The Synthesis of Tetra-acetic Acid Lactone and a Model for the Biosynthesis of 6-Methylsalicyclic Acid

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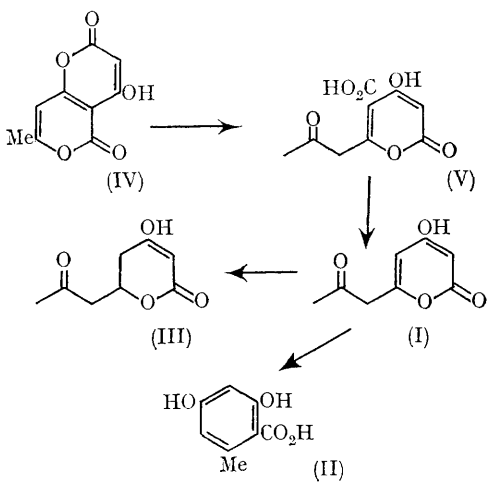
THE recent isolation and characterisation of tetra-acetic acid lactone (I) during studies with ethionine-inhibited *Penicillium stipitatum* cultures suggested the use of this compound in model studies related to aromatic biosynthesis. Thus, Bentley[1] showed that under extremely mild conditions (I) underwent hydrolysis and dehydrative cyclisation to orsellinic acid (II). The intervention of a polyketide chain in which one or more of the carbonyl groups not involved in the cyclisation mechanism is reduced and the resultant hydroxy-function subsequently lost [as in (VII; R = S-enzyme)] appears to play an important part in several biosynthetic pathways, the case of 6-methylsalicyclic acid being the prototype.[2] In order to study the model chemical reactions for this process and as part of our continuing synthetic requirement[3,4] for modification of the oxygenation patterns of complex phenolic systems we first evolved a synthesis of the lactone (I).

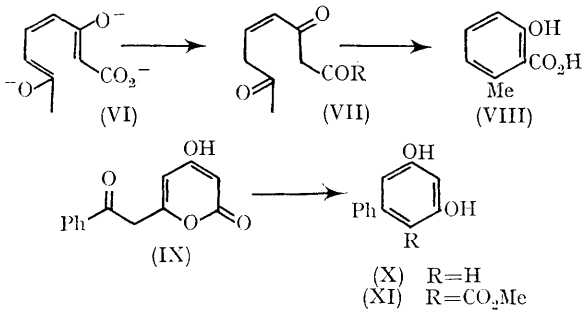
Controlled hydrolysis (1·0M-KOH solution; 5 min.; 20°) of the dioxopyranopyran[3a] (IV)

afforded the lactone carboxylic acid (V)† (90%), λ_{max} 255 and 286 mμ. Decarboxylation of (V) in refluxing dioxan solution in presence of copper bronze gave (I) (50%), m.p. 118°, identical in



every respect with an authentic sample.[1] Selective hydrogenation[5] of the 5,6-double bond of (I) was achieved in 75% yield to give the dihydropyrone (III), m.p. 129°, λ_{max} 238 mμ. When this lactone was treated with methanolic potassium hydroxide and then acidified to pH 2, 6-methylsalicylic acid (VIII) was isolated in 30% yield, the absorption spectrum of the alkaline reaction solution of (III), λ_{max} 397 mμ corresponding to participation of the enolate anion (VI). Several mechanisms can be considered for the conversion of (III) into (VIII) which require the intervention of (VII; R = OH) (or its double bond isomer) and the observed enolate (VI). 3,7-Dioxo-oct-4-enoic acid (VII) corresponds to the Lynen intermediate[2] (VII; R = S-enzyme) postulated for the cell-free biosynthesis of 6-methylsalicylic acid and it now becomes possible to evaluate the role of (III), (VI), and (VII) in cell-free extracts of *P. patulum*.

For comparative studies 4-hydroxy-6-phenacyl-2-pyrone (IX), m.p. 185°, was synthesised in 40%



yield from triacetic acid lactone and methyl benzoate by the sodamide–liquid ammonia technique.[6,7] In contrast to compounds (I), (III), and (IV) the phenacylpyrone (IX) was moderately stable to alkali and could be recovered unchanged after 1 hr. from 1·0 M-potassium hydroxide at 60°. However, after 1 hr. at 100° biphenyl-3,5-diol[8] (X) was formed (11%) and in methanolic sodium methoxide (30 min., reflux temperature) methyl 3,5-dihydroxybiphenyl-2-carboxylate[6,9] (XI), the product of methanolysis and aldol condensation, was isolated in 66% yield. These aldol-cyclisation reactions are perhaps closer models for aromatic biosynthesis than the systems used in our earlier studies.[3,4] Thus, the synthesis of (I) demonstrates a general method for the construction of poly-β-carbonyl chains lacking those additional carboxylic acid functions which, until now, have diminished the analogy of the previous models with respect to the decarboxylative–condensation step[2] in fatty acid and polyketide biosynthesis.

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† Satisfactory analytical and spectroscopic data have been obtained for all new compounds.

[1] R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, 1967, **89**, 676.
[2] F. Lynen and M. Tada, *Angew. Chem.*, 1961, **73**, 513.
[3] (a) T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, 1967, **23**, 3435; (b) F. W. Comer, T. Money, and A. I. Scott, *Chem. Comm.*, 1967, 231; (*c*) T. Money, J. L. Douglas, and A. I. Scott, *J. Amer. Chem. Soc.*, 1966, **88**, 624.
[4] D. G. Pike, J. J. Ryan, and A. I. Scott, *Chem. Comm.*, 1968, 629; A. I. Scott, *Chimia* (*Switz.*), 1968, in the press.
[5] J. R. Bartels-Keith and W. B. Turner, *J. Chem. Soc.*, 1960, 3413.
[6] T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, 1967, **89**, 6734, and references cited.
[7] T. M. Harris and C. M. Harris, *Chem. Comm.*, 1966, 699.
[8] C. M. Suter and P. G. Smith, *J. Amer. Chem. Soc.*, 1939, **61**, 166.
[9] J. L. Douglas and T. Money, *Canad. J. Chem.*, 1967, **45**, 1990.