

## 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<sup>1</sup> 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

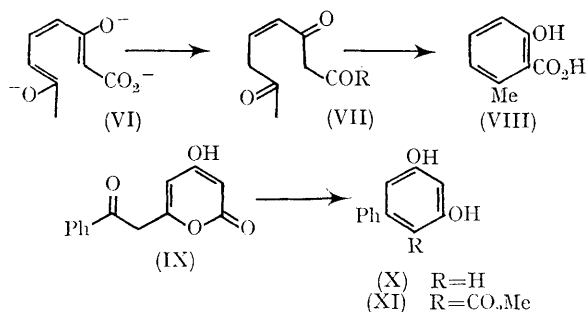
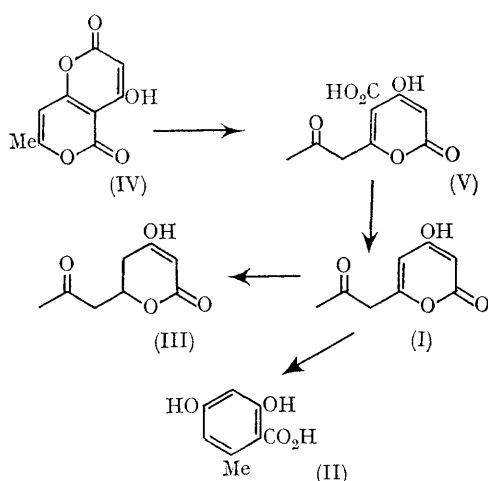
lost [as in (VII; R = S-enzyme)] appears to play an important part in several biosynthetic pathways, the case of 6-methylsalicyclic acid being the prototype.<sup>2</sup> In order to study the model chemical reactions for this process and as part of our continuing synthetic requirement<sup>3,4</sup> for 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<sup>3a</sup> (IV)

afforded the lactone carboxylic acid (V)<sup>†</sup> (90%),  $\lambda_{\max}$  255 and 286  $m\mu$ . Decarboxylation of (V) in refluxing dioxan solution in presence of copper bronze gave (I) (50%), m.p. 118°, identical in

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%



every respect with an authentic sample.<sup>1</sup> Selective hydrogenation<sup>5</sup> of the 5,6-double bond of (I) was achieved in 75% yield to give the dihydropyrone (III), m.p. 129°,  $\lambda_{\max}$  238  $m\mu$ . 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),  $\lambda_{\max}$  397  $m\mu$  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<sup>2</sup> (VII; R = S-enzyme) postulated for the cell-free biosynthesis of 6-methylsalicylic acid and it now becomes possible to

yield from triacetic acid lactone and methyl benzoate by the sodamide-liquid ammonia technique.<sup>6,7</sup> 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<sup>8</sup> (X) was formed (11%) and in methanolic sodium methoxide (30 min., reflux temperature) methyl 3,5-dihydroxybiphenyl-2-carboxylate<sup>6,9</sup> (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.<sup>3,4</sup> Thus, the synthesis of (I) demonstrates a general method for the construction of poly- $\beta$ -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<sup>2</sup> in fatty acid and polyketide biosynthesis.

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<sup>†</sup> Satisfactory analytical and spectroscopic data have been obtained for all new compounds.

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