A New Synthesis of Flavones by the Reaction of 2-Phenyl-2*H*-1-benzopyrans with Potassium Permanganate

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(Received April 11, 1977)

The oxidation of ten 2-phenyl-2*H*-1-benzopyrans with potassium permanganate in acetone has been found to give the corresponding flavones in 8—73% yields. The reaction mechanism is discussed on the basis of the substituent effect and the oxidations of related compounds.

Flavones can be synthesized from 2'-hydroxychalcones[1] or from flavanones[2] or they can be synthesized from *o*-benzoyloxyacetophenones by the Baker-Venkataraman rearrangement followed by cyclization[3] or from *o*-hydroxyacetophenones and aromatic acids by the Allan-Robinson condensation.[4] We have investigated the possibility of transforming 2-phenyl-2*H*-1-benzopyrans into flavones; this could be accomplished by the oxidation of the former with potassium permanganate. The procedure is very simple and can be utilized as an easy preparation method for flavones when 2-phenyl-2*H*-1-benzopyrans are readily available.

The 2-phenyl-2*H*-1-benzopyrans (IIa—IIj) were prepared from the corresponding 2'-hydroxychalcones (Ia—Ij) by sodium borohydride reduction, followed by treatment with aqueous acetic acid. The structures of the new 2-phenyl-2*H*-1-benzopyrans were confirmed by examining their NMR spectra and by elemental analyses.

When the 2-phenyl-2*H*-1-benzopyrans (IIa—IIj) were oxidized with potassium permanganate in a molar ratio of 1:4 in acetone, flavones (IIIa—IIIj) were obtained in 8—73% yields; they were identified by comparing their melting points with those reported and by examining their NMR spectra. When the reaction was carried out with potassium permanganate as an oxidizing reagent in a molar ratio less than 1:4 (Table 1, entries 5 and 12) or more than 1:4 (entries 9 and 24), it gave a rather poor yield because of the presence of some unchanged II or of tarry products. The change in the reaction time did not alter the yield significantly (entries 6, 7, and 8). However, 2-phenyl-2*H*-1-benzopyran (IIa) and 7-methoxy-2-phenyl-2*H*-1-benzopyran (IIb) had longer reaction times, 16 h (entry 2) and 12 h (entry 4), respectively, and the yields after 4 h were much lower (entries 1 and 3). It is thus considered that the 4'-methoxyl group and two methoxyl groups in the ring A may accelerate the reaction rate. The yield of 2',3',4',7-tetramethoxyflavone (IIIe) is extremely low (entry 16). This may indicate that the 2'-methoxyl group has a steric hindrance towards potassium permanganate which attacks the hydrogen at C(2)-position. There were many unidentified products in this case. When the reaction was conducted in pyridine in place of acetone, the yields and the reaction times were not affected (entries 14 and 21). The reaction in acetic acid, on the other hand, gave the lowest figure (entry 22). The change of the oxidizing reagent from potassium permanganate to chromium trioxide-pyridine complex[5] caused a decrease in the yield of III (entry 11).

In order to explain the above observations, we assumed three probable reaction mechanisms. The reaction may proceed through a cyclic intermediate (V) which is known to be involved in the reaction of olefins with potassium permanganate to give α-diols or α-ketols[6] (pathway a). The reaction could be of an ionic nature and proceed *via* flavylium cation (VI) (pathway b). Or the reaction may proceed *via* radical intermediate (VII) (pathway c).

Pathway a is not attractive since it fails to explain the facts that the reaction rate was enhanced by the 4'-methoxyl group and that the steric hindrance was exercised by the 2'-methoxyl group which is located far from the ethylenic double bond in IIe. Pathway a is completely excluded for the case when 7-methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (IV) was readily oxidized to give IIId in a yield comparable to that obtained in the oxidation of IId. Isomerization of IId to IV is not likely to occur in the reaction conditions, as IId was stable in 0.75% potassium hydroxide-moist acetone-d_6 even after 24 h, as observed by NMR spectra. The fact that the reaction time of IV (2.5 h) was shorter than that of IId (4 h) also argues against the pathway IV→IId→V (R=CH_3O–, Ar=*p*-CH_3O-C_6H_4–)→IIId.

Pathway b seemed to be consistent with all our observations. The electron-donating group, such as the methoxyl group in the rings A and B, would make the hydrogen at C(2)-position easier to be removed by an oxidant, and the methoxyl group at C(2')-position would hinder the approach of the oxidant by steric reasons. The fact that the oxidation of IV also yielded IIId may indicate that 4',7-dimethoxyflavylium ion (VI; R=CH_3O–, Ar=*p*-CH_3O-C_6H_4–) could be an intermediate. However, when we examined the oxidation of VI (R=CH_3O–, Ar=*p*-CH_3O-C_6H_4–) under similar conditions, it gave a complex mixture of products in which IIId was not found. This suggests that pathway b should also be eliminated.

Pathway c will account for the substituent effects due to the methoxyl groups in rings A and B, and for the identical results of the oxidations of 2-phenyl-2*H*-1-benzopyrans (II) and 2-phenyl-4*H*-1-benzopyran. When the reaction was carried out in the presence of 2,6-di-*t*-butylphenol (entry 15) in the hope of trapping the radical intermediate (VII), whose presence has been successfully demonstrated in the reaction of 2'-hydroxychalcone with lead tetraacetate using 3,5-dimethoxy-

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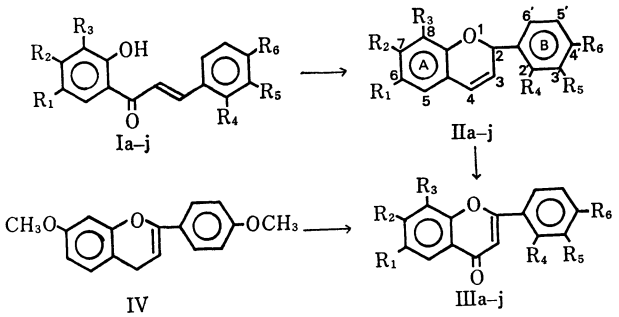
Table 1. The reactions of 2-phenyl-2*H*-1-benzopyrans(II) and 7-methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran(IV)

Entry	Substrate	Reaction conditions				Flavone (yield, %)
		Oxidant	Molar ratio	Time(h)	Solvnt	
1	IIa[12]	$KMnO_4$	1 : 4	4	acetone	IIIa[15] (27)
2	IIa	$KMnO_4$	1 : 4	16	acetone	IIIa (44)
3	IIb	$KMnO_4$	1 : 4	4	acetone	IIIb[16] (31)
4	IIb	$KMnO_4$	1 : 4	12	acetone	IIIb (50)
5	IIc[10]	$KMnO_4$	1 : 3	4	acetone	IIIc[17] (53)
6	IIc	$KMnO_4$	1 : 4	4	acetone	IIIc (59)
7	IIc	$KMnO_4$	1 : 4	5	acetone	IIIc (60)
8	IIc	$KMnO_4$	1 : 4	8	acetone	IIIc (60)
9	IIc	$KMnO_4$	1 : 4.5	5	acetone	IIIc (29)
10	IIc	$KMnO_4$[a]	1 : 4	4	acetone	IIIc (55)
11	IIc	CrO_3py_2	1 : 8	24	CH_2Cl_2	IIIc (34)
12	IId[10]	$KMnO_4$	1 : 3	4	acetone	IIId[18] (48)
13	IId	$KMnO_4$	1 : 4	4	acetone	IIId (72)
14	IId	$KMnO_4$	1 : 4	4	pyridine	IIId (73)
15	IId b)	$KMnO_4$	1 : 6	2	acetone	IIId (34)
16	IIe	$KMnO_4$	1 : 4	2	acetone	IIIe (8)
17	IIf	$KMnO_4$	1 : 4	2	acetone	IIIf[18] (58)
18	IIg[8]	$KMnO_4$	1 : 4	4	acetone	IIIg[19] (42)
19	IIh	$KMnO_4$	1 : 4	4	acetone	IIIh[20] (39)
20	IIi[13]	$KMnO_4$	1 : 4	4	acetone	IIIi[21] (64)
21	IIi	$KMnO_4$	1 : 4	4	pyridine	IIIi (51)
22	IIi	$KMnO_4$	1 : 4	4	CH_3COOH	IIIi (5)
23	IIj[8]	$KMnO_4$	1 : 4	4	acetone	IIIj[21] (68)
24	IIj	$KMnO_4$	1 : 5	2.5	acetone	IIIj (49)
25	IV[14]	$KMnO_4$	1 : 3	2.5	acetone	IIId (74)
26	IV	$KMnO_4$	1 : 4	2.5	acetone	IIId (33)
27	IV	CrO_3py_2	1 : 8	24	CH_2Cl_2	IIId (14)

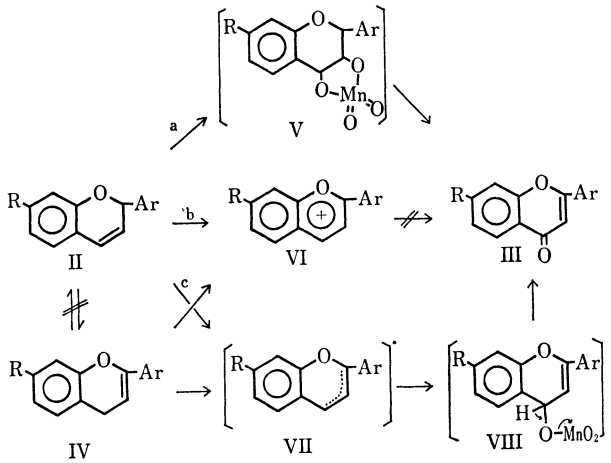
a) The reaction was carried out under nitrogen atmosphere. b) The reaction was carried out in the presence of 2,6-di-*t*-butylphenol (2 mmol).



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 $R_1=R_2=R_3=R_4=R_5=H$, $R_6=OCH_3$
d $R_1=R_3=R_4=R_5=H$, $R_2=R_6=OCH_3$
e $R_1=R_3=H$, $R_2=R_4=R_5=R_6=OCH_3$
f $R_3=R_4=R_5=R_6=H$, $R_1=R_2=OCH_3$
g $R_3=R_4=R_5=H$, $R_1=R_2=R_6=OCH_3$
h $R_1=R_4=R_5=R_6=H$, $R_2=R_3=OCH_3$
i $R_1=R_4=R_5=H$, $R_2=R_3=R_6=OCH_3$
j $R_1=R_4=H$, $R_2=R_3=R_5=R_6=OCH_3$

Scheme 1.

phenol,[7] it caused a decrease in the yield but no adduct was obtained. The reaction, carried out under nitrogen atmosphere, gave a flavone in a similar yield as well as in the same reaction time (entry 10).



Scheme 2. The possible reaction pathways of the oxidations of 2-phenyl-2*H*-1-benzopyrans and 2-phenyl-4*H*-1-benzopyran.

Nevertheless, it is likely that the oxidation of II and IV may proceed through the hydrogen abstraction at the C(2)-position in the case of II and at the C(4)-position in the case of IV giving the identical radical (VII), and that the attack of the permanganate ion to VII at the C(4)-position gave VIII and the elimination of reduced manganese species in VIII would give III.

The oxidations of the 2-phenyl-2*H*-1-benzopyrans are also interesting in connection with their biogenetic transformations into 3-flavanols,[8,9] 4-flavanols,[10,11] 3,4-flavandiols,[9,10] and 3,4-epoxyflavans.[9]

Experimental

All ^{1}H NMR spectra were recorded with a Hitachi R 24 NMR spectrometer with TMS as an internal standard, while the IR spectrum was recorded with a JASCO IRA-1 grating spectrometer. Melting points were determined on a Yanagimoto micro hot-stage and were uncorrected.

*Preparations of 2-Phenyl-2*H*-1-benzopyrans (IIb, IIe, IIf, and IIh).* A mixture of 2'-hydroxychalcone (6 mmol), sodium borohydride (12 mmol), and ethanol (100 ml) was stirred for 3 h at room temperature. After the removal of the ethanol, the resulting solid was treated with 10% aqueous acetic acid (100 ml) and then extracted with benzene. The benzene solution was separated and evaporated under reduced pressure. The resulting liquid was purified on a silica gel column (Wakogel C 100, 100 g) by eluting with benzene and by recrystallization or by distillation.

*7-Methoxy-2-phenyl-2*H*-1-benzopyran (IIb)*: $Bp_{0.02}$ 180 °C (bath temp), 35% yield, NMR (CCl_4) δ=3.66 (3H, s, OCH_3), 5.57 (1H, dd, J=9.6, 3.6 Hz, $H_{(3)}$), 5.83 (1H, dd, J=3.6, 1.6 Hz, $H_{(2)}$), 6.3—6.6 (3H, m), 6.85 (1H, m, $H_{(5)}$), and 7.1—7.6 (5H, m, Ph). Found: C, 80.37; H, 5.81%. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92%.

*7-Methoxy-2-(2,3,4-trimethoxyphenyl)-2*H*-1-benzopyran (IIe)*: $Bp_{0.02}$ 200 °C (bath temp), 41% yield, NMR (CCl_4) δ= 3.65 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.48 (1H, dd, J=9.0, 3.3 Hz, $H_{(3)}$), 6.10 (1H, dd, J=3.3, 1.7 Hz, $H_{(2)}$), 6.22—6.5 (3H, m), 6.40 (1H, d, J=10.0 Hz, $H_{(5')}$), 6.78 (1H, m, $H_{(5)}$), and 7.02 (1H, d, J=10.0 Hz, $H_{(6')}$). Found: C, 69.35; H, 6.17%. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%.

*6,7-Dimethoxy-2-phenyl-2*H*-1-benzopyran (IIf)*: Mp 79—80 °C (light petroleum), 67% yield, NMR (CCl_4) δ=3.62 (6H, s, 2×OCH_3), 5.47 (1H, dd, J=10.0, 3.5 Hz, $H_{(3)}$), 5.67 (1H, dd, J=3.5, 1.8 Hz, $H_{(2)}$), 6.30, (1H, dd, J=10.0, 1.8 Hz, $H_{(4)}$), 6.21 (1H, s, $H_{(8)}$), 6.37 (1H, s, $H_{(5)}$), and 7.20 (5H, m, Ph). Found: C, 75.95; H, 6.09%. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%.

*7,8-Dimethoxy-2-phenyl-2*H*-1-benzopyran (IIh)*: Mp 60—61 °C (MeOH), 53% yield, NMR (CCl_4) δ=3.63 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.64 (1H, dd, J=9.7, 3.5 Hz, $H_{(3)}$), 5.81 (1H, dd, J=3.5, 1.8 Hz, $H_{(2)}$), 6.28 (1H, d, $H_{(6)}$), and 6.56 (1H, d, $H_{(5)}$) (AB system, J_{AB}=8.0 Hz), 6.40 (1H, $H_{(4)}$, coincided with a part of the AB system), and 7.2—7.5 (5H, m, Ph). Found: C, 75.93; H, 6.01%. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%.

4',7-Dimethoxyflavylium Perchlorate (VI). Through a mixture of *p*-methoxyacetophenone (2.0 g), 2-hydroxy-4-methoxybenzaldehyde (2.5 g), and 85% formic acid (30 ml) was passed dry hydrogen chloride for 2.5 h at room temperature. 20% perchloric acid (27 ml) was added to the cooled reaction mixture, which was then left overnight. The precipitates were collected by filtration, giving a dark red powder, mp 265 °C (lit,[14] mp 270 °C) (3.05 g, 61%).

*7-Methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (IV).* 4',7-Dimethoxyflavylium perchlorate (1.83 g) in ethanol (50 ml) was reduced with sodium borohydride (51 mg) at 0 °C for 1 h. After the removal of the ethanol, the resulting solid was washed with ether. The ether was evaporated and the resulting substance was recrystallized to give colorless prisms, mp 137—139 °C (EtOH) (0.46 g, 35%).

*Oxidation of 2-Phenyl-2*H*-1-benzopyrans (IIa—IIj) with Potassium Permanganate.* A mixture of a 2-phenyl-2*H*-1-benzopyran (1 mmol), potassium permanganate (3—5 mmol), and a solvent (50 ml) was stirred at room temperature until all of II was consumed (the period of time is shown in the Table). The solvent was evaporated, and the resulting mixture was treated with 5% aqueous sodium hydrogen sulfite (20 ml) and acidified with concd sulfuric acid. The precipitates were collected and purified on a silica gel column by eluting with chloroform and by recrystallization to give II. In the case of IIe, the reaction mixture was filtered and the manganese dioxide was washed with chloroform. The combined filtrate was then evaporated, and the product was purified on TLC and by recrystallization. IIIa, mp 97 °C (MeOH) (lit,[15] mp 97 °C); IIIb, mp 107—108 °C (MeOH) (lit,[16] mp 110—111 °C); IIIc, mp 155—156 °C (MeOH) (lit,[17] mp 157—158 °C); IIId, mp 146—147 °C (MeOH) (lit,[18] mp 143—144 °C); IIIe. mp 164—165 °C (MeOH), IR ($CHCl_3$) 1635 cm^{-1} (C=O), NMR ($CDCl_3$) δ=3.87 (6H, s, 2×OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.78 (1H, d, J=8.1 Hz, $H_{(5')}$), 6.90 (1H, s, $H_{(3)}$), 6.85—7.05 (2H, m, $H_{(6)}$ and $H_{(8)}$), 7.49 (1H, d, J=8.1 Hz, $H_{(6')}$), and 8.09 (1H, m, $H_{(5)}$) [Found: C, 66.43; H, 5.36%. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.]; IIIf, mp 189—190 °C (MeOH) (lit,[18] mp 189 °C); IIIg, mp 181—182 °C (MeOH) (lit,[19] mp 184—185 °C); IIIh, mp 147—148 °C (MeOH) (lit,[20] mp 151 °C); IIIi, mp 192—194 °C (MeOH) (lit,[21] mp 189—190 °C); IIIj, mp 203—204 °C (MeOH) (lit,[21] mp 200 °C).

*Oxidation of 7-Methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (IV) with Potassium Permanganate.* The reaction was carried out in a manner similar to the above, giving IIId, mp 146—147 °C.

*Oxidation of 2-(*p*-Methoxyphenyl)-2*H*-1-benzopyran (IIc) with Chromium Trioxide–Pyridine Complex.* A mixture of IIc (1 mmol), chromium trioxide–pyridine complex[5] (8 mmol), and dichloromethane (30 ml) was stirred at room temperature under nitrogen atmosphere for 24 h. 5% aqueous sodium hydrogen sulfite (20 ml) and concd sulfuric acid (1 ml) were added to the reaction mixture, which was extracted with chloroform. The organic layer was separated, dried, and evaporated to dryness. The resulting solid was purified in a manner similar to the above, giving IIIc, mp 155—156 °C.

*Oxidation of 7-Methoxy-2-(*p*-methoxyphenyl)-4*H*-1-benzopyran (IV) with Chromium Trioxide–Pyridine Complex.* IV was oxidized with the reagent to give IIId, mp 146—147 °C.

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