Tetrahedron Letters No. 47, pp 4087 - 4090, 1974. Pergamon Press. Printed in Great Britain.

THE MICHAEL CONDENSATION OF γ-BUTYROLACTONES WITH CINNAMATE ESTERS

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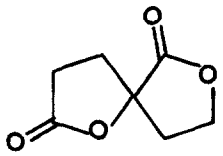
(Received in UK 30 September 1974; accepted for publication 10 October 1974)

Our work on the synthesis of the 1,7-dioxa-2,6-dioxo-spiro[4,4]nonane skeleton (1)[1] required a convenient procedure for the conjugate addition of the anion derived from a γ-lactone to a cinnamate ester. Although controlled alkylation of lactone enolates has been achieved through the agency of either lithium di-isopropylamide or lithium isopropyl-cyclohexylamide in tetrahydrofuran,[2] γ-butyrolactone and ethyl cinnamate did not furnish the Michael adduct under these conditions. The main product was identified as 2-(tetrahydro-furylidene-2')-γ-butyrolactone (2), which presumably arises from the lactone by way of nucleophilic attack of its enolate ion. With sodium ethoxide as the base, the only product isolated from the attempted Michael reaction was ethyl 4-cinnamoyloxybutyrate (3), whose



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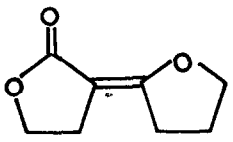

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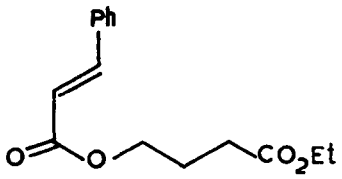
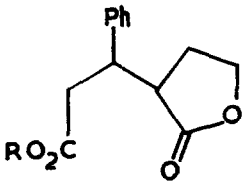


(3)

formation can be accounted for by ethanolysis of γ-butyrolactone to yield an alkoxy anion that subsequently causes the transesterification of ethyl cinnamate.

The desired reaction was accomplished by stirring a mixture of ethyl cinnamate and γ-butyrolactone with a suspension of sodium hydride in N,N-dimethylformamide for 16h at room temperature. Acid work-up and chromatography (silica gel) yielded, inter alia, ethyl 3-(γ-butyrolactone-2')-3-phenylpropionate (4, R=Et) (30%), b.p. 96°/0.02mm Hg, υ_{max}(film) 1765 (γ-lactone) and 1735 cm^{-1} (ester carbonyl), τ ($CDCl_3$): 2.76 (5H, s, aromatic protons), 5.98 (2H, q, OCH_2CH_3), 6.00 (2H, m, CH_2OCO), 6.80-7.10 (1H, m, PhCH), 7.0-7.35 (3H, overlapping m, CHCO), 7.80-8.16 (2H, m, $CHCH_2CH_2O$) and 8.90 (3H, 2 overlapping t, CH_2CH_3). This product yielded the hydroxydiamide (5) on treatment with ethanolic ammonia.



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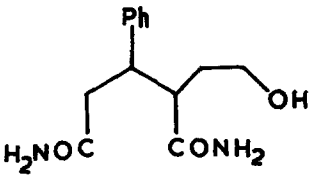
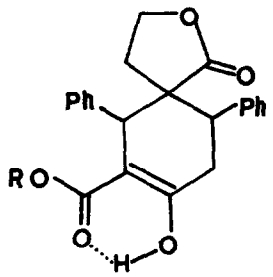


(5)

The main product ($C_{22}H_{24}O_5$) from the reaction was identified as 7-carboethoxy-2-oxa-1,8-dioxo-6,10-diphenylspiro[4,5] decane (6, R=Et) (40%), m.p. 198-200° (from ether), since, in addition to an absorption at 1765 cm^{-1} (γ-lactone), its i.r. spectrum contained absorptions at 1660 and 1615 cm^{-1} indicative of a β-keto ester in the chelated form.[3] In support of this structure, the n.m.r. spectrum ($CDCl_3$) contained a one-proton singlet at τ-2.68 characteristic of an enolic proton. Although stable to dilute alkali, the β-keto ester (6, R=Et) was smoothly converted into the ketone (7), υ_{max}(film) 1760 and 1720 cm^{-1}, on heating with a mixture of hydriodic and glacial acetic acids. A small amount (15%) of an isomeric product, m.p. 174-175° (from ether) was also recovered from the foregoing reaction. Reaction of methyl cinnamate with γ-butyrolactone under identical conditions afforded the analogues (4, R=Me) (20%), b.p. 122°/0.5mm Hg, (6, R=Me) (30%), m.p. 196-197° (from ether),[4] and its isomer (12%), m.p. 202-204° (from ether).



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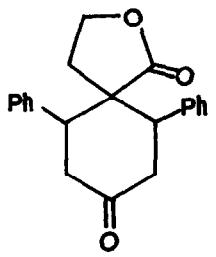
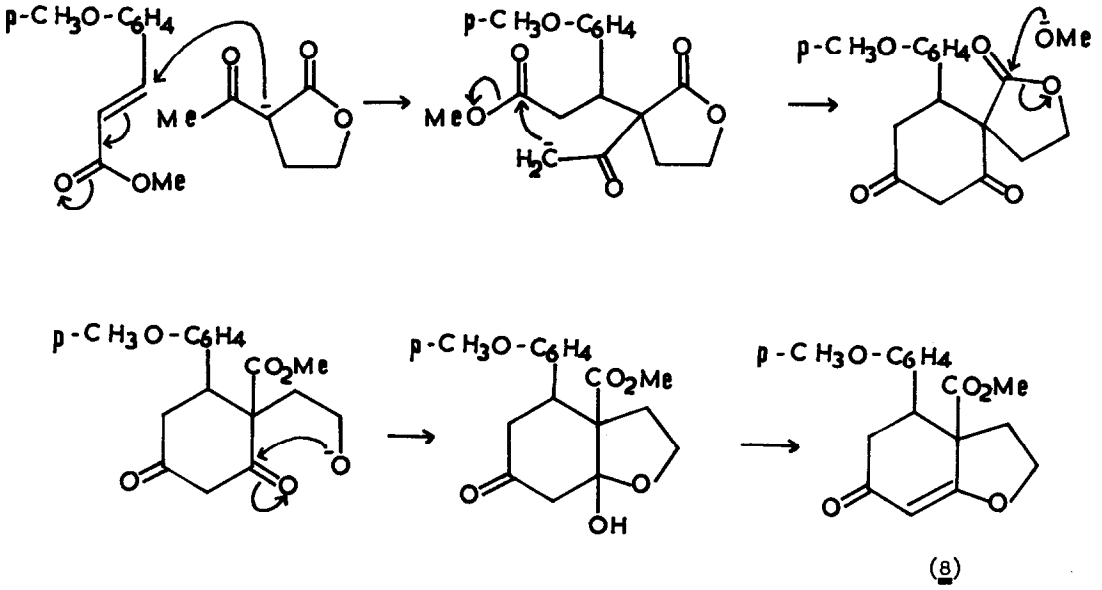


(7)

When γ-butyrolactone was replaced by 2-acetyl-γ-butyrolactone in a reaction with methyl p-methoxycinnamate, the only product isolated had the constitutional formula $C_{17}H_{18}O_5$ (mass spectrometry). Its infrared spectrum exhibited absorptions at 1745 (ester carbonyl), 1660 and 1625 cm^{-1} (β-keto enol ether)[5]; the presence of the β-keto enol ether was supported by the observation of a band at λ_{max} 259 nm (log ε 4.70) in the u.v. spectrum and the presence of a singlet at τ 4.43 (vinylic proton) in the n.m.r. spectrum. On the basis of these data, the product was assigned the structure (8), the formation of which may be visualized as involving the reactions shown in Scheme I.



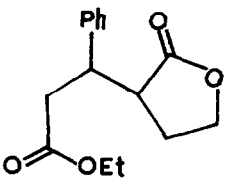
(8)

Scheme I

The isolation of such products as (6) and its isomer shows that addition of the enolate anion of γ-butyrolactone to cinnamate esters proceeds beyond the Michael product by addition of a second molecule of the α,β-unsaturated ester. The formation of these additional products should be prevented by internal dissipation of the anionic charge in the initial Michael product (4) before work-up. This was achieved by addition of γ-butyrolactone to a mixture of ethyl cis- and trans-β-chlorocinnamates (9), prepared by treating ethyl benzoylacetate with phosphorus pentachloride in benzene[6] followed by esterification.[7] Thus, rapid addition of a solution of the β-chlorovinyl esters (9)in tetrahydrofuran to a solution of the lithium salt[8] of γ-butyrolactone in tetrahydrofuran at -70° cleanly gave the unsaturated

adduct (10). Catalytic reduction then yielded ethyl 3-(γ-butyrolactone-2')-3-phenylpropionate (4, R=Et) (overall 60%), which was indistinguishable from that previously obtained.

(9)



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We thank the British Council for a grant in support of this work.

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8. The lithium enolate of the lactone was formed at -70° by slowly adding the lactone (1 mol. in tetrahydrofuran) to lithium di-isopropylamide (1 mol. in tetrahydrofuran), prepared by treating di-isopropylamide with n-butyllithium at 4° for 15 min.