Oxidation of 2-Aryl-4*H*-1-benzopyrans with Potassium Permanganate

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The oxidation of twelve 2-aryl-4*H*-1-benzopyrans with potassium permanganate in acetone gave the corresponding flavones in excellent yields.

Flavones can be synthesized from 2'-hydroxychalcones[1] or from flavanones[2] or they can be synthesized from *o*-(benzoyloxy)acetophenones by the Baker-Venkataraman rearrangement followed by cyclization[3] or from *o*-hydroxyacetophenone and aromatic acid anhydride by Allan-Robinson condensation.[4] Flavones can also be formed in reactions with flavylium chloride.[5] In a previous publication,[6] Ashihara *et al.* have reported that the oxidation of 2-aryl-2*H*-1-benzopyrans with potassium permanganate in acetone gives the corresponding flavones in moderate yields. The oxidation of twelve 2-aryl-4*H*-1-benzopyrans with potassium permanganate which produce flavones in 17—81% yields, are also reported by these authors. This procedure provides a simple method for the preparation of flavones.

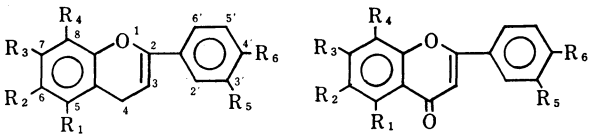
The 2-aryl-4*H*-1-benzopyrans (Ia—i) were prepared by lithium aluminium hydride reduction[7] of 2-aryl-1-benzopyrylium chlorides. The structures of the new 2-aryl-4*H*-1-benzopyrans were confirmed by examining their NMR spectra and by elemental analysis.

When 7-methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (Ig) was oxidized in acetone with potassium permanganate for molar ratios of 1:3, 1:4, and 1:5 (entries 7, 8, and 9 in Table 1), 4',7-dimethoxyflavone (IIg) was obtained in 74, 81, and 72% yields, respectively. Therefore, the oxidation of other 2-aryl-4*H*-1-benzopyrans was carried out for molar ratios of 1:4 until all the potassium permanganate added had been consumed. When the oxidation of Ig was carried out in pyridine or in *t*-butyl alcohol (entries 10 and 11), poor yields were observed (61% in pyridine and 65% in *t*-butyl alcohol). The oxidation of Ig in acetic acid (entry 12) gave *p*-anisic acid (III). Jurd[8] has reported that hydrolysis of Ig with aqueous acetic acid gives 3-(2-hydroxy-4-methoxyphenyl)-4'-methoxypropiophenone (IV). This indicates that Ig is unstable under the reaction conditions and, in fact, upon treatment of Ig with acetic acid containing a trace of water, IV was obtained. It appears that Ig was hydrolyzed under the reaction conditions to give IV, which was then oxidized with potassium permanganate to *p*-anisic acid (III). With 5,7-dimethoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (Ik), the yield of IIk was low (17%, entry 16) accompanied by many unidentified products. For the oxidation of 2-aryl-2*H*-1-benzopyran[6] with potassium permanganate, it was observed that the methoxyl group at position 2' causes a decrease in the yield of flavone and this is ascribed to the steric hindrance of the methoxyl group towards the attacking reagent. It appears that a similar steric effect could also explain the low yield of IIk: the methoxyl group at position 5 may hinder the approach of the reagent to the methylene group in Ik. An unsuccessful attempt was made to isolate products which could be formed by the attack of the reagent at position 2 or 3.

2-*p*-Tolyl-4*H*-1-benzopyran (Ie) gave 4'-methylflavone (IIe) (entry 5), indicating that the reaction can be adapted to the preparation of alkylated flavones.

Table 1. Oxidation of 2-aryl-4*H*-1-benzopyrans (I) with potassium permanganate

Entry	Substrate	Reaction conditions			Product (% yield)
		Molar ratio of I: $KMnO_4$	Time (h)	Solvent	
1	Ia[13]	1:4	1	acetone	IIa[18] (64)
2	Ib	1:4	1.5	acetone	IIb [5] (78)
3	Ic	1:4	3	acetone	IIc[19] (67)
4	Id[14]	1:4	2	acetone	IId[20] (72)
5	Ie	1:4	2.5	acetone	IIe[21] (64)
6	If[15]	1:4	2	acetone	IIf[22] (77)
7	Ig[16]	1:3	0.25	acetone	IIg[23] (74)
8	Ig	1:4	2.5	acetone	IIg (81)
9	Ig	1:5	10	acetone	IIg (72)
10	Ig	1:4	6	pyridine	IIg (61)
11	Ig	1:4	2.5	*t*-butyl alcohol	IIg (65)
12	Ig	1:4	7	acetic acid	III (97)
13	Ih	1:4	2	acetone	IIh[24] (77)
14	Ii	1:4	2	acetone	IIi (63)
15	Ij	1:4	3	acetone	IIj (71)
16	Ik[17]	1:4	1	acetone	IIk[26] (17)
17	Il	1:4	3	acetone	III [27] (74)



Ia—II IIa—III

a $R_1=R_2=R_3=R_4=R_5=R_6=H$
b $R_1=R_3=R_4=R_5=R_6=H$, $R_2=OCH_3$
c $R_1=R_2=R_4=R_5=R_6=H$, $R_3=OCH_3$
d $R_1=R_2=R_3=R_4=R_5=H$, $R_6=OCH_3$
e $R_1=R_2=R_3=R_4=R_5=H$, $R_6=CH_3$
f $R_1=R_3=R_4=R_5=H$, $R_2=R_6=OCH_3$
g $R_1=R_2=R_4=R_5=H$, $R_3=R_6=OCH_3$
h $R_1=R_2=R_4=R_5=H$, $R_3=OCH_3$, $R_6=OCH_2Ph$
i $R_1=R_2=R_3=R_5=H$, $R_4=R_6=OCH_3$
j $R_1=R_2=R_3=R_4=H$, $R_5=R_6=OCH_3$
k $R_2=R_4=R_5=H$, $R_1=R_3=R_6=OCH_3$
l $R_1=R_2=R_4=H$, $R_3=R_5=R_6=OCH_3$

Fig. 1.

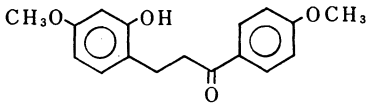


Fig. 2.

The oxidation of 2-(*p*-benzyloxyphenyl)-7-methoxy-4*H*-1-benzopyran (Ih) also gave the corresponding flavone (IIh) (entry 13). This suggests that a hydroxylated flavone can be synthesized by debenzylation of IIh.

It should be noted that the oxidation of 2-aryl-4*H*-1-benzopyran with potassium permanganate is also interesting in connection with the biogenetic type transformations of the 2-aryl-2*H*-1-benzopyrans into 3-flavanols,[9,10] 4-flavanols,[11,12] 3,4-flavandiols,[10,11] and 3,4-epoxyflavans.[10]

Experimental

All ^1H NMR spectra were recorded with a Hitachi R 24 NMR spectrometer with TMS as an internal standard. The IR spectra were recorded with a JASCO grating spectrometer. The UV spectra were recorded with a Hitachi EPS-3T spectrophotometer. Melting points were determined on a Yanagimoto micro hot-stage and are uncorrected.

Preparation of 2-Aryl-4H-1-benzopyrans (Ib,c,e,h,i,j, and l). A typical preparation of a 2-aryl-4*H*-1-benzopyran was carried out as follows. A mixture of 2-aryl-1-benzopyrylium chloride (10 mmol) (2-aryl-1-benzopyrylium chloride was prepared by condensing a *o*-hydroxybenzaldehyde and an acetophenone in ethyl acetate with dry hydrogen chloride), lithium aluminium hydride (0.7 g), and anhydrous ether (100 ml) was stirred at 0 °C until the color of the 2-aryl-1-benzopyrylium chloride disappeared (3—5 h). After the removal of the ether, the resulting solid was triturated with benzene and the benzene solution was then filtered through a short silica gel column. The filtrate was evaporated *in vacuo* to give 2-aryl-4*H*-1-benzopyran as crystals which were recrystallized from methanol. The 2-aryl-4*H*-1-benzopyrans were somewhat unstable compounds and colored on exposure to air at room temperature, but could be stored for a long time in a refrigerator.

6-Methoxy-2-phenyl-4H-1-benzopyran (Ib): Mp 104—105 °C, 74% yield, IR ($CHCl_3$) 1695 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 245 (23800) and 296 nm (4460), NMR (CCl_4) δ=3.50 (2H, d, J=3.5 Hz, $-CH_2-$), 3.69 (3H, s, OCH_3), 5.30 (1H, t, J=3.5 Hz, $H_{(3)}$), 6.54 (1H, d, J=2.5 Hz, $H_{(5)}$), 6.55 (1H, dd, J=9.0 and 2.5 Hz, $H_{(7)}$), 6.86 (1H, d, J=9.0 Hz, $H_{(8)}$), and 7.2—7.7 (5H, m, Ph). Found: C, 80.49; H, 5.83%. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92%.

7-Methoxy-2-phenyl-4H-1-benzopyran (Ic): Mp 65—66 °C, 61 % yield, IR ($CHCl_3$) 1695 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 237 (19100) and 279 nm (5550), NMR (CCl_4) δ=3.49 (2H, d, J=3.7 Hz, $-CH_2-$), 3.75 (3H, s, OCH_3), 5.42 (1H, t, J=3.7 Hz, $H_{(3)}$), 6.49 (1H, dd, J=9.5 and 2.5 Hz, $H_{(6)}$), 6.49 (1H, d, J=2.5 Hz, $H_{(8)}$), 6.87 (1H, m, $H_{(5)}$), and 7.2—7.7 (5H, m, Ph). Found: C, 79.13; H, 5.79%. Calcd for $C_{16}H_{14}O_2 \cdot 1/4\ H_2O$: C, 79.15; H, 6.02%.

2-p-Tolyl-4H-1-benzopyran (Ie): Mp 90—91 °C, 56% yield, IR ($CHCl_3$) 1695 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 244 (21900) and 281 nm (5310), NMR (CCl_4) δ=2.36 (3H, s, CH_3), 3.53 (2H, d, J=3.5 Hz, $-CH_2-$), 5.36 (1H, t, J=3.5 Hz, $H_{(3)}$), 6.7—7.3 (6H, m, $H_{(3')}$, $H_{(5')}$, and $H_{(5-8)}$), and 7.53 (2H, m, $H_{(2')}$ and $H_{(6')}$). Found: C, 86.16; H, 6.37%. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35%.

2-(p-Benzyloxyphenyl)-7-methoxy-4H-1-benzopyran (Ih): Mp 138—139 °C, 71% yield, IR ($CHCl_3$) 1690 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 249 (24500) and 277 nm (12100), NMR ($CDCl_3$) δ=3.47 (2H, d, J=3.8 Hz, $-CH_2-$), 3.76 (3H, s, OCH_3), 5.08 (2H, s, $-CH_2-$), 5.36 (1H, t, J=3.8 Hz, $H_{(3)}$), 6.58 (1H, dd, J=9.0 and 2.5 Hz, $H_{(6)}$), 6.58 (1H, d, J=2.5 Hz, $H_{(8)}$), 6.98 (3H, m, $H_{(5)}$, $H_{(3')}$, and $H_{(5')}$), 7.40 (5H, m, Ph), and 7.58 (2H, m, $H_{(2')}$ and $H_{(6')}$). Found: C, 80.07; H, 5.85%. Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85%.

8-Methoxy-(p-methoxyphenyl)-4H-1-benzopyran (Ii): Mp 91—92 °C, 49% yield, IR ($CHCl_3$) 1697 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 251 (22600) and 279 nm (9670), NMR (CCl_4) δ=3.48 (2H, d, J=3.5 Hz, $-CH_2-$), 3.72 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.31 (1H, t, J=3.5 Hz, $H_{(3)}$), 6.4—7.4 (3H, m, $H_{(5)}$, $H_{(6)}$, and $H_{(7)}$), 6.74 (2H, m, $H_{(3')}$ and $H_{(5')}$), and 7.53 (2H, m, $H_{(2')}$ and $H_{(6')}$). Found: C, 75.85; H, 6.07%. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%.

2-(3,4-Dimethoxyphenyl)-4H-1-benzopyran (Ij): Mp 107—108 °C, 35% yield, IR ($CHCl_3$) 1696 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 249 (17400) and 287 nm (8060), NMR (CCl_4) δ 3.54 (2H, d, J=3.5 Hz, $-CH_2-$), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.27 (1H, t, J=3.5 Hz, $H_{(3)}$), 6.6—7.3 (7H, m, aromatic). Found: C, 75.80; H, 5.95%. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%.

2-(3,4-Dimethoxyphenyl)-7-methoxy-4H-1-benzopyran (Il): Mp 128—129 °C, 66% yield, IR ($CHCl_3$) 1695 cm^{-1} (C=C), UV (MeOH) λ_{max} (ε) 249 (15600) and 280 (10100), NMR ($CDCl_3$) δ=3.46 (2H, d, J=3.5 Hz, $-CH_2-$), 3.77 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.36 (1H, t, J=3.5 Hz, $H_{(3)}$), and 6.5—7.4 (6H, m, aromatic). Found: 72.28; H, 6.11%. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08%.

Oxidation of 2-Aryl-4H-1-benzopyrans with Potassium Permanganate. A typical oxidation of a 2-aryl-4*H*-1-benzopyran with potassium permanganate was carried out as follows. A mixture of a 2-aryl-4*H*-1-benzopyran (1 mmol), potassium permanganate (3—5 mmol), and an appropriate solvent (30 ml) was stirred at room temperature until the color of the potassium permanganate disappeared (the time required is shown in the table). The 2-aryl-4*H*-1-benzopyran was also consumed within that time, as confirmed by TLC. The reaction mixture was filtered and the manganese dioxide formed was washed with chloroform. The combined filtrate was then evaporated and the resulting solid was recrystallized to give II. In the case of Ik, products were separated on TLC by eluting with chloroform and then recrystallized. The yields are based on the amount 2-aryl-4*H*-1-benzopyran used. IIa, mp 97 °C (benzene–light

petroleum) (lit,[18] mp 97 °C); IIb, mp 160—161 °C (MeOH) (lit,[5] mp 162 °C); IIc, mp 109—110 °C (MeOH) (lit,[19] mp 110—111 °C); IId, mp 153—154 °C (benzene–light petroleum) (lit,[20] mp 157—158 °C); IIe, mp 112—113 °C (aq MeOH) (lit,[21] mp 116 °C); IIf, mp 204—205 °C (MeOH) (lit,[22] mp 194—195 °C); IIg, 150—151 °C (MeOH) (lit,[23] mp 144 °C); IIh, mp 192—193 °C (MeOH) (lit,[24] mp 194 °C); IIi, mp 138—139 °C (MeOH), IR ($CHCl_3$) 1648 cm^{-1} (C=O), UV (MeOH) $\lambda_{max}(\varepsilon)$ 231 (19400), 270 (16300), and 324 nm (28000), NMR ($CDCl_3$) δ=3.88 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 6.70 (1H, s, $H_{(3)}$), 7.00 (2H, m, $H_{(3')}$ and $H_{(5')}$), 7.15 (1H, dd, J=9.0 and 2.5 Hz, $H_{(7)}$), 7.30 (1H, t, J=9.0 Hz, $H_{(6)}$), 7.38 (1H, dd, J=9.0 and 2.5 Hz, $H_{(5)}$), and 7.91 (2H, m, $H_{(2')}$ and $H_{(6')}$) (Found: C, 72.16; H, 5.02%. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%); IIj, mp 151—152 °C(MeOH) (lit,[25] mp 155 °C); IIk, mp 155—156 °C (MeOH) (lit,[26] mp 156 °C); IIl, mp 174—175 °C (MeOH) (lit,[27] mp 176 °C).

*Hydrolysis of 7-Methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (Ig)(3-(2-Hydroxy-4-methoxyphenyl)-4′-methoxypropiophenone(IV)).* A mixture of Ig (134 mg) and acetic acid (15 ml) containing a drop of water was stirred at room temperature for 2 h. After the removal of the acetic acid *in vacuo*, the resulting liquid was separated on a silica gel plate by eluting with chloroform. The crude material was recrystallized from aqueous methanol to give IV (109 mg, 73%), mp 77—78 °C (lit,[8] mp 78 °C).

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