4-methoxyphenyl)-8-methoxycoumarin (Id); mp 182—183 °C ($\mathrm{CHCl_3}$–EtOH), 83%, $\nu_{\max}^{\mathrm{KBr}}$: 3260 (OH) and 1700 cm^{-1} (C=O), δ: 3.80 (s, $\mathrm{OCH_3}$), 3.98 (s, $\mathrm{OCH_3}$), 6.4—7.4 (m, 6H), 7.81 (s, $\mathrm{H_{(4)}}$), and 8.1 (s, OH). Found: C, 68.21; H, 4.71%. Calcd for $\mathrm{C_{17}H_{14}O_5}$: C, 68.45; H, 4.73%.

6,7-Dimethoxy-3-(2-hydroxy-4-methoxyphenyl) coumarin (Ie); mp 200—201 °C ($\mathrm{CHCl_3}$), 84%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 3240 (OH) and 1700 cm^{-1} (C=O), $\delta_{\mathrm{CF_3COOH}}$: 4.00 (s, $\mathrm{OCH_3}$), 4.10 (s, $2\times\mathrm{OCH_3}$), 6.7—7.5 (m, 5H), and 8.15 (s, $\mathrm{H_{(4)}}$). Found: C, 65.56: H, 4.94%. Calcd for $\mathrm{C_{18}H_{16}O_6}$: C, 65.85; H, 4.91%.

3-(3,4-Dimethoxy-2-hydroxyphenyl) coumarin (If); mp 203—204 °C ($\mathrm{CHCl_3}$–EtOH), 95%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 3500 (OH) and 1740 cm^{-1} (C=O), δ: 3.86 (s, $\mathrm{OCH_3}$), 3.90 (s, $\mathrm{OCH_3}$), 6.42 (s, OH), 6.52 (d, J=9 Hz, $\mathrm{H_{(5')}}$), 7.0—7.6 (m, 5H), and 7.83 (s, $\mathrm{H_{(4)}}$). Found: C, 68.35; H, 4.78%. Calcd for $\mathrm{C_{17}H_{14}O_5}$: C, 68.45; H, 4.73%.

3-(3,4-Dimethoxy-2-hydroxyphenyl)-6-methoxycoumarin (Ig); mp 181—182°C (EtOH), 82%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 3500 (OH) and 1735 cm^{-1} (C=O), δ: 3.82 (s, $\mathrm{OCH_3}$), 3.88 (s, $\mathrm{OCH_3}$), 392 (s, $\mathrm{OCH_3}$), 6.55 (d, J=9 Hz, $\mathrm{H_{(5')}}$), 6.55 (s, OH), 6.9—7.5 (m, 4H), and 7.82 (s, $\mathrm{H_{(4)}}$). Found: C, 65.69; H, 4.98%. Calcd for $\mathrm{C_{18}H_{16}O_6}$: C, 65.85; H, 4.91%.

3-(3,4-Dimethoxy-2-hydroxyphenyl)-7-methoxycoumarin (Ih); mp 136—137 °C (EtOH), 76%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 3500 (OH) and 1730 cm^{-1} (C=O), δ: 3.88 (s, $2\times\mathrm{OCH_3}$), 3.92 (s, $\mathrm{OCH_3}$), 6.52 (d, J=9 Hz, $\mathrm{H_{(5')}}$), 6.55 (broad s, OH), 6.8—7.5 (m, 4H), and 7.82 (s, $\mathrm{H_{(4)}}$). Found: C, 65.58; H, 4.81%. Calcd for $\mathrm{C_{18}H_{16}O_6}$: C, 65.85; H, 4.91%.

3-(3,4-Dimethoxy-2-hydroxyphenyl)-8-methoxycoumarin (Ii); mp 186—188 °C ($\mathrm{CHCl_3}$–EtOH), 91%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 3500 (OH) and 1740 cm^{-1} (C=O), δ: 3.88 (s, $\mathrm{OCH_3}$), 3.92 (s, $\mathrm{OCH_3}$), 3.96 (s, $\mathrm{OCH_3}$), 6.51 (d, J=9 Hz, $\mathrm{H_{(5')}}$), 6.50 (s, OH), 6.9—7.4 (m, 4H), and 7.84 (s, $\mathrm{H_{(4)}}$). Found: C, 65.79; H, 4.91%. Calcd for $\mathrm{C_{18}H_{16}O_6}$: C, 65.85; H, 4.96%.

Oxidation of 3-(2-Hydroxyphenyl)coumarins with Lead Tetraacetate. The general procedure for the oxidation of 3-(2-hydroxyphenyl)coumarin was as follows: to a solution of 3-(2-hydroxyphenyl)coumarin (1 mmol) in anhydrous benzene (30 ml), lead tetraacetate (1.5 mmol) was added; the mixture was then heated under reflux for 30 min. After the removal of the lead diacetate by filtration, the benzene was evaporated *in vacuo*. The resulting mixture was purified either by TLC or by recrystallization.

Ia yielded 9-methoxy-6*H*-benzofuro[3,2-*c*][1] benzopyran-6-one (IIa); mp 212—213 °C (EtOH), 10%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1740 cm^{-1}, $\lambda_{\max}$ (ε): 242 (35000), 334 (31100), and 345 nm (26900), δ: 3.88 (s, $\mathrm{OCH_3}$) and 6.9—7.1 (m, 7H) (Found: C, 71.99; H, 3.74%. Calcd for $\mathrm{C_{16}H_{10}O_4}$: C, 72.18; H, 3.79%); and 3-(1-acetoxy-4-methoxy-2-oxo-3,5-cyclohexadienyl) coumarin (IIIa); mp 184—186 °C (EtOH), 32%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1680 and 1740 cm^{-1}, $\lambda_{\max}$ (ε): 285 (14000) and 318 nm (10600), δ: 2.15 (s, OAc), 3.76 (s, $\mathrm{OCH_3}$), 5.68 (d, J=2.5 Hz, $\mathrm{H_{(3)}}$), 6.25 (dd, J=2.5, 10 Hz, $\mathrm{H_{(5)}}$), 6.58 (d, J=10 Hz, $\mathrm{H_{(6)}}$), 7.0—7.7 (m, 4H), and 7.84 (s, $\mathrm{H_{(4)}}$) (Found: C, 65.95; H, 4.32%. Calcd for $\mathrm{C_{18}H_{14}O_6}$: C, 66.25; H, 4.32%).

Ib gave 2,9-dimethoxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (IIb)(mp 191—192 °C (EtOH), 22%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1740 cm^{-1}, $\lambda_{\max}$ (ε): 235 (38000), 320 (12300), and 345 nm (20200), δ: 3.90 (s, $2\times\mathrm{OCH_3}$), 7.0—7.6 (m, 5H), and 7.90 (d, $\mathrm{H_{(7)}}$) (Found: C, 68.81; 4.05%. Calcd for $\mathrm{C_{17}H_{12}O_5}$: C, 68.91; H, 4.08%)) and 3-(1-acetoxy-4-methoxy-2-oxo-3,5-cyclohexadienyl)-6-methoxycoumarin (IIIb) (mp 176—177 °C (EtOH), 16%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1670 and 1740 cm^{-1}, $\lambda_{\max}$ (ε): 284 (20500) and 344 nm (10900), δ: 2.17 (s, OAc), 3.82 (s, $2\times\mathrm{OCH_3}$) 5.71 (d, J=2.5 Hz, $\mathrm{H_{(3')}}$), 6.26 (dd, J=2.5, 10 Hz, $\mathrm{H_{(5')}}$), 6.45 (d, J=10 Hz, $\mathrm{H_{(6')}}$), 6.9—7.3 (m, 3H), and 7.8 (s, $\mathrm{H_{(4)}}$) (Found: C, 63.75; H, 4.52%. Calcd for $\mathrm{C_{19}H_{16}O_7}$: C, 64.04; H, 4.53%).

Ic yielded 3,9-dimethoxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (IIc); mp 198—199 °C (lit,[6] mp 197 °C), 12%.

Id gave 4,9-dimethoxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (IId) (mp 250—251 °C (EtOH), 14%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1740 cm^{-1}, $\lambda_{\max}$ (ε): 242 (28800) and 335 nm (19900), δ: 3.99 (s, $\mathrm{OCH_3}$), 4.05 (s, $\mathrm{OCH_3}$) and 6.9—7.8 (m, 6H) (Found: C, 68.77; H, 4.11%. Calcd for $\mathrm{C_{17}H_{12}O_5}$: C, 68.91; H, 4.08%) and 3-(1-acetoxy-4-methoxy-2-oxo-3,5-cyclohexadienyl)-8-methoxycoumarin (IIId) (mp 226—228 °C (EtOH), 38%, $\nu_{\max}^{\mathrm{KBr}}$: 1670, 1740, and 1770 cm^{-1}, $\lambda_{\max}$ (ε): 257 (15400) and 301 nm (13500), δ: 2.15 (s, OAc), 3.77 (s, $\mathrm{OCH_3}$), 3.80 (s, $\mathrm{OCH_3}$), 5.65 (d, J=2.5 Hz, $\mathrm{H_{(3')}}$), 6.13 (dd, J=2.5, 10 Hz, $\mathrm{H_{(5')}}$), 6.6—6.9 (m, 3H), 7.30 (d, $\mathrm{H_{(5)}}$), and 7.71 (s, $\mathrm{H_{(4)}}$) (Found: C, 63.74; H, 4.47%. Calcd for $\mathrm{C_{19}H_{16}O_7}$: C, 64.04; H, 4.53%)).

Ie yielded 2,3,9-trimethoxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (IIe); mp 253—254 °C (EtOH), 5%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1740 cm^{-1}, $\lambda_{\max}$ (ε): 235 (32900) and 353 nm (29800), δ: 3.90 (s, $\mathrm{OCH_3}$), 3.96 (s, $\mathrm{OCH_3}$) 4.00 (s, $\mathrm{OCH_3}$), 6.96 (s, 1H), 7.11 (s, 1H), 6.9—7.3 (m, 2H), and 7.88 (d, J=8.5 Hz, $\mathrm{H_{(7)}}$) (Found: C, 66.44; H, 4.39%. Calcd for $\mathrm{C_{18}H_{14}O_6}$: C, 66.25; H, 4.32%).

If gave 3-(1-acetoxy-3,4-dimethoxy-2-oxo-3,5-cyclohexadienyl)coumarin (IIIf); mp 145—146 °C (EtOH), 75%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1660 and 1740 cm^{-1}, $\lambda_{\max}$ (ε): 350 (12600) and 390 nm (inflection) (9720), δ: 2.15 (s, OAc), 3.52 (s, $\mathrm{OCH_3}$), 3.80 (s, $\mathrm{OCH_3}$), 5.53 (d, J=8.5 Hz, $\mathrm{H_{(5')}}$), 7.1—7.6 (m, 4H), 7.74 (d, J=8.5 Hz, $\mathrm{H_{(6')}}$), and 8.01 (s, $\mathrm{H_{(4)}}$) (Found: C, 63.39; H, 4.76%. Calcd for $\mathrm{C_{19}H_{16}O_7\cdot 1/2C_2H_5OH}$: C, 63.35; H, 5.02%.)

Ig yielded 2-(1-acetoxy-3,4-dimethoxy-2-oxo-3,5-cyclohexadienyl)-6-methoxycoumarin (IIIg); mp 190—192 °C (benzene), 82%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1650 and 1740 cm^{-1}, $\lambda_{\max}$ (ε): 376 nm (12700), δ: 2.18 (s, OAc), 3.49 (s, $\mathrm{OCH_3}$), 3.80 (s, $2\times\mathrm{OCH_3}$), 5.45 (d, J=8.5 Hz, $\mathrm{H_{(5')}}$), 6.8—7.3 (m, 3H), 7.70 (d, J=8.5 Hz, $\mathrm{H_{(6')}}$), and 7.94 (s, $\mathrm{H_{(4)}}$) (Found: C, 62.19; H, 4.71%. Calcd for $\mathrm{C_{20}H_{18}O_8}$: C, 62.14; H, 4.70%).

Ih yielded 3-(1-acetoxy-3,4-dimethoxy-2-oxo-3,5-cyclohexadienyl)-7-methoxycoumarin (IIIh); mp 178—179 °C (benzene–EtOH), 63%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1650 and 1740 cm^{-1}, $\lambda_{\max}$ (ε): 376 nm (12600), δ: 2.16 (s, OAc), 3.54 (s, $\mathrm{OCH_3}$), 3.69 (s, $\mathrm{OCH_3}$), 3.75 (s, $\mathrm{OCH_3}$), 5.50 (d, J=8.5 Hz, $\mathrm{H_{(5')}}$), 6.7—7.0 (m, 2H), 7.40 (d, $\mathrm{H_{(5)}}$), 7.68 (d, J=8.5 Hz, $\mathrm{H_{(6')}}$), and 7.92 (s, $\mathrm{H_{(4)}}$) (Found: C, 62.27; H, 4.78%. Calcd for $\mathrm{C_{20}H_{18}O_8}$: C, 62.17; H, 4.70%).

Ii gave 3-(1-acetoxy-3,4-dimethoxy-2-oxo-3,5-cyclohexadienyl)-8-methoxycoumarin (IIIi); mp 180—181 °C (benzene), 84%, $\nu_{\max}^{\mathrm{CHCl_3}}$: 1650 and 1740 cm^{-1}, $\lambda_{\max}$ (ε): 350 (11200) and 390 nm (inflection) (9100), δ: 2.15 (s, OAc), 3.47 (s, $\mathrm{OCH_3}$), 3.75 (s, $\mathrm{OCH_3}$), 3.91 (s, $\mathrm{OCH_3}$), 5.43 (d, J=8.5 Hz, $\mathrm{H_{(5')}}$), 6.9—7.3 (m, 3H), 7.80 (d, J=8.5 Hz, $\mathrm{H_{(6')}}$), and 7.96 (s, $\mathrm{H_{(4)}}$) (Found: 62.26; H, 4.73%. Calcd for $\mathrm{C_{20}H_{18}O_8}$: C, 62.17; H, 4.70%).

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