Rearrangement of 4-Ylidenebutenolides to Cyclopentene-1,3-diones: Synthesis of Calythrone and Related Compounds

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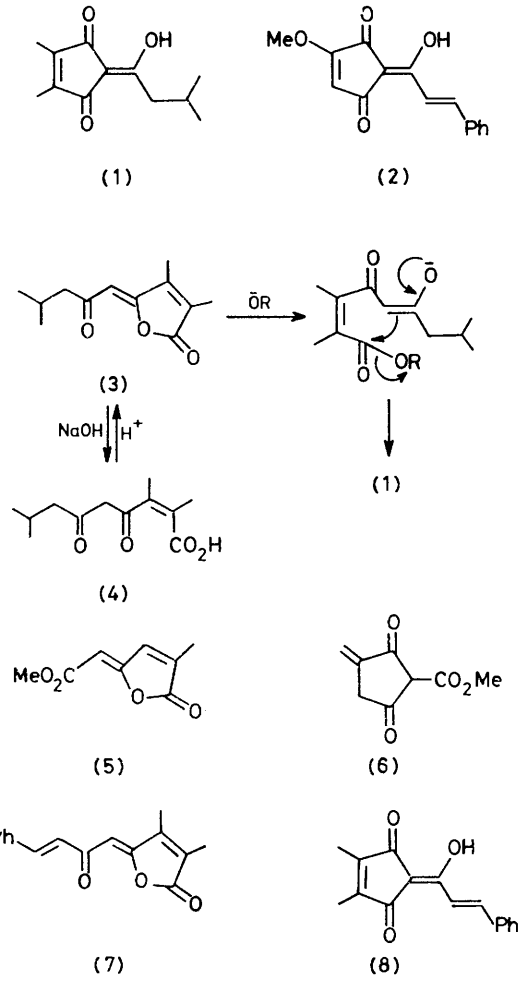
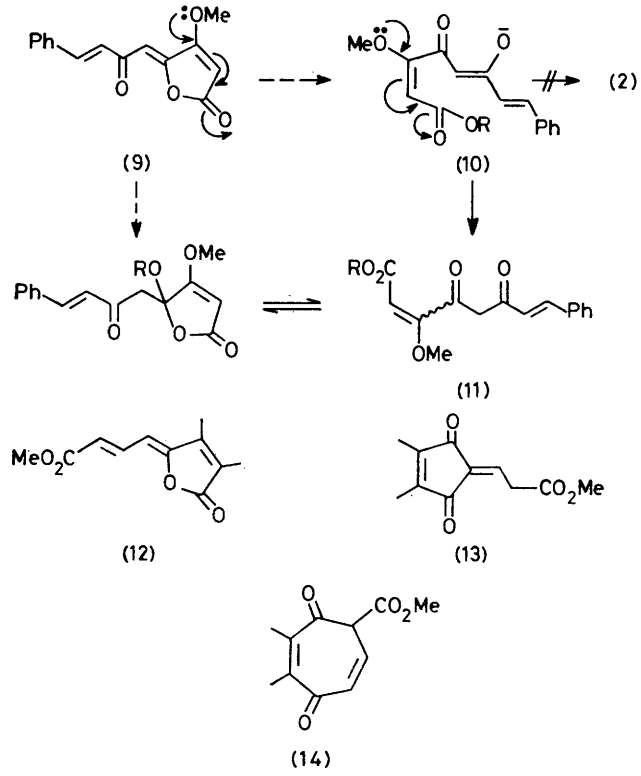
Summary Treatment of 4-ylidenebutenolides with NaOMe in MeOH results in rearrangement to the corresponding cyclopentene-1,3-diones in high yield; the general method is applied in a synthesis of calythrone (**1**) from *Calythrix tetragona*, and the related cyclopentene-1,3-diones (**6**), (**8**), and (**13**).

CALYTHRONE (**1**) and lucidone (**2**) are representative members of a unique group of naturally occurring cyclopentene-1,3-diones. Their biosynthesis has been suggested to involve ring contraction of appropriate acylphloroglucinol derivatives as a key stage.[1,2] The 4-ylidenebutenolide ring system (*viz.* **3**) is isomeric with the cyclopentene-1,3-dione system, and aromatic molecules are obligatory intermediates in the biosynthesis of several natural members of this class of compound.[3] The familial relationship between the two ring systems (*viz.* **1** and **3**) can be construed into suggesting that 4-ylidenebutenolides are implicated in the biosynthesis of cyclopentene-1,3-diones from aromatic precursors. In this paper we describe a synthesis of calythrone (**1**), and the related compounds (**6**), (**8**), and (**13**) modelled on this hypothesis.



Calythrix tetragona, was originally assigned the ylidenebutenolide structure (**3**) by Penfold and Simonsen,[6] but this was modified to (**1**) by Birch and his co-workers[7] largely on the basis of u.v. and i.r. absorption data. The ease with which (**3**) is rearranged to (**1**) in NaOMe–MeOH[8] might alternatively suggest that natural calythrone actually has the ylidenebutenolide structure (**3**), and that the cyclopentenedione (**1**) is an artifact produced during basic extraction and isolation. Indeed dissolution of the butenolide (**3**) in 10% aqueous sodium carbonate (25 °C, 24 h) followed by acidic work-up led to large amounts of the dione (**1**; 35%) together with the oxo-acid (**4**; 65%), ν_{max} 3350, 1750, and 1690 cm^{-1}, τ 3·5 (OH) and 7·22 ($CO.CH_2$ CO). Treatment of (**3**) with 2M NaOH, and acidic work-up however gave entirely the oxo-acid (**4**) which could be converted back into (**3**) on brief treatment with hot acid.

In a similar manner the ylidenebutenolide (**5**) on treatment with NaOMe–MeOH led to the dione (**6**), resulting from simultaneous rearrangement and allylic isomerisation,† and the cinnamoyl-butenolide (**7**) gave the analogue (**8**) of natural lucidone (**2**). The ylidenebutenolide isomer (**9**) of



Treatment of dimethylmaleic anhydride with 2-methylbutyrylmethylenetriphenylphosphorane (refluxing toluene; 16 h) gave the *Z*-butenolide (**3**), ν_{max} (film) 1785, 1760, and 1645 cm^{-1}, τ 4·41 (:CH), in 75% yield.[4] The butenolide was treated with sodium methoxide in dry methanol, and acidic work-up led to calythrone (**1**) in 80% yield, with identical spectral properties to those reported;[5] copper salt m.p. 208—210 °C (lit.[6] m.p. 208 °C). This synthesis can be commended not only for its brevity over existing routes to calythrone,[5] but also for its relevance to a possible biosynthetic route. Natural calythrone, from the oil of lucidone itself was also synthesised, but attempts to rearrange the molecule to lucidone under a variety of reaction conditions have this far been unsuccessful; the only product isolated has been the corresponding acyclic 4-oxo-unsaturated ester (**11**). This was found to be the outcome with a number of 3-methoxy-4-ylidenebutenolides investigated, and is presumably associated with the diminished electrophilicity of the acyl groups in the molecules [and/or the intermediates (*viz.* **10**) between (**9**) and (**2**)], as a result of their vinylogous disposition relative to the 3-methoxy substituents.

As a corollary to these investigations we also examined the rearrangement of the *E,E*-ylidenebutenolide (**12**) containing additional conjugation in its side chain. Treatment of (**12**) with NaOMe–MeOH led entirely to the cyclopentene-1,3-dione (**13**) (90%), ν_{max} 1735 and 1685 cm^{-1}, τ 3·06 (t, *J* 7 Hz, :CH), 5·9 (d, *J* 7 Hz, CH_2·CH:), 6·08 (OMe), and 7·73 (2 × :CMe); interestingly none of the isomeric 7-ring dione (**14**) could be detected in the crude reaction mixture.

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