treated with 1 ml of 30% H_2O_2 at 25° for 30 hr. The reaction flask was evacuated at 35° for 30 min. The residual solution was basified with aqueous NaOH to pH 10 and extracted with ether. The ether extract was dried (Na_2SO_4). Evaporation of the ether left 32 mg of unconverted 7-epideoxynupharidine. The aqueous layer was saturated with NaCl and extracted repeatedly with small amounts of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4). Evaporation of the CH_2Cl_2 left 108 mg of solid which from a column of alumina (5g of act. II) was eluted with two 20-ml portions of hexane–ether (95:5) to give fractions 1 (0.6 mg) and 2 (0.2 mg), 40 ml of benzene to give fraction 3 (1 mg), and 20 ml of benzene–$CHCl_3$ (1:1) to give fraction 4. Fraction 4 amounted to 66.2 mg of 7-epinupharidine: mp 199–202°; nmr ($CDCl_3$) 9.20 (d, 6.0 Hz, C-1 CH_3), 9.06 (d, 6.5 Hz, 1 H, C-7 CH_3), 7.23 (d of t, 12.5, 2.5, 2.5 Hz, 1 H, C-6 H), 6.85 (d of d, 7 and 2 Hz, 1 H, C-4 H), 6.09 (d of d, 12.5 and 2.5 Hz, 1 H, C-6 H), 3.25 (m, 1 H, β-furanyl H), 2.60 (m, 1 H, α-furanyl H), 2.33 (m, 1 H, α-furanyl H); ir (KBr) 6.28, 6.67, 11.5 μ.

In another preparation, 179 mg of 7-epideoxynupharidine in 2 ml of acetone was treated with 0.5 ml of 30% H_2O_2 at 25 for 1 week. After removal of the solvent by evaporation, the residue was chromatographed on 5 g of alumina (act. II) to obtain fractions 1 (50 ml of benzene, 25.7 mg), 2 (50 ml of CH_2Cl_2, 14.5 mg), and 3 (30 ml of methanol, 129 mg). Fractions 2 and 3 contained pure 7-epinupharidine (75% yield) according to tlc data (Al_2O_3, $CHCl_3$–Et_2NH (9:1), R_f 0.6).

Anal. Calcd for $C_{15}H_{23}NO_2$; C, 72.26; H, 9.29; N, 5.62. Found: C, 72.27; H, 9.40; N, 5.54.

Biogenetic-Type Synthesis of β-Resorcylic Acids. Isolation and Characterization of the Aldol Intermediate[1a]

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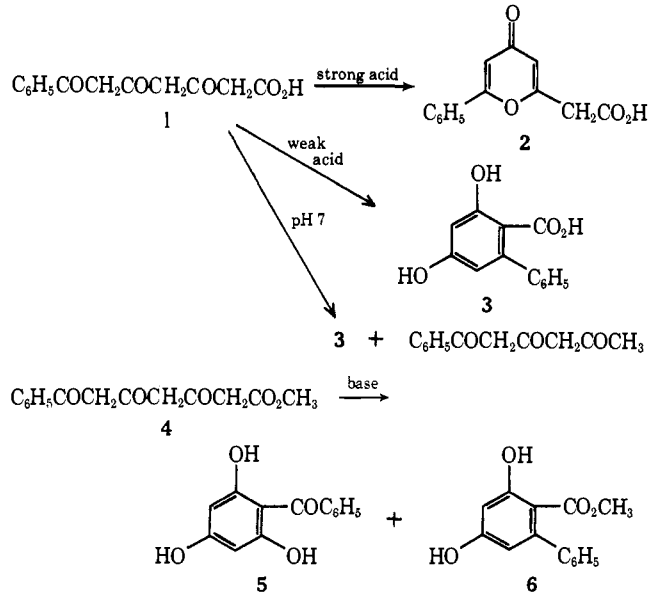
Contribution from the Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203. *Received February 9, 1970*

Abstract: The base-promoted cyclization of 3,5,7-trioxo-7-phenylheptanoic acid (**1**) afforded dianion **10** of hitherto unknown 6-hydroxy-2,4-dioxo-6-phenylcyclohexanecarboxylic acid; dehydration to form β-resorcylic acid **3** occurred when isolation of the free acid was attempted. The methyl ester of **1** cyclized similarly to give epimeric monoanions **12a** and **b**. Careful acidification afforded the major epimer **14a**, the relative configuration of which has been established. Epimerization of **12a** occurred in base primarily by ionization of the 1-proton rather than by reversal of the cyclization process. Facile aromatization of **14a** and **b** in acid gave β-resorcylic ester **6**. The stability of the cyclization products is discussed with reference to the role of similar compounds in the biosynthesis of naturally occurring, acetate-derived β-resorcylic acids and related compounds.

Recent reports from this laboratory have described the synthesis of a number of 3,5,7-triketo acids.[2] These compounds, although stable enough to be isolated and characterized, are highly reactive under some conditions. For example, in strongly acidic solutions **1** forms 4-pyronecarboxylic acid **2** and in weakly acidic solutions it is converted into 6-phenyl-β-resorcylic acid (**3**) by an intramolecular aldol condensation (Scheme I). At pH 7 decarboxylation of **1** becomes competitive with aldol cyclization. However, the corresponding triketo ester (**4**), which cannot decarboxylate, affords acylphloroglucinol **5** by an intramolecular Claisen condensation as well as resorcylic ester **6** when treated with basic reagents. All of these reactions occur at ambient temperature. The reactions are of interest because of their formal relationship to the postulated pathways by which acetate-derived phenolic natural products[3] are biosynthesized.[4,5]

Scheme I



In vivo studies have demonstrated the incorporation of acetate and/or malonate into phenolic metabolites in a number of instances.[5] However, more detailed study of the biosynthetic pathways has had to await the preparation and purification of cell-free extracts retaining aromatic synthetase activity. This problem has been under investigation in a number of laboratories.[6,7]

(1) (a) This research was supported by Research Grant GM-12848 from the National Institutes of Health, U. S. Public Health Service, and by the Alfred P. Sloan Foundation. (b) Research Career Development Awardee, K3-GM-27013, of the National Institutes of Health, U. S. Public Health Serivice.

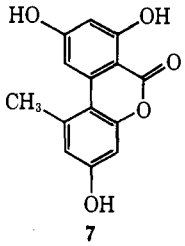
(2) T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, **88**, 2053, 5686 (1966); **89**, 6734 (1967); T. T. Howarth, G. P. Murphy, and T. M. Harris, *ibid.*, **91**, 517 (1969).

(3) The metabolites are often called polyketides or acetogenins.

(4) A. J. Birch and F. W. Donovan, *Aust. J. Chem.*, **6**, 360 (1953); A. J. Birch, *Proc. Chem. Soc. London*, 3 (1962).

(5) For a review, see J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W. A. Benjamin, New York, N. Y., 1964.

Recently, cell-free preparations have been obtained that bring about synthesis of three resorcinol derivatives. Gatenbeck and coworkers have reported an enzyme preparation from *Alternaria tenuis* capable of forming alternariol (**7**) from acetyl-CoA and malonyl-CoA.[8] Alternariol can be considered to arise from a hexaketo acid by two aldol condensations and a lactonization. Gaucher and Shepard have isolated orsellinic acid synthetase from the orsellinic acid (**8**) producing fungus, *Penicillium madriti*.[9] Gatenbeck and coworkers have also reported the formation of 5-methylorsellinic acid (**9**) and related metabolites by an enzyme preparation from *Aspergillus flaviceps*.[10] The three



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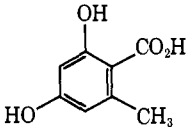

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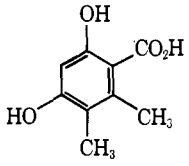

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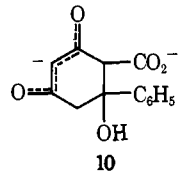
enzyme systems show activity in weakly alkaline solution. On account of these results, further investigation of the cyclization reactions of 3,5,7-triketo acids and esters was undertaken with emphasis on the unexplored, but apparently physiologically significant, alkaline region.[11]

Results

Initial attempts to cyclize 3,5,7-trioxo-7-phenylheptanoic acid (**1**) under basic conditions involved the use of methanolic sodium acetate. Under these conditions the predominant reaction was decarboxylation to give the corresponding triketone, 1-phenyl-1,3,5-hexanetrione. Under more basic conditions, *i.e.*, aqueous potassium hydroxide, decarboxylation of **1** was no longer a significant process and a cyclization reaction was observed. This reaction, when monitored by both nmr and uv spectroscopy, was found to be essentially complete within 2 hr at ambient temperature. The uv spectrum of the product contained a single, sharp maximum at 286 nm. This product was not the anticipated resorcylic acid **3**; the chromophore was identified as the anion of a 1,3-cyclohexanedione.[12] On the basis of this finding it is proposed that the species formed from **1** in alkaline solution is dianion **10** resulting from an intramolecular aldol-type reaction of an anion at the 2 position with the 7-carbonyl group.



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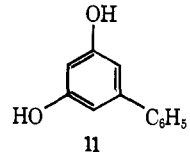
The nmr spectrum confirmed this assignment and indicated that only one epimer was present. The methylene protons at position 5 were chemically nonequivalent and appeared at 2.46 and 2.91 ppm. The geminal coupling constant was 17 Hz. The 1 proton appeared at 3.82 ppm. A signal at 5.15 ppm, which was partially obscured by the water signal, is tentatively assigned to the vinylic 3 proton.

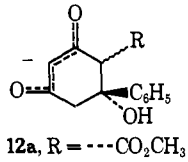
Acidification of the above reaction mixture to pH 3 followed by extraction gave only resorcylic acid **3**; none of the protonated tautomers of **10** could be detected. Further studies indicated that **10** was stable for several days at room temperature in the pH range 7–13. However, at pH 5.0 gradual dehydration occurred forming **3**. It was concluded that acid-catalyzed dehydration of protonated forms of **10** was too facile to permit isolation.

The thermal reactivity of dianion **10** was explored. 5-Phenylresorcinol (**11**) resulted from heating **10** in aqueous potassium hydroxide for 1 hr at 100°. Formation of resorcinol **11** requires loss of carbon dioxide and hydroxide ion. The sequence of these events is unknown; no intermediates were detected.[13]



11

Triketo ester **4** was cyclized in methanolic sodium acetate. The reaction was monitored by uv spectroscopy which showed it to be complete within 16 min at room temperature. The mixture was stable thereafter. Starting ester **4** gave maxima at 245, 292, and 346 nm; the product gave only a single, sharp maximum at 285 nm resulting from the cyclohexanedione anion.[12,14] The cyclization of **4** was also facile in aqueous sodium bicarbonate. Nmr spectra of the bicarbonate solutions showed the presence of two epimers (**12a** and **12b**) of the cyclization product. The epimers were not present in equal quantities. The methoxy group of the major epimer was less shielded than that of the minor one.



12a, R = ---CO_2CH_3
b, R = ◀CO_2CH_3

Careful acidification of the reaction mixtures gave the neutral aldol cyclization product. From methanolic sodium acetate yields up to 40% were obtained; the only other product was resorcylic ester **6**. However,

(6) 6-Methylsalicyclic acid and patulin from *Penicillium patulum*: E. W. Bassett and S. W. Tanenbaum, *Biochim. Biophys. Acta*, **40**, 535 (1960); F. Lynen and M. Tada, *Angew. Chem.*, **73**, 513 (1961); R. J. Light, *J. Biol. Chem.*, **242**, 1880 (1967); R. J. Light and L. P. Hager, *Arch. Biochem. Biophys.*, **125**, 326 (1968).

(7) Stipitatic acid from *Penicillium stipitatum*: S. W. Tanenbaum and E. W. Bassett, *Biochim. Biophys. Acta*, **59**, 524 (1962).

(8) S. Gatenbeck and S. Hermodsson, *Acta Chem. Scand.*, **19**, 65 (1965); S. Sjöland and S. Gatenbeck, *ibid.*, **20**, 1053 (1966).

(9) G. M. Gaucher and M. G. Shepherd, *Biochem. Biophys. Res. Commun.*, **32**, 664 (1968).

(10) S. Gatenbeck, P. O. Eriksson, and Y. Hansson, *Acta Chem. Scand.*, **23**, 699 (1969).

(11) A preliminary account has appeared describing certain features of this study: T. M. Harris and T. T. Howarth, *Chem. Commun.*, 1253 (1968).

(12) Resorcylic acid **3** in aqueous potassium hydroxide gives maxima at 225 and 312 nm, whereas 5,5-dimethyl-1,3-cyclohexanedione in aqueous potassium hydroxide gives a single sharp maximum at 281 nm.

(13) Resorcylic acid **3** decarboxylates rapidly under these conditions. Thus, even if hydroxide loss is the initial process, **3** would not be detected.

(14) In contrast resorcylic ester **6** under these conditions gives a maximum at 257 nm and a shoulder at 303 nm.

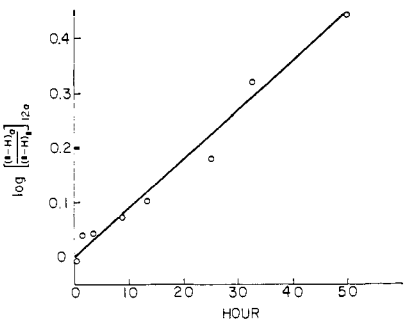
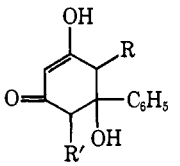


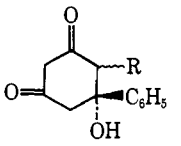
Figure 1. Protium loss from the 1 position of **12a** as a function of time during epimerization in deuterium oxide saturated with sodium bicarbonate.

in some cases the yield of aldol product diminished with corresponding increase in the yield of **6** due to the presence of acetic acid during work-up. Isolation from sodium bicarbonate solution was more satisfactory; the cyclization product was obtained in improved (53%) and reproducible yield.

Thorough examination of the product indicated that only one of the epimers had been isolated. Apparently the other had undergone aromatization and/or epimerization during the isolation procedure. In alcoholic solvents the epimer that had been isolated existed as enol tautomer **13a** and **b**; in anhydrous, ethanol-free chloroform it existed as diketo tautomer **14a** or **14b**.[15]

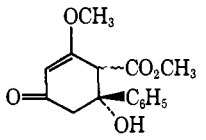


13a, R = CO_2CH_3; R′ = H
b, R = H; R′ = CO_2CH_3



14a, R = ···CO_2CH_3
b, R = ◀CO_2CH_3

In the accompanying paper the isolated epimer of **14** is correlated by a methylation reaction with one of the epimers of enol ether **15**.[17] The relative configuration of the latter has been deduced from spectroscopic data; consequently the isolable epimer of **14** can be assigned as that having the phenyl and carbomethoxy groups trans to each other, *i.e.*, **14a**.

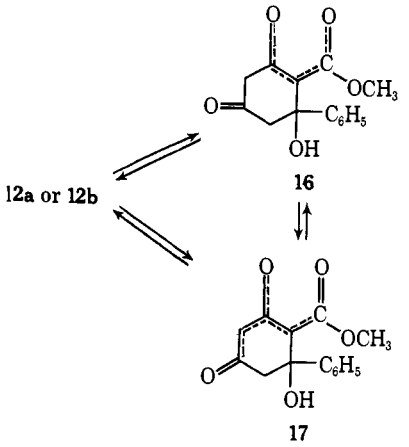


15

Epimerization of **14a** was studied. The cyclization of **4** in sodium bicarbonate-saturated water or deuterium oxide gave an initial epimer ratio of 2.3:1. Within several days this ratio dropped to 1.3:1 and was constant thereafter. Epimer **14a**, when freshly redissolved in deuterium oxide containing sodium bicarbonate, produced an nmr spectrum corresponding to that of the major epimer. Over a period of several days, this solution reached the same equilibrium mixture of epimers as had been observed before. It therefore follows that **12a**, which is the anion of **14a**, is the kinetically and thermodynamically preferred product.

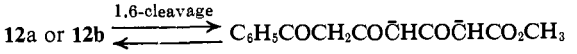
Several mechanisms can be proposed for the epimerization reaction. Epimerization at carbon 1 would occur by ionization of the 1-proton to give monoanion **16** or dianion **17** (Mechanism 1). Alternatively, epimer equilibration would result from retroaldol cleavage of the ring. Cleavage between carbons 1 and 6 (Mechanism 2), which is in effect reversal of the cyclization process, or cleavage between carbons 5 and 6 (Mechansim 3) would achieve this result. Consideration of the stabilities of the resultant anions suggest mechanism 2 is more probable than 3. Finally, epimerization at position 6 could result from solvolysis of the benzylic hydroxyl group (Mechanism 4), although this seems relatively unlikely under the reaction conditions that were employed. In summary, Mechanisms 1 and 2 are considered to be the only reasonable possibilities.

Mechanism 1



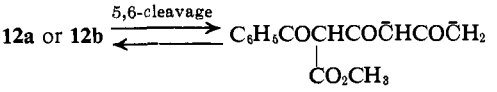
12a or 12b ⇌ **16** ⇌ **17**

Mechanism 2



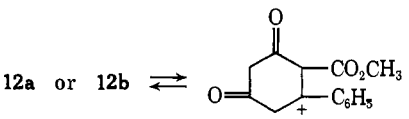
12a or **12b** $\xrightarrow{\text{1,6-cleavage}}$ $C_6H_5COCH_2CO\bar{C}HCO\bar{C}HCO_2CH_3$

Mechanism 3



12a or **12b** $\xrightarrow{\text{5,6-cleavage}}$ $C_6H_5COCHCO\bar{C}HCO\bar{C}H_2$, CO_2CH_3

Mechanism 4



12a or **12b** ⇌

Mechanisms 1 and 2 were supported by a comparison of the rate of deuterium exchange at position 1 of **12a** with the rate of epimerization to **12b**. An approximate pseudo-first-order rate constant (k_{exch}) of 0.021 hr^{-1} for the exchange reaction of **12a** in deuterium oxide saturated with sodium bicarbonate at ambient temperature was established by graphical solution (Figure 1) of the equation[18]

(15) The effect of solvent nucleophilicity upon enol–keto tautomerism of 1,3-cyclohexanediones is well known.[16] However, the effect is more pronounced in the present case than with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione. The latter compounds show concentration-dependent enolization in nonnucleophilic solvents such as chloroform because of dimeric and polymeric hydrogen bonding; enolization of cyclohexanedione **14** was not detected in chloroform. The difference can be ascribed to steric inhibition of intermolecular hydrogen bonding. Even 5,5-dimethyl-1,3-cyclohexanedione shows some steric inhibition of enolization in nonnucleophilic solvents; the equilibrium constant for enolization, K = (enol)/(keto),[2] has been estimated to be only about one-fourth that of 1,3-cyclohexanedione.[16]

(16) A. Yogev and Y. Mazur, *J. Org. Chem.*, **32**, 2162 (1967).

(17) T. M. Harris, T. T. Howarth, and R. L. Carney, *J. Amer. Chem. Soc.*, **93**, 2511 (1971).

(18) See A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

$$2.3 \log \left[\frac{(1\text{-H})_0}{(1\text{-H})_t}\right]_{12a} = k_{exch}t$$

The fraction of protium at the 1 position of **12a** (1-H) was obtained by determining the ratio of nmr signal areas for the 1-proton and methoxy protons of **12a**.

The epimerization reaction was considered similarly. The relative concentrations of **12a** and **12b** were determined by integration of the methoxy signals in the nmr spectra. The pseudo-first-order rate constant (k_{epim}) for conversion of **12a** to **12b** was estimated by graphical treatment (Figure 2) of the equation[18]

$$.2.3 \log \left[\frac{(12b)_\infty}{(12a)_t - (12a)_\infty}\right] = (k_{epim} + k_{epim}')t$$

where k_{epim}' is the rate constant for the reverse reaction and equals $k_{epim}\,(12a)_\infty/(12b)_\infty$ or $1.27k_{epim}$. The line in Figure 2 was calculated using 0.021 hr^{-1} (k_{exch} determined in Figure 1) as the value of k_{epim} and is in reasonable agreement with the experimental data. It can be concluded that k_{epim} and k_{exch} are equal.

It became possible to eliminate Mechanism 2 as a major contributor when the observation was made that **4**, under the conditions employed in epimerization, underwent exchange at all of the methylene positions more rapidly than it underwent cyclization, so that in deuterium oxide the resulting positions 1, 3, and 5 of **12a** and **12b** were totally deuterated. Thus, if epimerization of **12a** occurred *via* **4** (Mechanism 2), then **12b** would be obtained fully exchanged at the ring positions. On the other hand, epimerization *via* enolate anions **16** and **17** (Mechanism 1) would bring about exchange only at positions 1 and 3. The epimerization of **12a** in deuterium oxide gave **12b** with little exchange at the 5 position.[19] This indicated that the major pathway was Mechanism 1.

Nonaromatic ester **14a** was relatively stable in nonpolar solvents. In hydroxylic solvents, such as *tert*-butyl alcohol, the compound was slowly converted into resorcylic ester **6**. Aromatization also occurred in nonpolar solvents to which small quantities of acetic acid had been added. Treatment of **14a** with dry hydrogen chloride in tetrahydrofuran gave rapid formation of **6**. No cleavage to triketo ester **4** or formation of other products was observed.

In weak base, anions **12a** and **b** appeared to be stable indefinitely; no reaction, other than epimerization, was observed. On the other hand, when **14a** was dissolved in aqueous potassium hydroxide, the nmr spectrum after 30 min showed the presence of the potassio derivatives of resorcylic ester **6** and nonaromatic acid **10** in a ratio of 1:5. Thus saponification of the ester group of **12a** and **b** to give the stable anion **10** was the major reaction; aromatization of **12a** and **b** was less important. Tlc of the acidified reaction mixture indicated traces of benzoylphloroglucinol (**5**), which presumably was formed by retroaldol cleavage of **14a** and **b** and subsequent intramolecular Claisen condensation of intermediate triketo ester **4**.

(19) Accurate integration of nmr signals for the 5-methylene protons of **12b** was difficult because nonequivalence of the two hydrogens produced a doublet of doublets which was superimposed upon other signals in the spectrum. Visual analysis of the spectrum indicated that little exchange had occurred. However, mechanism 2 cannot be excluded as a possible minor contributor to epimerization.

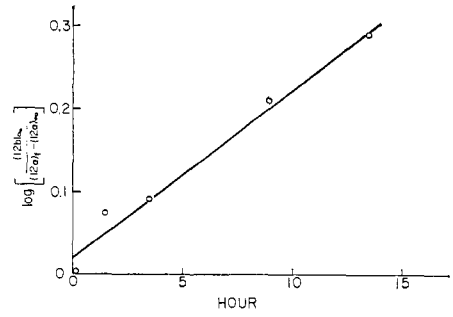
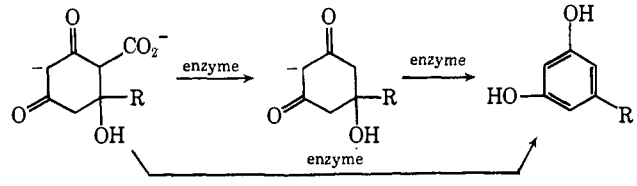


Figure 2. Epimerization of **12a** in deuterium oxide saturated with sodium bicarbonate plotted as a function of time.

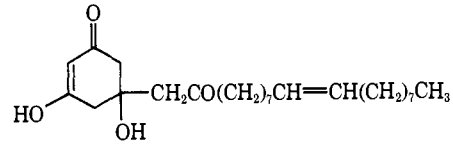
Discussion

In 1962, Birch speculated that nonaromatic aldol cyclization products comparable to **14** may be intermediates in the formation of β-resorcylic acids and related compounds from acyclic polyketide precursors. He suggested that these compounds might show relatively little tendency to revert to acyclic compounds and might be sufficiently stable to require enzyme-mediated dehydration to form β-resorcylic acids.

Furthermore, these compounds could be branching points for other pathways. For example, resorcinols, which are usually considered to arise by dehydration followed by decarboxylation, might in some cases arise by the reverse sequence or by a concerted process.



Reduction might occur at the nonaromatic stage to form salicylic acids and *m*-alkylphenols; the natural product **18** may arise by such a pathway.[20] C-Alkylation at position 3 and O-alkylation at 2 and 4 of the nonaromatic aldol product could lead to the corresponding alkylated β-resorcylic acids. Birch has suggested that O-methylation at this stage may be required in the biosynthesis of griseofulvin.[4]



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The studies described in this paper were carried out with a phenyl-substituted 3,5,7-triketo acid which was readily available and which had convenient physical properties. Unfortunately, the compound is of relatively little physiological importance. However, other more significant triketo acids can be prepared similarly[2] and it is probable that their nonaromatic aldol cyclization products will behave similarly to **10** and **12**. As a consequence, detection of such compounds in appropriate biological systems would now appear to be practicable. Moreover, the use of such aldol compounds in metabolic experiments may be feasible

(20) L. K. Dalton and J. A. Lamberton, *Aust. J. Chem.*, 11, 46 (1958).

leading to an evaluation of their role as biosynthetic branch points.

Experimental Section[21]

Cyclization of 3,5,7-Trioxo-7-phenylheptanoic Acid (1) in Base. (a) Triketo acid **1**[2] (225 mg, 0.9 mmol) was dissolved in aqueous 2 *M* potassium hydroxide (2.5 ml) and set aside at room temperature for 5 hr. The nmr and uv spectra indicated the presence of the dianion of 6-hydroxy-2,4-dioxo-6-phenylcyclohexanecarboxylic acid (**10**): nmr (aqueous 2 *M* KOH) δ 2.46 (d, 1, J = 17 Hz, 5-C*H*), 2.91 (d, 1, J = 17 Hz, 5-C*H*), 3.82 (s, 1, 1-C*H*), 5.15 (s, 1, 3-C*H*),[22] and 7.47 ppm (m, 5, C_6H_5); uv (aqueous 2 *M* KOH) 286 nm (log ϵ 4.32). The solution was acidified to pH 3, extracted with ether, and the ether extracts were dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave an oil (199 mg). Crystallization from chloroform–carbon tetrachloride gave 6-phenyl-β-resorcylic acid (**3**) as minute crystals (117 mg, 56%), mp 156–158°. The product was identical (tlc, nmr) with an authentic sample. No other products could be detected in the mother liquors from the crystallization.

(b) Attempted cyclization of **1** (250 mg) in methanol (70 ml) containing sodium acetate (2.8 g) at room temperature for 48 hr gave an oil (167 mg) which was shown (nmr, tlc) to be mainly 1-phenyl-1,3,5-hexanetrione.

Thermal Decarboxylation and Aromatization of 10. Triketo acid **1** (100 mg) was dissolved in aqueous 2 *M* potassium hydroxide (1 ml) and set aside at room temperature for 1 hr. The spectral properties of the solution indicated **10** was present. The solution was heated at 100° for 1.5 hr, during which time the gradual formation of the potassio salt of 5-phenylresorcinol (**11**) was observed (nmr). The solution was acidified with dilute hydrochloric acid, ether extracted, and the extracts were dried ($MgSO_4$). Evaporation *in vacuo* gave **11** as a buff solid. Recrystallization from ether–carbon tetrachloride gave minute prisms (50 mg, 67%), mp 156–157°. The product was identical (tlc, nmr) with an authentic sample. Under the same conditions resorcylic acid **3** also underwent complete decarboxylation to form **11**.

Cyclization of Methyl 3,5,7-Trioxo-7-phenylheptanoate (4) in Base. (a). Triketo ester **4**[2] (250 mg, 0.95 mmol) was dissolved in methanol (70 ml) containing sodium acetate (2.9 g) and left at room temperature for 10 min. After this time the absorption at 285 nm had reached a maximum. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The aqueous layer was acidified with dilute hydrochloric acid and extracted with two 50-ml portions of ether. The ether extract was dried ($MgSO_4$) and evaporated *in vacuo* to give an oil (230 mg). Trituration with chloroform–carbon tetrachloride gave methyl 6-hydroxy-2,4-dioxo-6-phenylcyclohexanecarboxylate (**14a**) as a microcrystalline solid (75 mg, 30%): mp 122–124° dec; uv (95% ethanol) 261 (log ϵ 4.00) and 285 nm (sh, 3.81); uv (ethanol-free chloroform) 247 (log ϵ 2.26), 252 (2.43), and 258 nm (2.26); ir (Nujol)[23] 3510, 1715, 1620, 1500–1540 cm^{-1}; ir (*tert*-butyl alcohol)[23] 1719, 1633 cm^{-1}; ir (ethanol-free chloroform)[23] 3470, 1748, 1719 cm^{-1}; ir (carbon tetrachloride)[24] 3480 cm^{-1}; nmr ($CDCl_3$) δ 2.94 (s, 2, 5-CH_2), 3.60 (s, 2, exchangeable with D_2O, 3-CH_2), 3.67 (s, 3, OCH_3), 4.43 (s, 1, 1-C*H*), 4.65 (broad, 1, exchangeable with D_2O, O*H*), and 7.55–7.4 ppm (m, 5, C_6H_5); nmr (*tert*-butyl alcohol) δ 2.81 (s, 2, 5-CH_2), 3.57 (s, 3, OCH_3), 4.08 (s, 1, 1-C*H*), 5.71 (s, 1, 3-C*H*), and 7.2 ppm (m, 5, C_6H_5); mass spectrum[25] (direct insertion) *m/e* 262 (1%, p^+), 230 (30), 229 (60), 212 (36), 184 (30), 153 (34), 128 (35), 105 (100), 95 (30), 91 (21), 81 (35), 79 (21), 77 (100), 69 (92), 67 (32), 57 (30), 55 (60), 51 (57), and 50 (25).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.24; H, 5.48.[26]

The mother liquors were shown by tlc to contain **14a** and methyl 6-phenyl-β-resorcylate (**6**). Chromatography on silicic acid gave 118 mg (51%) of **6**, mp 119–120°.

(b) To triketo ester **4** (600 mg) in methanol (40 ml) was added an equal volume of aqueous sodium bicarbonate solution. The solution was set aside for 20 min. It was diluted with water (100 ml) and extracted with five 50-ml portions of ether to remove most of the methanol. The aqueous layer was acidified with dilute hydrochloric acid and extracted with two 50-ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a colorless oil. Crystallization from chloroform–carbon tetrachloride gave 314 mg (53%) of ester **14a**, mp 120–123° dec.

(c) Triketo ester **4** (40 mg) was dissolved in 0.4 ml of water saturated with sodium bicarbonate. The nmr spectrum of the solution showed the presence of two epimeric anions (**12a** and **12b**). The methoxy signal of the major epimer (**12a**) appeared at δ 3.61 ppm and that of the minor epimer (**12b**) at δ 3.19 ppm. Much of the spectrum was obscured by the intense water signal and associated spin bands.

The cyclization was repeated in deuterium oxide. A spectrum recorded after 0.17 hr showed that cyclization was complete but that the only observable protons were the phenyl and methoxy groups of **12a** and **12b**. All other positions of both epimers were totally exchanged. The methoxy signals could be integrated with greater accuracy than for nondeuterated solutions because the other proton signals were not present and only a weak water signal was present. Gradual conversion of **12a** to **12b** occurred until an equilibrium mixture was obtained. The reaction period (hours) and ratio of **12a** to **12b** are as follows: (0.17) 2.3:1, (1.5) 2.1:1, (32) 1.5:1, (120) 1.4:1, (500) 1.3:1.

Epimerization of Anion 12a. Methyl ester **14a** freshly dissolved in sodium bicarbonate-saturated water initially displayed the nmr spectrum of anion **12a**: nmr δ 2.82 (m, 2, 5-CH_2), 3.61 (s, 3, OCH_3), 4.13 (s, 1, 1-C*H*), 5.18 (s, 1, 3-C*H*), and 5.42 ppm (m, 5, C_6H_5). Gradual epimerization occurred to give a mixture of **12a** and **12b**; nmr (**12b**) δ 2.52 (d, 1, J = 17 Hz, 5-C*H*), 3.19 (s, 3, OCH_3), 3.64 (d, 1, J = 17 Hz, 5-C*H*), and 5.26 ppm (s, 1, 3-C*H*). The phenyl signal of **12b** was superimposed on that of **12a**. The 1-proton signal of **12b** was not observed; it may have been obscured by the methoxy signal of **12a**.

The epimerization was repeated in deuterium oxide. The 3-proton of **12a** underwent rapid exchange with the medium. Gradual loss occurred at the 1 position due to reversibility of the ionization–epimerization process. Figure 1 is a plot of the exchange at this position *vs.* time. Relatively little loss of protium occurred at the 5 position of **12a**; **12b** was formed with little or no deuterium incorporation at this position. Precise measurement of exchange at the 5 position of these compounds was not possible because of the complexity of this portion of the spectra and the slowness of the exchange process. The 3 position of **12b** and presumably the 1 position were completely exchanged. The equilibrium was measured as a function of time and is plotted in Figure 2. The equilibrium ratio of **12a**:**12b**, determined after 500 hr, was 1.3:1.

Treatment of 14a with Dry Hydrogen Chloride. Dry hydrogen chloride was passed through a solution of 50 mg of **14a** in 10 ml of anhydrous tetrahydrofuran for 1 min. The solution was set aside for 1 hr at room temperature. The solvent was removed *in vacuo* and the residual oil was dissolved in ether, washed with water, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave an oil which crystallized from chloroform–hexane to give 25 mg (54%) of resorcylic ester **6**, mp 119–121°. The product was identical (tlc, nmr) with an authentic sample.

Treatment of 14a with Strong Base. A solution of **14a** (52 mg) in aqueous 2 *M* potassium hydroxide solution (0.4 ml) was allowed to stand at room temperature for 0.5 hr. Nmr indicated the presence of **10** and the anion of **6** in a ratio of 5:1 The solution was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated *in vacuo* to give an oil. Tlc indicated the presence of resorcylic ester **6**, resorcylic acid **3**, and a trace amount (<5%) of benzoylphloroglucinol (**5**).

(21) Melting points were determined with the Thomas-Hoover apparatus and are corrected. Thin layer chromatograms were run on silica gel GF (E. Merck A.-G., Darmstadt). Nmr spectra were obtained with a Varian A-60 spectrometer at ambient temperature. Tetramethylsilane was used as an internal standard in chloroform solutions and acetonitrile (δ = 2.00) in aqueous solutions. Uv spectra were recorded with Beckman DB and Cary 14 spectrophotometers.

(22) This peak is partially obscured by the water signal.

(23) Obtained with a Beckman IR-10 spectrophotometer.

(24) Obtained with a Perkin-Elmer 621 spectrophotometer employing 5-cm cells.

(25) We thank Dr. H. M. Fales of the National Heart Institute, Bethesda, Md., for obtaining this mass spectrum with the MS-9 mass spectrometer.

(26) Microanalysis by Galbraith Laboratories, Inc., Knoxville, Tenn.