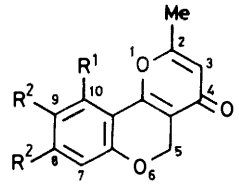
Studies of the Syntheses of Heterocyclic Compounds containing Benzopyrone. Part 3.[1] Synthesis of 2-Methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one, the Basic Skeleton in Citromycetin

Masashige Yamauchi,* Sadamu Katayama, Yoshihiko Nakashita, and Toshio Watanabe
Faculty of Pharmaceutical Sciences, Josai University, Keyakidai, Sakado, Saitama 350–02, Japan

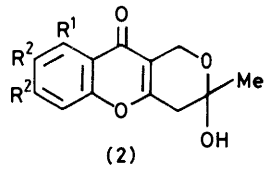
The synthesis of 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyrano-4-one (1b), the basic skeleton in citromycetin, is described. The alcohol (6a), chosen as the starting material, was oxidized to the dione (6c) which, after methylenation, was treated with concentrated hydrochloric acid–methanol (1 : 100) at ambient temperature to afford the pyrone (9a) regioselectively. Hydrogenation and bromine substitution of the pyrone (9a) gave the bromide (9e), which was converted into the benzopyranone (1b) with aqueous sodium hydrogen carbonate.

In our earlier studies [1,2] on the synthesis of heterocyclic compounds containing benzopyrone, we reported some syntheses of chromones. As part of our continuing interest in the synthesis of this ring system we focused our attention on the synthesis of fungal metabolites such as citromycetin (1a),[3] the ring system of which can be regarded as an enol form of benzopyrone, and fulvic acid (2a).[4] Biosyntheses of these two metabolites [5] have been proposed, and the hydroxymethyltrione (3)[5b] and the enetrione (4a),[5b,5c] respectively, are important intermediates. We thought that the enetrione (4a) could also be a synthetic intermediate for both citromycetin (1a) and fulvic acid (2a); that is, condensation between the benzoyl ketone moiety and the acetyl ketone (path a) would lead to citromycetin, and condensation between the ene and the acetyl ketone (path b) to fulvic acid (2a) (Scheme 1). The enetrione (4a) could be prepared from the aldol condensation of a suitably substituted *o*-hydroxyacetophenone with 3-oxobutanal followed by methylenation. As a preliminary approach to these metabolites we examined the condensation of the non-substituted enetrione (4b). In this paper we describe the synthesis of 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (1b), the basic skeleton in citromycetin, *via* the enetrione (4b).[6]



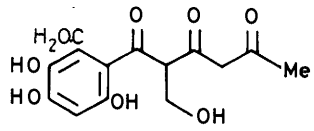
(1)

a; $R^1 = CO_2H, R^2 = OH$
b; $R^1 = R^2 = H$
c; $R^1 = CO_2Me, R^2 = R^2 = OMe$



(2)

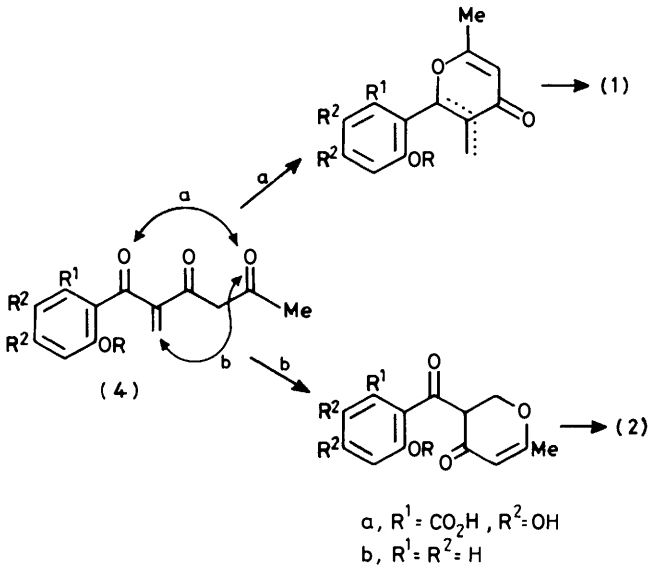
a; $R^1 = CO_2H, R^2 = OH$
b; $R^1 = R^2 = H$



(3)

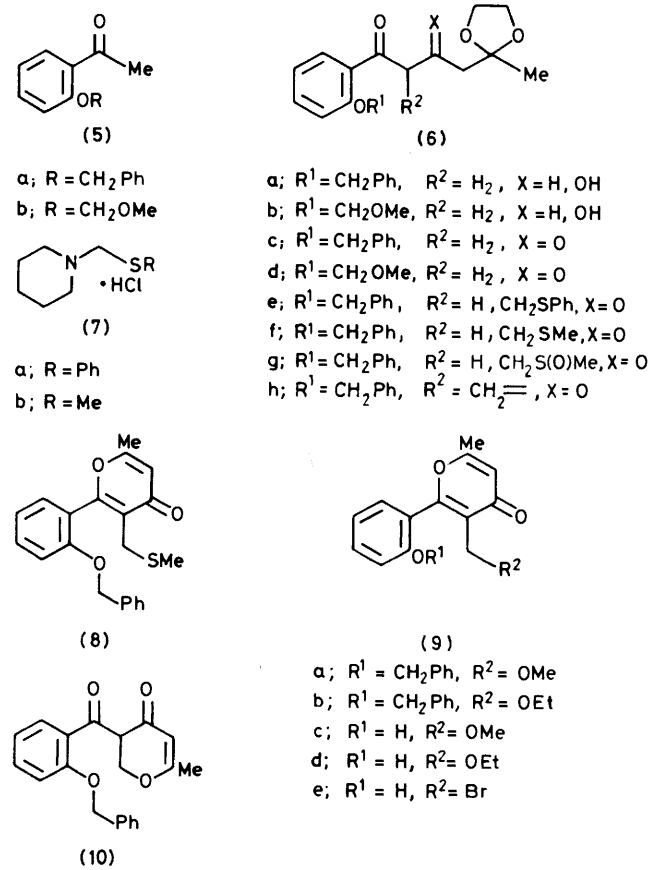
The aldol condensation of 2-benzyloxyacetophenone (5a) [7] with (2-methyl-1,3-dioxolan-2-yl)acetaldehyde [8] in the presence of lithium di-isopropylamide–magnesium bromide in tetrahydrofuran [9] gave the alcohol (6a). Using bases such as sodium hydride did not give satisfactory results. Oxidation of the alcohol (6a) with Collins reagent or PCC gave the diketone (6c) in low yield. Despite the presence of the acetal group, the best results were obtained from oxidation with chromic acid–sulphuric acid in dimethylformamide.[10] The methylenation of the diketone by many of the existing synthetic methods for α-methylenation of monocarbonyl compounds [11] was unsuccessful. Phenylthiomethylation of the dione (6c) with phenylthiomethylpiperidine hydrochloride (7a) [12] gave the phenylthiomethyl derivative (6e) in 81% yield. Oxidation and subsequent elimination, however, did not give the desired product. On the other hand, treatment of the dione (6c) with methylthiomethylpiperidine [13] hydrochloride (7b) [14] gave the methylthiomethyl derivative (6f) (90% yield) and the methylthiomethylpyrone (8) (9% yield). Oxidation of compound (6f) with sodium metaperiodate in methanol afforded the methylsulphinyl compound (6g); this, without further purification, was heated to give the desired product (6h) in 93% overall yield from (6f). This acetal (6h) is a protected form of the enetrione (4b).

A biogenetic-type cyclization was achieved by treatment of the acetal (6h) with concentrated hydrochloric acid–methanol (1 : 100) at ambient temperature to give the pyrone (9a) in 90% yield. This highly regioselective cyclization may be explained by the reaction mechanism shown in Scheme 2 *via* (i) hydrolysis of the acetal group, (ii) concerted methanol additive cyclization, and (iii) dehydration. The structure (9a) was confirmed by ^1H n.m.r. signals due to the methoxy group (δ 3.21) and a characteristic dienone olefinic proton signal (δ 6.07).[15] Treatment of (6h) with concentrated hydrochloric acid–ethanol (1 : 60) also gave the ethoxymethylpyrone (9b) but in low yield (42%). Under these conditions we did not detect another possible cyclization product, (10), which was obtained by treatment of (6h) with hydrochloric acid in tetrahydrofuran.[16] Details of this product (10) will be given in a later paper. Using a more labile phenol-protecting group such as methoxymethyl instead of benzyl would be expected to give spontaneous cyclization to (1b). However, thiomethylation of the acetal (6b), prepared from (5b) as for (5a), gave unidentified tarry products. Hydrogenolysis of the pyrone (9a) with 10% palladium–carbon in ethanol gave the phenol (9c) in 78% yield. Treatment of the phenol (9c) with dry hydrogen bromide in acetic acid gave the bromide (9e) in 70% yield. Finally, the bromide (9e) was converted quantitatively into 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (1b), the basic skeleton in citromycetin, with aqueous sodium hydrogen carbonate in methanol. The spectral data of

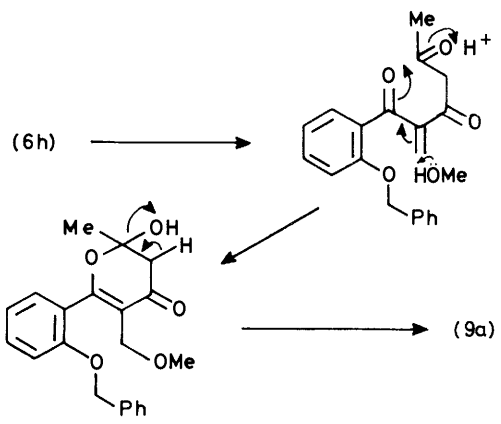


a, $R^1 = CO_2H$, $R^2 = OH$
b, $R^1 = R^2 = H$

Scheme 1.



(1b) [$\lambda_{max.}$ (log ε) (EtOH) 337 (3.90) 288 (4.08) 277 (4.12); δ_H 2.38 (3 H, s, Me), 5.23 (2 H, s, CH_2O), 6.20 (1 H, s, =CH), 6.82—7.72 (4 H, m, arom H); δ_C 19.96 (Me), 63.17 (C-5), 113.68 (C-4a), 114.46 (C-3), 176.47 (C-4)] closely resembled those reported [17] for citromycetin (1a) and methyl *O*-dimethylcitromycetin (1c). The pyranobenzopyran (1b) was also obtained from the ethoxymethylpyrone (9b), *via* the phenol (9d), using a similar method as for (9a), in low yield. Dean *et al.*[18]



Scheme 2.

have reported the synthesis of this ring system from chromanones. Our method supports the proposed biogenetic intermediacy of the enetrione (4a) in the production of citromycetin (1a).

Experimental

M.p.s and b.p.s are uncorrected. I.r. spectra were recorded on a Hitachi Model 215 spectrophotometer. U.v. spectra were recorded with a Hitachi Model 200-10 spectrophotometer. Mass spectra were taken on a Shimazu LKB-9000 mass spectrometer and high resolution mass spectra with a JEOL JMS-O1SG instrument. ^{1}H N.m.r. spectra were obtained with a JEOL 100 spectrometer and ^{13}C n.m.r. spectra with a JEOL JMN-GX 270 spectrometer. Chemical shifts are reported in p.p.m. (δ) relative to tetramethylsilane.

1-(2-*Benzyloxybenzoyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*propan*-2-*ol* (6a).—A solution of 2′-benzyloxyacetophenone (5a; R = CH_2Ph) (3.42 g, 15.1 mmol) in tetrahydrofuran (THF) (30 ml) was added to a solution of lithium di-isopropylamide (LDA) [from di-isopropylamine (1.91 g, 18.9 mmol) and 10 ml of 15w/w % Bu^{n}Li in pentane] in THF (20 ml) for 20 min at −78 °C under N_2. The resulting solution was stirred at −78 °C for 1 h and then treated with a mixture of 2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde (2.46 g, 18.9 mmol) and $MgBr_2$ [from ethylene dibromide (4.0 g, 21.3 mmol) and Mg (1.5 g, 62 mg-atom)] in THF (40 ml) at −78 °C. Vigorous stirring was continued for 30 min at the same temperature, and AcOH (1.5 ml) in Et_2O (50 ml) and then water (30 ml) were added to the mixture. The resulting solution was extracted with benzene (50 ml) and the benzene layer was washed with water (3 × 20 ml), dried and evaporated. The residue was subjected to column chromatography (Florisil, Wako) to elute (n-hexane–benzene, 1 : 1) 1-(2-*benzyloxybenzoyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*propan*-2-*ol* (6a) as a colourless oil (4.57 g, 85%); *m/z*, M^+ 356.1628 ($C_{21}H_{24}O_5$ requires M^+ 356.1617); $\nu_{max.}$ (neat) 3 525 and 1 670 cm^{-1}; δ($CDCl_3$) 1.30 (3 H, s, Me), 1.67 (2 H, d, *J* 6 Hz, CH_2C(Me)OCH_2CH_2O), 3.03 (2 H, d, *J* 6 Hz, CH_2CO), 3.82 (4 H, s, OCH_2CH_2O), 4.25 (1 H, m, *CH*OH), 5.10 (2 H, s, OCH_2Ph), and 6.73—7.73 (9 H, m, arom H).

1-(2-*Methoxymethoxybenzoyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*propan*-2-*ol* (6b).—A solution of 2-methoxymethoxyacetophenone (5b) (5.0 g, 27.8 mmol) in THF (20 ml) was added to a solution of LDA [from di-isopropylamine (3.5 g, 35 mmol) and 22 ml of 15 w/w% Bu^{n}Li in hexane solution] in

THF (15 ml) for 10 min at −78 °C under N_2. The resulting solution was stirred at −78 °C for 40 min and then treated with a mixture of 2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde (4.0 g, 30.1 mmol) and $MgBr_2$ [from ethylene dibromide (5.0 g, 26.6 mmol) and Mg (1.6 g, 65.8 mg-atom)] in THF (50 ml) at −78 °C. Stirring was continued for 30 min at the same temperature, and AcOH (2.5 ml) and then water (30 ml) were added to the mixture. The resulting solution was extracted with Et_2O (50 ml), and the ether layer was washed with water (30 ml), dried and evaporated. The residue was subjected to column chromatography (Florisil, Wako, n-hexane as eluant) to give 1-(2-methoxymethoxybenzoyl)-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-ol (6b) (6.73 g, 78%); $\nu_{max.}$ (neat) 3 500 and 1 660 cm^{-1}; δ($CDCl_3$) 1.33 (3 H, s, C(*Me*)OCH_2CH_2O), 1.90 (2 H, d, *J* 7 Hz, CH_2CHOH), 3.22 (2 H, d, *J* 7 Hz, $PhCH_2CHOH$), 3.60 (3 H, s, OMe), 4.08 (4 H, s, OCH_2CH_2O), 4.63 (1 H, tt, *J* 7 Hz, *CH*OH), 5.45 (2 H, s, OCH_2O), and 7.11—8.12 (4 H, m, arom H).

1-(2-*Benzyloxybenzoyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-*acetone* (6c).—Anhydrous chromic acid (1.4 g) was added in portions to a solution of 1-(2-benzyloxybenzoyl)-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-ol (6a) (408 mg, 1.15 mmol) in dimethylformamide (DMF) (18 ml) at 0 °C. To this homogeneous solution was added conc. H_2SO_4 (*ca.* 0.2 ml) dropwise by means of an injector syringe at −10 °C. Stirring was continued at 0 °C for 4 h, and the reaction mixture was then poured into ice-cooled saturated aqueous $NaHCO_3$ (30 ml) and extracted with Et_2O (3 × 20 ml). The organic layer was washed with saturated aqueous NaCl (3 × 20 ml), dried, and evaporated. The residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, benzene as eluant) to give 1-(2-*benzyloxybenzoyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-*acetone* (6c) (235 mg, 58%), as colourless needles (from benzene), m.p. 72.5—73.5 °C (Found: C, 71.2; H, 6.3. $C_{21}H_{22}O_5$ requires C, 71.16; H, 6.27%); $\nu_{max.}$ (KBr) 1 595 cm^{-1}; δ ($CDCl_3$) 1.37 (3 H, s, Me), 2.57 (2 H, s, $CH_2C(Me)OCH_2CH_2O$), 3.85 (4 H, s, OCH_2CH_2O), 5.13 (2 H, s, OCH_2Ph), 6.58 (1 H, s, =CHCO), and 6.87—8.17 (9 H, m, arom H); *m/z*, M^+ 354.1493 ($C_{21}H_{22}O_5$ requires M^+ 354.1461).

1-(2-*Methoxymethoxybenzoyl*)-3-(2-*methoxy*-1,3-*dioxolan*-2-*yl*)*acetone* (6d).—To a solution of 1-(2-methoxymethoxybenzoyl)-3-(2-methyl-1,3-dioxolan-2-yl)propan-2-ol (6b) (2.64 g, 8.5 mmol) in acetone (200 ml) was added Jones reagent (4 ml) at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h, then poured into saturated aqueous $NaHCO_3$ (50 ml). The precipitate was filtered off and the filtrate was concentrated to half its original volume and extracted with Et_2O (100 ml). The ether layer was washed with water (3 × 30 ml), dried, and evaporated. The residue was subjected to column chromatography (Florisil, Wako, Et_2O–n-hexane, 1 : 1 as eluant) to give 1-(2-methoxymethoxybenzoyl)-3-(2-methyl-1,3-dioxolan-2-yl)acetone (6d) (1.16 g, 44%); $\nu_{max.}$ (neat) 1 605 cm^{-1}; δ($CDCl_3$) 1.48 (3 H, s, C(*Me*)OCH_2CH_2O), 2.73 (2 H, s, $CH_2C(Me)OCH_2CH_2O$), 3.52 (3 H, s, OMe), 3.98 (4 H, br s, OCH_2CH_2O), 5.25 (2 H, s, OCH_2O), 6.53 (1 H, s, enolic H), and 6.91—7.95 (4 H, m, arom H).

3-(2-*Benzyloxybenzoyl*)-1-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*phenylthiobutan*-2-*one* (6e).—A suspension of 1-(2-benzyloxybenzoyl)-3-(2-methyl-1,3-dioxolan-2-yl)acetone (6c) (285 mg, 0.81 mmol) and phenylthiomethylpiperidine hydrochloride (218 mg, 0.90 mmol) in dioxane (10 ml) was refluxed for 12 h. The reaction mixture was poured into ice–water (10 ml), and extracted with Et_2O (10 ml). The ether layer was washed with water (3 × 5 ml), dried and evaporated. The residue was subjected to preparative t.l.c. (Kieselgel 60 PF_{254}, Merck) to isolate 3-(2-benzyloxybenzoyl)-1-(2-methyl-1,3-dioxolan-2-yl)-4-phenylthiobutan-2-one (6e) (310 mg, 81%) as a mixture of the keto and enol forms (keto : enol = 6 : 5); $\nu_{max.}$ (neat) 1 710, 1 660, and 1 595 cm^{-1}; δ($CDCl_3$) (keto form), 1.28 (3 H, s, Me), 2.63 (2 H, s, CH_2CO), 3.43 (2 H, d, *J* 7 Hz, SCH_2), 3.78 (4 H, br s, OCH_2CH_2O), 5.03 (2 H, s, OCH_2Ph), 5.03 (1 H, t, *J* 7 Hz, $CHCH_2S$), and 6.83—7.75 (14 H, m, arom H); δ(enol form) 1.43 (3 H, s, Me), 2.98 (2 H, s, CH_2CO) 3.62—3.86 (2 H, m, SCH_2), 3.78 (4 H, br s, OCH_2CH_2O), 5.08 (2 H, s, OCH_2Ph), 6.83—7.75 (14 H, m, arom H), and 16.68 (1 H, s, enolic OH).

3-(2-*Benzyloxybenzoyl*)-1-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*methylthiobutan*-2-*one* (6f).—A suspension of 1-(2-benzyloxybenzoyl)-3-(2-methyl-1,3-dioxolan-2-yl)acetone (6c) (1.19 g, 3.37 mmol) and methylthiomethylpiperidine hydrochloride (7b) (918 mg, 5.06 mmol) in dioxane (450 ml) was stirred at 80 °C for 24 h. After being cooled the precipitate was filtered off. The filtrate was dissolved in benzene (500 ml) washed with saturated aqueous NaCl (3 × 50 ml), dried, and evaporated. The residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, Merck, benzene as eluant) to give 3-(2-*benzyloxybenzoyl*)-1-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*phenylthiobutan*-2-*one* (6f) (1.25 g, 90%); *m/z*, M^+ 414.1514 ($C_{23}H_{26}O_5S$ requires M^+ 414.1499); $\nu_{max.}$ (neat) 1 715 and 1 665 cm^{-1}; δ($CDCl_3$) (enol form), 1.45 (3 H, s, Me), 1.80 (3 H, s, SMe), 3.02 (2 H, s, CH_2CO), 3.32 (2 H, s, CH_2S), 3.80 (4 H, s, OCH_2CH_2O), 5.07 (2 H, s, OCH_2Ph), and 6.83—7.73 (9 H, m, arom H); δ (keto form) 1.30 (3 H, s, Me), 1.93 (3 H, s, SMe), 2.70 (2 H, s, CH_2CO), 2.93 (2 H, d, *J* 7 Hz, CH_2S), 3.77 (4 H, br s, OCH_2CH_2O), 4.98 (1 H, t, *J* 7 Hz, $CHCH_2S$), 5.17 (2 H, s, OCH_2Ph), and 6.83—7.73 (9 H, m, arom H). Further elution with AcOEt–benzene (1 : 9) gave 2-(2-*benzyloxyphenyl*)-3-*methylthiomethyl*-6-*methyl*-4H-*pyran*-4-*one* (8) (110 mg, 9%); *m/z*, M^+ 352.1122 ($C_{21}H_{20}O_3S$ requires M^+ 352.1128); $\nu_{max.}$ (KBr) 1 660, 1 630, and 1 610 cm^{-1}; δ($CDCl_3$) 1.98 (3 H, s, Me), 2.13 (3 H, s, SMe), 3.24 (2 H, s, CH_2S), 5.07 (2 H, s, OCH_2Ph), 5.99 (1 H, s, =CH), and 6.80—7.54 (9 H, m, arom H).

3-(2-*Benzyloxybenzoyl*)-1-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*but*-3-*en*-2-*one* (6 h).—To a solution of 3-(2-benzyloxybenzoyl)-1-(2-methyl-1,3-dioxolan-2-yl)-4-methylthiobutan-2-one (6f) (161 mg, 0.38 mmol) in methanol (150 ml) was added a solution of $NaIO_4$ (500 mg, 2.3 mmol) in water (10 ml) at 0 °C. The resulting emulsion was stirred at ambient temperature for 24 h. The precipitate was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in benzene (50 ml) and washed with saturated aqueous NaCl (3 × 20 ml), dried and evaporated to give 3-(2-benzyloxybenzoyl)-1-(2-methyl-1,3-dioxolan-2-yl)-4-methylsulphinylbutan-2-one (6g) (160 mg), which was used for next step without purification. The sulphinyl compound (6g) (160 mg) was dissolved in toluene (50 ml), to this was added $CaCO_3$ (3 mg), and the mixture refluxed for 4 days. The reaction mixture was diluted with benzene (50 ml), washed with water (3 × 10 ml), dried, and evaporated to give 3-(2-*benzyloxybenzoyl*)-1-(2-*methyldioxolan*-2-*yl*)*but*-3-*en*-2-*one* (6h) [133 mg, 93% from (6f)]. This compound was too unstable to be purified by distillation or column chromatography; *m/z*, M^+ 366.1467 ($C_{22}H_{22}O_5$ requires M^+ 366.1461); $\nu_{max.}$ (neat) 1 658 and 1 590 cm^{-1}; δ($CDCl_3$) 1.23 (3 H, s, Me), 2.73 (2 H, s, CH_2CO), 3.67 (4 H, br s, OCH_2CH_2O), 4.90 (2 H, s, OCH_2Ph), and 5.70 (9 H, m, arom H).

2-(2-*Benzyloxyphenyl*)-3-*methoxymethyl*-6-*methyl*-4H-*pyran*-4-*one* (9a).—To a solution of 3-(2-phenylmethoxybenzoyl)-1-(2-methyl-1,3-dioxolan-2-yl)but-3-en-2-one (6h) (134 mg, 0.37 mmol) in MeOH (20 ml) was added conc. HCl (0.2 ml) and the resulting solution was stirred at ambient temperature for 20 h. The reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ (20 ml), and extracted with benzene (2 × 25 ml). The benzene layer was washed with saturated aqueous $NaHCO_3$ (10 ml) and water (3 × 10 ml), dried, and evaporated to give 2-(2-*benzyloxyphenyl*)-3-*methoxymethyl*-6-*methyl*-4H-*pyran*-4-*one* (9a) (111 mg, 90%); *m/z*, M^+ 336.1362 ($C_{21}H_{20}O_4$ requires M^+ 336.1356); $\nu_{max.}$ (neat) 1 655, 1 612, and 1 600 cm^{-1}; δ($CDCl_3$) 2.16 (3 H, s, =CMe), 3.21 (3 H, s, OMe), 4.00 (2 H, s, CH_2C=), 5.07 (2 H, s, OCH_2Ph), 6.07 (1 H, s, =CH), and 6.80—7.58 (9 H, m, arom H).

2-(2-*Benzyloxyphenyl*)-3-*ethoxymethyl*-6-*methyl*-4H-*pyran*-4-*one* (9b).—The enedione (6h) (575 mg, 1.57 mmol) and concentrated HCl (1 ml) in EtOH (60 ml) was stirred at ambient temperature for 17 h. The reaction mixture was concentrated to half its original volume, dissolved in benzene (50 ml), washed with water (3 × 30 ml), dried, and evaporated. The residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, Merck, benzene–AcOEt, 10 : 1 as eluant) to give 3-*ethoxymethyl*-6-*methyl*-2-(2-*benzyloxyphenyl*)-4H-*pyran*-4-*one* (9b) (229 mg, 42%); *m/z*, M^+ 350.1512 ($C_{22}H_{22}O_4$ requires M^+ 350.1512); $\nu_{max.}$ (neat) 1 662, 1 625, and 1 603 cm^{-1}; δ($CDCl_3$) 1.10 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.18 (3 H, s, $=CHCH_3$), 3.44 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.17 (2 H, s, $=CCH_2$), 5.10 (2 H, s, OCH_2Ph), 6.18 (1 H, s, =CH), and 6.88—7.62 (9 H, m, arom H).

2-(2-*Hydroxyphenyl*)-3-*methoxymethyl*-6-*methyl*-4H-*pyran*-4-*one* (9c).—2-(2-*Benzyloxyphenyl*)-3-*methoxymethyl*-6-*methyl*-4*H*-*pyran*-4-*one* (9a) (105 mg, 0.31 mmol) was hydrogenated with 10% Pd–C (20 mg) as catalyst at ambient temperature. After 1.1 mol of hydrogen gas had been consumed the catalyst was filtered off and the filtrate was distilled to dryness. The residue was dissolved in benzene (20 ml), washed with saturated aqueous NaCl (3 × 5 ml), dried, and evaporated to give 2-(2-*hydroxyphenyl*)-3-*methoxymethyl*-6-*methyl*-4H-*pyran*-4-*one* (9c) (60 mg, 78%), m.p. 81—84 °C (from benzene) (Found: C, 68.3; H, 5.7. $C_{14}H_{14}O_4$ requires C, 68.83; H, 5.87%), *m/z*, M^+ 246.0892 ($C_{14}H_{14}O_4$ requires 246.0888); $\nu_{max.}$ (KBr) 3 160, 1 655, and 1 590 cm^{-1}; δ($CDCl_3$) 2.28 (3 H, s, $=CCH_3$), 3.37 (3 H, s, OMe), 4.18 (2 H, s, OCH_2), 6.17 (1 H, s, =CH), 6.75—7.50 (4 H, m, arom H), and 8.65 (1 H, br s, OH).

3-*Ethoxymethyl*-2-(2-*hydroxyphenyl*)-6-*methyl*-4H-*pyran*-4-*one* (9d).—A solution of 2-(2-benzyloxyphenyl)-3-ethoxymethyl-6-methyl-4*H*-pyran-4-one (9b) (205 mg, 0.59 mmol) in 20 w/w % HBr–HOAc (6 ml) was stirred at ambient temperature for 19 h. The reaction mixture was poured into ice–water (10 ml) and extracted with Et_2O (50 ml). The ether layer was washed with water (5 × 10 ml), dried and evaporated. The residue was subjected to column chromatography (Kieselgel 60, 70—230 mesh, Merck, benzene–AcOEt, 1 : 1 as eluant) to give 3-ethoxymethyl-2-(2-hydroxyphenyl)-6-methyl-4*H*-pyran-4-one (9d) (90 mg, 59%); δ($CDCl_3$) 1.20 (3 H, t, *J* 7 Hz, OCH_2CH_3), 2.28 (3 H, s, $=CCH_3$), 3.60 (2 H, q, *J* 7 Hz, OCH_2CH_3), 4.28 (2 H, s, $=CCH_2$), 6.26 (1 H, s, =CH), 6.82—7.60 (4 H, m, arom H), and 8.62 (1 H, br s, OH).

3-*Bromomethyl*-2-(2-*hydroxyphenyl*)-6-*methyl*-4H-*pyran*-4-*one* (9e).—A solution of 2-(2-hydroxyphenyl)-3-methoxymethyl-6-methyl-4*H*-pyran-4-one (9c) (153 mg, 0.62 mmol) in 35 w/w % HBr–HOAc (5 ml) was stirred at ambient temperature for 24 h. The reaction mixture was poured into ice–water (20 ml) and extracted with a mixture of CH_2Cl_2 (30 ml) and Et_2O (60 ml). The organic layer was washed with saturated aqueous NaCl (5 × 10 ml), dried, and evaporated to give 3-*bromomethyl*-2-(2-*hydroxyphenyl*)-6-*methyl*-4H-*pyran*-4-*one* (9e) (128 mg, 70%), m.p. 166—168 °C (from benzene) (Found: C, 52.7; H, 3.8. $C_{13}H_{11}BrO_3$ requires C, 52.90; H, 3.76%); *m/z* 296 (M^+ + 2), and 294 (M^+); $\nu_{max.}$ (KBr) 3 100, 1 650, 1 602, and 1 580 cm^{-1}; δ($CDCl_3$) 2.29 (3 H, s, Me), 4.25 (2 H, s CH_2Br), 6.27 (1 H, s, =CH), 6.65—8.05 (4 H, m, arom H), and 8.80 (1 H, br s, OH).

2-*Methyl*-4H,5H-*pyrano*[3,2-c][1]*benzopyran*-4-*one* (1b).—To a solution of 3-bromomethyl-2-(2-hydroxyphenyl)-6-methyl-4*H*-pyran-4-one (9e) (54 mg, 0.18 mmol) in MeOH (60 ml) was added saturated aqueous $NaHCO_3$ (10 ml) at 0 °C. The reaction mixture was stirred at ambient temperature for 24 h, and extracted with a mixture of AcOEt (25 ml) and benzene (25 ml). The organic layer was washed with water (2 × 10 ml), dried and evaporated to yield 2-*methyl*-4H,5H-*pyrano*[3,2-c][1]*benzopyran*-4-*one* (1b) (38 mg, 97%), m.p. 155—156 °C (from benzene–n-hexane) (Found: C, 72.5; H, 4.9. $C_{13}H_{10}O_3$ requires C, 72.88; H, 4.71%); *m/z*, M^+ 124.0621 ($C_{13}H_{10}O_3$ requires M^+ 214.0627); $\nu_{max.}$ (KBr) 1 665, 1 620, and 1 600 cm^{-1}; $\lambda_{max.}$ (EtOH) 337 log ε (3.90), 288 (4.08), and 277 nm (4.12); δ($CDCl_3$) 2.38 (3 H, s, Me), 5.23 (2 H, s, CH_2O), 6.20 (1 H, s, =CH), and 6.82—7.72 (4 H, m, arom H); δ_C ($CDCl_3$) 19.86 (Me), 63.07 (C-5), 113.58 (C-4a), 114.36 (C-3), 116.06 (C-10a), 117.07 (C-7), 121.72 (C-9), 123.05 (C-8), 133.13 (C-10), 155.15 (C-6a), 156.76 (C-10b), 164.63 (C-2), and 176.37 p.p.m. (C-4).

References

1 Part 2, T. Watanabe, S. Katayama, Y. Nakashita, and M. Yamauchi, *J. Chem. Soc., Perkin Trans. 1*, 1978, 726.

2 T. Watanabe, Y. Nakashita, S. Katayama, and M. Yamauchi, *J. Chem. Soc., Chem. Commun.*, 1977, 493; T. Watanabe, S. Katayama, Y. Nakashita, and M. Yamauchi, *Chem. Pharm. Bull.*, 1977, **25**, 2778.

3 For isolation see A. C. Hetherington and H. Raistrick, *Philos. Trans. R. Soc. London, Ser. B*, 1931, **220**, 209 (*Chem. Abstr.*, 1932, **26**, 2485); for structure determination see J. B. D. Mackenzie, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 2965.

4 For isolation see A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, 1935, **29**, 1102; for structure determination see F. M. Dean, R. A. Eade, R. A. Moubasher, and A. Robertson, *Nature*, 1957, 3497.

5 (*a*) A. J. Birch, S. F. Hussiain, and R. W. Rickards, *J. Chem. Soc.*, 1964, 3494; A. J. Birch, P. Fitton, E. Pride, A. J. Ryan, H. Smith, and W. B. Whalley, *J. Chem. Soc.*, 1958, 4576; (*b*) W. B. Whalley, *Chem. Ind.*, 1958, 131; T. Money, *Nature*, 1963, 592; R. Thomas, *Biochem. J.*, 1961, **78**, 748; (*c*) I. Kurobane and C. R. Hutchinson, *Tetrahedron Lett.*, 1981, **22**, 493; G. E. Evans and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1976, 760.

6 Preliminary communication, T. Watanabe, S. Katayama, Y. Nakashita, and M. Yamauchi, *J. Chem. Soc., Chem. Commun.*, 1981, 761.

7 U. K. Pandit and T. C. Bruice, *J. Am. Chem. Soc.*, 1960, **82**, 3386.

8 Z. Horii, H. Hakusui, T. Sigeuchi, M. Hanaoka, and T. Momose, *Yakugaku Zasshi*, 1972, **92**, 503.

9 H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310.

10 G. Snatzke, *Chem. Ber.*, 1961, **94**, 729.

11 (*a*) For α-methylation and α-sulphenylation–oxidation–elimination sequences see D. Seebach and T. Teschner, *Tetrahedron Lett.*, 1973, 5113; B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, 1973, **95**, 6840; P. A. Grieco and J. J. Peap, *Tetrahedron Lett.*, 1974, 1097; (*b*) for α-thiomethylation–oxidation–elimin-

ation sequences see R. C. Ronald, *Tetrahedron Lett.*, 1973, 3831; H. J. Reich and J. M. Renga, *J. Chem. Soc., Chem. Commun.*, 1974, 135; I. Paterson and I. Fleming, *Tetrahedron Lett.*, 1979, 993, 995; (*c*) for dehydrobromination of α-bromo-α-methylketones see A. E. Greene, J.-C. Muller, and G. Ourisson, *Tetrahedron Lett.*, 1972, 3375; (*d*) for aminomethylation–dehydramination sequences see S. Danishefsky, T. Kitahara, R. Mckee, and P. F. Schucla, *J. Am. Chem. Soc.*, 1976, **98**, 6715.

12 G. F. Gillot, H. R. Felton, B. R. Garrett, H. Greenberg, R. Green, R. Clemmenti, and M. Moskowitz, *J. Am. Chem. Soc.*, 1954, **76**, 3969.

13 H. Böhme and H.-H. Otto, *Arch. Pharm.*, 1967, **300**, 647.

14 M. Yamauchi, S. Katayama, and T. Watanabe, *Synthesis*, 1982, 935.

15 K. Sato, S. Inoue, and M. Ohashi, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 1288; P. J. Wittek, K. B. Hindley, and T. M. Harris, *J. Org. Chem.*, 1973, **38**, 896.

16 M. Yamauchi, S. Katayama, Y. Nakashita, and T. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1983, 335.

17 For the u.v. spectrum of (1c), see A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1949, 848; for the ^{1}H n.m.r. spectrum of (1c) see F. M. Dean and D. R. Randell, *ibid.*, 1961, 798; for the ^{13}C n.m.r. spectrum of (1a) see ref. 5*d*.

18 F. M. Dean, S. Murray, and W. Taylor, *J. Chem. Soc., Chem. Commun.*, 1974, 440.

Received 11*th July* 1983; *Paper* 3/1178