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THE USE OF A PARAMAGNETIC SHIFT REAGENT FOR THE STRUCTURAL DETERMINATION OF ETHYL 4-OXO-4*H*-1-BENZOPYRAN-2-CARBOXYLATES

H. CAIRNS, D. HUNTER, J. KING* and N. H. ROGERS
Medicinal Chemistry Department, Pharmaceuticals Division, Fisons Ltd,
Bakewell Road, Loughborough, Leicestershire

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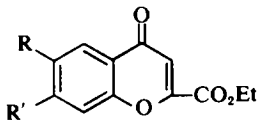
Abstract—The effect of a paramagnetic shift reagent on the PMR of ethyl 4-oxo-4*H*-1-benzopyran-2-carboxylates is described. Displacements of proton signals are discussed in terms of preferred co-ordination sites in the substrate molecules. The technique is shown to be particularly useful in distinguishing between structural isomers.

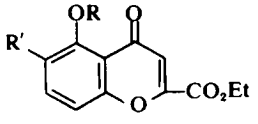
The use of PMR spectroscopy for the structure determination of disubstituted ethyl 4-oxo-4*H*-1-benzopyran-2-carboxylates has been described by Ellis and co-workers.[1-3] Using this technique the products obtained by bromination and nitration of the 6- and 7-hydroxy-substituted esters **1a** and **1b** were identified, the spectra permitting the unambiguous identification of the products through the ortho, meta or para coupling of the benzenoid protons.



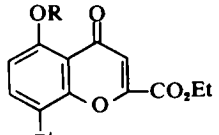
1

a: R = OH, R′ = H
b: R = H, R′ = OH

However, it is difficult to assign structure to isomeric esters **2a** and **2b** (e.g. where R = R′ = alkyl) by means of PMR spectroscopy. The two benzenoid protons in these isomers give ortho-coupled doublets and the observed differences in chemical shifts are difficult to interpret in terms of the substitution patterns.



2a

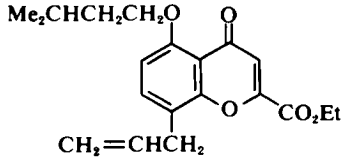


2b

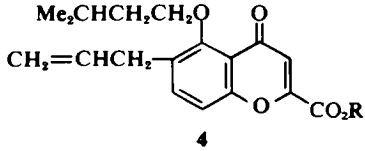
We have now shown that this difficulty can be overcome by the use of PMR spectroscopy in the presence of the paramagnetic shift reagent tris (1, 1, 1, 2, 2, 3, 3 - heptafluoro - 7, 7 - dimethyl - 4, 6 - octanedionato) europium, Eu(fod-d_9)$_3$.

While we were preparing this manuscript Okigawa, Kawano, Rahman and Dhar[4] published a paper describing similar work in which Eu(fod)$_3$ was used to distinguish protons in the 6- and 8-positions of 5-methoxyflavones. They claim that Eu(fod)$_3$ coordinates mostly at the pyrone carbonyl oxygen atom in these compounds. Although we agree with their structural assignments, we find that the oxygen atom of a 5-alkoxy substituent is the predominant coordination site in ethyl 4-oxo-4*H*-1-benzopyran-2-carboxylates.

In the course of chemical studies on benzopyrans we prepared two isomeric allyl-substituted derivatives of ethyl 5-(3-methylbutoxy)-4-oxo-4*H*-1-benzopyran-2-carboxylate. By chemical means we were able to assign the positions of the allyl groups unambiguously to the 8- and 6- positions (**3a** and **4a** respectively).



3a



4

a: R = Et
b: R = H

As mentioned above, the PMR spectra of the two isomers in $CDCl_3$ are very similar, the only significant differences being the chemical shifts of the

aromatic proton signals. For **3a** the 6- and 7- protons gave ortho-coupled doublets (J = 8·5 Hz) at $\tau = 3{\cdot}27$ and $\tau = 2{\cdot}61$ respectively, while the 7- and 8- protons in **4a** gave ortho-coupled doublets (J = 8·5 Hz) at $\tau = 2{\cdot}48$ and $\tau = 2{\cdot}76$ respectively. This difference of 0·51 ppm in the chemical shifts of the high-field signals is attributed to the different shielding effects of the 5-alkoxy and the pyran ring ether oxygen atoms. However, the difference in the PMR spectra would not be sufficiently characteristic to allow the identification of a single unknown isomer.

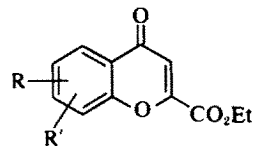
For our study of the effect of the paramagnetic shift reagent Eu(fod-d_9)$_3$ on the spectra of the two isomers **3a** and **4a**, it was first necessary to establish the preferred coordination sites for the shift reagent on esters of simpler substituted 4-oxo-4*H*-1-benzopyran-2-carboxylic acids.

The Table gives the values for the downfield shift (ΔEu)[5] in ppm that would be induced by the addition of a molar equivalent of Eu(fod-d_9)$_3$ to solutions of the esters in $CDCl_3$. These shifts were determined by extrapolation of the straight lines obtained from plots of induced shift against the Eu(fod-d_9)$_3$ to substrate molar ratio. The further a particular proton signal is shifted, the larger is its ΔEu value.

as in **5b** and **5c** contribute very little, if at all, to coordination with Eu(fod-d_9)$_3$. However, ethyl 5 - methoxy - 4 - oxo - 4*H* - 1 - benzopyran - 2 - carboxylate **5g** behaves differently because, in addition to a large shift in the methoxyl singlet, the shift of the 6-proton signal is much increased whilst that of the 3-proton signal is considerably reduced. It is apparent therefore that in the 5-methoxy derivative the ether oxygen atom makes a greater contribution to coordination than does the 4 - carbonyl oxygen atom. We have found this to be the case in all 5-alkoxy substituted compounds studied to date. Since there is a considerable difference in the induced shifts of the 6- and 8- protons in **5g**, then the 6- and 8- substituted derivatives of ethyl 5 - alkoxy - 4 - oxo - 4*H* - 1 - benzopyran - 2 - carboxylates should be readily distinguishable.

Induced shifts given by Eu(fod-d_9)$_3$ for the isomers **3a** and **4a** are shown below. Preferred coordination at the 5-ether oxygen atom in both isomers is confirmed by the small shift of the 3-proton resonance and the relatively large shift of the proton signals of the methylene groups in the alkoxy chain. As predicted, shifts of the benzenoid proton signals for the 6-allyl isomer **4a** are almost equal, whilst those for the 8-allyl isomer **3a** are in the ratio of 3·2 : 1.

Table



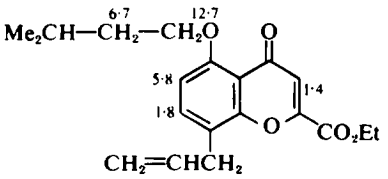
5

Compound	Ref	R	R'	Δ Eu in ppm of respective protons Ring Position					
				3	5	6	7	8	Ester CH_2
5a	6	6-Me	8-Me	11·3(H)	14·0(H)	1·2(Me)	1·9(H)	2·3(Me)	0·17
5b	7	7-Iodo	H	10·0(H)	12·0(H)	2·3(H)	—	2·7(H)	0·48
5c	8	6-Cl	8-Cl	11·2(H)	13·5(H)	—	2·4(H)	—	0·36
5d	9	6-OMe	H	9·7(H)	13·3(H)	1·2(Me)	2·4(H)	2·8(H)	0·29
5e	9	7-OMe	H	11·0(H)	13·7(H)	3·3(H)	1·7(Me)	3·0(H)	0·46
5f	10	8-OMe	H	9·5(H)	12·2(H)	2·5(H)	2·3(H)	1·7(Me)	0·45
5g	11	5-OMe	H	2·5(H)	13·1(Me)	6·6(H)	2·3(H)	2·3(H)	0·16

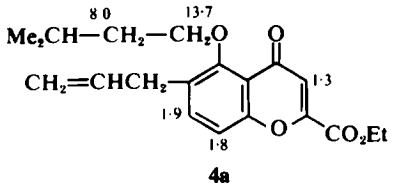
These results show that the pyrone carbonyl oxygen atom is the preferred coordination site in structures **5a–5f**. Signals of the protons in the 3- and 5- positions of the chromone nucleus, which lie close to this carbonyl oxygen atom, are shifted considerably further than the 6-, 7-, and 8-proton signals. The relatively weak coordination with the ester function is shown by the very small shift of the ester methylene quartet. Halogen substituents,

Chemical Synthesis and Proof of Structure

Ethyl 8-allyl-5-(3-methylbutoxy)-4-oxo-4*H*-1-benzopyran-2-carboxylate **3a** was synthesised by alkylation of 3-allyl-2,6-dihydroxyacetophenone[12] **6a** with isoamyl bromide to give the ether **6b**, which was condensed with diethyl oxalate followed by ring closure of the resulting α,γ-diketo ester, to give a product which was assigned structure **3a**. This assignment was based on the assumption that



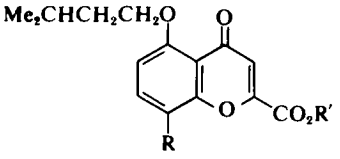
3a



4a

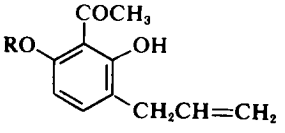
The data shown in these structures represent the induced shifts for the appropriate protons

alkylation of the acetophenone **6a** had occurred primarily on the 6-hydroxyl group rather than on the more sterically hindered 2-hydroxyl group, and confirmed by the following series of experiments.



3

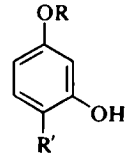
a: R = —$CH_2CH{=}CH_2$; R′ = Et
b: R = —$CH_2CH_2CH_3$; R′ = Et
c: R = —$CH_2CH_2CH_3$; R′ = H
d: R = —$CH_2CH{=}CH_2$; R′ = H



6

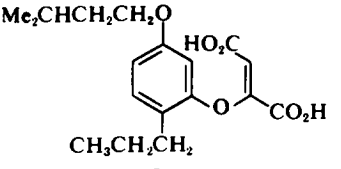
a: R = H
b: R = —$CH_2CH_2CHMe_2$

The product to which we assign structure **3a** was hydrogenated using Pd/C as catalyst to give the corresponding n-propyl derivative **3b**. This ester was then hydrolysed to the corresponding acid **3c** which was shown to be identical to authentic acid **3c** prepared in the following manner. Alkylation of 2,4-dihydroxypropiophenone **6a** with isoamyl bromide gave the ether **7b**, readily identifiable from its PMR spectrum which showed that the product contained an intramolecularly hydrogen-bonded hydroxyl group (singlet at $\tau = -2{\cdot}55$). The propiophenone ether **7b** was then reduced to 5-(3-methylbutoxy)-2-prophylphenol **7c** using the Clemmensen conditions. Michael type addition of **7c** to dimethyl acetylenedicarboxylate in the presence of Triton B, followed by hydrolysis, produced a mixture of the phenoxy-fumaric and maleic acids **8a** and **8b**. Treatment of the mixture of **8a** and **8b** with H_2SO_4 resulted in the cyclisation of **8a** to the acid **3c**. (This general route to 4-oxo-4*H*-1-benzopyran-2-carboxylic acids has recently been published by Cairns *et al.*[7]).

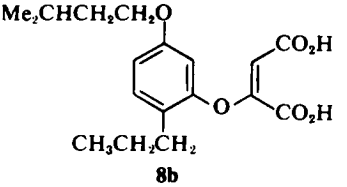


7

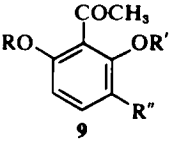
a: R = H; R′ = —$COCH_2CH_3$
b: R = —$CH_2CH_2CHMe_2$; R′ = —$COCH_2CH_3$
c: R = —$CH_2CH_2CHMe_2$; R′ = —$CH_2CH_2CH_3$



8a



8b



9

a: R = R″ = H; R′ = —$CH_2CH{=}CH_2$
b: R = *p*-$CH_3C_6H_4SO_2$—; R′ = —$CH_2CH{=}CH_2$; R″ = H
c: R = *p*-$CH_3C_6H_4SO_2$—; R′ = H; R″ = —$CH_2CH{=}CH_2$
d: R = *p*-$CH_3C_6H_4SO_2$—; R′ = —$CH_2CH_2CHMe_2$; R″ = —$CH_2CH{=}CH_2$
e: R = H; R′ = —$CH_2CH_2CHMe_2$; R″ = —$CH_2CH{=}CH_2$

The 6-allyl isomer of **3a** was prepared by the following route. The acetophenone **9a**[13] was esterified with p-toluenesulphonyl chloride to give **9b** which was thermally rearranged to **9c**. Alkylation of **9c** with isoamyl bromide gave the acetophenone **9d** which was hydrolysed to **9e**. Condensation of **9e** with diethyl oxalate followed by ring closure with HCl in EtOH produced 6-allyl-5-(3-methylbutoxy)-4-oxo-4*H*-1-benzopyran-2-carboxylic acid **4b** which on esterification gave **4a**.

EXPERIMENTAL

M.ps were determined on a Büchi melting point apparatus and are uncorrected. Mass spectra were recorded on a Hitachi-Perkin Elmer RMU 6 spectrometer. IR spectra were recorded on Perkin-Elmer 257 and 457 instruments using KBr discs, unless otherwise stated, and a Perkin-Elmer 402 Spectrometer was used to obtain UV spectra. PMR spectra were determined at 60 MHz on a Perkin-Elmer R 12 spectrometer (TMS as internal standard). For the shift reagent studies the spectrum of each substrate (10^{-4} M) dissolved in 0·5 ml $CDCl_3$ (dried over A4 molecular sieves) was recorded and re-run after successive additions of Eu(fod-d_9)$_3$. The molar ratio Eu(fod-d_9)$_3$/substrate did not exceed 0·5 and line broadening was found to be minimal.

3-Allyl-2-hydroxy-6-(3-methylbutoxy)acetophenone **6b**

A mixture of 3-allyl-2,6-dihydroxacetophenone[11] **6a** (96 g), isoamyl bromide (75·5 g), K_2CO_3 (70 g) and dry acetone (1·5 l) was stirred and heated under reflux for 60 h. The hot mixture was filtered and the residue was washed with acetone. The solvent was removed from the combined filtrate and washings, the residual oil was dissolved in Et_2O and washed with 5% NaOH, then water. After drying, the Et_2O was removed leaving the acetophenone **6b** as a yellow oil (110 g); τ($CDCl_3$) 2·90 (1H, d, H-4), 3·77 (1H, d, H-5), 4·1 (1H, m, allylic CH), 4·9 (2H, m, allylic CH_2), 6·05 (2H, t, OCH_2), 6·75 (2H, d, benzylic CH_2), 7·42 (3H, s, $COCH_3$), 8·25 (3H, m, $CHCH_2$), 9·03 (6H, d, protons of isopentyl methyl groups).

8-Allyl-5-(3-methylbutoxy)-4-oxo-4H-1-benzopyran-2-carboxylic acid **3d**

To a solution of NaOEt in EtOH, prepared from Na (41 g) and EtOH (600 ml), was added a solution of **6b** (110 g) and diethyl oxalate (160 g) in EtOH (900 ml). The mixture was stirred and heated under reflux for 4 h, cooled and poured into a mixture of EtOAc (1·5 l) and 1% HCl (10 l). The organic layer was separated and combined with EtOAc washings of the aqueous layer. Removal of solvent left an oil which was dissolved in EtOH (500 ml) containing conc HCl (0·5 ml) and the solution was heated under reflux for 0·5 h. The EtOH was then removed by evaporation and the resulting oily solid was extracted with hot aq. ethanolic $NaHCO_3$. Acidification of the cooled extract gave a yellow solid which was filtered off and crystallized from EtOAc to give **3d** (60·4 g) as yellow needles, m.p. 198–199°, ν_{max} 3200–2100 br (OH), 3080 (3 C-H), 1740 (carboxylate C=O) and 1640 (pyrone C=O) cm^{-1} (Found: C, 68·0; H, 6·4; $C_{18}H_{20}O_5$ requires C, 68·34; H, 6·37%); τ(DMSO-d_6) 2·34 (1H, d, H-7), 2·95 (1H, d, H-6), 3·22 (1H, s, H-3), 3·9 (1H, m, allylic CH), 4·8 (2H, m, allylic CH_2), 5·9 (2H, t, OCH_2), 6·44 (2H, d, benzylic CH_2), 8·25 (3H, m, $CHCH_2$), 9·04 (6H, d, protons of isopentyl methyl groups); *m/e* 316 (M^+), 273, 259 (base peak), 246, 245 and 219.

Ethyl 8-allyl-5-(3-methylbutoxy)-4-oxo-4H-1-benzopyran-2-carboxylate **3a**

A solution of **3d** (53 g) in EtOH (750 ml) containing conc H_2SO_4 (2 ml) was heated under reflux for 20 h. Evaporation of the solvent left an oil which crystallised on standing. A solution of this solid in $CHCl_3$ was washed with H_2O and then with $NaHCO_3$. After drying, solvent was removed and the residue was crystallised from Et_2O to give the ester **3a** (45 g) as yellow needles, m.p. 104–106°, ν_{max} 3090 (3 C—H), 1730 (ester C=O), 1665 (pyrone C=O) cm^{-1} (Found: C, 69·7; H, 7·22; $C_{20}H_{24}O_5$ requires C, 69·75; H, 7·02%); τ($CDCl_3$) 2·62 (1H, d, H-7) 3·12 (1H, s, H-3), 3·29 (1H, d, H-6), 4·1 (1H, m, allylic CH), 4·9 (2H, m, allylic CH_2), 5·63 (2H, q, ester CH_2), 5·95 (2H, t, OCH_2), 6·48 (2H, m, benzylic CH_2), 8·2 (3H, m, $CHCH_2$), 8·62 (3H, t, ester CH_3), 9·03 (6H, d, protons of isopentyl methyl groups); *m/e* 344 (M^+), 301, 288, 287 (base peak), 274 and 245.

Ethyl 5-(3-methylbutoxy-8-n-propyl-4-oxo-4H-1-benzopyran-2-carbooxylate **3b**

A suspension of **3a** (12 g) in EtOH (225 ml) was hydrogenated over 5% Pd/C (0·2 g) at 5 atmos. When the uptake of H_2 ceased, the catalyst was filtered off and the filtrate was concentrated and diluted with H_2O. **3b** (10·2 g) crystallised as pale yellow needles, m.p. 64·5–65°, ν_{max} 3080 (3 C—H), 1730 (ester C=O) and 1650 (pyrone C=O) cm^{-1} (Found: C; 69·2; H, 7·6; $C_{20}H_{26}O_5$ requires C, 69·35; H, 7·6%); τ ($CDCl_3$) 2·62 (1H, d, H-7), 3·10 (1H, s, H-3), 3·28 (1H, d, H-6), 5·61 (2H, q, ester CH_2), 5·94 (2H, t, OCH_2), 7·23 (2H, t, benzylic CH_2), 8·2 (5H, m, $CHCH_2$ and propyl CH_2), 8·6 (3H, t, ester CH_3), 9·0 (6H, d, protons of isopentyl methyl groups), 9·0 (3H, t, propyl CH_3); *m/e* 346 (M^+), 303, 289 (base peak), 276, 275, 261, 247, 231 and 219.

3b was hydrolysed with $NaHCO_3$ to give the corresponding acid **3c**, which crystallised from aqueous EtOH as yellow needles, m.p. 170–171°, ν_{max} 3300–2100 br (OH), 1740 (carboxylate C=O), 1640 (pyrone C=O) cm^{-1} (Found: C, 67·5; H, 6·97; $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·97%); τ(DMSO-d_6) 2·54 (1H, d, H-7), 3·1 (1H, d, H-6), 3·4 (1H, s, H-3), 6·01 (2H, t, OCH_2), 7·3 (2H, t, benzylic CH_2), 8·3 (5H, m, propyl CH_2 and $CHCH_2$), 9·1 (6H, d, protons of isopentyl methyl groups), 9·1 (3H, t, propyl CH_3); *m/e* 318 (M^+), 275, 261 (base peak), 248 and 219.

Unambiguous Synthesis of **3c**

2-(3-Methylbutoxy)-4-hydroxypropiophenone **7b**. A mixture of 2,4-dihydroxypropiophenone (166 g), isoamyl bromide (119·8 ml) and K_2CO_3 (140 g) in acetone (300 ml) was stirred and heated under reflux for 3 days. The reaction mixture was cooled and filtered. The residue was washed with acetone. The filtrate and washings were combined and evaporated to dryness. The remaining oil was taken up in Et_2O (500 ml) and the solution was washed with 2N HCl (100 ml), 5% KOH (6 × 50 ml), 2N HCl (100 ml) and finally H_2O (6 × 100 ml). The ethereal layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to dryness in vacuo to yield **7b** as an almost colourless oil, which solidified, as needles, on cooling, (107·9 g); m.p. 43–44°. The product was homogeneous by TLC (Found: C, 70·79; H, 8·42; $C_{14}H_{20}O_3$ requires C, 71·16; H, 8·53%); τ(CCl_4) −2·5 (1H, s, H-bonded 2-OH group), 2·5 (1H, meta d, H-6), 3·7 (2H, m, H-3 and H-5), 6·1 (2H, t, OCH_2), 7·3 (2H, q, ethyl CH_2), 8·4 (3H, m,

$CHCH_2$), 8·45 (3H, t, ethyl CH_3). 9·0 (6H, d, protons of isopentyl methyl); *m/e* 236 (M^+), 207, 186, 137 (base peak).

5-(3-*Methylbutoxy*)-2-*n*-*propylphenol* **7c**. Zinc amalgam was prepared by shaking zinc wool (100 g), $HgCl_2$ (10 g), conc HCl (5 ml) and H_2O (150 ml) for 5 min. The aqueous layer was decanted and the amalgamated zinc was covered with H_2O (150 ml) and conc HCl (200 ml). A solution of **7b** (47·2 g) in dioxan (200 ml) was added and the mixture was heated under reflux overnight. The mixture was cooled, filtered and the filtrate was extracted with Et_2O (2 × 200 ml). The ethereal extract was washed with H_2O (5 × 500 ml), dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to dryness in vacuo to give **7c** as a colourless oil, which solidified on cooling to a white crystalline solid (43·7 g); m.p. 40·0–40·5°. (Found: C, 75·94; H, 9·78 $C_{14}H_{22}O_2$ requires, C 75·63; H, 9·97%): τ(CCl_4) 3·12 (1H, ortho d, H-3), 3·62 (1H, meta d, H-6), 3·8 (1H, ortho-meta doublet of doublets, H-4), 4·2 (1H, s, OH), 6·2 (2H, t, OCH_2), 7·05 (2H, t, benzylic CH_2), 8·4 (5H, m, $CHCH_2$ and propyl CH_2), 9·1 (6H, d, protons of isopentyl methyl groups), 9·1 (3H, t, propyl CH_3); *m/e* 222 (M^+).

5-(3-*Methylbutoxy*-4-*oxo*-8-*n*-*propyl*-4*H*-1-*benzopyran* 2-*carboxylic acid* **3c**. The phenol **7c** (22·2 g) was dissolved in dimethyl acetylenedicarboxylate (14·2 g). Triton B (0·01 ml) was added to the solution, which was heated for 45 min on a steam bath. NaOH solution (45 ml of 25%) was added to the mixture and heating on the steam bath was continued for a further 2·5 h. The resulting homogeneous solution was cooled and acidified to pH 1 with 20% H_2SO_4. A yellow precipitate was produced and this was extracted into Et_2O (4 × 200 ml). The ethereal solution was washed with 2N H_2SO_4, H_2O, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness in vacuo. The residual yellow oil (30·9 g) quickly solidified and was dried at 80° at 0·05 mm. This crude mixture of [2-propyl-5-(3-methylbutoxy)phenoxy] fumaric and maleic acids (13·9 g), was crystallized from EtOAc-petrol (b.p. 60–80°), and dissolved portionwise in conc H_2SO_4 (70 ml) with cooling (ice bath). The orange solution was allowed to stand at room temp for 30 min and then added slowly into ice-H_2O. A yellow brown syrup was produced, which was extracted into EtOAc, and the organic layer was washed with 2N, H_2SO_4, H_2O, and dried over anhydrous $MgSO_4$, then filtered and evaporated to dryness in vacuo. The resulting brown oil was crystallized from EtOAc-petrol (b.p. 60–80°) to give **3c** as a yellow crystalline solid (1·90 g); m.p. 170–171°. The product obtained by this route was identical with that prepared by the preceding process (Found: C, 67·83, H, 6·83; $C_{18}H_{22}O_5$ requires C, 67·91; H 6·97%).

Synthesis of 6-*isomer* **4a**

2-*Acetyl*-3-*allyloxyphenyl toluene p*-*sulphonate* **9b**. 2-Allyloxy-6-hydroxyacetophenone[12] (96 g) was dissolved in NaOH (20 g in 1l of H_2O). A solution of toluene p-sulphonyl chloride (100 g) in acetone (1 l) was added and the resulting mixture was refluxed for 16 h. The acetone was removed by evaporation and the mixture was diluted with H_2O (1 l) and extracted with Et_2O (4 × 250 ml). The ethereal extract was washed with H_2O, cold 5% NaOH, H_2O, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to yield an oil which rapidly solidified. This material was crystallized from EtOH to give **9b** as white needles (114·4 g) m.p. 56·5–57·5°; ν_{max} 1700 (acetyl C=O) cm^{-1}; λ_{max} 217 nm (ϵ 20440) (Found: C, 62·8; H, 5·2; $C_{18}H_{15}O_5S$ requires C, 62·4; H, 5·2%); τ($CDCl_3$) 2·2–3·3 (7H, complex aromatic region), 4·1 (1H, m, allylic CH), 4·7 (2H, m, allylic CH_2), 5·5 (2H, m, OCH_2), 7·6 (3H, s, $COCH_3$), 7·6 (3H, s, tosyl CH_3); *m/e* 346 (M^+), 91 (base peak).

2-*Acetyl*-4-*allyl*-3-*hydroxyphenyl toluene p*-*sulphonate* **9c**. **9b** (114·3 g) was heated in an oil bath at 195–210° for 2 h. The dark mixture was cooled and dissolved in Et_2O (500 ml). The ethereal solution was washed with H_2O and extracted with 5% NaOH (8 × 250 ml). The latter was acidified to pH 1 with conc HCl and then extracted with Et_2O (5 × 100 ml). This ethereal solution was washed with H_2O, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness in vacuo to yield **9c** as a colourless oil (87·5 g). This oil was too involatile to be vacuum-distilled and the compound was used without further purification. ν_{max} (film) 1630 (acetyl C=O) cm^{-1}; τ($CDCl_3$) – 2·9 (1H, s, H-bonded OH), 2·2 and 2·6 (4H, AA′, BB′ for tosyl aromatic protons), 2·8 (1H, d, H-5), 3·6 (1H, d, H-6), 4·05 (1H, m, allylic CH), 4·92 (2H, m, allylic CH_2), 6·65 (2H, m, benzylic CH_2), 7·35 (3H, s, $COCH_3$), 7·56 (3H, s, tosyl CH_3).

2-*Acetyl*-4-*allyl*-3-(3-*methylbutoxy*)*phenyl toluene p*-*sulphonate* **9d**. A mixture of **9c** (87·5 g), isoamyl bromide (151 g) and anhydrous K_2CO_3 (138 g) in dry acetone (300 ml) was refluxed under anhydrous conditions for 5 days. The mixture was filtered and the residue was washed with acetone. The filtrate and washings were combined and evaporated to dryness in vacuo. The residue was taken up in Et_2O and the ethereal solution was washed with H_2O, cold 5% NaOH, 2N HCl and H_2O. The organic solution was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness in vacuo to give **9d** as an oil (94·6 g). This oil could neither be crystallized nor vacuum-distilled. The compound was homogeneous by TLC ν_{max} (film) 1700 (acetyl C=O) cm^{-1}; τ($CDCl_3$) 2·2 and 2·65 (4H, AA′, BB′ for tosyl aromatic protons), 2·8 (1H, d, H-5), 3·1 (1H, d, H-6), 4·2 (1H, m, allylic CH), 5·0 (2H, m, allylic CH_2), 6·3 (2H, t, OCH_2), 6·6 (2H, m, benzylic CH_2), 7·6 (3H, s, $COCH_3$), 7·6 (3H, s, tosyl CH_3), 8·4 (3H, m, $CHCH_2$), 9·1 (6H, d, protons of isopentyl methyl groups).

3-*Allyl*-2-(3-*methylbutoxy*)-6-*hydroxyacetophenone* **9e**. A solution of **9d** (94·6 g) in EtOH (450 ml) and 20% NaOH (250 ml) was refluxed for 24 h under N_2. The mixture was cooled after evaporation to small bulk, and the sodium salt of 3-allyl-2-(3-methylbutoxy)-6-hydroxyacetophenone crystallized out as plates. This was filtered off and washed with 40% NaOH then Et_2O. The sodium salt was then dissolved in H_2O and the solution was acidified to pH 1 with conc HCl. The resulting oil was extracted into Et_2O and the ethereal layer was washed with H_2O, $NaHCO_3$, H_2O, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness in vacuo to yield **9e** as a non-crystallizable oil (30·1 g); ν_{max} (film) 3400 (phenolic OH), 1640 (acetyl C=O) cm^{-1}; τ($CDCl_3$) –2·3 (1H, s, H-bonded OH), 2·7 (1H, d, H-4), 3·1 (1H, d, H-5), 4·1 (1H, m, allylic CH), 4·9 (2H, m, allylic CH_2), 6·2 (2H, t, OCH_2), 6·7 (2H, m, benzylic CH_2), 7·3 (3H, s, $COCH_3$), 8·3 (3H, m, $CHCH_2$), 9·1 (6H, d, protons of isopentyl methyl groups).

6-*Allyl*-5-(3 - *methylbutoxy*) - 4 - *oxo* - 4*H* - 1 - *benzopyran* - 2 - *carboxylic acid* **4b**. To a solution of Na (13·0 g) in EtOH (250 ml) was added **9e** (29·7 g) followed by diethyl oxalate (41·65 g). The resulting mixture was heated under reflux for 17 h. The organge reaction mixture was then cooled and evaporated to dryness. The dark residue was dissolved in H_2O (1·5 l) and the solution was acidified to pH 1 with conc HCl. The resulting sticky ma-

terial was extracted into $CHCl_3$, and extract was evaporated to dryness to leave an oil. The latter was heated under reflux for 1 h in EtOH (250 ml) and conc HCl (10 ml), and evaporated to dryness in vacuo to yield an oil, to which $NaHCO_3$ (40 g), H_2O (200 ml) and MeOH (150 ml) were added. This mixture was heated on a steam bath for 2 h, allowing the MeOH to evaporate slowly. The resulting aqueous solution was cooled in ice and the sodium salt of **4b** crystallized as plates, (29·8 g). This material was dissolved in hot H_2O (500 ml) and the solution was acidified to pH 1 with conc HCl. The resulting white precipitate was extracted into Et_2O and the ethereal solution was washed with H_2O, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to yield **4b** as a white solid. This material was crystallized from C_6H_6 as white plates (24 g); m.p. 144·5–145°. ν_{max} 3080 (3 C-H), 1725 (carboxylate C=O), 1630 (pyrone C=O) cm^{-1}; λ_{max} 210 nm (ϵ 20850), 320 nm (ϵ 4493) (Found: C, 68·06; H, 6·27; $C_{18}H_{20}O_5$ requires, C, 68·34; H, 6·37%); $\tau(CDCl_3)$ −0·88 (1H, s, CO_2H), 2·87 (1H, d, H-7), 3·1 (1H, d, H-8), 3·21 (1H, s, H-3), 4·5 (1H, m, allylic CH), 5·25 (2H, m, allylic CH_2), 6·31 (2H, t, OCH_2), 6·80 (2H, m, benzylic CH_2), 8·35 (3H, m, $CHCH_2$), 9·15 (6H, d, protons of isopentyl methyl groups); *m/e* 316 (M^+), 301, 245 (base peak).

The acid was esterified in the presence of H_2SO_4 to give ethyl 6 - allyl - 5 - (3- methylbutoxy) - 4 - oxo - 4*H* - 1 - benzopyran - 2 - carboxylate **4a** as a yellow oil; ν_{max} (film) 3080 (3 C—H), 1740 (carboxylate C=O), 1650 (pyrone C=O) cm^{-1} (Found: C, 69·67; H, 7·03; $C_{20}H_{24}O_5$ requires C, 69·75; H, 7·02%: $\tau(CDCl_3)$ 2·48 (1H, d, H-7), 2·77 (1H, d, H-6), 3·08 (1H, s, H-3) 4·1 (1H, m, allylic CH), 5·0 (2H, m, allylic CH_2), 5·61 (2H, q, ester CH_2), 6·08 (2H, t, OCH_2), 6·55 (2H, m, benzylic CH_2), 8·19 (3H, m, $CHCH_2$), 8·60 (3H, t, ester CH_3), 9·02 (6H, d, protons of isopentyl methyl groups); *m/e* 344 (M^+), 273 (base peak), 259, 247, 245, 231 and 219.

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