Heterodiene Cycloadditions of 3-Acylchromones with Enol Ethers

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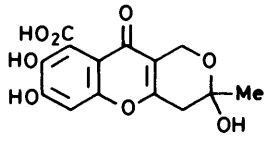
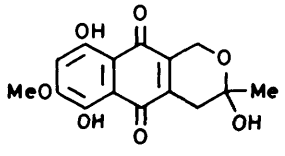
3-Formylchromones behave as heterodienes in stereoselective ($4\pi + 2\pi$)cycloadditions with enol ethers at 20 °C, the formal *endo*-addition product predominating. An electron-donor substituent (OH, OMe) in the aromatic ring retards the reaction and slightly increases *endo* selectivity, while an electron-withdrawing group (NO_2) has the reverse effect. 3-Acetyl- and 3-benzoyl-chromone react much more slowly but with similar stereoselectivity. The reaction of 3-formylchromone (**3a**) with t-butoxyethene is almost non-selective, while with dihydropyran it forms novel isomeric pyrano[2′,3′:6,5]pyrano[4,3-*b*][1]benzopyranones (**23**) and (**24**) in which the enol ether geometry is retained. Reaction rates and stereoselectivity vary slightly with solvent and temperature, and the results indicate a concerted cycloaddition mechanism with kinetically controlled stereoselection.

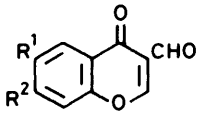
The structural resemblance of the fungal metabolites fulvic acid (**1**) and fusarubin (**2**) is consistent with their biosynthesis *via* a common polyketide-derived intermediate.[1] By the same token, a synthetic route to pyrano[4,3-*b*][1]benzopyrans such as (**1**) could also provide intermediates for conversion into the naphtho[2,3-*c*]pyran system, which is incorporated in compound (**2**) and several other biologically active molecules.[2] With this in mind we have examined the heterodiene cycloaddition of various 3-acylchromones to enol ethers, since this type of reaction appeared to offer a direct route to the tricyclic skeleton of (**1**), and according to precedent [3,4] should be facilitated by the electron-withdrawing chromone carbonyl group located in the α-position of the heterodiene component. We now describe the details of our study,[5] during the course of which others revealed similar observations[6] and a synthesis of fulvic acid (**1**) was completed.[7]



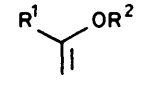
(**1**)



(**2**)

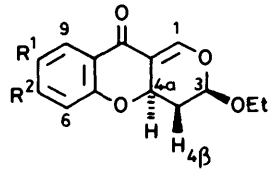


(**3**)

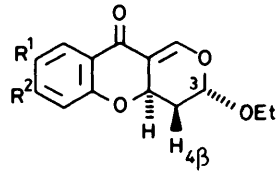


(**4**) R^1 = H, R^2 = Et
(**11**) R^1 = H, R^2 = Bu
(**12**) R^1 = H, R^2 = Bu^t
(**13**) R^1 = R^2 = Me

Treatment of 3-formylchromone (**3a**) with an excess of ethoxyethene (**4**) in dichloromethane at room temperature resulted in the simultaneous formation of two products. The major of these, (**5a**), was obtained by evaporation and crystallisation from ethanol. Chromatography of the mother liquors provided a further quantity of (**5a**), and an isomer (**6a**). The products were distinguished *via* 220 MHz ^{1}H n.m.r. spectroscopy, a diagnostic feature being the coupling constant $J_{3,4\beta}$, which had a value of 10 Hz in the major product (**5a**) and 2.8 Hz in the minor product (**6a**), indicating *trans*-diaxial and axial-equatorial arrangements of the respective vicinal hydrogens. It was therefore the formal *endo*-cycloaddition product (**5a**) which had predominated. Similar stereoselectivity was observed with a series of substituted 3-formylchromones (Table 1), and in each case the isomeric cycloadducts were distinguished *via* the respective ^{1}H n.m.r. signals associated with 4β-H.



(**5**)

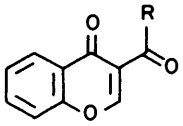


(**6**)

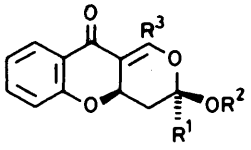
Table 1. Reactions of 3-formylchromones with ethoxyethene at 20 °C.

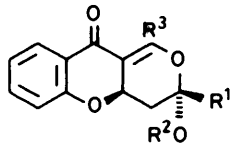
Substrate	R^1	R^2	Solvent	Reaction time (days)	Total yield (**5**) + (**6**) (%)	Ratio (**5**):(**6**)
(**3a**)	H	H	CH_2Cl_2	3	90	83:17
(**3b**)	OAc	H	CH_2Cl_2	3	94	88:12
(**3c**)	OMe	H	$CHCl_3$	7	91	88:12
(**3d**)	OH	H	THF	8	73	90:10
(**3e**)	NO_2	H	THF	2	66	77:23
(**3f**)	H	OAc	$CHCl_3$	3	96	89:11
(**3g**)	H	OMe	$CHCl_3$	7	95	89:11
(**3h**)	H	OH	DMF	14	67	90:10
(**3i**)	H	NO_2	THF	2	94	72:28

The effects of variation within the heterodiene and enol ether components are shown in Table 2. 3-Acetylchromone (**7**) and 3-benzoylchromone (**8**) reacted only slowly with ethoxyethene (**4**) at room temperature, but at 115 °C the cycloaddition was again efficient and stereoselective. Under these conditions the parent system (**3a**) predictably reacted more rapidly but less selectively with (**4**) than at room temperature. Reactions of compound (**3a**) with the enol ethers (**11**) and (**12**) at 20 °C were slower than with compound (**4**), and with the t-butyl ether (**12**) a significant decrease in *endo* selectivity was evident. By contrast, the extra methyl substituent in the propenyl ether (**13**) had no such effect on the stereochemical outcome of the reaction.

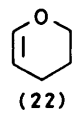


(7) R = Me
(8) R = Ph

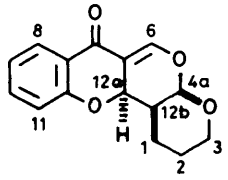




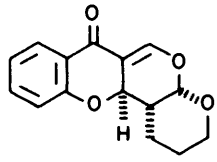
	R^1	R^2	R^3	
(9)	H	Et	Me	(10)
(14)	H	Et	Ph	(15)
(16)	H	Bu	H	(17)
(18)	H	Bu^t	H	(19)
(20)	Me	Me	H	(21)



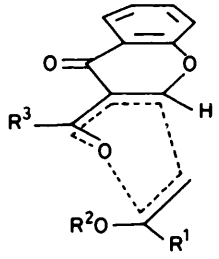
(22)



(23)



(24)



(25)

Table 2. Reactions of 3-acylchromones with enol ethers in dichloromethane.

Chromone	Enol ether	Temp. (°C)	Reaction time (days)	Products	Ratio	Total yield (%)
(7)	(4)	20	15	(9) + (10)	*a*	*a*
(7)	(4)	115	2	(9) + (10)	78:22	92
(8)	(4)	115	3	(14) + (15)	74:26	87
(3a)	(4)	115	1	(5a) + (6a)	75:25	95
(3a)	(11)	20	6	(16) + (17)	89:11	95
(3a)	(12)	20	7	(18) + (19)	55:45	43
(3a)	(13)	20	5	(20) + (21)	87:13	66
(3a)	(22)	115	5	(23) + (24)	56:44[b]	90[b]

[a] Reaction incomplete. Product (9) isolated in 28% yield by evaporation and trituration with petroleum and ether. [b] Determined by h.p.l.c.

With dihydropyran (22) at 115 °C, the chromone (3a) produced the novel tetracyclic systems (23) and (24). These structures were not assigned unequivocally since their ^{1}H n.m.r. spectra are similar. However, the allylic coupling constants $J_{1,4a}$ for *endo* (major) products (5) are consistently *ca.* 1 Hz, while for *exo* (minor) products (6) they are consistently 1.5 Hz. The observed values for the corresponding coupling in compounds (23) and (24) maintain this pattern, and therefore invite assignment as depicted. Although the coupling between 4a-H and 12b-H in compounds (23) and (24) is not a distinguishing feature (*J* 2.5 and 2 Hz respectively), neither value is consistent with a *trans*-diaxial relationship, and this confirms that the *cis*-geometry of the 2π cycloaddend is retained in each product. Mechanistically the above results are consistent with a concerted (4π + 2π) cycloaddition which proceeds preferentially *via* the *endo* transition state (25) under kinetic control. Predictably the *exo*-cycloadducts (6) are thermodynamically more stable due to the anomeric effect;[3] equilibration of (5a) or (6a) with acid produces identical mixtures in which the latter predominates by almost 7:1.* Although not directly comparable due to the variation in solvent, the results in Table 1 indicate that donor substituents (OH, OMe) in the aromatic ring reduce the overall electrophilicity of the heterodiene, resulting in a slower reaction and increased stereoselectivity. The reduced reactivity of compounds (7) and (8) reflect the increasing steric interaction between R^3 and the chromone carbonyl oxygen as the 4π component assumes the planar *cisoid* rearrangement required for cycloaddition, while the increased bulk of R^2 in (12) also destabilises (25), thus increasing the proportion of *exo* cycloaddition observed with this enol ether.

Table 3. Effect of variation of conditions on stereoselectivity in the reaction of 3-formylchromone with ethoxyethene.

Solvent	Temp. (°C)	Relative rate[a]	% (5a) in product mixture[a,b]
Acetone	20	0.55	85.5
MeCN	20	0.81	87.5
CH_2Cl_2	20	1.00	83.5
DMF	20	1.07	79.0
CH_2Cl_2	−5	0.13	87.6
CH_2Cl_2	40	1.62	80.4

[a] Calculated using a calibrated h.p.l.c. system. [b] Accuracy estimated to be ±0.4; balance to 100% is (5b).

In a brief study of solvent and temperature effects (Table 3), the reaction between compounds (3a) and (4) was monitored using calibrated h.p.l.c. The rate and stereoselectivity of the cycloaddition process varied only slightly with solvent, indicating little or no increase in polarity in attaining the transition state (25). It is likely that the solvent influences primarily the extent of intramolecular hydrogen bonding between the formyl hydrogen atom and the chromone carbonyl oxygen. Such hydrogen bonding is a feature of 3-formylchromones,[8] and stabilises the *cisoid* conformation of the 4π component required for cycloaddition. The extremely slow reaction of the hydroxychromone (3h) with (4) in DMF is

* This and other aspects of the chemistry of the cycloadducts will be described in detail elsewhere.

Table 4. Analytical data for heterodiene cycloaddition products.

Compd. (Formula)	Solvent	M.p. (°C)	Found % (Requires) C	H	N
(5a)	EtOH	176—177	68.35	5.6	
(6a)	Petroleum (60—80 °C)	83—84	68.2	5.8	
($C_{14}H_{14}O_4$)			(68.3)	(5.7)	
(5b)	EtOAc	172—173	63.3	5.3	
(6b)	Petroleum	88—89	63.3	5.3	
($C_{16}H_{16}O_6$)			(63.15)	(5.3)	
(5c)	EtOAc	159—161	65.0	5.7	
(6c)	Petroleum	83—84	65.1	6.0	
($C_{15}H_{16}O_5$)			(65.2)	(5.8)	
(5d)	MeOH	188—189	64.0	5.45	
(6d)	EtOAc	193—194	64.0	5.4	
($C_{14}H_{14}O_5$)			(64.1)	(5.4)	
(5e)	DMF	208—209	57.6	4.5	4.6
(6e)	EtOAc	152—153	57.6	4.6	4.65
($C_{14}H_{13}NO_6$)			(57.7)	(4.5)	(4.8)
(5f)	EtOAc	176—177	63.4	5.2	
(6f)	Ether	115—116	63.0	5.4	
($C_{16}H_{16}O_6$)			(63.15)	(5.3)	
(5g)	EtOAc	152	65.0	5.7	
(6g)	Petroleum	96—97	65.1	5.9	
($C_{15}H_{16}O_5$)			(65.2)	(5.8)	
(5h)	EtOH	209—211	64.2	5.55	
(6h)	EtOAc	215—216	64.0	5.4	
($C_{14}H_{14}O_5$)			(64.1)	(5.4)	
(5i)	EtOH	159—160	57.7	4.4	4.8
(6i)	Petroleum–ether	141—143	57.9	4.5	4.7
($C_{14}H_{13}NO_6$)			(57.7)	(4.5)	(4.8)
(9)	MeOH	106—107	69.3	6.3	
(10)	MeOH	115—116	69.2	6.3	
($C_{15}H_{16}O_4$)			(69.2)	(6.2)	
(14)	MeOH	150—152	74.5	5.6	
(15)		oil	74.3	5.6	
($C_{20}H_{18}O_4$)			(74.5)	(5.6)	
(16)	EtOAc	120—121	70.0	6.6	
(17)	Petroleum	50—51	70.2	6.6	
($C_{16}H_{18}O_4$)			(70.1)	(6.6)	
(18)	Petroleum	100—101	70.1	6.6	
(19)		oil	70.1	6.7	
($C_{16}H_{18}O_4$)			(70.1)	(6.6)	
(20)	Ether	114—115	68.1	5.8	
(21)	Petroleum	127—128	68.4	5.7	
($C_{14}H_{14}O_4$)			(68.3)	(5.7)	
(23)	EtOH	115—116	69.8	5.5	
(24)	EtOH	152—153	69.8	5.3	
($C_{15}H_{14}O_4$)			(69.8)	(5.5)	

probably due to an adverse combination of electronic and hydrogen bonding effects which interfere with the reactivity and conformation of the heterodiene unit. From a synthetic viewpoint, the results in Table 3 suggest that by judicious choice of temperature and solvent, these ($4\pi + 2\pi$) cycloadditions can be moderated and the kinetically controlled stereoselectivity thereby optimised.

Experimental

M.p.s were determined using an Electrothermal melting point apparatus and are uncorrected. I.r. spectra, unless otherwise stated, were of liquid paraffin mulls on sodium chloride plates, recorded on a Perkin-Elmer 297 instrument. Except where stated, ^{1}H n.m.r. spectra were measured for solutions in deuteriochloroform with tetramethylsilane as the internal standard, on Perkin-Elmer R32 (90 MHz) or R34 (220 MHz) instruments. U.v. spectra were recorded for ethanolic solutions using a Pye-Unicam SP800A spectrometer. Mass spectra were measured on a Kratos MS30 instrument with a 70 eV electron impact source, and peak abundances are quoted as a percentage of the base peak. H.p.l.c. was carried out on a Waters 6000 Series system fitted with a Z Module 10 μm silica column and a Rheodyne 7125 injector (20 μl loop). Eluate (3 ml min^{-1}) was monitored at 254 nm using a Pye-Unicam 4020 u.v. detector coupled to a Pye-Unicam DP 88 computing integrator.

Starting materials and solvents were routinely purified by conventional techniques,[9] unless stated. Organic solutions were concentrated by rotary evaporation. T.l.c. was carried out on Camlab Polygram SIL G/UV$_{254}$ silica gel precoated plates, and preparative (column) chromatography was carried out using 60H silica gel (Merck 7736) and hand-bellows pressure. Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, b.p. 40—60 °C, unless otherwise stated.

Starting Materials. The chromones (**3a**—i),[8, 10-13] (**7**),[14] and (**8**)[14] are available using literature procedures, as is the enol ether (**12**).[15] Ethoxyethene (**4**) (Lancaster) and butoxyethene (**11**) (B.D.H.) were used without further purification. The enol ethers (**13**) (Lancaster) and (**22**) (Aldrich) were distilled[9] prior to use.

General Procedure for Cycloadditions of 3-Formylchromones with Ethoxyethene.—A solution of the chromone (**3a**—**i**) (2—7 mmol) in the solvent (Table 1) was stirred with the enol ether (**4**) (20 equiv.) at 20 °C until t.l.c. [ethyl acetate–petroleum (1:9 or 1:4)] showed that the starting chromone had been consumed and two less polar products had been formed. The solution was then evaporated to dryness, and the residue crystallised from a suitable solvent. The mother liquors from this crystallisation were then chromatographed on a column of silica gel, eluting with ethyl acetate–petroleum, to obtain the less polar minor cycloadduct and a further small quantity of the major product. Analytical samples were obtained by crystallisation and the data are recorded in Table 4. ^{1}H N.m.r. spectral data are given in Tables 5, 6, and 7.

3-*Ethoxy*-4,4a-*dihydro*-3H,10H-*pyrano*[4,3-b][1]*benzopyran*-10-*ones* (**5a**) *and* (**6a**).—The chromone (**3a**) (2.5 mmol) in dichloromethane (10 ml) was treated with ethoxyethene (**4**) as above. The *cycloadduct* (**5a**) was obtained from ethanol as colourless needles (0.456 g, 74%) (in two crops); $\lambda_{max.}$ 218, 272infl, 284.5, and 330 nm (log ε 4.290, 4.009, 4.045, and 3.664); $\nu_{max.}$ 1 665 and 1 600 cm^{-1}; *m/z* 246 (M^+).

The minor *cycloadduct* (**6a**) (0.094 g, 15%) formed colourless prisms; $\nu_{max.}$ 1 665 and 1 600 cm^{-1}; *m/z* 246 (M^+).

8-*Acetoxy*-3-*ethoxy*-4,4a-*dihydro*-3H,10H-*pyrano*[4,3-b][1]-*benzopyran*-10-*ones* (**5b**) *and* (**6b**).—The chromone (**3b**) (5 mmol) in dichloromethane (20 ml) was treated with ethoxyethene (**4**) as above. The *cycloadduct* (**5b**) (1.25 g, 83%) formed colourless needles; $\nu_{max.}$ 1 745, 1 665, 1 615, and 1 595 cm^{-1}; *m/z* 304 (M^+, 22%) and 262 (99). The minor *cycloadduct* (**6b**) (0.170 g, 11%) formed colourless prisms; $\nu_{max.}$ 1 745, 1 660, and 1 600 cm^{-1}; *m/z* 304 (M^+, 23%) and 262 (94).

3-*Ethoxy*-4,4a-*dihydro*-8-*methoxy*-3H,10H-*pyrano*[4,3-b]-[1]*benzopyran*-10-*ones* (**5c**) *and* (**6c**).—The chromone (**3c**) (6 mmol) in chloroform (30 ml) was treated as described above. The *cycloadduct* (5c) (1.32 g, 80%) formed colourless plates; $\nu_{max.}$ 1 665, 1 615, and 1 600 cm^{-1}; *m/z* 276 (M^+, 87%).

The minor *cycloadduct* (**6c**) (0.19 g, 11%) formed pale yellow prisms; $\nu_{max.}$ 1 665, 1 610, and 1 595 cm^{-1}; *m/z* 276 (M^+, 48%).

Table 5. ^{1}H N.m.r. data for the *endo*-cycloadducts (**5a**—**i**).

Compd.	1-H	3-H	4a-H	4α-H ddd	4β-H dt	7-H	6-H	8-H	9-H	Me[b] t	Remarks/Others
(**5a**)	7.57 d	5.22 dd	5.19 ddd	2.58	2.31	7.44 ddd	6.94 dd	7.04 ddd	7.95 dd	1.28	At 220 MHz
(**5b**)	7.54 br s	5.30—5.02 m		2.60	2.28	7.15 dd	6.92 d		7.61 d	1.27	2.26 s (OCOMe)
(**5c**)	7.55 br s	5.30—5.00 m		2.58	2.28	7.06 dd	6.88 d		7.39 d	1.28	3.79 s (OMe)
(**5d**)[a]	7.50 br s	5.37 dd	5.19 ddd	2.53	2.04	6.68—6.94 m			7.12 d	1.18	9.35 s (OH)
(**5e**)[a]	7.57 br s	5.55—5.30 m		2.59	2.12	8.26 dd	7.15 d		8.48 d	1.14	
(**5f**)	7.55 br s	5.35—5.10 m		2.58	2.29		6.72—6.86 m		7.96 d	1.28	2.28 s (OCOMe)
(**5g**)	7.50 br s	5.30—5.05 m		2.58	2.28		6.41 d	6.61 dd	7.87 d	1.27	3.82 s (OMe)
(**5h**)	7.45 br s	5.45—5.15 m		2.54	2.06		6.33 d	6.54 dd	7.67 d	1.18	10.5 s (OH)
(**5i**)	7.63 br s	5.40—5.15 m		2.66	2.29		7.80 d	7.85 dd	8.10 d	1.29	

[a] In $(CD_3)_2SO$. [b] All $-OCH_2Me$ appeared as complex multiplets centred at δ *ca.* 3.8.

Table 6. ^{1}H N.m.r. data for the *exo*-cycloadducts (**6a**—**i**).

Compd.	1-H d	3-H	4a-H	4α-H ddd	4β-H ddd	7-H	6-H	8-H	9-H	Me[b] t	Remarks/Others
(**6a**)	7.54	5.31 dd	5.20 ddd	2.54	2.18	7.44 ddd	6.94 dd	7.04 ddd	7.97 dd	1.18	At 220 MHz
(**6b**)	7.53	5.31 t	5.20 ddd	2.55	2.15	7.18 dd	6.94 d		7.65 d	1.18	2.27 s (OCOMe)
(**6c**)	7.54	5.29 t	5.13 ddd	2.53	2.14	7.06 dd	6.89 d		7.40 d	1.18	3.80 s (OMe)
(**6d**)[a]	7.50	5.47 t	5.00 ddd	2.47	2.10	6.80—7.07 m			7.16 d	1.13	9.36 s (OH)
(**6e**)[a]	7.60	5.45—5.20 m		2.61	2.20	8.29 dd	7.07 d		8.84 d	1.20	
(**6f**)	7.50	5.28 t	5.22 ddd	2.52	2.13		6.67—6.85 m		7.96 d	1.17	2.26 s (OCOMe)
(**6g**)	7.47	5.29 t	5.19 ddd	2.52	2.15		6.40 d	6.60 dd	7.88 d	1.17	3.81 s (OMe)
(**6h**)[a]	7.43	5.43 t	5.07 ddd	2.48	2.10		6.34 d	6.54 dd	7.68 d	1.13	10.55 s (OH)
(**6i**)	7.61	5.20—5.40 m		2.62	2.20		7.80 d	7.85 dd	8.13 d	1.21	

[a] In $(CD_3)_2SO$. [b] All $-OCH_2Me$ appeared as complex multiplets centred at δ *ca.* 3.7

Table 7. ^{1}H N.m.r. coupling constants *J* (Hz) for the cycloadducts (**5**) and (**6**).

Compd.	1,4a	3,4α	3,4β	4α,4β	4a,4α	4a,4β	6,7	6,8	7,8	7,9	8,9	1′,2′
(**5a**—**i**)	*ca.* 1	2.5—3	9.5—10	13	6.5—7	9.5—10	8.5—9	1—2.5	7	2—3	8—9	6.5—7
(**6a**—**i**)	1.5	2.5—3	2.5—3	13	6.5—7	10—10.5	8.5—9	1—2.5	7	2—3	8—9	6.5—7

3-*Ethoxy*-4,4a-*dihydro*-8-*hydroxy*-3H,10H-*pyrano*[4,3-b]-[1]*benzopyran*-10-*ones* (**5d**) *and* (**6d**).—The chromone (**3d**) (5 mmol) in tetrahydrofuran (35 ml) was treated as above. The major *cycloadduct* (**5d**) (0.86 g, 65.5%) formed yellow needles; $\nu_{max.}$ 3 180, 1 640, 1 625, and 1 590 cm^{-1}; *m/z* 262 (M^+, 41%).

The minor *cycloadduct* (**6d**) (0.10 g, 7.5%) formed yellow prisms; $\nu_{max.}$ 3 175, 1 645, 1 625, and 1 590 cm^{-1}; *m/z* 262 (M^+, 68%).

3-*Ethoxy*-4,4a-*dihydro*-8-*nitro*-3H,10H-*pyrano*[4,3-b][1]-*benzopyran*-10-*ones* (**5e**) *and* (**6e**).—The chromone (**3e**) (7 mmol) in tetrahydrofuran (35 ml) was treated as above. The major *cycloadduct* (**5e**) (1.04 g, 51%) formed pale yellow prisms; $\nu_{max.}$ 1 670, 1 600, and 1 515 cm^{-1}; *m/z* 291 (M^+, 9%).

The minor *cycloadduct* (**6e**) (0.31 g, 15%) formed colourless needles; $\nu_{max.}$ 1 670, 1 600, and 1 510 cm^{-1}; *m/z* 291 (M^+, 43%).

7-*Acetoxy*-3-*ethoxy*-4,4a-*dihydro*-3H,10H-*pyrano*[4,3-b][1]-*benzopyran*-10-*ones* (**5f**) *and* (**6f**).—The chromone (**3f**) (6 mmol) in chloroform (30 ml) was treated as above. The major *cycloadduct* (**5f**) (1.57 g, 86%) formed colourless needles; $\nu_{max.}$ 1 750, 1 660, and 1 600 cm^{-1}; *m/z* 304 (M^+, 16%).

The minor *cycloadduct* (**6f**) (0.19 g, 10%) formed colourless needles; $\nu_{max.}$ 1 750, 1 660, and 1 600 cm^{-1}; *m/z* 304 (M^+, 15%).

3-*Ethoxy*-4,4a-*dihydro*-7-*methoxy*-3H,10H-*pyrano*[4,3-b]-[1]*benzopyran*-10-*ones* (**5g**) *and* (**6g**).—The chromone (**3g**) (4 mmol) in chloroform (30 ml) was treated as above. The major *cycloadduct* (**5g**) (0.93 g, 84%) formed colourless needles; $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; *m/z* 276 (M^+, 27%).

The minor *cycloadduct* (**6g**) (0.12 g, 11%) formed colourless plates; $\nu_{max.}$ 1 665 and 1 660 cm^{-1}; *m/z* 276 (M^+, 44%).

3-*Ethoxy*-4,4a-*dihydro*-7-*hydroxy*-3H,10H-*pyrano*[4,3-b]-[1]*benzopyran*-10-*ones* (**5h**) *and* (**6h**).—The chromone (**3h**) (5 mmol) in *N*,*N*-dimethylformamide (30 ml) was treated as above. The major *cycloadduct* (**5h**) (0.79 g, 60%) formed yellow prisms; $\nu_{max.}$ 3 100, 1 645, 1 610, and 1 585 cm^{-1}; *m/z* 262 (M^+, 15%).

The minor *cycloadduct* (**6h**) (0.09 g, 7%) formed colourless needles; $\nu_{max.}$ 3 100, 1 660, 1 600, and 1 575 cm^{-1}; *m/z* 262 (M^+, 23%).

3-*Ethoxy*-4,4a-*dihydro*-7-*nitro*-3H,10H-*pyrano*[4,3-b][1]-*benzopyran*-10-*ones* (**5i**) *and* (**6i**).—The chromone (**3i**) (1.73 mmol) in tetrahydrofuran (30 ml) was treated as above. The major *cycloadduct* (**5i**) (0.342 g, 68%) formed pale yellow needles; $\nu_{max.}$ 1 670, 1 600, and 1 530 cm^{-1}; *m/z* 291 (M^+, 7%).

The minor *cycloadduct* (**6i**) (0.13 g, 26%) formed pale yellow crystals; $\nu_{max.}$ 1 680, 1 600, and 1 530 cm^{-1}; *m/z* 291 (M^+, 7%).

General Procedure for Cycloadditions of 3-*Acylchromones with Compound* (**4**) *at* 115 °C.—A mixture of the chromone (2 mmol), ethoxyethene (0.4 ml, 4.2 mmol), and dichloromethane (3.6 ml) was heated at 115 °C in a sealed tube for the times

indicated in Table 2. The contents of the tube were then frozen by immersion in liquid nitrogen, the tube opened, and the thawed reaction mixture removed using dichloromethane. The products were then isolated by evaporation, crystallisation, and chromatography as above.

3-*Ethoxy*-4,4a-*dihydro*-1-*methyl*-3H,10H-*pyrano*[4,3-b][1]-*benzopyran*-10-*ones* (**9**) *and* (**10**).—The chromone (**7**) (0.376 g) was treated with compound (**4**) in a sealed tube as above. The major *cycloadduct* (**9**) (0.374 g, 72%) formed colourless plates; $\lambda_{max.}$ 219.5, 266, 290, and 329 nm (log ε 4.305, 3.930, 4.086, and 3.790); $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; δ 1.27 (3 H, t, *J* 7 Hz, CH_2Me), 2.37 (3 H, d, *J* 1.5 Hz, 1-Me), 2.12—2.73 (2 H, m, 4-H_2), 3.5—4.2 (2 H, m, CH_2Me), 5.0—5.2 (2 H, m, 3-H and 4a-H), 6.9—7.1 (2 H, m, 6-H and 8-H), 7.3—7.5 (1 H, m, 7-H), and 7.97 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 260 (M^+).

The minor *cycloadduct* (**10**) (0.103 g, 20%) formed colourless prisms; $\nu_{max.}$ 1 655 and 1 600 cm^{-1}; δ 1.20 (3 H, t, *J* 7 Hz, CH_2Me), 2.05—2.60 (2 H, m, 4-H_2), 2.40 (3 H, d, *J* 1.5 Hz, 1-Me), 3.45—4.1 (2 H, m, CH_2Me), 5.0—5.2 (1 H, m, 4a-H), 5.21 (1 H, t, *J* 3 Hz, 3-H), 6.88—7.13 (2 H, m, 6-H and 8-H), 7.3—7.5 (1 H, m, 7-H), and 7.98 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 260 (M^+).

3-*Ethoxy*-4,4a-*dihydro*-1-*phenyl*-3H,10H-*pyrano*[4,3-b][1]-*benzopyran*-10-*ones* (**14**) *and* (**15**).—The chromone (**8**) (0.50 g) was treated with compound (**4**) in a sealed tube as above. The major *cycloadduct* (**14**) (0.37 g, 57%) formed pale yellow prisms; $\lambda_{max.}$ 219, 237sh, 267, 313infl, and 334 nm (log ε 4.253, 4.090, 3.962, 3.959, and 3.978); $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; δ 1.28 (3 H, t, *J* 7 Hz, CH_2Me), 2.43 (1 H, ddd, *J* 8, 8, 13 Hz, 4β-H), 2.64 (1 H, ddd, *J* 3, 7, 13 Hz, 4α-H), 3.55—4.25 (2 H, m, CH_2Me), 5.22 (1 H, dd, *J* 7, 8 Hz, 4a-H), 5.31 (1 H, dd, *J* 3, 8 Hz, 3-H), 6.9—7.1 (2 H, m, 6-H and 8-H), 7.3—7.55 (7 H, m, 7-H and Ph), and 7.91 (1 H, dd, *J* 2, 8.5 Hz, 9-H); *m/z* 322 (M^+).

The minor *cycloadduct* (**15**) (0.148 g, 23%) was obtained as a colourless gum; $\nu_{max.}$(neat) 1 660br and 1 600—1 560br cm^{-1}; δ 1.25 (3 H, t, *J* 7 Hz, CH_2Me), 2.37—2.52 (2 H, m, 4-H_2), 3.5—4.2 (2 H, m, CH_2Me), 5.20 (1 H, dd, *J* 7, 7.5 Hz, 4a-H), 5.34 (1 H, t, *J* 3 Hz, 3-H), 6.9—7.05 (2 H, m, 6-H and 8-H), 7.3—7.6 (7 H, m, 7-H and Ph), and 7.90 (1 H, dd, *J* 2, 8.5 Hz, 9-H); *m/z* 322 (M^+).

The starting material (**8**) (0.023 g, 4.6%) was recovered from the column.

3-*Butoxy*-4,4a-*dihydro*-3H,10H-*pyrano*-[4,3-b][1]*benzopyran*-10-*ones* (**16**) *and* (**17**).—3-Formylchromone (**3a**) (0.696 g, 4 mmol) in dichloromethane (20 ml) was stirred with butoxyethene (**11**) (10.3 ml, 80 mmol) at 20 °C for 6 days. The residue on evaporation was crystallised from ethyl acetate, to give the major *cycloadduct* (**16**) (0.68 g, 62%) (in two crops) as colourless needles; $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; δ 0.92 (3 H, t, 4′-H_3), 1.2—1.8 (4 H, m, 2′,3′-H), 2.25 (1 H, ddd, *J* 10, 10, 13 Hz, 4β-H), 2.56 (1 H, ddd, *J* 3, 7, 13 Hz, 4α-H), 3.4—4.1 (2 H, m, OCH_2), 5.05—5.30 (2 H, m, 3-H and 4a-H), 6.92 (1 H, d, *J* 8 Hz, 6-H), 7.00 (1 H, t, *J* 8 Hz, 8-H), 7.40 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), 7.52 (1 H, br s, 1-H), and 7.91 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 274 (M^+, 23%).

Chromatography using ethyl acetate–petroleum (1:19) gave the minor *cycloadduct* (**17**) (0.11 g, 10%) which formed colourless needles; $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; δ 0.88 (3 H, t, 4′-H_3), 1.1—1.7 (4 H, m, 2′-, 3′-H), 2.15 (1 H, ddd, *J* 3, 10, 13 Hz, 4β-H), 2.55 (1 H, ddd, *J* 3, 7, 13 Hz, 4α-H), 3.4—3.95 (2 H, m, OCH_2), 5.21 (1 H, m, 4a-H), 5.30 (1 H, m, 3-H), 6.94 (1 H, d, *J* 8 Hz, 6-H), 7.03 (1 H, t, *J* 8 Hz, 8-H), 7.42 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), 7.53 (1 H, d, *J* 1.5 Hz, 1-H), and 7.97 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 274 (M^+, 19%).

Chromatography also yielded a further portion of the cycloadduct (**16**) (0.25 g, 23%).

3-t-*Butoxy*-4,4a-*dihydro*-3H,10H-*pyrano*[4,3-b][1]*benzopyran*-10-*ones* (**18**) *and* (**19**).—3-Formylchromone (**3a**) (0.300 g, 1.72 mmol) in dichloromethane (10 ml) was stirred with t-butoxyethene (2.0 g, 20 mmol) at 20 °C for 6 days. The solution was evaporated and the residue chromatographed using ethyl acetate–petroleum (1:4) as the eluant. The major; *cycloadduct* (**18**) (0.111 g, 23.5%) formed colourless prisms from petroleum; $\nu_{max.}$ 1 665, 1 655, and 1 605 cm^{-1}; δ 1.30 (9 H, s, CMe_3), 2.20—2.55 (2 H, m, 4-H_2), 5.22 (1 H, ddd, *J ca.* 1, 7, 10 Hz, 4a-H), 5.42 (1 H, dd, *J* 4, 8.5 Hz, 3-H), 6.91 (1 H, dd, *J* 1.5, 8 Hz, 6-H), 7.01 (1 H, ddd, *J* 1.5, 8, 8 Hz, 8-H), 7.41 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), 7.53 (1 H, br s, 1-H), and 7.92 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 274 (M^+, 2%).

The minor *cycloadduct* (**19**) (0.091 g, 19.3%) was obtained as a colourless oil; $\nu_{max.}$(neat) 1 670 and 1 610 cm^{-1}; δ 1.27 (9 H, s, CMe_3), 2.14 (1 H, ddd, *J* 3, 10, 13 Hz, 4β-H), 2.41 (1 H, ddd, *J* 2.5, 6, 13 Hz, 4α-H), 5.23 (1 H, m, 4a-H), 5.57 (1 H, m, 3-H), 6.92 (1 H, dd, *J* 1.5, 8 Hz, 6-H), 7.00 (1 H, ddd, *J* 1.5, 8, 8 Hz, 8-H), 7.42 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), 7.52 (1 H, d, *J* 1.5 Hz, 1-H), and 7.96 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 274 (M^+, 1%).

3-*Methoxy*-3-*methyl*-4,4a-*dihydro*-3H,10H-*pyrano*[4,3-b]-[1]*benzopyran*-10-*ones* (**20**) *and* (**21**).—3-Formylchromone (**3a**) (1.220 g, 7.01 mmol) in dichloromethane (28 ml) was stirred with 2-methoxypropene (**13**) (13.4 ml, 140 mmol) at 20 °C for 5 days. The residue on evaporation was crystallised from ether to give the major *cycloadduct* (**20**) (0.84 g, 49%) (in two crops) as colourless needles; $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; δ 1.45 (3 H, s, 3-Me), 2.28 (1 H, dd, *J* 8, 13 Hz, 4β-H), 2.48 (1 H, dd, *J* 9, 13 Hz, 4α-H), 3.39 (3 H, s, OMe), 5.05 (1 H, ddd, *J ca.* 1, 8, 9 Hz, 4a-H), 6.92 (1 H, d, *J* 8 Hz, 6-H), 7.00 (1 H, t, *J* 8 Hz, 8-H), 7.42 (1 H, ddd, *J* 2, 8, 8 Hz, 7-H), 7.55 (1 H, d, *J ca.* 1 Hz, 1-H), and 7.94 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 246 (M^+, 28%).

Chromatography using ethyl acetate–petroleum (1:9) gave the minor *cycloadduct* (**21**) (0.15 g, 9%) which formed needles from petroleum; $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; δ 1.56 (3 H, s, 3-Me), 2.05 (1 H, dd, *J* 11, 13 Hz, 4β-H), 2.57 (1 H, dd, *J* 7, 13 Hz, 4α-H), 3.28 (3 H, s, OMe), 5.18 (1 H, ddd, *J* 1.5, 7, 11 Hz, 4a-H), 6.94 (1 H, d, *J* 8 Hz, 6-H), 7.02 (1 H, t, *J* 8 Hz, 8-H), 7.44 (1 H, ddd, *H* 2, 8, 8 Hz, 7-H), 7.50 (1 H, d, *J* 1.5 Hz, 1-H), and 7.96 (1 H, dd, *J* 2, 8 Hz, 9-H); *m/z* 246 (M^+, 3%).

The chromatography also yielded a further quantity (0.14 g, 8%) of the cycloadduct (**20**).

2,3,12a,12b-*Tetrahydro*-1H,4aH,7H-*pyrano*[2′,3′:6,5]*pyrano*-[4,3-b][1]*benzopyran*-7-*ones* (**23**) *and* (**24**).—3-Formylchromone (**3a**) (0.20 g, 1.15 mmol), dihydropyran (**22**) (1.05 ml, 11.5 mmol), and dichloromethane (4 ml) were heated in a sealed tube at 115 °C for 5 days. The contents of the tube were then isolated as described above, crystallising from ethanol. This gave the minor *cycloadduct* (**24**) (0.080 g, 27%) (in two crops) as colourless needles; $\nu_{max.}$ 1 670 and 1 610 cm^{-1}; δ 1.5—2.2 (4 H, m, 1-, 2-H), 2.4—2.7 (1 H, m, 12b-H), 3.7—4.0 (2 H, m, 3-H_2), 5.30 (1 H, dd, *J* 1.5, 6.5 Hz, 12a-H), 5.48 (1 H, d, *J* 2 Hz, 4a-H), 6.90 (1 H, d, *J* 8 Hz, 11-H), 7.01 (1 H, t, *J* 8 Hz, 9-H), 7.42 (1 H, ddd, *J* 2, 8, 8 Hz, 10-H), 7.62 (1 H, d, *J* 1.5 Hz, 6-H), and 7.93 (1 H, dd, *J* 2, 8 Hz, 8-H); *m/z* 258 (M^+, 3%).

Continuation of the crystallisation from ethanol produced a third crop which consisted of the isomeric *cycloadduct* (**23**) (0.040 g, 13.5%) as colourless plates; $\nu_{max.}$ 1 670 and 1 620 cm^{-1}; δ 1.6—2.1 (4 H, m, 1-,2-H), 2.3—2.55 (1 H, m, 12b-H), 3.6—4.2 (2 H, m, 3-H_2), 4.79 (1 H, d, *J* 6 Hz, 12a-H), 5.22 (1 H, d, *J* 3 Hz, 4a-H), 6.97 (1 H, d, *J* 8 Hz, 11-H), 7.05 (1 H, t, *J* 8 Hz, 9-H), 7.46 (1 H, ddd, *J* 2, 8, 8 Hz, 10-H), 7.54 (1 H, d, *J ca.* 1 Hz, 6-H), and 7.97 (1 H, dd, *J* 2, 8 Hz, 8-H); *m/z* 258 (M^+, 9%).

Attempts to isolate the remainder of (**23**) and (**24**) by column chromatography were unsuccessful. However, using the isolated products it was possible to analyse a sample of the crude reaction mixture by quantitative h.p.l.c. [eluant iso-octane–

ethyl acetate (9:1)]. This indicated an approximate molar ratio for (**3a**):(**23**):(**24**) of 10:50:40.

The structural assignments for compounds (**23**) and (**24**) are tentative and may be reversed.

Effects of Variation of Solvent and Temperature on the Reaction of Compound (**3a**) *with Compound* (**4**).—(*a*) Solutions of 3-formylchromone (**3a**) (0.100 g, 0.57 mmol) and ethoxyethene (**4**) (1.0 ml, 11.4 mmol) in the solvents indicated in Table 3 (10 ml) were stirred at 20 °C for 3 days. Each was then evaporated to dryness under reduced pressure, and the residue dissolved in h.p.l.c. grade ethyl acetate (50 ml). After filtration each solution was made up to 100 ml in a graduated flask, and examined by h.p.l.c. [eluant iso-octane–ethyl acetate (4:1)]. The h.p.l.c. system was calibrated using three solutions containing known concentrations of analytically pure (**5a**) and (**6a**). Each result was calculated using the average peak area integrals from six separate 10 μl injections. Retention times were: (**3a**), 259 s; (**5a**), 175 s; (**6a**), 133 s.

(*b*) Solutions of (**3a**) and (**4**) in dichloromethane as in (*a*) above were stirred for 1 day at the temperatures indicated in Table 3. Each was then evaporated and analysed by h.p.l.c. as described in (*a*).

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