Lithiation in Flavones, Chromones, Coumarins, and Benzofuran Derivatives

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Flavones are lithiated at position 3 by lithium di-isopropylamide in tetrahydrofuran at −78 °C and the products are stable at that temperature. Appropriate reagents replace the lithium by carboxy, ethoxycarbonyl, mercapto, methylthio, trimethylsilyl, hydroxy, and other groups, sometimes giving products not previously available.

Benzofurans are preferentially lithiated at position 2 if this is free, and may not be attacked if it is blocked, but if there is an activating group (*i.e.*, one able to co-ordinate with the lithium cation) at position 2, then lithiation occurs at position 3. In the benzofuran series ring-opening is easier and lithiation often leads directly to acetylenic phenols. Chromones can be lithiated at positions 2 and 3 depending upon the substitution pattern and whether the substituents are activating. Aurones are not easily deprotonated, and only the acetylenic phenol arising from ring opening was found in the one successful case. Coumarins tend to behave simply as esters and give amides with the lithiating reagent, but 4-methoxycoumarin is readily lithiated at position 3.

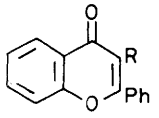
It is suggested that 3-deprotonation in ethers occurs easily only when there is an ether link antiperiplanar to the proton removed, and that the lithiated species are really unstable intermediates in *trans*-eliminations leading to alkyne derivatives.

As we have already reported briefly,[1] flavone is immediately attacked by lithium di-isopropylamide in tetrahydrofuran at −78 °C giving a 3-lithio derivative (**1**) which is converted by carbon dioxide into the carboxylic acid (**2**) in high yield. This lithiation allows a number of new derivatives of flavone to be prepared easily. The ester (**3**) can be obtained by acylation with either ethyl carbonate or ethyl chloroformate. Iodine gives 3-iodoflavone (**4**), and chlorotrimethylsilane the trimethylsilyl derivative (**5**). Sulphur affords the thiol (**6**) which can be methylated but the sulphide (**7**) is more easily made by letting the lithioflavone react with dimethyl disulphide. Aldol condensations are possible, as is shown by the reaction with furan-2-carbaldehyde to give the alcohol (**8**); it appears that transmetallation of the furan ring is not competitive.

Direct oxidations of 3-lithioflavone have not yielded satisfactory results. An attempt to induce radical coupling at the 3-position by means of copper(II) chloride led only to recovery of flavone, but the reaction with methyl borate and then hydrogen peroxide[2] supplied flavonol (**9**) in good yield, thus providing a new route to this important type of compound.

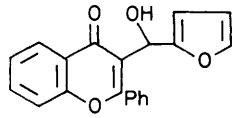
3-Lithioflavone shares with other organolithium compounds an inability to add unsaturated compounds in Michael reactions; acrylonitrile regenerates flavone, and dimethyl butyndioate gives a mixture containing both flavone and what may be acylated products. Reactions also fail if the reagent contains 'acidic' hydrogen adjacent to the reaction centre; thus cyclohexanone regenerates flavone in preference to undergoing an aldol condensation. Disappointingly, iodomethane failed to give 3-methylflavone, only flavone resulting. Presumably the reagent lost a proton to the base, and was itself lost as carbene, which we know from other work hardly reacts with flavone. A brief survey of the literature showed that the alkylation of organolithium compounds by iodomethane is very variable, yields varying from as little as 4% to nearly quantitative for no clear reason. Table 1 summarizes the results for 3-lithioflavones in this work; the presence of methyl groups seems to reduce the yield of the acid (**10**), whereas the methoxy group in (**11**) attended a near quantitative yield.

Such lithiations do not fall into any established class.[3] There is no directly attached heteroatom such as that known to permit metallation of furans at the 2-position. The carbonyl group

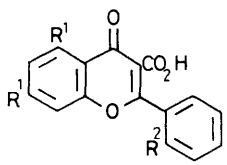


R

(**1**) Li
(**2**) CO_2H
(**3**) CO_2Et
(**4**) I
(**5**) $SiMe_3$
(**6**) SH
(**7**) SMe
(**9**) OH



(**8**)

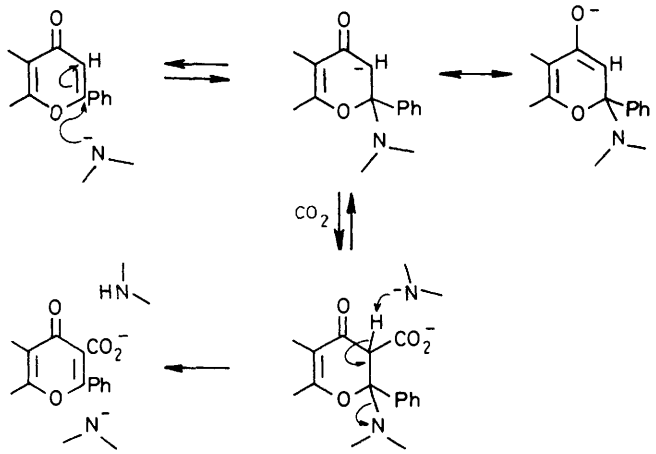


(**10**) R^1 = Me ; R^2 = H
(**11**) R^1 = H ; R^2 = OMe

Table 1. Reactions of 3-lithioflavone at −78 °C in THF

Electrophile	Product	Yield (%)	Note
CO_2	(**2**)	92	
$(EtO)_2CO$	(**3**)	51	*a*
EtOCOCl	(**3**)	48	*a*
Me_3SiCl	(**5**)	86	
MeI		0	*b*
Iodine	(**4**)	93	
Sulphur	(**6**)	97	
MeSSMe	(**7**)	92	
Furan-2-CHO	(**8**)	60	
$(MeOCO)_2C_2$		0	*c*
CH_2=$CHCH_2Br$		0	*c*
Cyclohexanone		0	*b*
CH_2CHCN		0	*c*
$B(OMe)_3$–H_2O_2	(**9**)	92	

[a] Based on isolated product. Spectroscopic results indicate a much higher true yield. [b] Most of the flavone was recovered. [c] Some flavone was recovered but the main product was an unresolved mixture.



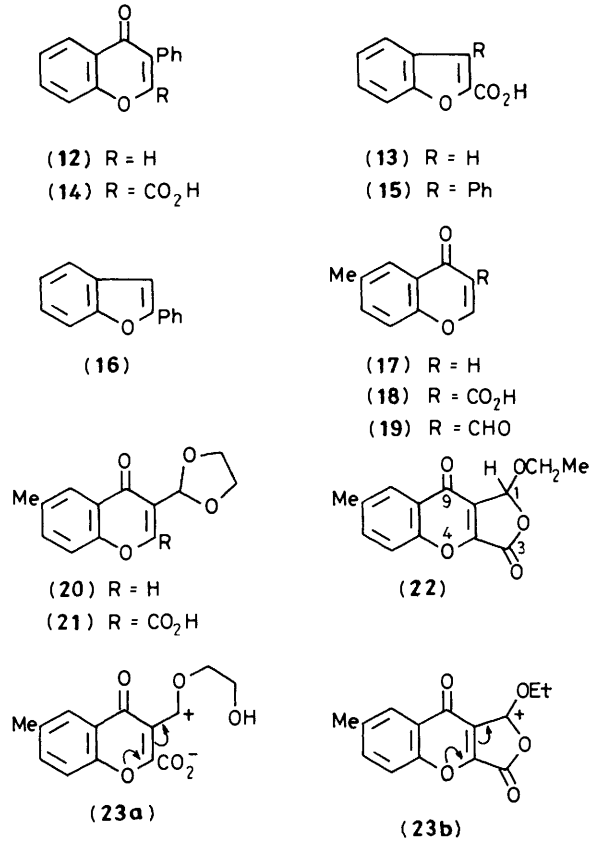
Scheme 1.

cannot stabilise the charge by delocalising it because the π-system does not overlap the σ-orbital in which the charge lies. We find that chalcone, for example, is not lithiated under these conditions. It might be possible to rationalise the formation of carboxylic acids without assuming lithiation if the base adds to the flavone and is eliminated again after the carboxy group has been introduced (Scheme 1), but several features render this idea unattractive. The lithiation is faster at −78 °C than the reaction of flavones and other chromones with unhindered bases at ambient temperatures; when pyrone rings are opened by nitrogen bases the products invariably retain the nitrogen atom,[4] which does not happen here. Moreover, silylation is almost specific for oxygen if charge is available there, so the reaction at carbon is very strong evidence that there is no delocalisation onto oxygen as in Scheme 1. Flavone is not affected by other bases such as sodium butoxide or potassium carbonate in conjunction with the complexing agent 18-crown-6. Lithium 2,2,6,6-tetramethylpiperidide reacts sluggishly, and the more bulky lithium bistrimethylsilylamide not at all. Butyllithium reacts, though not usefully since the product is complex. The best yields are obtained with exactly 1 mol equiv. of lithium di-isopropylamide, the yields falling off if an excess is used.

Isoflavone (**12**) was subjected to lithiation in order to compare the 2-position of a chromone with the 2-position in benzofuran. Whereas benzofuran was lithiated extensively [some was recovered after carbonation to the acid (**13**)], isoflavone did not react so easily, since the yield of the 2-carboxylic acid (**14**) was low, and it appeared not to react at all with the lithium bistrimethylsilylamide reagent. Similarly, 3-phenylbenzofuran gave the acid (**15**); some was recovered so the lithiation is incomplete or reversible. 2-Phenylfuran (**16**) was inert, notwithstanding its possession of a hydrogen at the 3-position rather like that in flavone, and we take this as evidence that the carbonyl group of flavone plays some part in the lithiation though it cannot delocalise the negative charge.

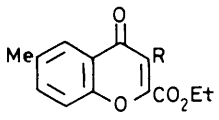
The lithiation of 6-methylchromone (**17**) is complex, since both the 2- and the 3-positions are available, and since the absence of substituents allows the base relatively free access to the 2-position and consequently to nucleophilic attack and other ring-opening reactions. In practice, most of the compound was converted by lithiation and treatment with carbon dioxide into neutral products.* Operating at a lower temperature (−95 °C) secured some improvement; the acid fraction was still small and mixed but the 3-carboxylic acid (**18**) was obtained pure. Although the evidence it is not strong, it does support a preference for 3- over 2-lithiation. Lithiation at both positions can be improved by appropriate substituents. With a formyl group at position 3 as in (**19**) the compound proved unstable to the conditions employed, but the derived dioxolane (**20**) was readily lithiated and carboxylated giving, we presume, the acid (**21**). Necessarily slightly acidic, and also involving ethanol at one stage, the work-up stripped off the dioxolane protection and esterified the resulting pseudoacid giving the lactone (**22**). The particular sensitivity of the dioxolane grouping is probably partly due to the ability of the chroman ring oxygen atom to aid in stabilising the intermediate carbenium ion as indicated in diagram (**23a**). The lactone loses a single hydrogen atom easily in the mass spectrometer, the resulting peak being as strong as that from the parent molecular ion, and we also attribute this property to the acetal methine hydrogen which would leave behind a carbenium centre stabilised by three oxygen atoms, two attached directly and one vinylogously, as in (**23b**). The lactonic band at 1 780 cm^{-1} is typical of a substituted butenolide,[5] while the attachment of the ethoxy group to a chiral centre is clearly supported by the ^1H n.m.r. spectrum, in which the ethyl group displays an ABX_3 instead of the usual A_2X_3 spin pattern.

A carboxy group at the 2-position of chromone could be expected to assist 3-lithiation, but in the event 2-carboxychromone provided problems for which unfavourable solubility relations were partly responsible. On the other hand, the ethyl ester (**24**) was easily attacked and appeared to have been lithiated as expected, because, after carboxylation, some of the acid (**25**) was isolated. The major product, however, was the ring-opened acetylenic amide (**26**). The ring must open before the amide is formed, because the (preformed) chromone amide

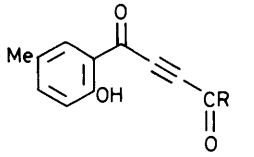


* In this paper the term neutral products covers those that are acidic only by virtue of a phenolic hydroxy group.

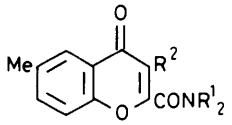
(**28**), which shows by its temperature-dependent ^{1}H n.m.r. spectrum clear evidence for slow amidic rotation (Table 2), can be transformed by lithiation into the 3-carboxylic acid (**29**) in high yield. Nevertheless, we did not actually find the ester (**27**) in the reaction mixture, but assume that it was formed by what amounts to *trans*-elimination in the chromone. The subsequent amide formation is remarkably rapid considering the hindered nature of the base and the low temperature; moreover, the base is not the amide (which must all be used up generating the anionic centre), but the amine. In an acetylenic ester like (**27**), of course, there is almost nothing in the space around the carbonyl group to prevent the approach of the amine.



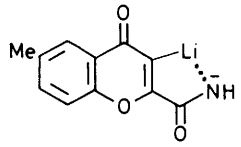
(**24**) R = H
(**25**) R = CO_2H



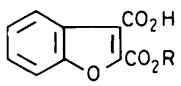
(**26**) R = $N(CHMe_2)_2$
(**27**) R = OMe



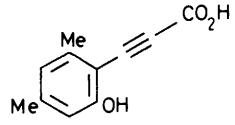
(**28**) $R^1 = (CHMe_2)_2$; $R^2 = H$
(**29**) $R^1 = (CHMe_2)_2$; $R^2 = CO_2H$
(**30**) $R^1 = H$; $R^2 = H$
(**31**) $R^1 = H$; $R^2 = CO_2H$



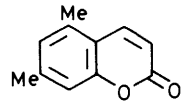
(**32**)



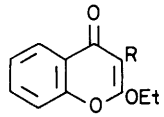
(**33**) R = H
(**34**) R = Me



(**35**)



(**36**)



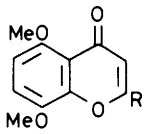
(**37**) R = H
(**38**) R = CO_2H

The simpler amide (**30**) can also be readily transformed into the 3-carboxylic acid (**31**), despite a report[6] that the amino-carbonyl group does not support *ortho*-lithiation in the benzene series. Although the removal of both amino protons has been observed in some amides,[7] here the best yields were secured by the use of only 2 equivalents of base, thus showing that the effective intermediate is (**32**) and disclosing the relative acidities of the hydrogen atoms concerned. Attempts were made to cyclise the amido acid (**31**) to imide without success; the only observation of interest was that neat sulphuric acid stripped off both acid functions leaving 6-methylchromone (**17**) itself.

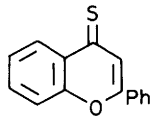
Again in the benzofuran series, a carboxylic function at position 2 promotes lithiation at position 3, a point that did not emerge from earlier studies because these were conducted in the main with butyl-lithium acting on bromobenzofurans.[8] Thus benzofuran-2-carboxylic acid (**13**) affords the 2,3-dicarboxylic acid (**33**) and its methyl ester affords the half ester (**34**) accompanied, however, by large amounts of by-products (not isolated) with the spectroscopic characteristics of alkyne derivatives. Lithiation of 4,6-dimethylbenzofuran-2-carboxylic acid led solely to the alkyne acid (**35**), a ring scission of a kind well known in type, though not in dependence upon the benzenoid substituents.[9] Evidently the energy differences that determine whether the lithio-derivative survives or suffers ring scission are small. A similar ring opening could account for the relatively low yield of the acid (**10**). Semi-hydrogenation of the alkyne acid (**35**) generated 5,7-dimethylcoumarin (**36**) in high yield.

In the chromone as in the benzene series, alkoxy groups promote *ortho*-lithiation. Thus, 2-ethoxychromone (**37**) was easily lithiated, the lithio derivative was comparatively stable thermally, and the acid (**38**) obtainable in high yield. This enol ether acid is of a kind not previously accessible.

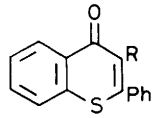
Attempts to lithiate sulphur analogues of some of these oxygen derivatives were almost wholly unsuccessful, complex mixtures resulting from the sulphide (**39**), the sulphoxide (**40**) (both available from other studies), the pyranthione (**41**), and the thiapyran (**42**). Upon lithiation and carbonation, only the last gave a small amount of an acid, and this behaved as expected for thiin-4-carboxylic acid (**43**). The nitrogen analogue (**44**) also failed to give useful results.



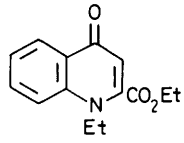
(**39**) R = SEt
(**40**) R = S(O)Et



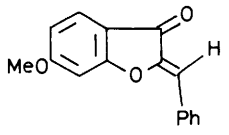
(**41**)



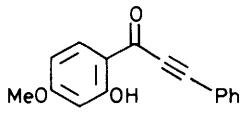
(**42**) R = H
(**43**) R = CO_2H



(**44**)



(**45**)

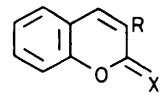


(**46**)

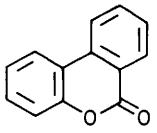
We turned next to an examination of other ways in which the structural elements of chromone can be assembled. Aurone appeared to react to some extent with the reagent, but was mostly recovered after carbonation and work-up. Nor did any acid result from similar attempts with 6-methoxyaurone (**45**), but in this case there must have been some lithiation (or at least deprotonation), because the neutral fraction contained not only recovered methoxyaurone, but also the acetylenic ketone (**46**).

The coumarins offer another structural alternative to the chromones. The reactions with coumarin itself (**47**) and with thiocoumarin (**48**) were complex and yielded no acid fraction after carbonation; they were not examined more closely. Undoubtedly amide formation was important, however, because 3-phenylcoumarin (**49**), 3-methoxycoumarin (**50**), and the dibenzopyrone (**51**) were converted into their amides, (**52**), (**53**) and (**54**), respectively, and there was no other reaction. 4-Lithiation also failed with 3-benzoylcoumarin, carbonation yielding no acid. The contrast between 3-phenylcoumarin (**49**)

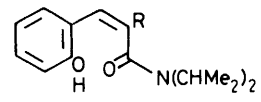
and its isomer, flavone (**1**), is striking, and is attributed to the importance of the co-ordination of lithium with a carbonyl oxygen atom in a four-membered transition state, which determines the sequel. In the lactone, the base cannot reach a labile proton, but it can attack the carbonyl carbon atom and form an amide with ring opening even though there must be substantial steric hindrance. In the flavone a similar co-ordination with the carbonyl group cannot lead to ring-opening because the base is too far from position 2, but there is now a labile proton (at the 3-position) within easy reach so lithiation occurs. Furthermore 4-phenylcoumarin and its 7-methoxy derivative (**55**) gave only complex, neutral products under



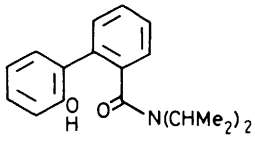
	R	X
(**47**)	H	O
(**48**)	H	S
(**49**)	Ph	O
(**50**)	OMe	O



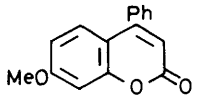
(**51**)



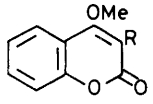
(**52**) R = Ph
(**53**) R = OMe



(**54**)



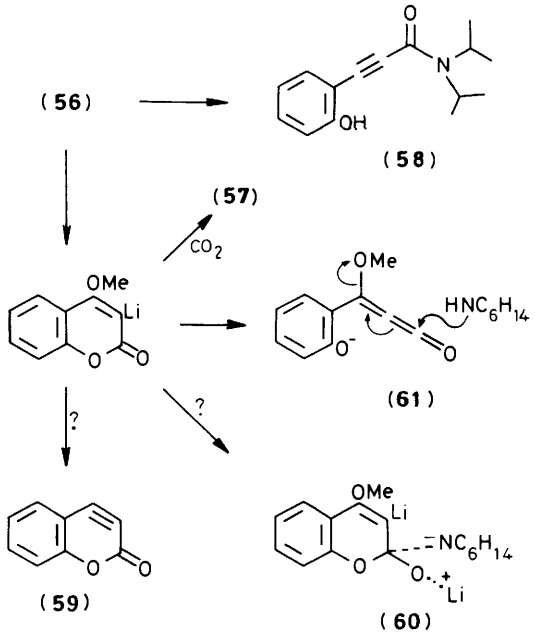
(**55**)



(**56**) R = H
(**57**) R = CO_2H

various conditions with the lithiating reagent and carbon dioxide and no sign of an acid. It seems that even when a proton is available at the 3-position reactions other than lithiation are preferred.

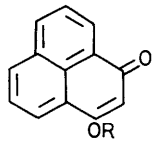
As in other cases, however, 3-lithiation of a coumarin does succeed if there is an *ortho*-alkoxy group to assist it. Thus 4-methoxycoumarin (**56**) is readily lithiated, and provided that carbonation is conducted immediately the acid (**57**) is readily obtained. Even a short delay, however, permits ring scission and the formation of an acetylenic amide (**58**) (Scheme 2). There are four reactions here: lithiation, extrusion of the methoxy group, amide formation, and ring opening, and it is not immediately obvious how they are connected. No doubt lithiation is the first step, but if the methoxy group is lost in the second then a very strained heterocycle (**59**) would result. We are not aware of any close precedent for this. If amide formation is next it has to be combined with the ring opening and presumably occurs in the same way as for the coumarins (**49**)—(**51**) discussed above; that is, it requires a *second* equivalent of amide as in (**60**) (Scheme 2), the first having been used up in removing the 3-proton. But the reaction proceeds well with only 1 equivalent in all. We are left with a purely thermal ring opening to a ketene derivative (**61**). This should react at once with amine (no amide is now present) and the gain in bond energy could well be enough to eliminate the methoxy group at the same time as shown in Scheme 2. We prefer this to the other possibilities. A closely similar lithiation of monocyclic 4-meth-



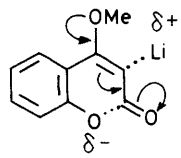
Scheme 2.

oxy-2-pyrones is on record but no ring opening, amide formation *etc.*, was observed.[10]

Finally, we examined the behaviour of the alkoxyphenalones[11] (**61**) and (**62**), which offer yet another way of arranging



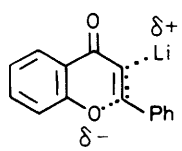
(**61**) R = Me
(**62**) R = Et



(**63**)

the structural components of the chromone system. They appeared not to react at all with lithium di-isopropylamide or with lithium bistrimethylsilylamide, notwithstanding the seemingly close parallel with 4-methoxycoumarin and with flavone itself. The mere derivation of the system from naphthalene can hardly be responsible; there is much precedent to support the view that that side of the system would have no great importance in lithiations, and no current theory of lithiation would ascribe a role to it.[3] Instead, it seems very probable that some essential structural feature has been lost in the transition from flavone to the alkoxyphenalones, and we suggest that this is the presence of an ether oxygen atom *within* the ring. From that we conclude that for a successful lithiation (or even a simple deprotonation) similar to that in flavone there must be an ether oxygen antiperiplanar to the proton being removed.

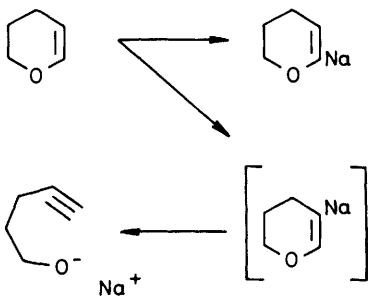
The antiperiplanar arrangement could assist lithiation or at least the removal of the proton by absorbing some of the negative charge into the carbon–oxygen bond:



Obviously, if this transfer continued it would end in ring-opening and the formation of an acetylenic product (*i.e. trans*-elimination) as is actually found in several examples. It is also obvious that lithium, more than other metals, will oppose this transfer of charge at some stage because of its tendency to form covalent bonds rather than to exist as a simple cation, so that a delicate balance of forces results and the lithiated species is an intermediate in *trans*-elimination, occupying a shallow energy minimum on the reaction co-ordinate. Though formally of the correct geometry, the aurones like (**45**) do not have their carbon–oxygen and carbon–hydrogen bonds properly parallel which, we suggest, is why they react sluggishly and suffer immediate ring-scission. The strain in the five-membered ring will also favour the scission. In coumarins such as (**55**) there is no corresponding strain and the bonds are correctly disposed for lithiation, but here the carbon–oxygen bond is part of an ester function the delocalisation in which will strongly oppose bond lengthening.

We therefore suggest that the 4-methoxy group in coumarin (**56**) (Scheme 2) is not only helpful in stabilising the lithium cation by co-ordination, but also feeds electrons into the carbonyl group, thus allowing the ring oxygen atom to move away without much loss of delocalisation energy, as indicated in diagram (**63**).

The lithiation of flavone is easier than that of simple vinyl ethers, which usually require alkyl-lithium and temperatures near to ambient.[12,13] Moreover, the lithiation of such ethers occurs only at the 2-position, in accordance with the view that co-ordination of the metal with the oxygen atom is important for orientation. Significantly, attack of 3,4-dihydro-2*H*-pyran by alkylsodium is unselective, occurring at position 2 to give an alkylsodium, but at position 3 to effect ring scission and the formation of an alkyne:



The lithiation of flavone, therefore, depends also upon the carbonyl group at the 4-position, which probably assists it by helping to remove charge through the σ-system to the small extent that is possible in the absence of true delocalisation. More importantly, the carbonyl oxygen atom would direct the lithium to the adjacent site because this oxygen atom is a highly negatively charged one in a pyrone system. Similarly in benzofuran derivatives, the 3-position is not attacked unless there is a carbonyl group at position 2 which can direct the lithium reagent appropriately.

There remains the question of 2-lithiation in chromones. There is a suggestion that the kinetic acidity at the 2-position is rather less in the dihydropyran series than in the dihydrofuran series, but its authors regard the (spectroscopic) evidence as very weak.[13] Certainly, 2-lithiation in chromones is much less satisfactory than in furans or benzofurans, and requires assistance from a 3-substituent to proceed adequately. Views as to the origin of the acidity at the 2-position in furan derivatives seem to apply equally to the 2-position in chromone, so we seek no further explanation there. But the carbonyl group which in flavones promotes 3-lithiation will for the same reason *oppose* 2-lithiation in chromones; it will tend to take up most of the lithium and keep it in a position where no lithiation can ensue at all if there is a 3-substituent as in isoflavone. With a good ligand (dioxolane ring) at the 3-position as in (**20**), however, the lithium can again reside near the 2-position and 2-lithiation can proceed.

Experimental

The ^{1}H n.m.r. spectra were recorded for solutions in deuteriochloroform, unless another solvent is specified, on a Perkin-Elmer R34 spectrophotometer, operating at 220 MHz with tetramethylsilane as internal standard: coupling constants were obtained by first-order analysis only. I.r. spectra measured on a Perkin-Elmer 125 spectrophotometer for KBr discs (unless other techniques are stated), and are quoted only for OH and double-bond stretching regions. Molecular weights were determined by mass spectroscopy using an AEI MS12 spectrometer, and the direct inlet technique; peaks other than that of the molecular ion are recorded only for support, *e.g.* when the molecular ion is very weak. Solutions were dried by means of magnesium sulphate. Tetrahydrofuran was purified by distillation from sodium. Carbon dioxide gas was dried by passage through sulphuric acid and over calcium chloride. Ether refers to diethyl ether.

Spectra not tabulated in Tables 2 and 3 are recorded below. All compounds recorded were pure by t.l.c. standards.

Standard Procedure for Lithiations and Carboxylations.—Standard solutions of lithium di-isopropylamide (0.01 mol) were prepared by allowing butyl-lithium (2M solution in hexane; 5 ml) to react with di-isopropylamine (1.5 ml, 0.01 mol) in tetrahydrofuran (40 ml) at −78 °C under nitrogen. The solution was stirred during the addition of the flavone or other pyrone.

For carboxylations, the system was saturated with carbon dioxide as rapidly as possible and water (10 ml) was added before the mixture was allowed to attain room temperature. Dilution with water (100 ml) was followed by extraction, usually into ethyl acetate (3 × 30 ml), to isolate the neutral components; acidification of the aqueous layer with dilute hydrochloric acid provided the acidic components, often as a precipitate.

Reactions of 3-Lithioflavone.—For the purposes of the survey, standard solutions of 3-lithioflavone were made by adding flavone (2.22 g, 0.01 mol) in tetrahydrofuran (20 ml) to the standard lithium di-isopropylamide reagent (0.01 mol). The resulting solution was usually kept at −78 °C for 5 min before use.

(i) *Carbon dioxide.* A rapid stream of carbon dioxide during 15 min bleached the colour of the standard 3-lithioflavone preparation. Work-up gave a negligible neutral fraction and an acid fraction that crystallised from acetone–ether giving *4-oxo-2-phenyl-4H-1-benzopyran-3-carboxylic acid* (**2**) as long needles (2.5 g), m.p. 177—179 °C, $\nu_{max.}$ *ca.* 2 000—3 000 (CO_2H), 1 722, 1 609, and 1 572 cm^{-1}; δ 8.32 (dd, *J* 9, 2 Hz, 5-ArH), 7.81 (t, *J ca.* 7 Hz, 7-ArH), 7.5—7.7 (other ArH), and 14.1 (br, exchange with D_2O, CO_2H). (Found: C, 72.4; H, 3.8%; *M*, 266.0588. $C_{16}H_{10}O_4$ requires C, 72.2; H, 3.8%; *M*, 266.0579).

(ii) *Ethyl carbonate.* Ethyl carbonate (1.21 ml, 0.01 mol) in tetrahydrofuran (10 ml) was added in one portion to the standard 3-lithioflavone solution at −78 °C and the mixture stirred for 5 min before being quenched with water (10 ml) and allowed to regain room temperature. The product was isolated by dilution with water (100 ml) and extraction into ethyl acetate (3 × 40 ml), dried, and recovered by evaporation of the solvents under reduced pressure. Crystallisation of the yellowish residue

Table 2. ^{1}H N.m.r. spectra of derivatives of chromone (4*H*-1-benzopyran-4-one) other than flavones

Substituents	Compound Number	Field (MHz)	Solvent	Chromone nucleus (H or Me) 2	3	5[d]	6[e]	7[f]	8[g]	OCH_2Me[a] or OMe	OH[b] or NH[b]	$NCHMe_2$[c]
6-Me	(**17**)	220	$CDCl_3$	7.83[h]	6.32[h]	8.00	2.43	7.48	7.36			
3-CO_2H		60	$(CD_3)_2SO$	9.12		8.13	--- 7.4—8.0 ---					
6-Me, 3-CO_2H	(**18**)	60	$CDCl_3$	9.07		8.18	2.56	-- *ca.* 7.6 --				
6-Me, 2-CO_2H		60	$CDCl_3$–$(CD_3)_2SO$		7.13	8.02	2.51	-- *ca.* 7.6 --				
6-Me, 2-CO_2Et	(**24**)	220	$CDCl_3$		7.12	8.00	2.46	7.57	7.53	4.49 (OCH_2) 1.44 (Me)		
6-Me, 2-CO_2Me		220	$CDCl_3$		6.99	7.87	2.45	7.45	7.39	3.91		
6-Me, 2-CO_2Et, 3-CO_2H	(**25**)	60	$CDCl_3$			8.14	2.54	-- *ca.* 7.6 --		4.57 (OCH_2) 1.26 (Me)		
6-Me, 2-$CONH_2$	(**30**)	220	$CDCl_3$–TFA		7.37	8.12	2.50	7.72	7.56		7.75, 7.95	
6-Me, 2-$CONH_2$, 3-CO_2H	(**31**)	60	$CDCl_3$			8.23	2.60	-- *ca.* 7.7 --			5.80, 6.70, 7.60	
6-Me, 2-$CON(CHMe_2)_2$ at 0 °C	(**28**)	220	$CDCl_3$		6.40	8.00	2.44	7.52	7.39			3.59, 3.91 1.54, 1.27
6-Me, 2-$CON(CHME_2)_2$ at 110 °C	(**28**)	220	$(CD_3)_2SO$		6.30	7.85	2.43	7.63	7.52			3.77 (CH) 1.32 (Me)
6-Me, 2-$CON(CHMe_2)_2$ 3-CO_2H	(**29**)	220	$CDCl_3$			8.05	2.52	7.65	7.50		13.7	3.61 (CH) 1.61, 1.23 (Me)
2-OEt	(**37**)	60	$CDCl_3$		5.61	8.17	--- 7.2—7.8 ---			4.28 (OCH_2) 1.49 (Me)		
2-OEt, 3-CO_2H	(**38**)	60	$(CD_3)_2SO$			8.21	--- 7.5—7.9 ---			4.96 (OCH_2) 1.64 (Me)		
6-Me, 3-$C_3H_7O_2$	(**20**)	60	$CDCl_3$	8.13		8.03	2.46	7.48	7.35	6.08 (OCHO) 4.09 (OCH_2)		

[a] Methylenic protons appear as quartets, methyl protons as triplets, *J* 8 Hz. [b] Broad. [c] Methine protons appear as multiplets, usually 7 lines seen, methyl protons as doublets, *J* 7 Hz. [d] Doublets, *J ca.* 2 Hz, or doublets of doublets, *J* 8, *ca.* 2 Hz. [e] Methyl bands form slightly broadened singlets. Aromatic protons appear as fairly well resolved 'triplets,' *J* 7—8 Hz. [f] When resolved, these bands appear as doublets of doublets, *J* 8, *ca.* 2 Hz, or as irregular 'triplets,' *J ca.* 8, *ca.* 7, and *ca.* 2 Hz. [g] Doublets, *J* 8 Hz. [h] *J* 7 Hz.

Table 3. U.v. spectra[a] of some derivatives of chromone (4*H*-1-benzopyran-4-one)

Substituents	Compound Number	λ/nm	log ε	λ/nm	log ε
2-Ph, 3-I	(**4**)	246	4.23	311	3.90
2-Ph, 3-SH	(**6**)	248	4.22	340	3.50
2-Ph, 3-SMe	(**7**)	247	4.21	288	3.91
2-Ph, $SiMe_3$	(**5**)	241	4.30	304	3.91
2-Ph, 3-CO_2H	(**2**)	247	4.25	308	4.46
2-Ph, 3-CO_2Et	(**3**)	247	4.28	286	4.16
				304infl.	
2-Ph, 3-$C_5H_5O_2$[b]	(**8**)	243	4.22	280	3.89
				302	3.86
2-Ar,[c] 3-CO_2H	(**11**)	234	4.27	306	3.40
2-OEt	(**37**)	220	4.27	285	3.91
		267	4.03		
2-OEt, 3-CO_2H	(**38**)	250	3.95	290	3.91
				336	3.69
2-$CONH_2$, 3-CO_2H, 6-Me	(**31**)	241	4.28	308	3.27

[a] For solutions *ca.* 10^{-3}M in EtOH. [b] (2-Furyl)hydroxymethyl. [c] 2′-Methoxyphenyl.

from ether–pentane gave *ethyl* 4-*oxo*-2-*phenyl*-4H-1-*benzopyran*-3-*carboxylate* (**3**) as long needles (1.82 g), m.p. 89—90 °C, $\nu_{max.}$ 1 731sh, 1 722, 1 635, 1 615, and 1 610 cm^{-1}; δ 8.28 (dd, *J* 8, 2, 5-ArH), 7.40—7.80 (other ArH), 4.27 (q, *J* 7 Hz, OCH_2Me), and 1.17 (t, *J* 7 Hz, OCH_2Me) (Found: C, 73.6; H, 4.9%; *M*, 294. $C_{18}H_{14}O_4$ requires C, 73.5; H, 4.8%; *M*, 294). This ester (32 mg) was hydrolysed by hydrobromic acid (48%; 0.2 ml) in acetic acid (0.5 ml) at 80 °C during 1.5 h. Removal of the solvent and reagent by azeotropic distillation with benzene left the acid (**3**) (30 mg) spectroscopically identical with a sample made as in (i).

(iii) *Ethyl chloroformate.* The above experiment was repeated, but with ethyl chloroformate (0.96 ml, 0.01 mol) instead of ethyl carbonate. Ethyl 4-oxo-2-phenyl-4*H*-1-benzopyran-3-carboxylate (1.4 g), m.p. 89—90 °C, was obtained.

(iv) *Furan-2-carbaldehyde.* Experiment (ii) was repeated with furan-2-carbaldehyde (0.83 ml, 0.01 mol) instead of ethyl carbonate, but after dilution with water the mixture was adjusted to pH 3 with dilute hydrochloric acid before extraction into ethyl acetate. The product crystallised from aqueous acetone giving 3-[*hydroxy*-(2-*furyl*)*methyl*]-2-*phenyl*-4H-1-*benzopyran*-4-*one* (**8**) as long needles, m.p. 188 °C, $\nu_{max.}$ 3 360br; 1 618, 1 561, 1 461, 1 450, and 1 380 cm^{-1}; δ[$(CD_3)_2SO$], 8.08 (1 H, dd, *J* 8, 2, 5-ArH), 7.81 (1 H, 't', *J ca.* 8 Hz, 7-ArH), 7.61—7.70 (3 H, m, ArH), 7.45—7.56 (5 H, m, ArH + furan 5′-H), 6.31 (1 H, dd, *J* 3.5, 2 Hz, furan 4′-H), 6.23 (1 H, d, *J* 3.5 Hz, furan 3′-H), 5.80 (1 H, d, *J* 7 Hz, CHOH), and 5.71 (1 H, d, *J* 7 Hz, OH) (Found: *M*, 318.0873. $C_{20}H_{14}O_4$ requires *M*, 318.0879).

(v) *Chlorotrimethylsilane.* When ethyl carbonate in experiment (ii) was replaced by chlorotrimethylsilane (1.3 ml, 0.01

mol) in tetrahydrofuran (7 ml) the product was 3-*trimethylsilylflavone* (**5**) which separated from ethyl acetate as plates (2.82 g), m.p. 126 °C, $\nu_{max.}(CCl_4)$ 1 611, 1 559, 1 461, 1 407, and 1 340 cm^{-1}; δ 7.41—8.36 (9 H, mm, ArH) and 0.21 (9 H, s, Si*Me*) (Found: C, 73.2; H, 6.15%; *M*, 294 (M^+), 279 (M^+ − Me). $C_{18}H_{18}O_2Si$ requires, C, 73.4; H, 6.2%; *M*, 294).

(vi) *Iodine*. A solution of iodine (2.6 g, 0.01 mol) in tetrahydrofuran (6 ml) was added to the standard solution of 3-lithioflavone at −78 °C. The colour faded rapidly. The product was isolated as a golden yellow oil that solidified when kept for some time and then crystallised from ethyl acetate giving 3-*iodoflavone* (**4**) as small cubes (3.2 g), m.p. 128 °C, $\nu_{max.}(CCl_4)$ 1 640, 1 607, 1 460, 1 339, 1 332, and 1 141 cm^{-1}; δ 8.35 (dd, *J* 8, 2, 5-ArH) and 7.41—7.90 (other ArH) (Found: C, 51.8; H, 2.7%; *M*, 348.966 80, (M^+), 222 (M^+ − I). $C_{15}H_9O_2I$ requires C, 51.75; H, 2.6%; *M*, 348.966 72).

(vii) *Sulphur*. Finely powdered sulphur (0.32 g, 0.01 mol) was added to a vigorously stirred solution of 3-lithioflavone. After 35 min at −78 °C the mixture was allowed to attain room temperature and was then poured into water (100 ml). The aqueous solution was washed with ether (2 × 50 ml) and acidified with dilute hydrochloric acid and the product isolated by extraction into ethyl acetate (3 × 40 ml). Recovered in the usual manner, the product crystallised from ethyl acetate giving 3-*mercapto*-2-*phenyl*-4H-1-*benzopyran*-4-*one* (**6**) as prisms (2.46 g), m.p. 115 °C, $\nu_{max.}$ 1 621, 1 606, 1 546, 1 462, and 1 360 cm^{-1}; δ 8.35 (1 H, m, ArH), 8.0 (2 H, m, ArH), 7.5—7.8 (6 H, m, ArH), and 5.35 (1 H, s, SH) [Found: *M*, 254.0370, (M^+), 222 (M^+ − S), 194 (M^+ − S − CO). $C_{15}H_{10}O_2S$ requires *M*, 254.0382].

The experiment was repeated, but after the sulphur had reacted iodomethane (1.42 g, 0.01 mol) was added and stirring at −78 °C was continued for another 10 min; acidification during work-up was omitted. The product failed to crystallise but appeared homogeneous in chromatographic systems and after isolation from a silica column it provided 3-*methylthio*-2-*phenyl*-4H-1-*benzopyran*-4-*one* (**7**) as a yellow oil (2.4 g), $\nu_{max.}$ 1 634, 1 609, 1 535, 1 460, and 1 347 cm^{-1}, δ 8.26 (1 H, m, 5-ArH), 6.9—7.9 (8 H, m, ArH), and 2.1 (3 H, s, SMe) [Found: *M*, 268.0536 (M^+), 222 (M^+ − SCH_2). $C_{16}H_{12}O_2S$ requires *M*, 268.0545].

(viii) *Dimethyl disulphide*. Dimethyl disulphide (0.94 g, 0.01 mol) in tetrahydrofuran (5 ml) was added to the lithioflavone solution in one portion. After 5 min standard work-up and chromatography on silica gave the 3-methylthiobenzopyrone (**7**) as an oil (2.47 g) identical (n.m.r., i.r., m.s.) with a sample made as in (vii).

(ix) *Trimethyl borate/hydrogen peroxide*. The dropwise addition of trimethyl borate (1.13 ml, 0.01 mol) in tetrahydrofuran (10 ml) to the standard solution of 3-lithioflavone at −78 °C produced a white sludge. After being stirred at that temperature for a further 35 min the mixture was treated first with acetic acid (0.9 g, 0.015 mol) and then with hydrogen peroxide (27%; 1.15 ml, 0.011 mol) and permitted to reach room temperature. The mixture was shaken with saturated aqueous sodium hydrogen carbonate (50 ml) and the product extracted into ethyl acetate (3 × 40 ml) and isolated in the usual way. The product imparted an intense brown-purple colour to ethanolic iron(III) chloride and crystallised from ethyl acetate giving, 3-hydroxyflavone (**9**) as small yellow cubes (2.24 g), m.p. 169 °C (lit.,[15] 169 °C), δ 8.30 (3 H, m, 5-ArH, 2′-ArH, 6′-ArH), 7.4—7.8 (6 H, m, other ArH) (Found: C, 75.6; H, 4.3%; *M*, 238. Calc. for $C_{15}H_{10}O_3$: C, 75.6; H, 4.3%; *M*, 238).

A similar reaction carried out on 6-methylflavone instead of flavone gave 3-hydroxy-6-methylflavone, m.p. 203 °C (lit.,[16] 197 °C), δ 8.3 (2 H, m, 2′-ArH and 6′-ArH), 8.08 (1 H, br s, 5-ArH), 7.4—7.6 (5 H, m, other ArH), and 2.47 (3 H, s, Me) (Found: *M*, 252.0765. Calc. for $C_{16}H_{12}O_3$: *M*, 252.0774).

5,7-*Dimethyl*-4-*oxo*-2-*phenyl*-4H-1-*benzopyran*-3-*carboxylic Acid* (**10**).—5,7-Dimethylflavone[17] had δ (at 60 MHz) *ca.* 7.92 (2 H, m, 2′- and 6′-ArH), *ca.* 7.53 (3 H, m, 3′-, 4′-, and 5′-ArH), 7.21 (1 H, s, 8-ArH), 6.97 (1 H, s, 6-ArH), 6.70 (1 H, s, 3-H), 2.85 (3 H, s, 5-Me), and 2.42 (3 H, s, 7-Me). This flavone (0.65 g, 2.6 mmol) when lithiated by the standard solution (3.0 mM) rapidly became deeply green-black; carbon dioxide was introduced after 20 s and the colour became orange. Work-up gave a neutral fraction (0.2 g; discarded) and an acid fraction which, purified from ethyl acetate, gave the *acid* (0.28 g), m.p. 195—197 °C, δ (60 MHz) 7.59 (5 H, m, Ph), 7.23 (1 H, s, 6-ArH), 7.15 (1 H, s, 8-ArH), 2.87 (3 H, s, 5-Me), and 2.47 (3 H, s, 7-Me) (Found: *M*, 294. $C_{18}H_{14}O_4$ requires *M*, 294).

2-(2-*Methoxyphenyl*)-4-*oxo*-4H-1-*benzopyran*-3-*carboxylic Acid* (**11**).—A reaction similar to that above but with 2′-methoxyflavone[18] (2.52 g, 0.01 mol) in tetrahydrofuran (15 ml) added to the lithiation mixture (0.01 mol) and kept for 35 min before carbonation provided the *acid* separating from ethyl acetate as plates (2.9 g), m.p. 194 °C, $\nu_{max.}$ 2 900br, 1 705, 1 603, 1 460, and 1 384 cm^{-1}; δ 8.38 (1 H, dd, *J* 8, 2 Hz, 5-ArH), 6.9—7.8 (7 H, m, other ArH), and 3.82 (3 H, s, OMe) (Found: C, 68.95; H, 4.15%; *M*, 296. $C_{17}H_{12}O_5$ requires C, 68.9; H, 4.1%; *M*, 296).

The Carboxylation of Isoflavone (**12**).—An attempt was made to carboxylate isoflavone (1.11 g, 0.5 mmol) using lithium diisopropylamide as for flavone, and 20 min was allowed for metallation before carbon dioxide was introduced. Nearly all the isoflavone was recovered in the neutral fraction, but a small acid fraction yielded 4-oxo-3-phenyl-4*H*-1-benzopyran-2-carboxylic acid (**14**) which separated from trichloromethane–hexane as needles (50 mg), m.p. 212 °C, (lit.,[19] 212—213 °C), $\nu_{max.}$(Nujol) *ca.* 2 500vbr, 1 730br, 1 620, and 1 590 cm^{-1} (Found: *M*, 266. Calc. for $C_{16}H_{10}O_4$: *M*, 266).

Carboxylation of 3-*Phenylbenzofuran*.—3-Phenylbenzofuran (**13**) (0.49 g, 2.5 mmol) was lithiated by the standard reagent (2.5 mM) and saturated with carbon dioxide after a short period (*ca.* 4 min) during which a precipitate appeared. Work-up gave a negligible neutral fraction and an acid fraction (0.48 g) consisting almost entirely of 3-phenylbenzofuran-2-carboxylic acid (**15**) which separated from methanol–dichloromethane as thin rods, m.p. 234—236 °C (transition at 170—180 °C) (lit.,[20] 232—233 °C), $\nu_{max.}$ 2 500—3 100 (CO_2H), 1 675, 1 600, 1 570, 1 540, and 1 490 cm^{-1} (Found: *M*, 238. Calc. for $C_{15}H_{10}O_3$: *M*, 238). Since the ^1H n.m.r. spectrum contained too many overlapping lines for it to be assigned unambiguously, the ^{13}C spectrum was obtained and a doublet at δ 142.2 ($CDCl_3$; $SiMe_4$ internal standard) characterising 2-H of the benzofuran nucleus was found to have been replaced by a singlet at δ 140.4 in the desired acid, a new band at δ 160.1 being assigned to the carboxy group.

Carboxylation of Chromone.—A solution of lithium 2,2,6,6-tetramethylpiperidide (0.01 mol) in tetrahydrofuran (40 ml) was prepared by treating tetramethylpiperidine (1.68 ml) with 2M-butyl-lithium in hexane (5 ml) at −78 °C. The solution was cooled to −95 °C and chromone (1.46 g) in tetrahydrofuran (6 ml) was added and the reaction immediately quenched with carbon dioxide. The standard work-up furnished a neutral fraction shown by t.l.c. to consist of more than 12 components. The aqueous solution yielded a small amount of an acid that was isolated using ethyl acetate and purified from the same solvent giving 4-oxo-4*H*-1-benzopyran-3-carboxylic acid (**18**) (0.095 g), m.p. 200 °C (lit.,[21] m.p. 203 °C, $\nu_{max.}$ 1 750, 1 620, 1 481, and 1 363 cm^{-1} (Found: *M*, 190. Calc. for $C_{10}H_6O_4$; *M*, 190).

Reactions of 6-*Methyl*-4-*oxo*-4H-1-*benzopyran*-3-*carbaldehyde* (**19**).—(i) *Direct lithiation.* The aldehyde (1.7 g) was not very soluble in tetrahydrofuran so it was added as a powder to the standard lithiation reagent (0.01 mol). The mixture became black at once, and was saturated with carbon dioxide after a delay of 15 min. The neutral fraction contained starting material and at least four other substances; the acid fraction was also complex and no pure material was obtained from it.

(ii) *Lithiation of the dioxolane derivative.* The aldehyde (3 g) and ethane-1,2-diol (2 g) were heated in benzene (50 ml) containing a small crystal of 4-methylbenzenesulphonic acid in a Dean-Stark apparatus for 60 h. The solution was washed with water and dried and the solvent was removed under reduced pressure giving 2-(4-*oxo*-6-*methyl*-4H-1-*benzopyran*-3-*yl*)-1,3-*dioxolane* (**20**) (3.2 g), m.p. 142 °C, $\nu_{max.}$ 1 638, 1 607, 1 580, 1 480, and 1 440 cm^{-1}; [Found: *M*, 232 (M^+), 231 ($M^+ - 1$, equally strong). $C_{13}H_{12}O_4$ requires *M*, 232]. This compound (2.32 g) in tetrahydrofuran (20 ml) was added to the standard lithiation (0.01 mol) and the mixture saturated with carbon dioxide after 5 min.The acid fraction (0.22 g) was isolated by means of ethyl acetate but failed to crystallise well, except from ethanol–hexane when it supplied 1-*ethoxy*-7-*methyl*-1H-*furo*[3,4-b][1]*benzopyran*-3,9-*dione* (**22**), m.p. 155—157 °C, $\nu_{max.}$ 1 780, 1 672, 1 656, 1 610, and 1 477 cm^{-}, δ (at 220 MHz) 8.07 (1 H, d, *J* 2 Hz, 8-ArH), *ca.* 7.59 (2 H, m, 5- and 6-ArH), 6.43 (1 H, s, OCHO), 4.01 (2 H, m, *J ca.* 7 Hz, $-OCH_2Me$), 2.50 (3 H, s, Ar*Me*), and 1.35 (3 H, t, *J* 7 Hz, CH_2Me) [Found: C, 64.3; H, 4.6%; *M*, 260 (*m/z* 259 equally strong.)] $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.65%; *M*, 260).

Reactions of Ethyl 6-*Methyl*-4-*oxo*-4H-1-*benzopyran*-2-*carboxylate* (**24**).—The ester (2.32 g) in tetrahydrofuran (20 ml) was treated with lithium di-isopropylamide (0.01 mol) in tetrahydrofuran (40 ml) and the system was immediately saturated with carbon dioxide and worked up in the usual manner. Isolated by extraction into ethyl acetate, the neutral fraction was obtained as a faintly yellow solid that crystallised from ethyl acetate to give 4-(2-*hydroxy*-5-*methylphenyl*)-N,N-*bis*(1-*methylethyl*)-4-*oxobut*-2-*ynamide* (**26**) as plates (2.6 g), m.p. 189 °C, $\nu_{max.}$ 2 225, 1 668, 1 649, and 1 603 cm^{-1}; δ($CDCl_3$), 8.00 (1 H, s, benzoyl 6-H), 7.72 (1 H, d, *J* 8 Hz, benzoyl 4-H), 7.56 (1 H, d, *J* 8 Hz, benzoyl 3-H), 2.22 (3 H, s, benzoyl Me), 3.34 (2 H, m, C*H* Me_2), and 1.56 (12 H, d, *J* 7 Hz, CHMe_2) (Found: C, 71.2; H, 7.4%; *M*, 287. $C_{17}H_{21}NO_3$ requires C, 71.0; H, 7.4%; *M*, 287).

Acidification of the aqueous phase and extraction with ethyl acetate (3 × 30 ml) supplied 2-*ethoxycarbonyl*-6-*methyl*-4-*oxo*-4H-1-*benzopyran*-3-*carboxylic acid* (**25**) (0.2 g), m.p. 149—151 °C (from ethanol), $\nu_{max.}$ 2 900br, 1 710, 1 694, 1 617, and 1 584 cm^{-1} [Found: C, 60.6; H, 4.7%; *M*, 276 (M^+), 232 ($M^+ - CO_2$). $C_{14}H_{12}O_6$ requires C, 60.9; H, 4.4%; *M*, 276].

Carboxylation of 6-*Methyl*-N,N-*bis*(1-*methylethyl*)-4-*oxo*-4H-1-*benzopyran*-2-*carboxamide* (**28**).—The amide was prepared by heating 6-methyl-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (6.12 g) with thionyl chloride (2.19 ml) and *N*,*N*-dimethylformamide (five drops) in benzene (100 ml) for 4 h, removing the volatile materials, and treating the residue in benzene (100 ml) with di-isopropylamine (4.2 ml) in benzene (15 ml) (with ice cooling). Purified from ethyl acetate, the product furnished the *carboxamide* as needles (7.49 g), m.p. 287 °C, $\nu_{max.}$(Nujol), 1 649 and 1 611 cm^{-1} (Found: *M*, 287.1512. $C_{17}H_{21}NO_3$ requires *M*, 287.1515).

This amide (2.87 g) in tetrahydrofuran (20 ml) was lithiated by lithium di-isopropylamide (0.01 mol) in the standard manner and after 5 min at −78 °C was subjected to a fast stream of carbon dioxide. Isolated by the standard procedure the acid product crystallised from ethyl acetate giving 6-*methyl*-2-*bis*(1-*methylethyl*)*aminocarbonyl*-4-*oxo*-4H-1-*benzopyran*-3-*carboxylic acid* (**29**) as plates (2.85 g), m.p. 228 °C, $\nu_{max.}$ 1 750, 1 651, 1 610, 1 449, and 1 374 cm^{-1} (Found: *M*, 331.1424. $C_{18}H_{21}NO_5$ requires *M*, 331.1423).

2-*Aminocarbonyl*-6-*methyl*-4-*oxo*-4H-1-*benzopyran*-3-*carboxylic Acid* (**31**).—6-Methyl-4-oxo-4*H*-1-benzopyran-2-carboxamide[22] (**30**) (1.93 g, 0.01 mol) was added as a powder to a standard solution of lithium di-isopropylamide (0.02 mol) in tetrahydrofuran (60 ml). It dissolved during 25 min and a stream of carbon dioxide was then passed in. Work-up followed after a further 25 min and the aqueous solution, having been extracted with ethyl acetate, was acidified with dilute hydrochloric acid and the precipitate collected. A suitable solvent for recrystallisation could not be found (partly because the material is rather insoluble but is sensitive to strong heating) but the precipitate, when thoroughly washed with water and dried in air, gave satisfactory spectroscopic results and is considered to be the desired *acid* (**31**) (1.16 g), m.p. 176 °C, $\nu_{max.}$(Nujol) 3 380, 3 260, 2 690, 1 695, 1 621, and 1 580 cm^{-1} [Found: *M*, 247 (M^+), 203 ($M^+ - CO_2$). $C_{12}H_9NO_5$ requires *M*, 247].

This acid (0.2 g) was warmed briefly with sulphuric acid (3 ml) on a steam-bath. Dilution with water and extraction into dichloromethane gave 6-methylchromone (0.08 g), identical with an authentic specimen.

Ring-opening of 4,6-*Dimethylbenzofuran*-2-*carboxylic Acid.*—The acid[23] (1.9 g) in tetrahydrofuran (50 ml) was added to the lithiation reagent (0.01 mol) and the green-brown mixture either kept for 25 min before admitting carbon dioxide or treated with carbon dioxide with the minimum delay. The results were the same. The neutral fraction was very small and was disregarded. The acid fraction was isolated by means of ethyl acetate and gave, almost quantitatively, 3-(2-*hydroxy*-4,6-*dimethylphenyl*)*propynoic acid* (**35**), m.p. 145—147 °C, $\nu_{max.}$ (Nujol) 3 380br (phenolic OH?), 2 570 (carboxylic OH?), 2 180 (C≡C), 1 600br, 1 500, and 1 450 cm^{-1}; δ[$(CD_3)_2SO$] 10.24br (1 H, removed by D_2O, OH), 6.46 (2 H, s, ArH), and 2.28 and 2.19 (each 3 H, s, ArMe). (Found: *M*, 190. $C_{11}H_{10}O_3$ requires *M*, 190).

Semi-hydrogenation of the propynoic acid (0.095 g) in methanol (40 ml) using an excess of palladium–barium sulphate catalyst (5%) required 2.5 h but supplied, in almost quantitative yield, 5,7-dimethylcoumarin (**36**), m.p. 132 °C (lit.,[24] 133—134 °C), identical with an authentic specimen.

Carboxylation of Benzofuran.—Benzofuran (1.2 ml, 0.01 mol) in tetrahydrofuran (15 ml) was lithiated by lithium di-isopropylamide (0.01 mol) by the standard method and formed a precipitate after *ca.* 10 min. Carbonation produced a yellow colour, and work-up (with dichloromethane for extractions) furnished a neutral fraction consisting mainly of benzofuran (0.3 g) and an acid fraction (0.9 g) which crystallised from benzene giving benzofuran-2-carboxylic acid (**13**) as needles (0.63 g), m.p. 190 °C (lit.,[8] 192 °C), spectroscopically identical with an authentic specimen.

Carboxylation of Benzofuran-2-*carboxylic Acid* (**13**) *and its Methyl Ester.*—The reaction was conducted as for flavone, using the acid[8] (0.81 g) in tetrahydrofuran (35 ml) and lithium di-isopropylamide solution (0.01 mol, 2 equiv.) A metallation time of 25 min was allowed before carbonation. The products were rather insoluble in convenient solvents and repeated extraction with ethyl acetate was necessary. No pure material was obtained from the neutral fraction. The acid fraction (0.5 g) supplied benzofuran-2,3-dicarboxylic acid (**13**) separating from acetic acid as small prisms, m.p. 245—249 °C (decomp.) lit.,[25] 249—250 °C lit.,[8] 260 °C, $\nu_{max.}$(Nujol) 2 200—3 100 (CO_2H),

1 700br, 1 590, and 1 540 cm^{-1}; δ[$(CD_3)_2CO$] 8.25 (1 H, d, *J* 8 Hz, 4-ArH), 7.72 (1 H, d, *J* 8 Hz, 7-ArH), 7.61 (1 H, t, *J* 8 Hz, 5-ArH), 7.49 (1 H, t, *J* 8 Hz, 6-ArH), and 10.8 (2 H, br, removed by D_2O, CO_2H) (Found: *M*, 206. Calc. for $C_{10}H_6O_5$: *M*, 206). The mother liquors appeared from spectroscopic evidence to contain an acetylenic acid but this was not obtained pure.

Methyl benzofuran-2-carboxylate (0.83 g) was treated with only 1 equivalent of base; the products were more soluble and could be isolated into dichloromethane. The large neutral fraction was a complex mixture that could not be resolved easily. The acid fraction (0.15 g) crystallised from ether giving *2-methoxycarbonylbenzofuran-3-carboxylic acid* (**34**) as thin rectangular plates, m.p. 176—178 °C, $\nu_{max.}$(Nujol), 2 600(vbr, CO_2H), 1 725, 1 670, 1 600, and 1 440 cm^{-1}, δ 11.6 (1 H, vbr, CO_2H), 8.49 (1 H, *d*, *J* 8 Hz, 4-ArH), 7.57 (2 H, m, 6- and 7-ArH) and 7.46 (1 H, m, 5-ArH) (these three aromatic protons constitute an ABC spin system not amenable to first order analysis), and 4.19 (3 H, s, OMe) (Found: C, 59.7; H, 3.8%; *M*, 220. $C_{11}H_8O_5$ requires C, 60.0; H, 3.6%; *M*, 220).

2-Ethoxy-4-oxo-4H-1-benzopyran-3-carboxylic Acid (**38**).—2-Ethoxychromone (**37**) was prepared by the method of Cry and Poulton,[26] and a sample (1.9 g) in tetrahydrofuran (30 ml) was added to the standard lithium di-isopropylamide solution (0.01 mol) and carboxylated after being stirred for 1 min. Isolated in the usual way, the product was recrystallised from ethanol giving the *acid* as plates (2.14 g), m.p. 200 °C, $\nu_{max.}$ 2 900br, 1 778, 1 663, 1 612, 1 566, 1 509, and 1 456 cm^{-1} (Found: *M*, 234.0519. $C_{12}H_{10}O_5$ requires *M*, 234.0532).

4-Oxo-2-phenyl-4H-1-benzothiin-3-carboxylic Acid (**43**).—Thiaflavone (**42**) (2.38 g) in tetrahydrofuran (10 ml) was added gradually to the standard lithium di-isopropylamide solution at −78 °C and was followed immediately by a stream of carbon dioxide. The usual isolation procedure supplied only a very small acid fraction which separated from ethyl acetate to give the *acid* as a powder (34 mg), m.p. 220 °C, $\nu_{max.}$ 2 900br, 1 724, 1 567, 1 537, and 1 435 cm^{-1}, δ 8.61 (1 H, m, ArH), 7.38—7.52 (8 H, mm; other ArH) (Found: *M*, 282.0340. $C_{16}H_{10}O_3S$ requires *M*, 282.0344).

Ring-opening of (E)-*2-Benzylidene-6-methoxybenzofuran-2(3H)-one* (**45**).—The benzofuranone[27] (1.26 g) in tetrahydrofuran (25 ml) was added to the lithiation solution (0.5 mM) and the orange solution left for 35 min before the system was flooded with carbon dioxide. The acid fraction was small and was rejected. The neutral fraction contained three components separated by chromatography on silica from petroleum–benzene and later benzene-ethyl acetate mixtures. The main yellow fraction was starting material. An orange fraction could not be obtained pure. A pale yellow fraction crystallised from benzene–hexane giving 1-(*2-hydroxy-4-methoxyphenyl*)-*3-phenylpropynone* (**46**) as pale yellow prisms, m.p. 96—97 °C, $\nu_{max.}$(Nujol), 2 195 (C≡C), 1 630 (Ar C=C), and 1 575 (amide C=O) cm^{-1}; δ 12.33 (removed by D_2O, OH), 7.95 (1 H, d, *J* 8 Hz, 6′-ArH), 7.7 and 7.5 (mm, ArH), 6.38 (1 H, d, *J* 2 Hz, 3′-ArH), *ca.* 6.55 (2 H, m, 2″ and 6″ ArH), and 3.82 (3 H, s, OMe) (Found: C, 76.3; H, 4.7%; *M*, 252. $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8%; *M*, 252).

Ring-opening of 3-Methoxycoumarin.—A solution of 3-methoxy-coumarin (0.88 g, 0.005 mol) in tetrahydrofuran (5 ml) was added in one portion to a standard solution of lithium di-isopropylamide (0.005 mol) and after 1 min the system was quenched with carbon dioxide. Work-up with water and extraction of the products into ethyl acetate furnished a solid that crystallised from ethyl acetate giving (E)-3 (*2-hydroxyphenyl*)-*2-methoxy*-N,N-*bis*(*1-methylethyl*)*propenamide* (**53**) as cubes (1.32 g), m.p. 170 °C, $\nu_{max.}$ 1 648, 1 598, 1 413, and 1 400 cm^{-1}; δ 8.90 (1 H, s, OH), 7.28 (1 H, d, *J* 8 Hz, 6-ArH), 6.98 (1 H, t, *J* 8 Hz, 4-ArH), 6.79 (1 H, d, *J* 8 Hz, 5-ArH), 5.89 (1 H, s, alkene CH), 3.71 (3 H, s, OMe), 4.02 (1 H, m, CH_aMe_2), 1.35 (6 H, d, *J* 7 Hz, $CH_a\mathit{Me}_2$), 3.30 (1 H, m, CH_bMe_2), and 0.84 (6 H, d, *J* 7 Hz, $CH_b\mathit{Me}_2$) (Found: C, 69.2; H, 8.4; N, 5.0%; *M*, 277. $C_{16}H_{23}NO_3$ requires C, 69.3; H, 8.4; N, 5.05%; *M*, 277).

Ring-opening of 3-Phenylcoumarin.—3-Phenylcoumarin (1.11 g) in tetrahydrofuran (30 ml) was added slowly to the lithiation reagent (0.5 mM) giving a red solution that was saturated with carbon dioxide after 20 min. The acid fraction was negligible. The neutral fraction was found by t.l.c. to contain a little starting material; when purified from acetone it gave (Z)-3-(*2-hydroxyphenyl*)-N,N-*bis*(*1-methylethyl*)-*2-phenylpropenamide* (**52**) as rectangular prisms (0.8 g), m.p. 215—217 °C, $\nu_{max.}$ (Nujol), 3 200br and 1 570; δ[$(CD_3)_2CO$], 7.76, 7.59, 7.4, 7.10, 6.91 and 6.76 (9 H, mm, unassigned ArH), 4.08 (1 H, m, NCH_aMe_2), 3.43 (1 H, m, NCH_bMe_2), 1.52 (3 H, d, *J* 7 Hz, $NCH\mathit{Me}_a$), 1.43 (3 H, d, *J* 7 Hz, $NCH\mathit{Me}_a$), 0.85 (3 H, d, *J* 7 Hz, $NCH\mathit{Me}_b$), and 0.67 (3 H, d, *J* 7 Hz, $NCH\mathit{Me}_b$) (Found: *M*, 323. $C_{21}H_{25}NO_2$ requires *M*, 323).

Ring-opening of 6H-*Dibenzo*[c,e]*pyran-6-one* (**51**).—The pyrone (0.98 g) was subjected to the action of lithium di-isopropylamide (0.005 mol) followed by carbon dioxide. There was no acid product. From the neutral fraction small amounts of soluble materials were removed by extraction with dichloromethane leaving 2-(*2-hydroxyphenyl*)-N,N-*bis*(*1-methylethyl*)-*benzamide* (**54**), m.p. 200—202 °C, $\nu_{max.}$ 3 200br, 1 605, 1 595, 1 585, 1 510, and 1 485 cm^{-1}; δ{$CDCl_3$ + 4 drops of [$(CD_3)_2SO$]}, 8.25 (OH; removed by D_2O), 7.34—6.80 (mm, ArH), 3.60 (1 H, m, *J* 7 Hz, NCH_aMe_2), 3.29 (1 H, m, *J* 7 Hz, NCH_bMe_2), 1.46 (3 H, d, *J* 7 Hz, Me_a), 1.09 (3 H, d, *J* 7 Hz, Me_a), 1.00 (3 H, d, *J* 7 Hz, Me_b), and 0.70 (3 H, d, *J* 7 Hz, Me_b) (Found: *M*, 297. $C_{19}H_{23}NO_2$ requires *M*, 297).

Reactions of 4-Methoxycoumarin.—(i) *Immediate carboxylation.* A solution of 4-methoxycoumarin (0.88 g, 0.005 mol) in tetrahydrofuran (25 ml) was added in one portion to a standard solution of lithium di-isopropylamide (0.005 mol) giving a yellow solution which was at once saturated with carbon dioxide and kept for 40 min. Work-up supplied only a trace of neutral materials (ignored), but the acidic fraction from the aqueous layer formed a powder (0.9 g) that separated from acetone–ether giving *2-oxo-4-methoxy-2H-1-benzopyran-3-carboxylic acid* (**57**), m.p. 153—154 °C, $\nu_{max.}$(Nujol), 1 730, 1 650, 1 600, and 1 555 cm^{-1}; δ 8.03 (1 H, d, *J* 8 Hz; 5-ArH), 7.70 (1 H, t, 6-ArH), 7.41 (1 H, t, 7-ArH), and 7.39 (1 H, d, 8-ArH). This acid was too unstable to give a satisfactory molecular ion under electron-impact conditions so its molecular weight was determined by converting a sample into the methyl ester by brief treatment with ethereal diazomethane, and submitting the ester to mass spectrometry (Found: *M*, 234. $C_{12}H_{10}O_5$ requires *M*, 234).

(ii) *Delayed carboxylation.* The experiment in (i) was repeated except that carbon dioxide was not introduced until 25 min after the addition of the methoxycoumarin. The acidic and the neutral fractions were separated using dichloromethane. The benzopyrancarboxylic acid was obtained in small amounts (0.21 g). The neutral fraction crystallised from acetone–ether to furnish 3-(*2-hydroxybenzoyl*)-N,N-*bis*(*1-methylethyl*)*propynamide* (**58**) as large, pale yellow prisms (0.9 g), m.p. 174—176 °C, $\nu_{max.}$(Nujol), 3 050br, 2 195 (C≡C), and 1 570 (amide) cm^{-1}; δ{$CDCl_3$ + 3 drops [$(CD_3)_2SO$]}, 9.5 (1 H, br s, removed by D_2O, OH), 7.38 (1 H, d, 6′-ArH), 7.22 (1 H, t, 4′-ArH), 6.96 (1 H, d, 3′-ArH), 6.80 (1 H, t, 5′-ArH), 4.75 (1 H, m, NCH_aMe_2), 3.68 (1 H, m, NCH_bMe_2), 1.38 (6 H, d, *J* 7 Hz, $NCH_a\mathit{Me}_2$), and 1.28 (6

H, d, *J* 7 Hz, NCH_bMe_2) (Found: *M*, 245. $C_{15}H_{19}NO_2$ requires *M*, 245).

Hydrogenation of the amide (0.2 g) in methanol (50 mol) was effected with hydrogen gas at ordinary pressure and a palladium—carbon catalyst (10%, 20 mg) and the required volume of hydrogen (45 ml) was absorbed in 20 min. T.l.c. indicated that only one compound was present; this was isolated in the usual way and purified from methanol to give 3-(2-*hydroxybenzoyl*)-N,N-*bis*(1-*methylethyl*)*propanamide* as stout needles, m.p. 99—101 °C, $\nu_{max.}$ 3 200br, 1 610, and 1 595 cm^{-1}; δ 7.03 (1 H, t, 4′-ArH), 6.97 (1 H, d, 6′-ArH), 6.82 (1 H, d, 3′-ArH), 6.72 (1 H, t, 5′-ArH), 3.92 (1 H, m, *J* 7 Hz, NCH_aMe_2), 3.42 (1 H, m, *J* 7 Hz, NCH_bMe_2), 2.91 (2 H, m, *J* 6 Hz, $ArCH_2CH_2CO$), 2.66 (2 H, m, *J* 6 Hz, $ArCH_2CH_2CO$), 1.32 (6 H, d, *J* 7 Hz, CH_aMe_2), and 1.11 (6 H, d, *J* 7 Hz, CH_bMe_2) (Found: *M*, 249. $C_{15}H_{23}NO_2$ requires *M*, 249).

(iii) *Lithium hexamethyldisilazide as base.* A reaction was conducted as in (i) but using 1,1,1,3,3,3-hexamethyldisilazane instead of di-isopropylamine to prepare the reagent (0.01 mol). To this reagent was added 4-methoxycoumarin (1.76 g) in tetrahydrofuran (35 ml) and the yellow mixture was left for 35 min and then saturated with carbon dioxide. Work-up furnished the benzopyrancarboxylic acid in small yield (0.13 g, 7%) and a neutral fraction consisting almost enitrely of unchanged methoxycoumarin (1.64 g, 93%).

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