Biogenetically Modeled Synthesis of β-Resorcylic Acids[1]

Sir:

The biosynthesis of "polyketide"-derived natural products can be rationalized on the basis of condensations of acetate and malonate units to form polyketo acids (*e.g.*, **1**), which are cyclized by aldol condensations to aromatic compounds.[2,3] However, little is actually known concerning the intermediates in this pathway.[3] For example, triketo acids **1** remain undetected in biological systems and relatively inaccessible synthetically.[4]

$$RCOCH_2COCH_2COCH_2CO_2H$$
1

resorcylic acids **4** were isolated, although the yields were not reported. This system has provided interesting results, but the relevance to biological reactions is open to question because of the strongly alkaline (potassium hydroxide) conditions employed.

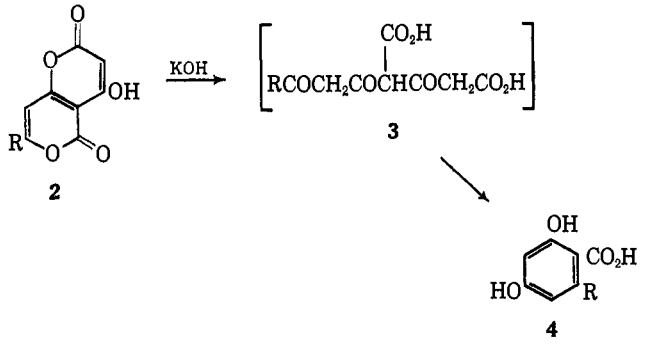
In our investigation of this problem a method has been devised to prepared many of the triketo acids **1**.[6] 1,3,5-Triketones on treatment with 3 or more equiv of alkali amide in liquid ammonia were converted to mixtures of the di- and trianions. Treatment of the mixtures in ether or tetrahydrofuran with carbon dioxide afforded the triketo acids **1**. The yields of triketo acids **1** varied widely as shown in Table I. Triketo acids **1a–d** were crystalline compounds and afforded satisfactory elemental analyses. Triketo acids **1e** and **1f** were formed in amounts too small to purify and were employed in crude form in the subsequent cyclization reactions.

Table I. Formation of Triketo Acids **1** by Carboxylation of Triketones; Cyclization of Triketo Acids **1** to β-Resorcylic Acids **4**

	Carboxylation			Cyclization		
R	Product	Yield, %[a]	Mp, °C	Product	Yield, %[a]	Mp, °C
C_6H_5	7-Phenyl-3,5,7-trioxoheptanoic acid (**1a**)	38[b]	100–101 dec	6-Phenyl-β-resorcylic acid (**4a**)	80	156–158 dec
$C_6H_5CH{=}CH$	9-Phenyl-3,5,7-trioxo-8-nonenoic acid (**1b**)	52	125–126 dec	Pinosylvic acid (**4b**)	88	158–161 dec
n-C_7H_{15}	3,5,7-Trioxotetradecanoic acid (**1c**)	30	82–83	Spheropherolcarboxylic acid (**4c**)	95	142–144[c]
n-C_5H_{11}	3,5,7-Trioxododecanoic acid (**1d**)	14	80–81	Olivetolcarboxylic acid (**4d**)	90	142.5–143[d]
n-C_3H_7	3,5,7-Trioxodecanoic acid (**1e**)	Low[e]	...	Divaric acid (**4e**)	Good[e]	180–181 dec[f]
CH_3	3,5,7-Trioxooctanoic acid (**1f**)	Trace[g]	...	Orsellinic acid (**4f**)	Good[g]	...

[a] Yields are reported in some cases of material melting slightly lower than the reported melting point. [b] Previously reported; see ref 4. [c] Reported mp 140°: A. Hasimoto, *J. Pharm. Soc. Japan*, 58, 776 (1938); *Chem. Abstr.*, 33, 2504 (1939). [d] Reported mp 142°: Y. Asahina and M. Yasue, *Ber.*, **70B**, 206 (1937). [e] Acid **1e** was not purified. It was converted to divaric acid (**4e**) in 1.8% yield based on triketone. [f] Reported mp 179° dec; Y. Asahina and H. Akagi, *Ber.*, **68B**, 1130 (1935). [g] Acid **1f** was not purified. However, the conversion to **4f** appeared to occur in good yield. Acid **4f** was identified by thin layer chromatography; see text.

Recently, Money, Scott, and co-workers reported that dipyrones **2** can be used to study the chemistry of this pathway, since alkaline hydrolysis apparently affords the closely related triketo dicarboxylic acids **3**.[5] Under their reaction conditions the acids **3** were not isolated, but instead derivatives resulting from aldol condensations and decarboxylation reactions were obtained. Under one set of conditions β-



2 **3** **4**

$$RCOCH_2COCH_2COCH_3 \xrightarrow{\text{excess } NH_2^-} RCO\bar{C}HCO\bar{C}HCO\bar{C}H_2 \xrightarrow{CO_2} \mathbf{1}$$
$$+$$
$$RCO\bar{C}HCO\bar{C}HCOCH_3 \xrightarrow{\text{pH 5}} \mathbf{4}$$

The cyclization of **1a** to resorcylic acid **4a** was investigated under a variety of conditions. Optimum results (80% yield) were obtained in aqueous buffer at pH 5. Cyclization was complete within 16 hr at 25°. More rapid cyclization occurred in solutions closer to neutrality, but decarboxylation of **1a** and of **4a** competed significantly.

The other triketo acids **1b–f** were treated similarly to afford good yields of the corresponding β-resorcylic acids **4b–f** (see Table I). Resorcylic acid **4a** analyzed satisfactorily, but analyses of **4b** differed from theory significantly more (~0.6%) than experimental error. Although the latter appeared to be chromatographically pure, the elemental analysis (and neutralization equivalent) varied with recrystallization solvent and drying conditions. Possibly, the crystals were partially solvated. Facile decarboxylation of the acid prevented

(1) Supported by grants from the National Institute of General Medical Sciences (5-RO1-GM12848-02) and from the Research Corporation.

(2) A. J. Birch and F. W. Donovan, *Australian J. Chem.*, **6**, 360 (1953).

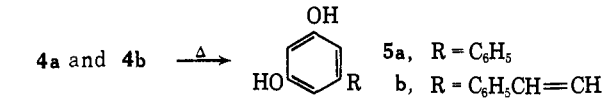
(3) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W. A. Benjamin, Inc., New York, N. Y., 1964.

(4) K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965).

(5) T. Money, I. H. Qureshi, G. B. Webster, and A. I. Scott, *J. Am. Chem. Soc.*, **87**, 3004 (1965); T. Money, J. L. Douglas, and A. I. Scott, *ibid.*, **88**, 624 (1966).

(6) We have previously described the synthesis of one of these.[4] In that report the generality of the reaction was questioned because of the failure of 2,4,6-heptanetrione to be converted to significant amounts of the corresponding acid **1**.

drying at a temperature sufficiently high to assure removal of this solvation. Acids **4a** and **4b** were decarboxylated; they afforded good yields of 5-phenylresorcinol (**5a**), mp 157–158° (reported[7] mp 157–158°), and pinosylvin (**5b**), mp 152–155° (reported[8] mp 156°), respectively. The melting points of resorcylic acids **4c–e** conformed satisfactorily to reported values. Only a small quantity of orsellinic acid (**4f**) was obtained, although the yield based on **1f** appeared to be good. Orsellinic acid was identified by thin layer chromatographic comparison with authentic material.[9]



The 6-alkyl-β-resorcylic acids **4c–f** are common metabolites of lichens and **4f**, the simplest of the series, is produced by fungi, as well.[3] Pinosylvin (**5b**) is found in the heartwood of pines, and is probably formed from **4b**.[2,3] The conversion of triketo acids **1** to resorcylic acids **4** in high yields under mild "physiological" conditions lends support to the postulate that triketo acids (or their esters) are precursors of such resorcylic acids in living systems. The ease with which these cyclizations occur in aqueous solutions tempts us to question whether they are of necessity effected enzymatically.

Variations in the cyclization conditions are currently being investigated to determine whether other equally mild conditions may lead to acylphloroglucinols or other aromatic condensation products.

(7) C. M. Suter and P. G. Smith, *J. Am. Chem. Soc.*, 61, 166 (1939).
(8) H. Erdtman, *Ann.*, 539, 116 (1939).
(9) The authentic sample was kindly furnished by Dr. R. J. Light, Florida State University.

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Allylic Oxidation of Olefins by Palladium Acetate[1]

Sir:

As reported recently,[2] allylic oxidation of certain 1- and 2-olefins by mercuric acetate in acetic acid involves S_Ei' formation of allylic mercurials which rapidly equilibrate in favor of the primary isomer. This undergoes a unique S_Ni demercuration reaction leading to secondary allylic acetate, and thus pure secondary ester is obtained from either the 1- or 2-olefinic isomer. In this communication we report the contrasting allylic oxidation of olefins by palladium acetate.

The oxidation of olefins by Pd^{II} salts under aqueous conditions to yield carbonyl compounds is well known,[3] and certain features of the mechanism have been recognized.[3,4] However, allylic oxidation of olefins by Pd^{II} salts has received little attention, and the pathways to allylic products have been far from clear. Only in the case of cyclohexene has clean allylic oxidation been effected,[5] Δ^2-cyclohexenyl acetate being essentially the sole product[6] from oxidation with $Pd(OAc)_2$ in AcOH. Further investigation, the results of which are now reported, shows that in olefin–$Pd(OAc)_2$ oxidation: (i) 1-olefins give mainly enol acetate while 2-olefins give mainly allylic acetate; (ii) 1-olefins and 2-olefins give different allylic acetates.

Oxidation of excess propene (Ia), 1-butene (Ib), *cis*- and *trans*-2-butene (IIb), 1-pentene (Ic), and *cis*-2-pentene (IIc) by $Pd(OAc)_2$ in AcOH proceeds smoothly at 25° to give high yields of monoacetate products. Any diacetates formed represent <2% of the product. From the 1-olefins, the predominant monoacetates are enol acetates, allylic acetate being a minor product. Thus, the monoacetate product from propene consists of 98.6% isopropenyl acetate[7d] (Va), *ca.* 0.5% *cis*- and *trans*-propenyl acetates[7c,8c] combined (VIa), and *ca.* 0.9% allyl acetate[7c] (VIIa). From 1-butene, the monoacetate product contains somewhat more allylic acetate, *ca.* 9% being observed. This material is purely primary (>99.5%), the crotyl acetate[7b] (VIIb) showing an 80:20 *trans*:*cis* ratio. The major product (*ca.* 80%) is the enol acetate[7a] Vb, other products being enol acetate[7c,8b] VIb (*ca.* 9%) and a material having the same vpc characteristics as 3-buten-1-yl acetate[8a] (*ca.* 2%). The product from 1-pentene contained *ca.* 10% of allylic acetate, >98% primary[7b] (VIIc), *ca.* 85% of an enol acetate[7a] Vc, and *ca.* 5% of two other materials with vpc behavior appropriate for enol acetates.

As in the case of cyclohexene,[5] oxidation of *cis*- or *trans*-2-butene leads nearly exclusively (>97%) to allylic acetate.[9] The latter is exclusively (>99.2%)

(1) (a) Research sponsored by the U. S. Army Research Office (Durham); (b) research supported in part by the National Science Foundation.
(2) Z. Rappoport, P. D. Sleezer, S. Winstein, and W. G. Young, *Tetrahedron Letters*, No. 42, 3719 (1965).
(3) J. Smidt, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, 1, 80 (1962), and references there cited.
(4) P. M. Henry, *J. Am. Chem. Soc.*, 86, 3246 (1964), and other included references; see the suggestion of J. Halpern quoted by R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1964, p 88.
(5) C. B. Anderson and S. Winstein, *J. Org. Chem.*, 28, 605 (1963).
(6) Other reports of allylic oxidation have appeared. *E.g.*, see I. I. Moiseev, *et al.*, *Dokl. Akad. Nauk SSSR*, 133, 377 (1960), and subsequent papers. These workers reported that oxidation of propene by $PdCl_2$ in AcOH yielded 15% allyl acetate. The $Pd(OAc)_2$–AcOH system is mechanistically simpler than $PdCl_2$–AcOH–NaOAc where questions of ligand competitions on Pd arise.
(7) (a) Identified by nmr and infrared spectra. A useful diagnostic feature of the infrared spectra of allylic and enol acetates concerns the relative intensities of the C=O and C=C absorptions. In allylic acetates, the former is far more intense, but the intensities are more nearly equal in enol acetates. (b) Identified by comparison of vpc characteristics and infrared spectra with those of an authentic sample. (c) Identified by peak enhancement experiments with an authentic sample. (d) Identified by comparisons of infrared and nmr spectra with those of an authentic sample.
(8) (a) Prepared according to S. Olsen, *Acta Chem. Scand.*, 4, 901 (1950). (b) Prepared by a modification of the procedure described by P. Z. Bedoukian, *J. Am. Chem. Soc.*, 66, 1325 (1944). The nmr spectrum indicated a *trans* geometry (J = 12.5 cps). (c) Prepared according to D. Y. Curtin and M. J. Hurwitz, *ibid.*, 74, 5381 (1952), and shown to be a 60:40 *cis*:*trans* mixture by vpc and nmr studies (J_{trans} = 12.5 cps and J_{cis} = 7 cps).
(9) Contrasting results, the reasons for which are not clear to us, have been very recently reported. Thus, D. R. Bryant, J. E. McKeon, and P. S. Starcher (Abstracts, Second International Symposium on Organometallic Chemistry, Madison, Wis., Aug 1965, p 94) describe *trans*-crotyl acetate and 3-buten-1-yl acetate as the major products from oxidation of 1-butene by $Pd(OAc)_2$ in AcOH, with *cis*- or *trans*-2-butene leading to *trans*-crotyl acetate and α-methylallyl acetate in roughly equal amounts. Propene was reported to yield quite high (*ca.* 90%) proportions of allyl acetate. In contrast, a buffered system of $PdCl_2$ in AcOH yields predominantly isopropenyl and propenyl acetates. E. W. Stern, *Proc. Chem. Soc.*, 111 (1963) and I. I. Moiseev, A. D. Belov, and Y. K. Syrkin, *Izv. Akad. Nauk, Ser. Khim.*, No. 8, 1527 (1963); *Chem. Abstr.*, 59, 14022 (1963).