

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

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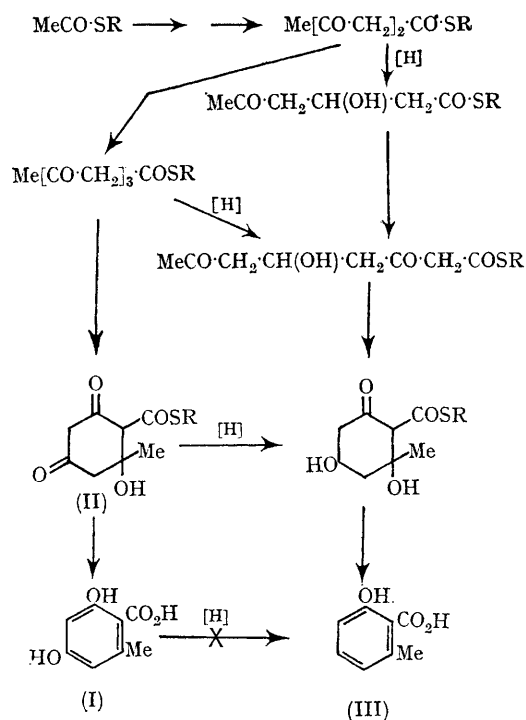
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ACCORDING to Birch,¹ the naturally occurring, acetate-derived 2,4-dihydroxybenzoic acids (I) arise by intramolecular condensation of 3,5,7-triketo-acids (or esters) (Scheme). Birch also suggested that the initial non-aromatic cyclization product (II) 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 laboratory² 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

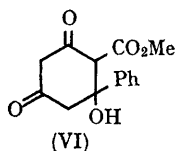
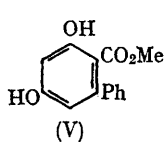
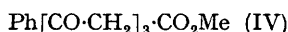
346 m μ was replaced by one sharp maximum at 286 m μ . This is not the spectrum of the benzoate



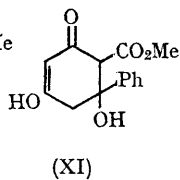
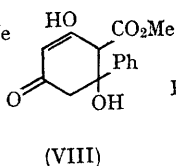
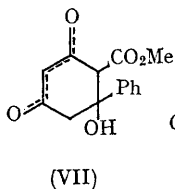
SCHEME

(V), in which a maximum is observed at 303 m μ and a shoulder at 257 m μ . However, 5,5-dimethylcyclohexane-1,3-dione shows a similar, sharp maximum at 282 m μ 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



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.



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 $\text{m}\mu$ (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 $\text{m}\mu$ (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), 4.2.9 (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.

We thank Dr. H. M. Fales of the National Heart Institute, Bethesda, Maryland, for the mass spectrum, the U.S. Public Health Service for financial support, and the Alfred P. Sloan Foundation for a fellowship (to T.M.H.).

(Received, July 8th, 1968; Com. 922.)

¹ A. J. Birch, *Proc. Chem. Soc.*, 1962, 3.

² T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, 1967, 89, 6734.