Isolation of the Intermediate in 2,4-Dihydroxybenzoate Formation from a 3,5,7-Triketo-ester

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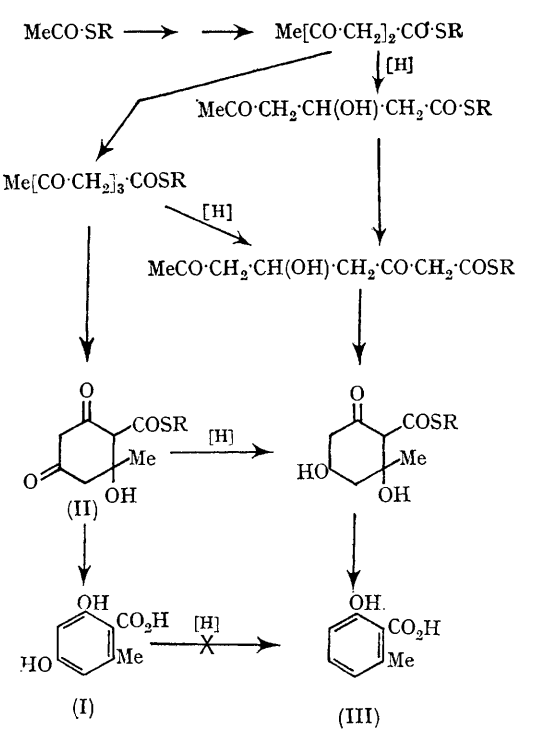
ACCORDING to Birch,[1] the naturally occurring, acetate-derived 2,4-dihydroxybenzoic acids (I) arise by intramolecular consensation of 3,5,7-triketo-acids (or esters) (Scheme). Birch also suggested that the initial non-aromatic cyclization product (II) might have considerable stability and that subsequent dehydration to the 2,4-dihydroxybenzoic acid could require a separate, enzymic process.[1] Furthermore, because it is unlikely that the 2,4-dihydroxybenzoic acids (I) are reduced to the 2-hydroxybenzoic acids (III) *in vivo*, the biosynthetic path to 2-hydroxybenzoic acids requires a reduction process prior to aromatization. The process might involve reduction of either an acyclic polyketo-acid or a cyclic, non-aromatic intermediate (II) (Scheme). Verification of the point of divergence of 2-hydroxybenzoate and 2,4-dihydroxybenzoate biosynthesis awaits the synthesis of precursors involved in the Scheme. Therefore, the synthesis of the hitherto unknown 6-hydroxy-2,4-dioxocyclohexanecarboxylate system (*cf.* II) was attempted.

A report from this laboratory[2] concerning biogenetically modelled syntheses of phenolic compounds described the cyclization of methyl 7-phenyl-3,5,7-trioxoheptanoate (IV) to form methyl 2,4-dihydroxy-6-phenylbenzoate (V) in excellent yield under mildly basic conditions. Further investigation has shown that, under suitable conditions, the desired structural type (VI) can be isolated in satisfactory yield.

The cyclization of ester (IV) in 0·5M-methanolic sodium acetate was monitored by u.v. spectroscopy, to show that the reaction was complete within 16 min. at room temperature and the mixture was stable thereafter. The characteristic spectrum of the triketo-ester (IV) with maxima at 245, 292, and 346 mμ was replaced by one sharp maximum at 286 mμ. This is not the spectrum of the benzoate



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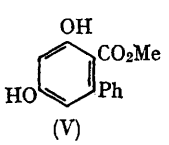
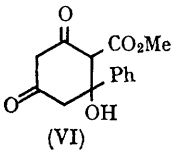
(V), in which a maximum is observed at 303 mμ and a shoulder at 257 mμ. However, 5,5-dimethylcyclohexane-1,3-dione shows a similar, sharp maximum at 282 mμ under the same conditions.

On the basis of this correlation it is suggested that the species present in solution is the anion (VII). The n.m.r. spectrum of cyclization product (VII) in

$Ph[CO{\cdot}CH_2]_3{\cdot}CO_2Me$ (IV)

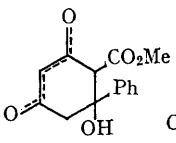


(V)

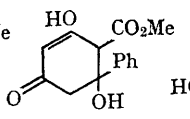


(VI)

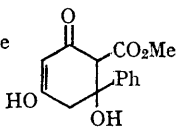
aqueous sodium hydrogen carbonate, formed by cyclization of (IV) in this solution, confirmed this assignment and indicated that the solution contained a mixture of the two epimers of (VII). The methyl protons of the major and minor epimers were respectively at 1·0 and 1·3 p.p.m. higher field than water.



(VII)



(VIII)



(XI)

Careful acidification of reaction mixtures and crystallization from chloroform–carbon tetrachloride afforded 40% of the neutral hydroxy-ester; benzoate ester (V) was the other product. The hydroxy-ester, methyl 6-hydroxy-2,4-dioxo-6-phenylcyclohexanecarboxylate, was isolated as a single epimer and existed as the diketo-form (VI) in anhydrous, ethanol-free chloroform: m.p. 122—124° (decomp.); ν_{max} (ethanol-free $CHCl_3$) 1748 and 1716 cm.$^{-1}$; λ_{max} (ethanol-free $CHCl_3$) 247 (ϵ 670), 252 (697), and 258 mμ (670); n.m.r. ($CDCl_3$) τ 7·06 (s, 2H, 5-CH_2), 6·40 (s, 2H, exchangeable with D_2O, 3-CH_2), 6·33 (s, 3H, CH_3), 5·57 (s, 1H, CH), 5·35 (br, 1H, exchangeable with D_2O, OH), and 2·45—2·60 (m, 5H, C_6H_5), *M*, 262 (mass spectroscopy). In hydroxylic solvents the hydroxy-ester existed as enol (VIII) and/or (IX): ν_{max} (Bu^tOH) 1720, 1632, and 1602 cm.$^{-1}$; λ_{max} (95% EtOH) 261 (ϵ 10,400), and 285 mμ (sh; 6400); n.m.r. (Bu^tOH) τ 7·19 (s, 2H, 5-CH_2), 6·43 (s, 3H, CH_3), 5·92 (s, 1H, 1-CH), 42·9 (s, 1H, 3-CH), and 2·8 (m, 5H, C_6H_5).

The hydroxy-ester (VI) was relatively stable in non-polar organic solvents and could be recrystallized from chloroform–heptane mixtures. The anion (VII) in dilute base was also stable and was unchanged after several days. In hydroxylic solvents, (*e.g.* t-butyl alcohol) the hydroxy-ester was slowly converted into the benzoate (V). Aromatization also occurred in the presence of acetic acid, and treatment of the compound with hydrogen chloride in tetrahydrofuran gave rapid and quantitative formation of the benzoate (V); retro-aldol condensation could not be detected. In the earlier study of the cyclization of triketo-ester (IV), acid-catalyzed dehydration of (VI) presumably occurred during product isolation.[2]

This reaction system provides the first route to the 6-hydroxy-2,4-dioxocyclohexanecarboxylate system.

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[1] A. J. Birch, *Proc. Chem. Soc.*, 1962, 3.
[2] T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, 1967, **89**, 6734.