Kinetic and Thermodynamic Control in the Lithiation of 2,6-Dimethylchromone, and Selective Lithiations in 2-(*x*-Furyl)chromones and in Furanochromones Related to Khellin

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The addition of 2,6-dimethylchromone to lithium di-isopropylamide (LDA) allows formation, under thermodynamic control, of the 2-methylene carbanion (**3**), but this seems to react at the carbonyl oxygen atom with carbon dioxide so no carboxylic acid can be isolated. With ethyl chloroformate (but not diethyl carbonate) this carbanion does afford the expected ethyl chromon-2-ylacetate (**1d**). The chromonylacetic acid is also obtainable if the starting chromone bears a free hydroxy group at position 5 as in (**4a**).

From the addition of 2,6-dimethylchromone to a mixture of LDA and diethyl carbonate there results ethyl 2,6-dimethylchromone-3-carboxylate (**9b**) because the chromone 3-carbanion formed under kinetic control is trapped before it isomerises. The reaction resembles that found in flavones.

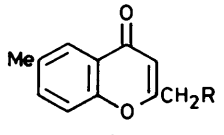
Flavone (at the 3-position) and furan or benzofuran (at the 2-position) are about equally effective in competing for deprotonation by LDA. Khellin (**14a**) is probably deprotonated by LDA at both furan and pyrone sites but carboxylation affords only the furan carboxylic acid (**14b**) and unchanged khellin. This accords with the above results, as does the deprotonation and carboxylation of the phenol (**15b**), norvisnagin, which affords the chromonylacetic acid (**16**).

With LDA followed by carbon dioxide the 2-(2-furyl)chromone (**18a**) surprisingly gives only the dicarboxylic acid (**18b**); apparently the dicarbanion is more stable than either monocarbanion. The isomeric 2-(3-furyl)chromone (**20a**) under similar conditions affords only the chromone-3-carboxylic acid (**20b**); the furan ring is untouched.

We have already described the surprisingly easy removal of methine protons from positions 3 in flavone and other chromone derivatives, and from certain coumarins, by means of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF).[1,2] Other workers have described similar deprotonations for monocyclic pyrones[3] and for comparable 4-methoxybutenolides.[4] We are concerned here with the question of relative acidity, and describe a number of situations in which two or more acidic centres are present that can compete either externally or internally.

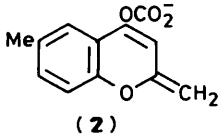
In chromones like (**1a**) the 2-methyl group has long been recognised as acidic, being vinylogous with a methyl ketone. Relatively weak bases suffice to form carbanions, sodium ethoxide being used to catalyse the aldol condensation of 2-methylchromones with aromatic aldehydes.[5] Monocyclic 2-methylpyrones behave in the same way, aqueous alkali being adequate.[6] As there is no report that the 3-proton can be disturbed by such treatment we examined this point initially by treating a solution of 2,6-dimethylchromone (**1a**) in [$^2H_4$]-methanol with sodium [$^2H_3$]methoxide and following the consequences by ^1H n.m.r. spectroscopy. The signal from the methyl group faded rapidly (30 min) compared with that from the 3-proton; mass spectrometry showed the recovered chromone to contain four deuterium atoms eventually.

Next we treated 2,6-dimethylchromone with LDA in THF at −78 °C and observed the deep red colour associated with carbanion formation; this colour faded when carbon dioxide was introduced, exactly as if the salt corresponding to the expected acid (**1b**) had been produced. Yet work-up merely recovered the original 2,6-dimethylchromone and no acid fraction was found, as if there had been a spontaneous decarboxylation. An acid with structure (**1b**) would hardly be so sensitive, so we surmised that the intermediate must be the salt (**2**) of carbonic acid formed because the electrophilic centre in carbon dioxide is very 'hard', and reacts with the 'hardest' centre in the chromone carbanion (**3**) which is the oxygen atom rather than the terminal carbon atom.

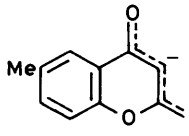


(**1**)

a; R = H
b; R = CO_2H
c; R = COPh
d; R = CO_2Et



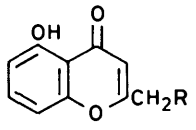
(**2**)



(**3**)

To test this point we subjected 5-hydroxy-2-methylchromone (**4a**) to LDA; again the red colour was seen, and it faded when carbon dioxide was introduced, but this time the expected acid (**4b**) was obtained in good yield without difficulty. In contrast, the methyl ether (5-methoxy-2-methylchromone) behaved like dimethylchromone and furnished no acid product. It appeared to us that the phenoxide group would ensure the presence of two lithium cations close enough to the carbonyl oxygen atom to co-ordinate with it strongly [diagram (**5**)], and that access to an electrophile at this point would, therefore, be impeded leaving the terminal methylene free to react. It is also important that the

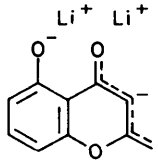
5-hydroxy group cannot be supposed to function simply by stabilising the acid (**4b**) towards decarboxylation during work-up; rather the reverse, since hydrogen-bonding would assist loss of carbon dioxide as indicated in diagram (**6**). The acid is unstable to heat at its m.p., and even during recrystallisation under some conditions.



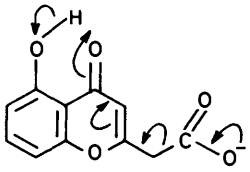
(**4**)

a; R = H

b; R = CO_2H



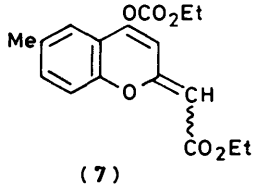
(**5**)



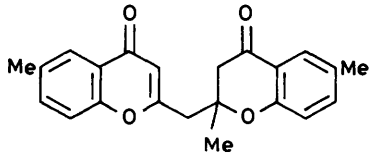
(**6**)

Nucleophiles softer than carbon dioxide react as desired at the chromone methyl group, and 2,6-dimethylchromone readily affords the benzoyl derivative (**1c**) with benzoyl chloride and the chromonylacetate (**1d**) with ethyl chloroformate, the second reaction also giving what ^1H n.m.r. and i.r. spectra show to be a mixture of geometrical isomers corresponding to the double-acylation product (**7**). Double acylations are perhaps unavoidable because there is always some time during acylation when the carbanion and the first acylation product (**1d**) co-exist, thus allowing removal of a second proton and so a second electrophilic attack; however, double acylation has not been serious in the examples studied so far. It will be noted that this reaction supports the idea of reversible carboxylation at carbonyl oxygen mooted above.

In contrast to acid chlorides, esters did not react with the chromone carbanion and failed to discharge its red colour. A new compound was sometimes found in traces during these attempts; it was highly fluorescent and eventually identified as the chromone-chromanone (**8**) formed by Michael addition of the chromone carbanion to a second molecule of chromone. The loss, in one residue, of the chromone 2,3-double bond has a marked effect (upfield shift) on all the associated aromatic resonances so that the two systems are easily distinguished by ^1H n.m.r. spectroscopy. Conducted stoicheiometrically, the reaction produces the new compound in high yield which is interesting because simple, classical Michael additions to chromones are rare [7] though several accompanied by secondary reactions are known and cuprate reagents are successful.[8]

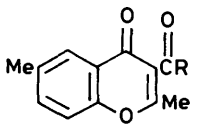


(**7**)



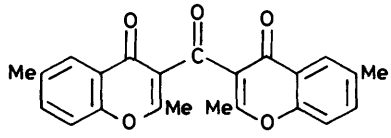
(**8**)

Esters can be made to react with chromones under other circumstances. Because esters react rather slowly with LDA it is feasible to mix these two components first and then add the chromone. There ensues a reaction between the ester and the chromone which is of a different type and occurs at position 3. Thus, 2,6-dimethylchromone with ethyl benzoate gives the 3-benzoyl derivative (**9a**), and with diethyl carbonate the 3-carboxylate (**9b**). Ester delocalisation is much less in this product than in diethyl carbonate itself, so the product is the more reactive and there is considerable secondary condensation resulting in the ketone (**10**).



(**9**) **a**; R = Ph

b; R = OEt



(**10**)

Carbanions of type (**3**) allow for electrophilic attack at the 3-position in the sense that the negative charge can be mobilised there, and in simple conjugated carbonyl compounds kinetic attack is indeed at the equivalent position [equation (1)].[9] A

$$RCH_2CH{=}CH\underset{|}{C}{=}O \xrightarrow[\text{ii, MeI}]{\text{i, base}} RCH{=}CHCMe_2\underset{|}{C}{=}O \quad (1)$$

heteroatom X at the β-position, however, re-directs electrophilic attack to the terminal site [equation (2)].[10]

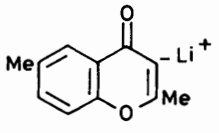
$$RCH_2\underset{|}{\overset{X}{C}}{=}CH\underset{|}{C}{=}O \xrightarrow[\text{ii, MeI}]{\text{i, base}} RCMe_2\underset{|}{\overset{X}{C}}{=}CH\underset{|}{C}{=}O \quad (2)$$

The reaction of the chromone carbanion at the terminal carbon is therefore entirely in line with precedent and the same carbanion cannot be used to explain attack at the 3-position. We have to accept that a different carbanion is required for 3-substitution, that it must have structure (**11**) as for the flavone carbanions discussed already,[2] and that it is formed under kinetic control but isomerises rapidly to the other carbanion (**3**) under thermodynamic control. As usual, the kinetically formed species is the more reactive and can attack esters, whereas the thermodynamically formed species is less reactive and reacts only with acid chlorides.

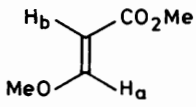
There may be a similar situation in the chemistry of 4-methoxybutenolides since it is known that LDA removes the 3-methine proton selectively from 5-arylidene derivatives,[4] whereas other bases remove a proton selectively from a 5-methylene group if there is one.[11] No direct comparison appears to have been reported, so further discussion is impossible at present.

Thus the 3-methine group is kinetically more acidic than a 2-methyl group in a chromone system. It is also of interest to compare a 3-methine group with a 2-methine group in an unsubstituted chromone, but attempts to do this failed because 2-unsubstituted chromones react too easily in other ways with nucleophiles.[2] A similar situation exists in an acyclic analogue[12] (**12**) which exhibits kinetic acidity at H_a but thermodynamic acidity about equally at H_a and H_b. This suggests that in a chromone the 2-methine group should be the more acidic kinetically, but about the same as a 3-methine group thermodynamically. However, the analogy is poor stereochemically, since in (**12**) the ester is on the wrong side of the double bond and can exert co-ordination effects not possible in chromones.

No such difficulty arises in comparing the 3-position in a chromone with the 2-position in a furan or benzofuran. When flavone (1 mol) and furan (1 mol) compete for LDA (1 mol) and



(11)



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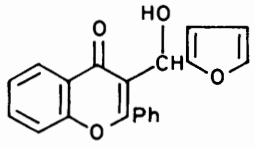
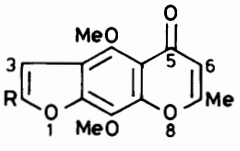


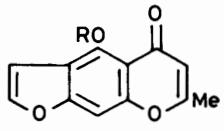
(13)

the reaction is quenched by carbon dioxide, almost equal amounts of flavone-3-carboxylic acid and furan-2-carboxylic acid are obtained no matter how short the competition time. The same result is obtained when preformed flavone 3-carbanion is allowed to react with furan or preformed furan 2-carbanion is allowed to react with flavone. Evidently the 3-position in flavone and the 2-position in furan or benzofuran have the same thermodynamic acidity, the relative kinetic acidities remaining unknown. We can now understand why, in earlier work,[2] the interaction of flavone 3-carbanion with furan-3-carboxaldehyde gave rather a low yield of the aldol (**13**) in a type of reaction that is usually very efficient; proton-exchange must have been competing with the aldol reaction.

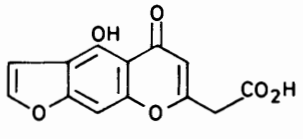
Studies were also made of compounds containing both pyrone and furan rings that could compete internally. The furochromone khellin (**14a**), when treated with 1 equiv. of LDA and then carbon dioxide, gave both the furan-2-carboxylic acid derivative (**14b**) (35%) and recovered khellin (45%). This result conforms to the previous results in that the pyrone methyl group is the most acidic of the three centres present, but that carboxylation of the pyrone occurs at carbonyl oxygen and is reversed upon work-up, leaving the pyrone segment apparently



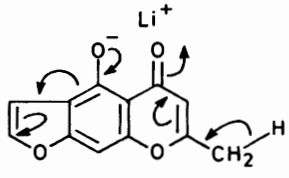
(14) **a**; R = H
b; R = CO_2H



(15) **a**; R = Me
b; R = H



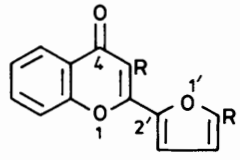
(16)



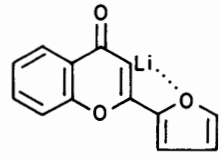
(17)

unchanged. From visnagin (**15a**) we obtained a mixture that we failed to separate or interpret, so we demethylated the compound (boron chloride[13] being better than the published methods[14]) and examined the behaviour of norvisnagin, the phenol (**15b**), towards 2 mol equiv. of LDA. A high yield (81%) of carboxylic acid resulted; this was a single acid readily identified as the chromone-2-acetic acid (**16**) as we now expect for a 5-hydroxychromone derivative. In view of the behaviour of khellin the absence of carboxylation at the furan ring is surprising and to explain it we suggest that the hydroxy group is again the directing feature. Since it will instantly be ionised by the reagent it will presumably be associated with a lithium cation which will also be co-ordinated with the adjacent carbonyl oxygen atom as in diagram (**17**). Hence this lithium cation can be expected to increase the acidity of the methyl group by withdrawing electrons from it. At the same time electrons can be released from the phenolic anion and reduce the acidity of the furan segment.

A quite different phenomenon was encountered in the furan analogue (**18a**) of flavone. With 1 equiv. of LDA followed by carbonation this compound gave a mixture of the *di*carboxylic acid (**18b**) and unchanged chromone in about equal proportions; with 2 equiv. of LDA the dicarboxylic acid was formed almost exclusively. Although cases are known where parent carbon acids, monocarbanions, and dicarbanions exist in equilibrium,[15] this example of dicarbanion being formed in *preference* to any monocarbanion has no parallel currently. In explanation, we suggest that the 3-carbanion is formed first and is stabilised by association of the lithium cation with the furan oxygen atom as in diagram (**19**), and that, in turn, the diminished electron density around this oxygen atom increases its inductive effect at the furan 2-position to that this is more acidic in the carbanion than any other position even in the parent molecule.

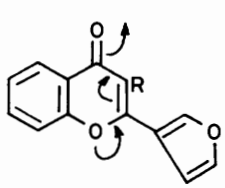


(18) **a**; R = H
b; R = CO_2H

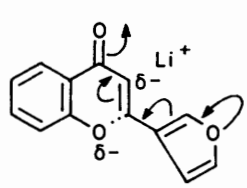


(19)

To check these ideas we finally studied the isomeric furylchromone (**20a**) which was converted by 1 equiv. of LDA and then carbon dioxide into the single acid (**20b**) in high yield (82%). Since the furan oxygen atom is sterically unable to co-ordinate with a 3-lithium cation in the intermediate, the importance of this possibility in the previous example is substantiated. The result also supports the suggestion that 3-lithiation, rather than furan lithiation, is the first step, but this itself requires explanation in view of the fact that, as separate molecules, furan and chromone (flavone) are about equally acidic. We adapt an explanation already put forward to explain why 4-methoxycoumarin can be readily lithiated at its 3-position.[2] To accommodate high negative charge in the σ-system at the 3-position of a chromone, the bond linking the 2-carbon atom and the ring oxygen atom probably has to lengthen somewhat, the oxygen atom bearing some of the excess of negative charge (in extreme cases the ring opens). But this lengthening is opposed by the π-system because there is strong interaction between the ring oxygen atom and the carbonyl group (vinylogous ester) with charge flowing from the ring oxygen into the carbonyl oxygen atom. The furan nucleus, however, is electron-excessive and electrons can flow from its π-system into the carbonyl group, thus making up the loss from the receding oxygen atom. Diagram (**21**) attempts to portray the two effects operating simultaneously.



(20) **a**; R = H
b; R = CO_2H



(21)

Experimental

Light petroleum refers to the fraction b.p. 60—80 °C. All solvents and liquid reagents were distilled before use. THF was purified by means of sodium–benzophenone and then distilled over lithium aluminium hydride. Carbon dioxide was dried by passage through sulphuric acid before being used for carbonations. Solutions were normally dried over Na_2SO_4.

Only diagnostic peaks are recorded for i.r. spectra which were determined for mulls in Nujol if no other phase is specified. ^1H N.m.r. spectra were obtained from solutions in $CDCl_3$ with $SiMe_4$ as internal reference; analyses of spin systems are first-order only; in general a Perkin-Elmer R34 spectrometer was used, but for the furylchromones a Bruker WM250 instrument was used.

All lithiations were conducted under nitrogen or argon.

Deuteriation Experiments.—A solution of 2,6-dimethylchromone (**1a**) (21 mg) in [$^2H_4$]methanol (0.6 ml) at probe temperature (28 °C) was treated with a solution of 0.1M-sodium [$^2H_3$]methoxide in the same solvent (0.1 ml) and was monitored at intervals by ^1H n.m.r. spectroscopy at 60 MHz. The signal near δ 2 from the 2-methyl group disappeared during 30 min without any change in other signals. A slow diminution of the signal near δ 6 from the 3-proton seemed to be complete after about 3 days. The substrate was recovered by precipitation by deuterium oxide and when purified from EtOD/D_2O formed crystals m.p. 101 °C (unaffected by admixture with the parent chromone) (Found: M^+, 178.0934. $C_{11}H_6D_4O_2$ requires M, 178.0933). The i.r. spectrum (KBr) of the deuteriated product resembles that of the parent compound; it lacks strong bands at 1 375, 965, 847, 816, and 570 cm^{-1} but has new ones at 795 and 610 cm^{-1}.

(5-*Hydroxy*-4-*oxo*-4H-*chromen*-2-*yl*)*acetic Acid* (**4b**).—A solution of LDA was prepared at 0 °C from di-isopropylamine (13 g) and n-butyl-lithium (M in hexane; 20 ml) in THF (100 ml). To the stirred solution was added, during 10 min, a solution of 5-hydroxy-2-methylchromone (freshly resublimed; 7.6 g) in THF (50 ml). After 1 h the red mixture was saturated with carbon dioxide and became yellow. Nex day the solvent was removed under reduced pressure, the residue was treated with ice–M-sulphuric acid (50 ml), the product was collected into ethyl acetate (2 × 50 ml), and the solution washed with a little cold water. The acid fraction was isolated using aqueous sodium hydrogen carbonate (5%; 50 ml) at 0 °C and precipitated by ice-cold dil. sulphuric acid at once. The solid (6.1 g, 64%) could be recrystallised from methanol to give (5-hydroxy-4-oxo-4*H*-chromen-2-yl)acetic acid, m.p. 153 °C (rapid heating; decomp.), but since this seemed to be unstable it was characterised by esterification in methanol with diazomethane in ether. The *methyl ester* crystallised from benzene–light petroleum in prisms, m.p. 85—86 °C; δ([$^2H_5$]pyridine) 3.89 (2 H, s, CH_2CO_2Me) and 6.50 (1 H, s, pyrone H) (Found: C, 61.8; H, 4.3%; M^+, 234. $C_{12}H_{10}O_5$ requires C, 61.5; H, 4.3%; M, 234). The compound was soluble in dil. aqueous hydroxide and imparted an intense dark red colour to ethanolic iron(III) chloride.

6-*Methyl*-2-*phenacyl*-4H-1-*benzopyran*-4-*one* (**1c**).—A solution of 2,6-dimethylchromone (**1a**) (0.52 g) in THF (3 ml) was added to LDA [from di-isopropylamine (0.35 g) and butyl-lithium (1.5M-solution in hexane; 2 ml)] at −78 °C, and was followed after 20 min by a solution of benzoyl chloride (0.44 g) in THF (3 ml), injected as rapidly as possible. The reaction was quenched after 2 min by acetic acid (0.5 ml) and then water (100 ml). The products were collected into ether (3 × 30 ml) and freed from acid by successive washings with aqueous sodium hydrogen carbonate and water, and finally was dried (Na_2SO_4). Removal of the solvents under reduced pressure left an oil that crystallised when kept for some hours. Residual oil was removed by rapid washing with cold ether and the solid could then be recrystallised from benzene–light petroleum to give the *benzopyranone* (**1c**) as long prisms (0.35 g, 42%), m.p. 169—170 °C; $\nu_{max.}$ 1 685 (ethanone CO), 1 640, 1 610, 1 590, and 1 575 cm^{-1} (pyrone and aromatic pattern); δ 2.43 (3 H, s, Ar*Me*), 4.29 (2 H, s, CH_2CO), 6.30 (1 H, s, 3-H), 7.30 (1 H, d, *J* 8 Hz, 8-H), 7.46 (1 H, dd, *J* 8 and 2 Hz, 7-H), 7.53 (2 H, poor t, *J ca.* 7 Hz, 3′- and 5′-H), 7.64 (1 H, poor t, *J ca.* 7 Hz, 4′-H), 7.98 (1 H, d, *J* 2 Hz, 5-H), and 8.02 (2 H, poor d, *J ca.* 7 Hz, 2′- and 6′-H) (Found: C, 77.5; H, 5.0%; M^+, 278. $C_{18}H_{14}O_3$ requires C, 77.7; H, 5.1%; M, 278).

Ethyl(6-*Methyl*-4-*oxo*-4H-*chromen*-2-*yl*)*acetate* (**1d**).—A solution of 2,6-dimethylchromone (**1g**) (0.87 g) in THF (5 ml) was added to a solution of LDA prepared from di-isopropylamine (5 ml) and butyl-lithium (1.5M-solution in hexane; 13.3 ml) in THF (40 ml) at 77 °C. After 20 min, ethyl chloroformate (5 ml) was added. After a further 3 h the reaction was quenched with saturated aqueous ammonium chloride (20 ml) and the mixture was diluted with water (200 ml). The product was isolated by means of ether (3 × 100 ml) and was recovered in the usual way as a syrup from which ethyl di-isopropylcarbamate was removed by distillation as an oil (3 g), b.p. 50 °C/1 mmHg. The residue partly sublimed at 100 °C/0.1 mmHg to give 2,6-dimethylchromone (**1a**) (0.5 g recovery) as sublimate, and left a brown oil, which was purified by chromatography from ether–light petroleum (1:1 v/v) on silica and then sublimation at 120 °C/0.05 mmHg to give the *ester* (**1d**) as prisms (0.25 g, 20% conversion, 48% yield), m.p. 97 °C; $\nu_{max.}$ 1 733 (carboxylate), 1 640, 1 610, and 1 572 cm^{-1} (chromone pattern); δ 1.27 (3 H, t, *J* 7 Hz, *Me*CH_2), 2.44 (3 H, s, Ar*Me*), 3.64 (2 H, q, OCH_2Me), 6.28 (1 H, s, 3-H), 7.34 (1 H, d, *J* 8 Hz, 8-H), 7.47 (1 H, dd, *J* 8 and 2 Hz, 7-H), and 7.97 (1 H, d, *J* 2 Hz, 5-H) (Found: C, 68.5; H, 6.0%; M^+, 246. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%; M, 246).

Another reaction was conducted in the same way but the products, isolated by means of extraction (ether), were chromatographed from ether–light petroleum (1:9 v/v) without intervening steps and gave, in addition to the compounds already found, a yellow, moisture-sensitive powder (47 mg) that is believed to be ethyl (4-ethoxycarbonyloxy-6-methyl-2*H*-chromen-2-ylidene)acetate [as a mixture of geometrical isomers of structure (**7**)] and had *m/z* 318 corresponding to $C_{17}H_{18}O_6$, and exhibited a partly dual set of ^1H n.m.r. resonances, thus: δ 1.28 and 1.41 (both 3 H, t, *J* 7 Hz, CH_2Me), 2.32 (3 H, s, Ar*Me*), 4.14 and 4.34 (both 2 H, q, *J* 7 Hz, OCH_2Me), 4.95 (0.1 H, s, 2-*exo*-methine, minor isomer), 5.35 (0.9 H, s, 2-*exo*-methine, major isomer), 6.37 (0.1 H, s, 3-H, minor isomer), 6.93 (1 H, d, *J* 8 Hz, 8-H), 7.16 (1 H, dd, *J* 8 and 2 Hz, 7-H), 7.19 (1 H, d, *J* 2 Hz, 5-H), and 7.96 (0.9 H, s, 3-H, major isomer).

3-*Benzoyl*-2,6-*dimethyl*-4H-1-*benzopyran*-4-*one* (**9a**).—A solution of LDA was prepared as in the preceding experiment and kept at —77 °C during the sudden addition of ethyl benzoate (0.5 ml), followed immediately by the sudden addition of a solution of 2,6-dimethylchromone (**1a**) (0.52 g) in THF (3 ml). After 3 h, acetic acid (0.5 ml) and then water (100 ml) were added and the products were isolated by means of ether in the usual way. An oil was obtained, which was taken up in light petroleum and the solution was cooled to below −50 °C to yield a solid that could be recrystallised from ether–light petroleum, to give the *benzoylchromone* (**9a**) as platelets (0.38 g, 46%), m.p. 65—70 °C (decomp.); $\nu_{max.}$ 1 667 (benzoyl CO), 1 635, 1 615, 1 595, 1 580, and 1 567 cm^{-1} (chromone and other aromatic bands); δ 2.37 (3 H, s, 2-Me), 2.44 (3 H, s, Ar*Me*), 7.38 (1 H, d, *J* 8 Hz, 8-H), 7.58 (1 H, poor t, *J ca.* 7 Hz, 4′-H), 7.92 (2 H, poor d, *J ca.* 7 Hz, 2′- and 6′-H), 7.95 (1 H, d, 2 Hz, 5-H), and

7.42—7.53 (3 H, mm, other ArH) (Found: C, 77.5; H, 5.3%; M^+, 278. $C_{18}H_{14}O_3$ requires C, 77.7; H, 5.1%; M, 278).

*Ethyl 2,6-Dimethyl-4-oxo-*4H*-1-benzopyran-3-carboxylate* (**9b**).—To a solution of LDA in THF (40 ml) [made from di-isopropylamine (5 ml) and butyl-lithium (1.5M-solution in hexane; 13.3 ml)] at −77 °C was added diethyl carbonate (5 ml), and immediately afterwards was added a solution of 2,6-dimethylchromone (**1a**) (0.87 g) in THF (5 ml). After 1 h the mixture was treated with saturated aqueous ammonium chloride (20 ml) and poured into water (200 ml). The products were extracted into ether (3 × 100 ml), the extracts were washed with water, and the products were recovered in the usual way for purification by chromatography on silica (250 g) from ether–light petroleum (2:3 v/v). The main band eluted provided a powder (0.74 g) that crystallised from light petroleum to give two components. The major, more soluble component was further purified by sublimation at 80 °C/0.05 mmHg to provide the *ester* (**9b**) as small prisms (0.5 g, 42%), m.p. 82 °C; $\nu_{max.}$ 1 723 (ester), 1 640, 1 615, and 1 570 cm^{-1} (chromone pattern); δ 1.40 (3 H, t, *J* 7 Hz, CH_2*Me*), 2.43 (3 H, s, Ar*Me*), 2.49 (3 H, s, 2-Me), 4.39 (2 H, q, *J* 7 Hz, OCH_2), 7.28 (1 H, d, *J* 8 Hz, 8-H), 7.45 (1 H, dd, *J* 8 and 2 Hz, 7-H), and 7.97 (1 H, d, *J* 2 Hz, 5-H) (Found: 68.3; H, 5.7%; M^+, 246. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%; M, 246).

The minor, less soluble component crystallised from light petroleum to give *bis-(2,6-dimethyl-4-oxo-*4H*-1-benzopyran-3-yl) ketone* (**10**) as needles (0.16 g, 17%), m.p. 203 °C; $\nu_{max.}$ 1 662 (CO bridge), 1 640, 1 614, and 1 560 cm^{-1} (chromone pattern); δ 2.38 (3 H, s, Ar*Me*), 2.64 (3 H, s, 2-Me), 7.34 (1 H, d, *J* 8 Hz, 8-H), 7.46 (1 H, dd, *J* 8, 2, 7-H), and 7.46 (1 H, d, *J* 2 Hz, 5-H) (Found: C, 73.8; H, 4.9%; M^+, 374. $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.9%; M, 374).

Competitive Carboxylation of Furans and Flavone.—A solution of flavone (2.22 g, 0.01 mol) and furan (0.73 ml, 0.01 mol) in THF (25 ml) was added gradually to a stirred solution of LDA (0.01 mol) in THF (40 ml) held at −78 °C under nitrogen. After 15 min, the system was saturated with carbon dioxide and after a further 20 min water (10 ml) was added and the temperature allowed to rise. The products were liberated from their salts by dil. hydrochloric acid, and extracted into ethyl acetate (5 × 30 ml); the extracts were dried, and the products recovered by evaporation of the solvents under reduced pressure. The residue was dissolved in trichloromethane (50 ml) and treated with a slight excess of ethereal diazomethane. Removal of volatile materials under reduced pressure left material shown by g.l.c. (0.3 mm capillary, 25 m; OV 1 packing; programmed 120—200 °C, with N_2 as carrier gas, and flame ionisation detection) to consist of flavone (24.0), furan (24.2), methyl 4-oxo-2-phenyl-4*H*-1-benzopyran-3-carboxylate[2] (23.9), and methyl furan-2-carboxylate (23.9%).

When under the same conditions flavone was first converted into its 3-lithio derivative and then furan was added, the product was a mixture of flavone (25.1), furan (24.6), methyl 4-oxo-2-phenyl-4*H*-1-benzopyran-3-carboxylate (23.9), and methyl furan-2-carboxylate (24.0%). When furan was first converted into its 2-lithio derivative and flavone was added, the product was a mixture of flavone (23.0), furan (23.6), methyl 4-oxo-2-phenyl-4*H*-benzopyran-3-carboxylate (23.2), and methyl furan-2-carboxylate (23.1%). Similar results were obtained from benzofuran.

The Carboxylation of Khellin (**14a**).—A 0.01M solution of LDA was prepared from di-isopropylamine (1.5 ml) and n-butyl-lithium (2M-solution in hexane; 5 ml) in freshly purified THF (40 ml) at −78 °C. To this stirred solution was added a selection of khellin (2.6 g) in THF (15 ml), in one portion, under nitrogen. After 30 s, the mixture was saturated with carbon dioxide gas, and after 30 min water was added and the temperature allowed to rise to ambient. The mixture was extracted with ethyl acetate (3 × 30 ml), the extract was dried ($MgSO_4$), and the solvent was evaporated off to leave khellin (**14a**) (1.17 g recovery). The aqueous phase was acidified with cold dil. hydrochloric acid and the product was isolated, by means of ethyl acetate (4 × 30 ml), as a gum which crystallised from acetonitrile–ethanol to furnish 4,9-*dimethoxy-7-methyl-5-oxo-*5H*-furo*[3,2-g][1]*benzopyran-2-carboxylic acid* (**14b**) as tiny prisms (1.06 g, 35% conversion, 65% yield), m.p. 230 °C; $\lambda_{max.}$(MeOH) 242, 272, and 321 nm (log ε 4.57, 3.86, and 3.61); $\nu_{max.}$(KBr) 3 470br, 1 721, 1 646, 1 569, 1 480, 1 435, and 1 398 cm^{-1}; δ 7.78 (1 H, s, 3-H), 6.00 (1 H, s, 6-H), 4.21 and 4.10 (each 3 H, s, OMe), and 2.43 (3 H, s, 7-Me) (Found: M^+, 304.0553. $C_{15}H_{15}O_7$ requires M, 304.0563). The mass spectrum also contained strong fragment ions at m/z 260 ($M - CO_2$) and 245 ($M - CO_2 - Me$).

Carboxylation of Norvisnagin (**15b**).—Visnagin (**15a**) (2.3 g) in dichloromethane (30 ml) was demethylated by boron trichloride (2.2 g) in dichloromethane (12 ml) at room temperature for 30 min. Isolated in the usual way, norvisnagin (**15b**) crystallised from ethanol as needles (2.0 g), m.p. 156 °C (lit.,[16] 156 °C).

A solution of norvisnagin (2.16 g) in THF (40 ml) was added in one portion at −78 °C to a stirred solution of LDA (0.02 mol) in THF (40 ml). After 30 s, the mixture was saturated with a rapid stream of carbon dioxide, and after 30 min water was added and the mixture was left to attain room temperature. Extraction with ethyl acetate (4 × 30 ml) furnished norvisnagin (0.39 g). The aqueous layer was acidified with cold dil. hydrochloric acid and again extracted with ethyl acetate (4 × 30 ml) to give, after work-up, (*4-hydroxy-5-oxo-*5H*-furo*[3,2-g][1]*benzopyran-7-yl)acetic acid* (**16**) which separated from ethanol as faintly yellow plates (2.11 g, 81%), m.p. 169 °C; $\lambda_{max.}$(MeOH) 252, 260, and 335 nm (log ε 4.52, 4.41, and 3.41); $\nu_{max.}$(KBr) 2 900br, 1 722, 1 650, 1 622, 1 586, and 1 461 cm^{-1}; δ([$^2H_5$]pyridine) 7.78 and 7.07 (each 1 H, d, *J* 3 Hz, 2- and 3-H), 7.14 (1 H, s, 9-H), 6.55 (6-H), and 3.95 (2 H, s, CH_2CO_2H) (Found: C, 59.9; H, 3.4%; M^+, 260.0328. $C_{13}H_8O_6$ requires C, 60.0; H, 3.1%; M, 260.0325).

The Carboxylation of 2-(2′-*Furyl*)*chromone*[17] (**18a**).—A solution of the furylchromone (**18a**) (2.12 g, 0.01 mol) in THF (15 ml) was added in one portion to a stirred solution of LDA (0.01 mol) in THF (40 ml) at −78 °C under nitrogen. After 1 min, the system was flooded with carbon dioxide, and after 30 min it was treated with water (10 ml) and allowed to attain room temperature. Then it was diluted with water (45 ml) and washed with dichloromethane (2 × 30 ml). The aqueous solution was acidified with dil. hydrochloric acid to give a precipitate that was collected, washed with water, and dried in air. Crystallisation from aqueous dimethylformamide gave 2-(*5′-carboxy-2′-furyl*)-4-*oxo-*4H*-1-benzopyran-3-carboxylic acid* (**18b**) as small prisms (1.26 g, 42%), m.p. 240 °C (decomp.); $\nu_{max.}$ 3 350br, 1 750, 1 738, 1 600, 1 560, 1 455, and 1 374 cm^{-1} (Found: M^+, 300.0280. $C_{15}H_8O_7$ requires M, 300.0283). A similar reaction but with only 0.005 mol of the furylchromone heated with 0.01 mol of LDA generated the same dicarboxylic acid in a higher yield (1.12 g, 75%).

2-(3′-*Furyl*)-4H-1-*benzopyran-4-one* (**20a**).—3-Furoyl chloride (13 g) was added to a stirred solution of 2-hydroxyacetophenone (13.6 g) in pyridine (dried by distillation from calcium hydride; 20 ml). After 1 h, the solution was poured into dil. hydrochloric acid (500 ml) and the precipitate was collected, washed with water, dried at 60 °C in air, and dissolved in

pyridine (40 ml). To this solution was added powdered potassium hydroxide (30 g) in small portions and with agitation. After 5 min, dil. acetic acid (300 ml) was used to precipitate the product which was collected and heated for 40 min, in neat acetic acid containing conc. hydrochloric acid (1 ml). The product separated on being cooled and, after purification from ethyl acetate, furnished 2-(3′-*furyl*)-4H-1-*benzopyran*-4-*one* (**20a**) as plates (15.5 g, 74% based on furoyl chloride), m.p. 119—120 °C; $\nu_{max.}$ 1 662, 1 650, 1 600, 1 454, and 1 370 cm^{-1}; δ 6.52 (1 H, s, 3-H), 6.77 (1 H, d, *J* 3 Hz, 4′-H), 7.41 (1 H, t, *J* 8 Hz, 7-H), 7.47 (1 H, d, *J* 8 Hz, 8-H), 7.56 (1 H, d, *J* 3 Hz, 5′-H), 7.69 (1 H, t, *J* 8 Hz, 6-H), 8.10 (1 H, s, 2′-H), and 8.24 (1 H, dd, *J* 8, 2 Hz, 5-H) (Found: C, 73.6; H, 3.8%; M^+, 212.0463. $C_{13}H_8O_3$ requires C, 73.6; H, 3.8%; *M*, 212.0473).

The Carboxylation of 2-(3′-*Furyl*)-4H-1-*benzopyran*-4-*one* (**20a**).—The chromone (**20a**) (2.12 g; 0.01 mol) was treated with LDA (0.01 mol) as in the preceding example and carbonation gave 2-(3′-*furyl*)-4-*oxo*-4H-1-*benzopyran*-3-*carboxylic acid* (**20b**) which separated from ethyl acetate as plates (2.10 g, 71%), m.p. 278 °C; $\nu_{max.}$ 1 709, 1 634, 1 602, 1 582, 1 478, and 1 371 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 7.12 (1 H, d, *J* 3 Hz, 4′-H), 7.29 (1 H, d, *J* 3 Hz, 5′-H), 7.49 (1 H, t, *J* 8 Hz, 7-H), 7.61 (1 H, d, *J* 8 Hz, 8-H), 7.79 (1 H, t, *J* 8 Hz, 6-H), 7.90 (1 H, s, 2′-H), and 8.13 (1 H, dd, *J* 8 and 2 Hz, 5-H) (Found: M^+, 256.037 93. $C_{14}H_8O_5$ requires *M*, 256.037 96).

2-(3′,4′-*Dihydro*-2′,6′-*dimethyl*-4′-*oxo*-2′H-1′-*benzopyran*-2′-*yl*)*methyl*-6-*methyl*-4H-1-*benzopyran*-4-*one* (**8**).—A solution of 2,6-dimethylchromone (**1a**) (0.35 g) in THF (10 ml) was added to a solution of LDA [from di-isopropylamine (0.28 ml) and the requisite amount of butyl-lithium in hexane] in THF (25 ml) at −25 °C. After 20 min, a similar solution of the chromone was added and the red colour of the mixture faded slowly. After 5 h, the reaction was terminated by successive addition of acetic acid (5 ml) and then water (200 ml). The product was extracted into ether and isolated in the usual manner as an oil (0.73 g) which was dissolved in dichloromethane–ethyl acetate (4:1 v/v) and passed through silica gel (100 g) to remove highly polar impurities. The filtrate furnished a mixture, which was separated by preparative t.l.c. on silica plates with ether as developer, and a brilliantly fluorescent band was removed and extracted to give the *benzopyranone* (**8**) which crystallised from ether as plates (0.34 g, 97%), m.p. 124—126 °C; $\nu_{max.}$(KBr) 1 690 (dihydropyrone CO), 1 642br, 1 612, and 1 572 cm^{-1} (benzopyrone bands); δ 1.54 (3 H, s, 2′-Me), 2.30 (3 H, s, 6′-Me), 2.46 (3 H, s, 6-Me), 2.82 and 2.94 (each 1 H, d, *J* 14 Hz, 2-CH_2), 2.96 and 3.08 (each 1 H, d, *J* 14 Hz, 3′-H_2), 6.22 (1 H, s, 3-H), 6.89 (1 H, d, *J* 8 Hz, 8′-H), 7.32 (1 H, d, *J* 8 Hz, 8-H), 7.35 (1 H, dd, *J* 8 and 2 Hz, 7′-H), 7.50 (1 H, dd, *J* 8 and 2 Hz, 7-H), 7.68 (1 H, d, *J* 2 Hz, 5′-H), and 8.00 (1 H, d, *J* 2 Hz, 5-H) (Found: C, 75.8; H, 5.8%; M^+, 348. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%; *M*, 348).

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