Some Reactions of Carbenoids with Chromone-2-carboxylic Esters

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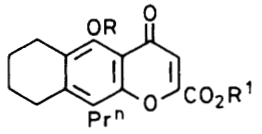
Ethyl 5-hydroxy-4-oxo-8-propyl-4*H*-[1]benzopyran-2-carboxylate (3a) reacts with chloroacetone under basic conditions to yield (1α, 1aα, 7aα)- and (1β, 1aα, 7aα)-ethyl 1-acetyl-1,1a,7,7a-tetrahydro-6-hydroxy-7-oxo-3-propylbenzo[*b*]cyclopropa[*e*]pyran-1a-carboxylate (4a) and (5a), products of cyclopropanation of the chromone 2,3-double bond, as well as ethyl 1,7-diacetyl-7, 7a-dihydro-5-propyl-6a*H*-cyclopropa[*b*]furo[4,3,2-*de*][1]benzopyran-6a-carboxylate (6a), representing a novel ring system. The corresponding tetrahydronaphthopyran (3b) gives analogous products (4b), (5b), and (6b). The thiochromone analogue of (3a), (8), gives only the furan annelated product ethyl 2-acetyl-6-propylthiopyrano[4,3,2-*cd*]benzofuran-4-carboxylate (9) under similar conditions. The reaction of the chromone (3b) with dimethylsulphoxonium methylide to yield the isomeric naphthofuranones (16a) and (17a) is also described.

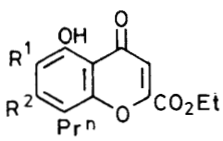
For the purpose of preparing certain 5-alkoxy derivatives of the anti-allergic compound proxicromil[1] (1), we wished to synthesise the 5-acetonyloxy compound (2). Compound (2) was eventually obtained in 39% yield by treatment of the ester (3b) with bromoacetone in refluxing butan-2-one in the presence of potassium carbonate. However, our earlier attempts at the preparation of the compound gave a number of unexpected products from reactions in which the halogenoacetone was acting as a carbenoid species, as described below.



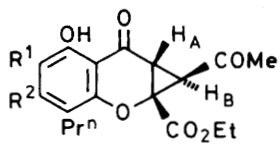
(1) R = R^1 = H
(2) R = MeCOCH$_2$, R^1 = Et

Results and Discussion

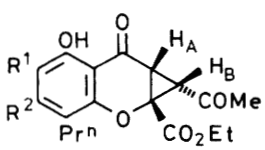
When the 5-hydroxychromone-2-carboxylic esters (3) were treated at room temperature in dimethylformamide (DMF) with chloroacetone in the presence of either potassium carbonate or sodium hydride and the reaction mixture was chromatographed on silica, several compounds were obtained, some of which were the result of a cyclopropanation of the pyrone ring system. Thus compounds (3a) and (3b) give rise respectively to the products (4a)—(7a) and (4b)—(6b) as summarised in the Table. The stereochemistry of the annelated cyclopropane ring followed from the coupling constants of the protons H_A and H_B in compounds (4), (5), and (6). In (4) and (6) J_{AB} is 7 Hz whereas in (5) it is 11 Hz, the latter being consistent with a *cis* arrangement of the cyclopropane protons. Thus (5) has *endo*- and (4) and (6) have *exo*-acetyl substituents.



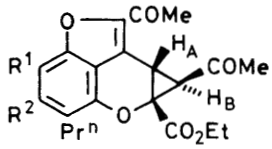
(3)
a ; R^1 = R^2 = H
b ; R^1R^2 = $(CH_2)_4$



(4)
a ; R^1 = R^2 = H
b ; R^1R^2 = $(CH_2)_4$



(5)
a ; R^1 = R^2 = H
b ; R^1R^2 = $(CH_2)_4$



(6)
a ; R^1 = R^2 = H
b ; R^1R^2 = $(CH_2)_4$

The thiochromone (8) corresponding to the chromone (3a) behaved differently. Treatment of compound (8) with chloroacetone and potassium carbonate in DMF at 60 °C gave 35% of the furan compound (9) only. No cyclopropane derivatives were observed.

The scope of the reaction was further examined by treating the cyclohexenyl fused compounds (10) and (11) with chloroacetone and potassium carbonate in DMF, but no reactions were observed. On reaction of (12) [the 2-unsubstituted derivative of (3b)] with chloroacetone, only the ' normal ' product (13) could be identified albeit in low yield.

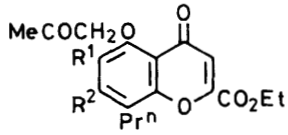
The observed products (4)—(6) probably arise from an initial conjugate addition of the anion of chloroacetone to the pyrone ring, followed by expulsion of chloride with consequent cyclopropane ring formation (Scheme 1). The reaction is in fact analogous to the Darzens glycidic ester condensation.[2a] Related cyclopropanation reactions of enones are also known (for example see ref. 2*b* and references cited therein). Under the conditions employing potassium carbonate, subsequent 1,2-addition of a second molecule of chloroacetone to the carbonyl group of compound (4) or (5) occurred followed by nucleophilic displacement of chloride by the 5-hydroxy group and elimination of water giving rise to the furan analogues (6) in low yield. Only *exo* products were isolated.† The fact that the observed furano products were always cyclopropanated suggests that cyclopropanation

† Under the basic reaction conditions employed, the products (4), (5), and (6) are probably subject to thermodynamic control. Predominance of the *exo* products may be due to their greater stability or to the isolation conditions. Inspection of Dreiding models of (4a) and (5a) shows that no serious strain is present in either stereoisomer. However, electronic repulsions between the acetyl group and the heterocyclic ring system in the *endo* isomer would energetically disfavour its formation.

Table. Reaction of chromone-2-carboxylic esters with chloroacetone

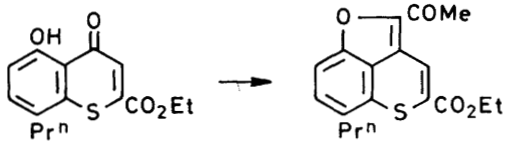
Chromone-2-carboxylic ester	Base	Temp. (°C)	Products	Yield (%)
(3a)	K_2CO_3	R.t.[a]	(3a)	17
			(4a)	14
			(5a)	3.5
			(6a)	1.5
			(7a)	4
(3a)	NaH	60	(3a)	40
			(4a)	10
			(5a)	0
			(6a)	0
			(7a)	2
(3b)	K_2CO_3	R.t.	(3b)	10
			(4b)	10
			(5b)	0
			(6b)	1.6
(3b)	NaH	60	(3b)	39
			(4b)	8
			(5b)	1.3
			(6b)	0

[a] R.t. = room temperature.

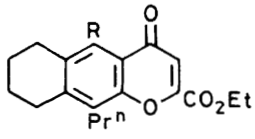


(7)

a; $R^1 = R^2 = H$



(8) (9)

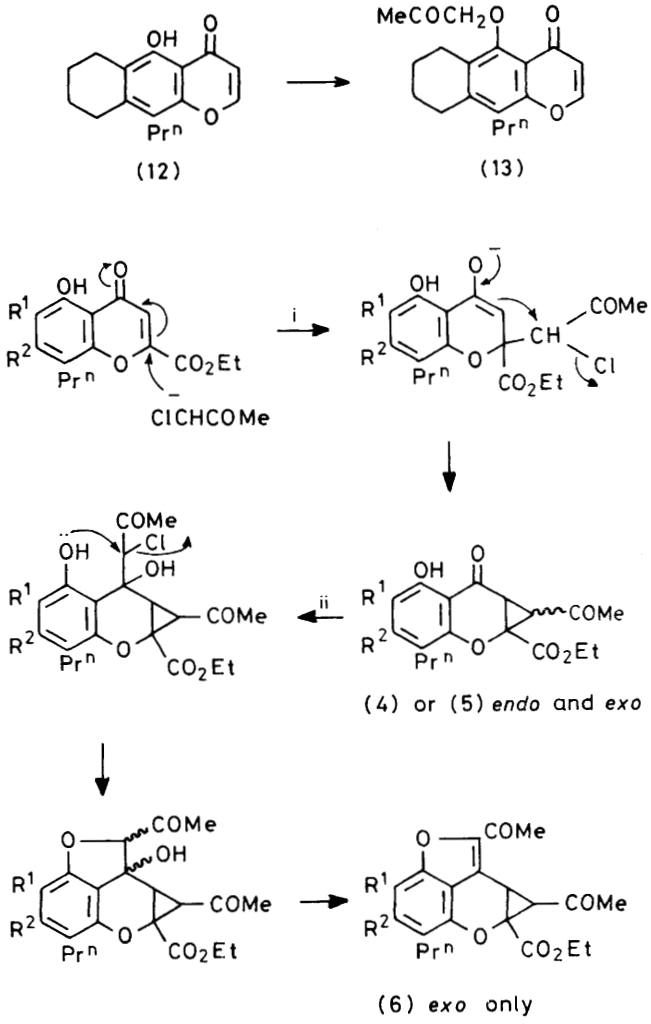


(10) R = OMe

(11) R = H

occurs initially, *via* 1,4-conjugate addition to the chromones, and furanation is subsequent to this. Since 5-hydroxy and 2-carboxy moieties are essential for the production of the carbenoid products [(4)—(6)], it appears that the reactions depend on the Michael acceptor properties of the chromone. Both these groups increase the electrophilicity of the enone system, the hydroxy group by virtue of the strong H-bond formed between it and the carbonyl group at C-4.

Conversely, initial addition to the thiochromone enone system (8) occurs in a 1,2-manner and no cyclopropanation subsequently takes place. We have also noted that thio-



(12) (13)

(4) or (5) *endo* and *exo*

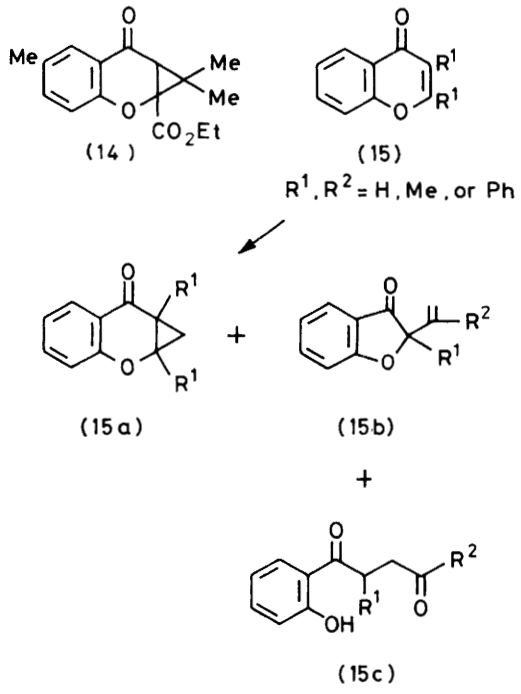
(6) *exo* only

Scheme 1. *Reagents:* i, NaH or K_2CO_3; ii, $ClCHCOMe$, K_2CO_3

chromone-2-carboxylic esters are stable to aqueous base in contrast to the well-known ring opening of chromone-2-carboxylic esters under these conditions.[3] This is a further indication of the different behaviour of the two systems. The stronger $-I$ effect of oxygen may be responsible for the facile nucleophilic attack on the 2-position of chromones compared to their thio analogues.

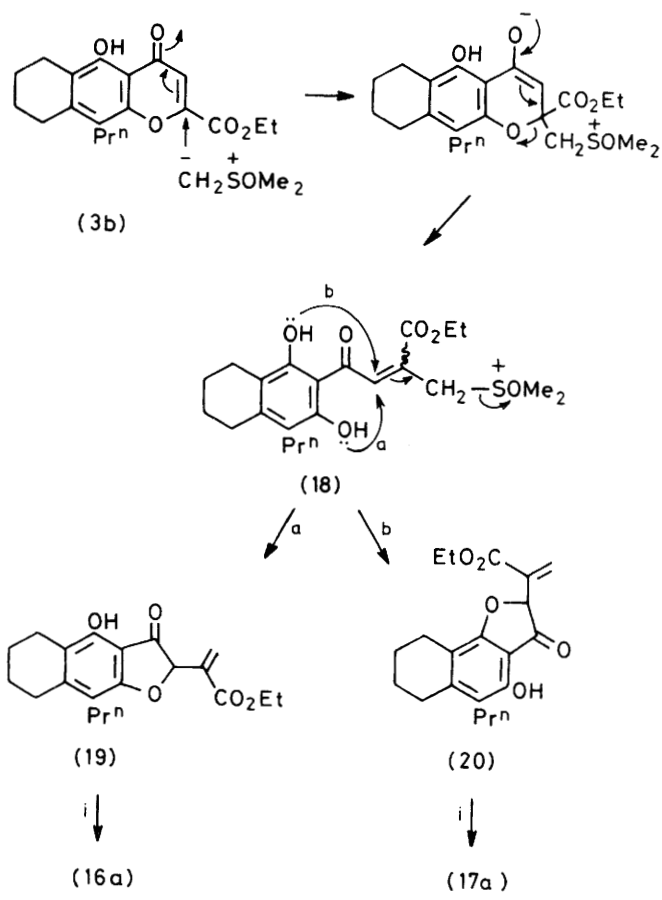
The reaction of compound (3b) to yield the desired acetonyloxy compound (2) was only achieved with bromoacetone and potassium carbonate in butan-2-one. Any changes in reagents or solvent resulted in a mixture of carbenoid products as described above. The unique ability of the solvent (butan-2-one) to give rise to the expected product (in contrast to acetone in particular) is puzzling. However, the weaker acidity of bromoacetone (compared to chloroacetone) coupled with the lower basicity of potassium carbonate would reduce the extent of deprotonation of the reagent resulting in an increased likelihood that electrophilic rather than nucleophilic behaviour would be displayed by this reagent.

There have been some reports of 'carbenoid' addition reactions to chromones giving cyclopropanes. Dean [4] observed that diazopropane will react with electron deficient chromones to give cyclopropane derivatives. For instance, the cyclopropane derivative (14) was obtained in 25% yield from 6-methylchromone-2-carboxylate. Ollis [5] reported that chromones and isoflavones can give rise to one or more of three

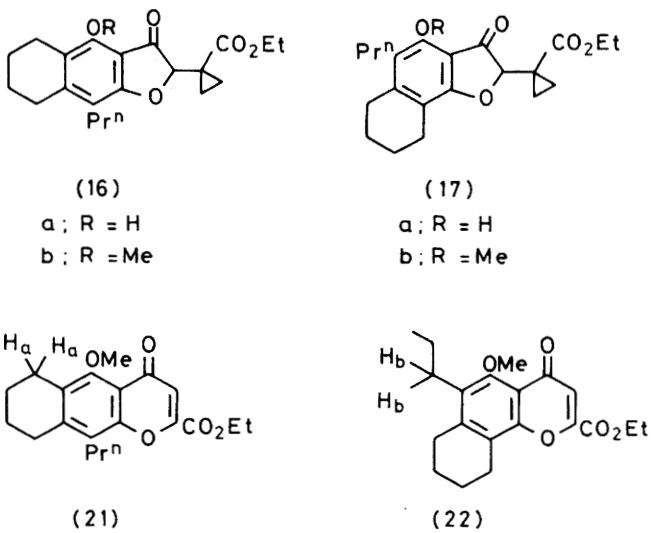


products (15a), (15b), or (15c) when made to react with dimethylsulphoxonium methylide. Donnelly [6] described similar products resulting from the reaction of this reagent with chalcones, thought to involve chromones as intermediates. Cyclopropanation of pyrones and chromones has also been shown to result from the reaction of the same ylide using a dimethyl sulphoxide–hexamethylphosphoric triamide medium.[7]

It was also of interest to examine the behaviour of our more electron deficient 2-ethoxycarbonyl system (3) towards this ylide reagent. Reaction of (3b) with excess of trimethylsulphoxonium iodide and sodium hydride in dimethyl sulphoxide (DMSO) at room temperature gave a 44% yield of the two isomeric compounds (16a) and (17a). No other products could be detected. We suggest (Scheme 2) that the formation of these two isomers arises from initial nucleophilic attack by the ylide to give the ring opened species (18). DMSO is then eliminated by attack from either of the phenolic oxygen atoms to produce the linear or angular vinyltetrahydrofuranone (19) or (20) *via* paths a and b respectively. These intermediates (not isolated) are analogous to the final products (15b) in the corresponding chromone or isoflavone reactions. Compounds (19) and (20), however, are susceptible to Michael additions by virtue of the ethoxycarbonyl substituents and consequently each undergoes cyclopropanation with a second mole of the ylide yielding (16a) and (17a). We could not assign structures unambiguously to these isomers although both were obtained in the pure state. Methylation of each compound with diazomethane gave the corresponding methyl ethers (16b) and (17b), which could not be differentiated by ^{1}H n.m.r. spectroscopy using the shift reagent Eu(fod)$_3$. In an analogous study in our laboratories,[8] the methyl ether (21) was readily distinguishable from its angular isomer (22) because complexation with the shift reagent occurred in the vicinity of the methoxy group, thereby inducing a shift in the protons H_a and H_b respectively [see structures (21) and (22)]. In the present investigation, however, the shift reagent does not co-ordinate predominantly with the 5-alkoxy group, as evidenced by large induced shifts in the cyclopropyl protons. Therefore, the isomers (16b) and (17b) could not be distinguished using this technique.



Scheme 2. *Reagents:* i, $\bar{C}H_2\overset{+}{S}OMe_2$



Experimental

M.p.s were determined with a Büchi apparatus. Mass spectra were recorded with a Kratos MS 30 or MS 50, and n.m.r. spectra with either a Bruker WP-80 FT or a Varian EM 390 spectrometer, using tetramethylsilane as internal standard. U.v. spectra were run in ethanol solution and were recorded on a Perkin-Elmer 552S spectrometer and i.r. spectra were recorded as KBr discs with a Perkin-Elmer 297 spectrometer. Anhydrous sodium sulphate was used as a drying agent for

solutions in organic solvents and light petroleum refers to the fraction boiling at 60—80 °C unless otherwise stated. Ether refers to diethyl ether. The syntheses of compounds (1),[9] (3a),[10] (3b),[9] (8),[11] (10),[9] and (11)[9] have previously been described.

Ethyl 6,7,8,9-*Tetrahydro*-4-*oxo*-5-(2-*oxopropoxy*)-10-*propyl*-4H-*naphtho*[2,3-b]*pyran*-2-*carboxylate* (2).—Ethyl 6,7,8,9-tetrahydro-5-hydroxy-4-oxo-10-propyl-4*H*-naphtho[2,3-*b*]-pyran-2-carboxylate (3b) (33 g, 0.1 mol), bromoacetone (20.6 g, 0.15 mol), anhydrous potassium carbonate (27.2 g, 0.2 mol), and potassium iodide (100 mg) in butan-2-one (800 ml) were heated under reflux for 6 h and a further aliquot (20.6 g) of bromoacetone added after 3 h. The reaction mixture was cooled, poured into water and allowed to stand in a fume cupboard overnight to allow the majority of the butanone to evaporate. The resulting suspension was extracted with ethyl acetate (3 ×) and the organic extracts were washed with water, dried ($MgSO_4$), and evaporated to yield a dark brown solid which was chromatographed on a silica column (1 kg). 25% Light petroleum in ether eluted starting material (4 g, 12%) and the *ester* (2) as a yellow solid (15.1 g, 39%), m.p. 96—97 °C (Found: C, 68.0; H, 7.0. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.7%); $\lambda_{max.}$ 212 (ε 29 517), 256 (16 278), and 275 nm (10 979); $\nu_{max.}$ 1 740 cm^{-1}; δ ($CDCl_3$; 90 MHz) 1.02 (3 H, t, *J* 4 Hz), 1.43 (3 H, t, *J* 7 Hz), 1.8 (6 H, m), 2.4 (3 H, s), 2.82 (6 H, m), 4.40 (2 H, q, *J* 7 Hz), 4.45 (2 H, s), and 6.9 (1 H, s); *m/z* 386 (M^+, 1%), 343 ($M^+ - COCH_3$, 19), 329 ($M^+ - CH_3COCH_2$, 100), 301 (41), and 273 (14).

Reaction of Chloroacetone with 5-Hydroxychromone-2-carboxylates

(*a*) *Ethyl* 5-*Hydroxy*-4-*oxo*-8-*propyl*-4H-*benzopyran*-2-*carboxylate* (3a) *with Potassium Carbonate as Base*.—A mixture of the title compound (24.8 g, 0.09 mol), chloroacetone (18.5 g, 0.2 mol), anhydrous potassium carbonate (30.3 g, 0.22 mol) and potassium iodide (0.2 g) in DMF (250 ml) was stirred at room temperature for 22 h, then poured into water (1 l) and extracted with ethyl acetate. The organic extract was washed with water, dried, and evaporated. The residue (*ca.* 28 g) was chromatographed on silica, eluting initially with a mixture of 10% ether in light petroleum, gradually increasing the concentration of ether to 80%. Five products were eluted in the following order.

(i) Unchanged starting material. Trituration with cold pentane gave a yellow crystalline solid, m.p. 57—58 °C (4.3 g, 17%).

(ii) *Ethyl* 1α-*acetyl*-1,1a,7,7aα-*tetrahydro*-6-*hydroxy*-7-*oxo*-3-*propylbenzo*[b]*cyclopropa*[e]*pyran*-1aα-*carboxylate* (4a), isolated as a yellow solid (4.3 g, 14.4%), m.p. 75—76 °C (Found: C, 65.3; H, 6.0. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.0%); $\lambda_{max.}$ 215 (ε 19 549) and 275 nm (9 123); $\nu_{max.}$ 1 735, 1 718, and 1 640 cm^{-1}; δ ($CDCl_3$) 0.95 (3 H, t, *J* 7.6 Hz, Me of propyl), 1.30 (3 H, t, *J* 6.9 Hz, Me of ethyl ester), 1.60 (2 H, m, CH_2 of propyl), 2.35 (3 H, s, COMe), 2.5 (2 H, m, $ArCH_2$), 2.71 (1 H, d, *J* 7.0 Hz, H in cyclopropane ring), 3.32 (1 H, d, *J* 7.0 Hz, cyclopropyl H), 4.31 (2 H, q, *J* 6.9 Hz, CH_2 of ethyl ester), 6.52 (1 H, d, *J* 8.2 Hz, ArH), 7.25 (1 H, d, *J* 8.2 Hz, ArH), and 11.40 (1 H, s, OH exchangeable); *m/z* 332 (M^+, 8%), 303 (M^+ — Et, 4), 259 ($M^+ - CO_2Et$, 100), 178 (17), 155 (42), 150 (45), 149 (47), and 127 (35).

(iii) *Ethyl* 1-β-*acetyl*-1,1a,7,7aα-*tetrahydro*-6-*hydroxy*-3-*propylbenzo*[b]*cyclopropa*[e]*pyran*-1aα-*carboxylate* (5a), a yellow solid, isolated by trituration with cold pentane (0.9 g, 3.5%), m.p. 107.5—108 °C (Found: C, 65.3; H, 6.1. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.0%); $\lambda_{max.}$ 208 (ε 16 994) and 278 nm (8 646); $\nu_{max.}$ 1 730, 1 712, and 1 645 cm^{-1}; δ ($CDCl_3$) 0.95 (3 H, t, *J* 7.0 Hz, Me of propyl), 1.42 (3 H, t, *J* 6.50 Hz, Me of ethyl ester), 1.65 (2 H, m, CH_2 of propyl), 2.32 (3 H, s, COMe), 2.5 (2 H, m, $ArCH_2$), 2.74 (1 H, d, *J* 11.0 Hz, H of cyclopropane), 3.26 (1 H, d, *J* 11.0 Hz, H of cyclopropane), 4.28 (2 H, q, *J* 6.5 Hz, CH_2 of ethyl ester), 6.51 (1 H, d, *J* 8.0 Hz, ArH), 7.22 (1 H, d, *J* 8.0 Hz, ArH), and 11.4 (1 H, s, OH-exchangeable); *m/z* 332 (M^+, 18%), 303 (M^+ — Et, 2), 259 ($M^+ - CO_2Et$, 54), 178 (40), 155 (100), 150 (96), 149 (74), and 127 (79).

(iv) *Ethyl* 1,7α-*diacetyl*-7,7aα-*dihydro*-5-*propyl*-6a-*cyclopropa*[b]*furo*[4,3,2-de][1]*benzopyran*-6aα-*carboxylate* (6a), obtained as a colourless solid by trituration with ether–pentane (1 : 1) followed by boiling with ether and recovery of the insoluble material (0.4 g, 1.8%), m.p. 185—187 °C (Found: C, 67.5; H, 6.2. $C_{21}H_{22}O_6$ containing 1% water requires C, 67.5; H, 6.2%); $\lambda_{max.}$ 243 (ε 13 519) and 300 nm (15 653); $\nu_{max.}$ 1 725 and 1 670 cm^{-1}; δ ($CDCl_3$; 90 MHz) 0.95 (3 H, t, *J* 7.5 Hz, Me of propyl), 1.32 (3 H, t, *J* 7.0 Hz, Me of ethyl ester), 1.72 (2 H, m, CH_2 of propyl), 2.40 (3 H, s, COMe), 2.62 (3 H, s, COMe), 2.65 (2 H, m, $ArCH_2$), 2.73 (1 H, d, *J* 8.0 Hz, H of cyclopropane), 3.76 (1 H, d, *J* 8.0 Hz, H of cyclopropane), 4.33 (2 H, q, *J* 7.0 Hz, CH_2 of ethyl ester), 6.94 (1 H, d, *J* 8.5 Hz, ArH), and 7.27 (1 H, d, *J* 8.5 Hz, ArH); *m/z* 370 (M^+, 1%), 327 (M^+ — COMe, 100), 299 ($M^+ - COMe - C_2H_4$, 65), 255 (52), and 229 (12).

(v) *Ethyl* 4-*oxo*-5-(2-*oxopropyloxy*)-8-*propyl*-4H-1-*benzopyran*-2-*carboxylate* (7a), obtained as a colourless solid (1.2 g, 4%), m.p. 141—142 °C by trituration with ether (Found: C, 65.1; H, 6.3. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.05%); $\lambda_{max.}$ 220 (ε 17 464), 238 (15 216), 266 (9 337), and 275 nm (9 337); $\nu_{max.}$ 1 730 and 1 665 cm^{-1}; δ ($CDCl_3$; 90 MHz) 1.02 (3 H, t, *J* 7.1 Hz, Me of propyl), 1.45 (3 H, t, *J* 7.0 Hz, Me of ethyl ester), 1.73 (2 H, m, CH_2 of propyl), 2.46 (3 H, s, COMe), 2.81 (2 H, t, *J* 7.5 Hz, $ArCH_2$), 4.44 (2 H, q, *J* 7.0 Hz, CH_2 of ethyl ester), 4.56 (2 H, s, OCH_2CO), 6.65 (1 H, d, *J* 8.5 Hz, ArH), 6.95 (1 H, s, ArH), and 7.42 (1 H, d, *J* 8.5 Hz, ArH); *m/z* 332 (M^+, 4%), 289 (M^+ — COMe, 100), 261 ($M^+ - COMe - C_2H_4$, 75), and 232 (17).

(*b*) *Ethyl* 6,7,8,9-*Tetrahydro*-5-*hydroxy*-4-*oxo*-10-*propyl*-4H-*naphtho*[2,3-b]*pyran*-2-*carboxylate* (3b) *with Potassium Carbonate*.—The title compound (15 g, 0.05 mol) was treated under the same conditions as those described for (3a) and gave the following mixture of products.

(i) Unchanged starting material (1.8 g, 10%).

(ii) *Ethyl* 1α-*acetyl*-1,1a,4,5,6,7,9,9aα-*octahydro*-8-*hydroxy*-9-*oxo*-3-*propylcyclopropa*[b]*naphtho*[2,3-e]*pyran*-1aα-*carboxylate* (4b), isolated as yellow-green needles (1.8 g, 10%), m.p. 134—135 °C (Found: C, 68.7; H, 7.1. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%); $\lambda_{max.}$ 211 (ε 19 678) and 285 nm (12 488); $\nu_{max.}$ 1 739 cm^{-1}; δ ($CDCl_3$; 80 MHz) 0.98 (3 H, t, *J* 7.1 Hz, Me of propyl), 1.32 (3 H, t, *J* 7.32 Hz, Me of ethyl ester), 1.7—1.85 (6 H, m, non-benzylic CH_2), 2.33 (3 H, s, COMe), 2.5 (6 H, m, $ArCH_2$), 3.31 (1 H, d, *J* 7.03 Hz, H in cyclopropane ring), 2.57 (1 H, d, *J* 7.03 Hz, H in cyclopropane ring), 3.76 (2 H, q, *J* 7.32 Hz, CH_2 of ethyl ester), and 11.81 (1 H, s, exchangeable, OH); *m/z* 386 (M^+, 18%), 357 (M^+ — Et, 19), 232 (63), and 203 (55).

(iii) *Ethyl* 2,3α-*diacetyl*-2bα,3,6,7,8,9-*hexahydro*-5-*propyl*-3H-*cyclopropa*[b]*furo*[4,3,2-de]*naphtho*[b]*pyran*-3aα-*carboxylate* (6b), isolated as pale yellow needles (0.28 g, 1.6%), m.p. 181—182 °C (Found: C, 70.4; H, 7.0. $C_{25}H_{28}O_6$ requires C, 70.7; H, 6.65%); $\lambda_{max.}$ 252 (ε 14 300) and 312 nm (14 600); $\nu_{max.}$ 1 720 and 1 688 cm^{-1}; δ ($CDCl_3$; 80 MHz) 1.0 (3 H, t, *J* 6.73 Hz, Me of propyl), 1.32 (3 H, t, *J* 7.03 Hz, Me of ethyl ester), 1.58 (2 H, m, CH_2 of propyl), 1.84 (4 H, m, CH_2 of cyclohexane ring), 2.39 (3 H, s, COMe), 2.62 (3 H, s, COMe), 2.9 (6 H, m, $ArCH_2$), 2.82 (1 H, d, *J* 7.9 Hz, H of cyclo-

propyl), 3.72 (1 H, d, *J* 7.9 Hz, H of cyclopropyl), and 4.28 (2 H, q *J* 7.04 Hz, CH_2 of ester); *m/z* 424 (M^+, 6%), 382 (M^+ − 42, 100), 381 (M^+ − COMe, 42), 353 (M^+ − COMe − C_2H_4, 85), 309 (41), and 283 (6).

(*c*) *Reaction of the Chromone* (3a) *using Sodium Hydride as Base*.—To a solution of (3a) (5.45 g, 0.02 mol) in DMF (50 ml) was added sodium hydride (57% in oil; 0.84 g, 0.02 mol). The mixture was stirred at room temperature for 20 min after which was added sodium iodide (0.1 g) and chloroacetone (2.3 g, 0.025 mol). The mixture was stirred for 12 h at 60—70 °C and allowed to cool. A further quantity of chloroacetone (2.0 ml) was added and heating was continued for a further 3 h during which time no further change was observed. The mixture was poured into water (400 ml) and extracted with ethyl acetate. The organic extracts were washed with water and brine then dried. Evaporation gave a red oil which was chromatographed on silica, eluting initially with a mixture of 10% ether in light petroleum, gradually increasing the concentration of ether to 80%. Three products, starting material (40%), (4a) (10%), and (7a) (2%), were isolated.

(*d*) *Reaction of the Naphthopyranone* (3b) *using Sodium Hydride*.—The title compound was treated as described above for (3a) to yield the following. (i) Unchanged starting material (39%). (ii) Cyclopropanaphthopyran (4b) (8%). (iii) *Ethyl* 1β-*acetyl*-1,1a,4,5,6,7,9,9aα-*octahydro*-8-*hydroxy*-9-*oxo*-3-*propylcyclopropa*[b]*naphtho*[2,3-e]*pyran*-1aα-*carboxylate* (5b), isolated as pale yellow plates after trituration with cold pentane (0.37 g, 1.3%), m.p. 112—113 °C (Found: C, 68.5; H, 7.0. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.7%); $\lambda_{max.}$ 210 (ε 20 352) and 287 nm (11 930); $\nu_{max.}$ 1 725 cm^{-1}; δ ($CDCl_3$; 80 MHz) 0.98 (3 H, t, *J* 6.74 Hz, Me of propyl), 1.36 (3 H, t, *J* 7.33 Hz, Me of ethyl ester), 1.7 (6 H, m, CH_2), 2.28 (3 H, s, COMe) 2.6 (6 H, m, $ArCH_2$), 2.75 (1 H, d, *J* 10.84 Hz, H of cyclopropyl), 3.21 (1 H, d, *J* 10.8 Hz, H of cyclopropyl), 4.32 (2 H, q, *J* 7.03 Hz, CH_2 of ethyl ester), and 11.79 (1 H, s, exchangeable OH); *m/z* 386 (M^+, 27%), 357 (M^+ − Et, 14), 313 (75), 232 (100), and 203 (66).

Reaction of Chloroacetone with Ethyl 6,7,8,9-*Tetrahydro*-4-*oxo*-10-*propyl*-4H-*naphtho*[2,3-b]*pyran*-2-*carboxylate* (11).—A mixture of the ester (11) (5.8 g, 0.02 mol), potassium carbonate (7 g, 0.05 mol), chloroacetone (3.68 g, 0.04 mol), and potassium iodide (0.05 g) in dry DMF (75 ml) was stirred overnight at room temperature, after which time only starting material was present. A further quantity of chloroacetone (3.0 g) was added and the mixture was stirred for a further 3 h at 50 °C. No reaction occurred.

Reaction of Chloroacetone with Ethyl 6,7,8,9-*Tetrahydro*-5-*methoxy*-4-*oxo*-10-*propyl*-4H-*naphtho*[2,3-b]*pyran*-2-*carboxylate* (10).—A mixture of the ester (10) (2.2 g, 7 mmol), chloroacetone (1.85 g, 20 mmol), potassium carbonate (4.15 g, 30 mmol), and potassium iodide (0.1 g) in DMF (40 ml) was stirred at room temperature for 16 h. No reaction was observed. The mixture was heated on the steam-bath for 3 h. Again no reaction was observed.

Ethyl 2-*Acetyl*-6-*propylthiopyrano*[4,3,2-cd]*benzofuran*-4-*carboxylate* (9).—Ethyl 5-hydroxy-4-oxo-8-propyl-4*H*-[1]-benzothiopyran-2-carboxylate (8) (1.46 g, 5 mmol) was heated under reflux with bromoacetone (1.4 g, 10 mmol), potassium carbonate (2.8 g, 20 mmol), and potassium iodide (2 crystals) in butan-2-one (30 ml) for 24 h with addition of a further aliquot of bromoacetone (1 g) after 4.5 h. The mixture was poured into water (100 ml) and extracted with chloroform (3 × 50 ml). The combined organic extracts were washed with water (1×), 2M-HCl (1×), and water (1×), dried and evaporated to yield a yellow oil which was chromatographed on silica. 20% Ether–light petroleum eluted a red solid (0.6 g, 35%), m.p. 105—106 °C (Found: C, 65.4; H, 5.7; S, 9.7. $C_{18}H_{18}O_4S$ requires C, 65.4; H, 5.5; S, 9.7%); $\lambda_{max.}$ 246 (ε 22 160), 322 (9 460), and 428 nm (6 010); $\nu_{max.}$ 1 718, 1 660, and 1 625 cm^{-1}; δ ($CDCl_3$; 80 MHz) 0.95 (3 H, t), 1.4 (3 H, t), 1.55 (2 H, m), 2.60 (3 H, s), 2.65 (2 H, t), 4.35 (2 H, q), 7.1 (2 H, ABq), and 8.12 (1 H, s); *m/z* 330 (M^+), 301 (M^+ − Et, 100%), and 292.

6,7,8,9-*Tetrahydro*-5-*hydroxy*-10-*propylnaphtho*[2,3-b]-*pyran*-4-*one* (12).—6,7,8,9-Tetrahydro-5-hydroxy-4-oxo-10-propyl-4*H*-naphtho[2,3-*b*]pyran-2-carboxylic acid (1) (1.51 g, 5 mmol) was dissolved in quinoline (15 ml) and copper-bronze (100 mg) was added. The mixture was heated under reflux under N_2 for 10 min, cooled, diluted with ether (60 ml), and filtered. The filtrate was washed with 2M-HCl (3 × 50 ml), water (1×), and brine (1×), dried ($MgSO_4$), and evaporated affording an orange solid which was recrystallised from light petroleum to yield the naphthopyranone (12) as brown plates (0.84 g, 64%), m.p. 100—101 °C (Found: C, 74.4; H, 7.3. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%); $\lambda_{max.}$ 227 (ε 15 662) and 261 nm (17 488); $\nu_{max.}$ 1 645, 1 615, and 1 585 cm^{-1}; δ ($CDCl_3$; 80 MHz), 1.0 (3 H, t, Me of propyl), 1.4 (2 H, m, CH_2 of propyl), 1.7 (4 H, m, non benzylic CH_2), 2.7 (6 H, m, $ArCH_2$), 6.2 and 7.8 (2 H, ABq), and 12.5 (1 H, s, OH, exchangeable); *m/z* 258 (M^+), 229 (M^+ − Et, 100%), and 201.

6,7,8,9-*Tetrahydro*-5-(2-*oxopropyloxy*)-10-*propylnaphtho*-[2,3-b]*pyran*-4-*one* (13).—A stirred mixture of the hydroxy compound (12) (2.0 g, 7.75 mmol), chloroacetone (1.6 ml, 1.85 g, 20 mmol), anhydrous potassium carbonate (4.15 g, 30 mmol), and potassium iodide (0.1 g) in dry DMF (40 ml), was maintained at room temperature overnight, then heated on a steam-bath for 4 h. More chloroacetone (1.6 ml) was added and heating was continued for a further 2 h. After standing overnight the mixture was poured into water, acidified by addition of conc. HCl and extracted into ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and evaporated, affording a dark oil. Purification was by column chromatography on silica, eluting with ether–light petroleum mixtures. After removal of the starting material and very minor impurities, the required compound (13) was isolated from the relevant fractions and washed with 10% ether in pentane, giving an almost colourless solid (0.19 g, 8%), m.p. 118—119 °C (Found: C, 72.2; H, 7.3. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%); $\lambda_{max.}$ 227 (ε 21 433), 251 (15 718), and 257 nm (15 360); $\nu_{max.}$ 1 730 and 1 650 cm^{-1}; δ ($CDCl_3$; 80 MHz) 1.01 (3 H, t, *J* 7 Hz, propyl Me), 1.9—1.4 (6 H, m, non benzylic CH_2), 2.44 (3 H, s, COMe), 2.9—2.6 (6 H, m, $ArCH_2$), 4.48 (2 H, s, OCH_2CO), 6.19 (1 H, d, *J* 6 Hz, H_3), and 7.77 (1 H, d, *J* 6 Hz, H_2); *m/z* 314 (M^+, 1%), 271 (M^+ − COMe, 23), 257 (100), 229, and 215.

Reaction of Ethyl 6,7,8,9-*Tetrahydro*-5-*hydroxy*-4-*oxo*-10-*propyl*-4H-*naphtho*[2,3-b]*pyran*-2-*carboxylate* (3b) *with Dimethylsulphoxonium Methylide*.—Sodium hydride (57% oil suspension, 0.524 g, 21.8 mmol) was added at room temperature under N_2 to the title compound (3b) (3.3 g, 10 mmol), in dry dimethyl sulphoxide (DMSO) (75 ml). The dark brown suspension was stirred for 0.5 h, and trimethylsulphoxonium iodide (2.42 g, 11 mmol) was then added during 20 min causing a slightly exothermic reaction. After being stirred for 48 h with addition of a further aliquot of trimethylsulphoxonium iodide (2.42 g, 11 mmol) after 18 h, the mixture was poured into dil. aqueous HCl (250 ml) and extracted with methylene dichloride (3×). The organic extracts were washed

with water (4×), dried, and evaporated to yield a brown oil. Chromatography on silica using 15% ether–light petroleum as eluant, yielded starting material (0.9 g, 27%) and a mixture of ethyl 1-(2,3,5,6,7,8-hexahydro-4-hydroxy-3-oxo-9-propyl-2*H*-naphtho[2,3-*b*]furan-2-yl)cyclopropanecarboxylate (16a) and ethyl 1-(2,3,6,7,8,9-hexahydro-4-hydroxy-3-oxo-5-propyl-2*H*-naphtho[1,2-*b*]furan-2-yl)cyclopropanecarboxylate (17a) (1.65 g, 46%). H.p.l.c. (Waters Prep 500) separation of the two products yielded the following products.

(i) A cream coloured solid, after recrystallisation from light petroleum (270 mg, 7.5%), m.p. 105—106 °C (Found: C, 70.3; H, 7.2. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%); δ ($CDCl_3$; 90 MHz) 0.93 (3 H, t, *J* 7.0 Hz, Me of propyl), 0.98 (3 H, t, *J* 6.5 Hz, Me of ester), 1.1—1.9 (10 H, m, non-benzylic CH_2), 2.62 (6 H, m, $ArCH_2$), 4.00 (2 H, q, *J* 6.5 Hz, CH_2 of ester), 4.16 (1 H, s, H_2), and 7.53 (1 H, s, OH, exchangeable); *m*/*z* 358 (M^+), 329 (M^+ − Et, 100%), 312, 284, and 255.

(ii) A cream coloured solid from light petroleum (310 mg, 8.7%), m.p. 81—82 °C (Found: C, 70.2; H, 7.1. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%); δ ($CDCl_3$; 90 MHz) 0.93 (3 H, t, *J* 7.0 Hz, Me of propyl), 0.95 (3 H, t, *J* 6.5 Hz, Me of ester), 1.0—1.95 (10 H, m, non benzylic CH_2), 2.60 (6 H, m, $ArCH_2$), 3.96 (2 H, q, *J* 6.5 Hz, CH_2 of ester), 4.20 (1 H, s, H_2), and 7.65 (1 H, s, OH, exchangeable); *m*/*z* 358 (M^+), 329 (M^+ − Et, 100%), 312, 284, and 255.

Attempted Differentiation of the Isomers (16a) *and* (17a).—Each of the isomers (10 mg, 0.028 mmol) was treated separately with diazomethane generated from Diazald (5 mmol) and the ether solvent was allowed to evaporate in a fume cupboard overnight. Two methyl ethers were obtained as white solids which were investigated by ^1H n.m.r.

(i) Methyl ether (16b) or (17b) derived from phenol of m.p. 105 °C, δ ($CDCl_3$; 80 MHz) 0.97 (3 H, t, Me of propyl), 1.02 (3 H, t, Me of ester), 1.1—1.9 (10 H, m), 2.6 (6 H, m, $ArCH_2$), 4.05 (3 H, s, OMe), and 4.1 (2 H, q, CH_2 of ester).

(ii) Methyl ether (17b) or (16b) derived from phenol of m.p. 81 °C, δ ($CDCl_3$; 80 MHz), 0.95 (6 H, t), 1.2—1.9 (10 H, m), 2.7 (6 H, m), 4.05 (3 H, s), 4.1 (2 H, q), and 7.3 (1 H, s).

Addition of $Eu(fod)_3$ to the above n.m.r. samples resulted in downfield shifts of the cyclopropyl and ethoxy protons only.

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