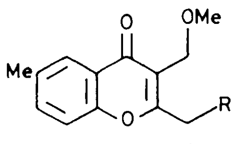
Two Exceptional Lithiations in the Chromone Series

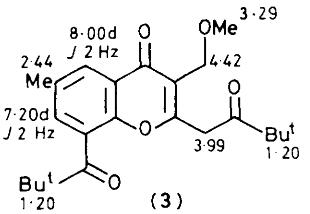
Ana M. B. S. R. C. S. Costa, Francis M. Dean,* Michael A. Jones, and Dennis A. Smith
Robert Robinson Laboratories, The University of Liverpool, Liverpool L69 3BX, U.K.

With lithium di-isopropylamide in tetrahydrofuran at −70 °C followed by pivaloyl chloride the 2-pivaloylmethyl-3-methoxymethylchromone (**1**) affords by a novel aromatic substitution the 8-pivaloylchromone (**3**); lithiation of the 2-(2-furyl)chromone (**7**) with one mol. equiv. of the reagent followed by carbonation leads not to monocarboxylic acids but to a 50% yield of the dicarboxylic acid (**8**).

The pivaloylmethylchromone (**1**) is readily obtained from 3-methoxymethyl-2,6-dimethylchromone (**2**) by lithiation with lithium di-isopropylamide (LDA) in tetrahydrofuran at −70 °C and addition of pivaloyl chloride as in the acylations described recently.[1] Attempts to introduce a second pivaloyl residue by treating the ketone (**1**) with another mol. equiv. of reagent gave awkward mixtures but a three-fold excess of the reagent permitted a smooth conversion unexpectedly giving the 8-pivaloylchromone (**3**), m.p. 145—148 °C, ν_{max} 1 720, 1 690, 1 640, 1 608, and 1 588 cm^{-1}, m/z 386 (M^+), the orientation of which is established by the ^1H n.m.r. details (δ scale for solutions in $CDCl_3$) appended to the structure. It appears that although the expected anion (**4**) must be present the anionic system does not itself react at any of the four sites available in theory. Steric hindrance may account for this failure but not for the unexpected aromatic acylation. We have confirmed that the reagent does not normally attack aromatic ethers (*e.g.*, 1,3,5-trimethoxybenzene; flavone) from which we conclude that the anionic side chain curls around so as to form, with the heterocyclic oxygen atom, a nesting site highly suitable for a lithium cation, as indicated in diagram (**5**), thus attracting an amide molecule into the right place for removing the 8-proton.



(1) R = COBu^t
(2) R= H



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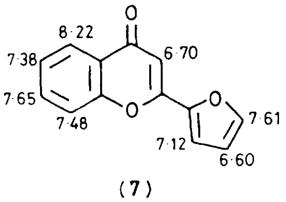

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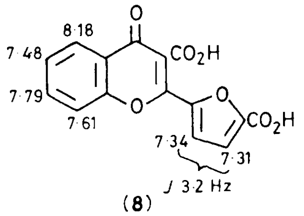

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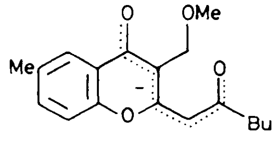

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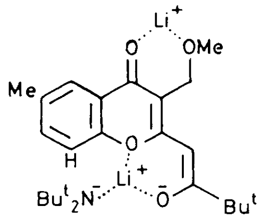

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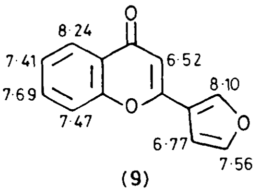

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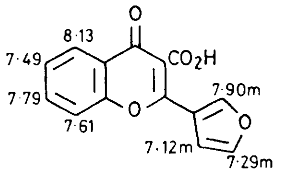

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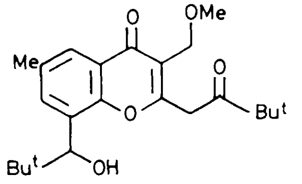

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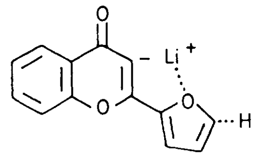

(11)

In the absence of a 6-methyl group the reaction still occurs selectively at position 8. At higher temperatures (near 0 °C), however, the alcohol (**6**) is produced instead of the ketone. Such reductions are known and are now believed to have radical intermediates;[2] in the present example, severe steric compression would prevent the formation of Meerwein–Ponndorf complexes of the kind originally proposed and so support the radical mechanism.

In another series of lithiations, LDA (2 mol. equiv.) converted 2-(2-furyl)chromone[3] (**7**) into a dianion that reacted with carbon dioxide giving in high yield the diacid (**8**), m.p. 240 °C (decomp.), m/z 300.0280 [^{1}H n.m.r. details as in diagram (**8**); δ scale for solution in Me_2SO]. Surprisingly, however, the use of only one mol. equiv. of LDA led to the *same* diacid in 42% yield (by isolation), starting chromone being recovered. In careful chromatographic searches monocarboxylic acids were not detected even in traces: evidently the intermediate di-anion is substantially more stable than either monoanion. This situation seems to be unique although equilibria between mono- and di-anions are known to exist.[4] The effect depends upon the orientation of the furan ring. From the isomeric 2-(3-furyl)chromone (**9**), m.p. 119—200 °C, one mol. equiv. of reagent produces a good yield (82% by isolation) of the monoacid (**10**), m.p. 278 °C, m/z 256.0379 [^{1}H n.m.r. assignments as in diagram (**10**) for a solution in $CDCl_3$–Me_2SO]. No diacid was detected. Although furan oxygen is usually rated as a poor donor to cations,[5] in structure (**11**) it is well placed to co-ordinate with a lithium cation at position 3. If it does, its own electrophilic character would be increased and consequently it would be able to activate position 2 in the furan ring better in the mono-anion than in the original neutral molecule (**7**).

We thank S.E.R.C. and Fisons plc, Pharmaceutical Division for financial support, and Drs. I. M. Dicker and J. L. Suschitzky for discussions.

Received, 16th June 1983; Com. 796

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