Models of the Biogenesis of Polyketide-Type Phenolic Ethers[1a]

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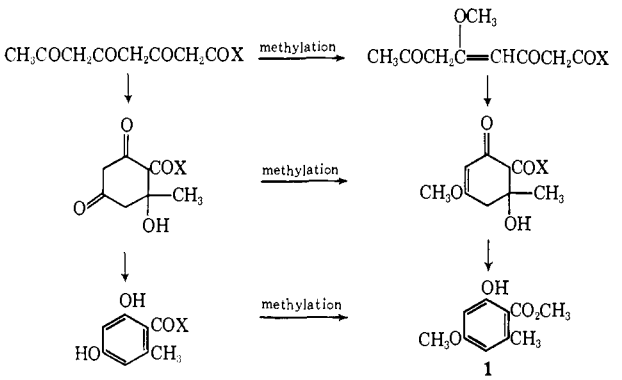
Abstract: Methylation of 3,5,7-trioxo-7-phenylheptanoic acid (**2b**) with diazomethane gave a mixture from which 3-methoxy ester **3**, cyclohexenone **4**, and pyrone **5** were isolated by chromatography. Cyclization of **3** in the pH range 5.0–9.5 gave pyrone **5**, cyclohexenone **9**, benzoate **12**, and benzophenone **13**. Methylation of cyclohexanedione **14a** gave cyclohexenones **4** and **8**; methylation of a mixture of epimers **14a** and **b** gave cyclohexenones **4**, **8**, and **9** and benzoate **10**. The structures and relative configurations of **4**, **8**, and **9** were assigned by dehydration to give benzoates **10** and **12** and by spectral studies. The methylation reactions are discussed in relation to proposed pathways for the biogenesis of O-alkylated, acetate-derived phenols.

Surveys of the structures of polyketide-type phenolic natural products readily demonstrate the ubiquity of alkylated derivatives;[2] methyl, glycosyl, and terpenoid substituents are all quite common. The site of attachment of the alkyl group may be either carbon or oxygen. In the biosynthesis of these metabolites the alkylation step could conceivably occur at any of several stages in the generation of the aromatic ring system. For example, the alkylation step required for the formation of sparassol (**1**), which is the 4-methyl ether of methyl orsellinate, may occur after the aromatic ring is formed. On the other hand, alkylation preceding aromatization may occur at either the poly(keto acid) stage or the aldol stage (Scheme I).

Scheme I



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In this and many other cases the timing of the alkylation step is unknown, but there are several examples in which evidence has been obtained that is relevant to this question. Alkylation after aromatization is proven readily by isotopic labeling studies; by this method, the methyl ether of alternariol has been shown to arise by methylation of alternariol itself.[3] Alkylation prior to aromatization is much more difficult to establish and is usually inferred from unsuccessful attempts to alkylate aromatic systems *in vivo*. Indirect evidence suggests that the methyl ether of the resorcinol ring of griseophenones A, B, and C (and the methyl ether on the cyclohexanone ring of griseofulvin) is introduced prior to aromatization.[4–6] Strong arguments have been made for methylation occurring prior to aromatization in the biosynthesis of 5-methylorsellinic acid.[7,8] Similar situations appear to exist in the formation of clavatol,[9] usnic acid,[10] and the tetracyclines.[11]

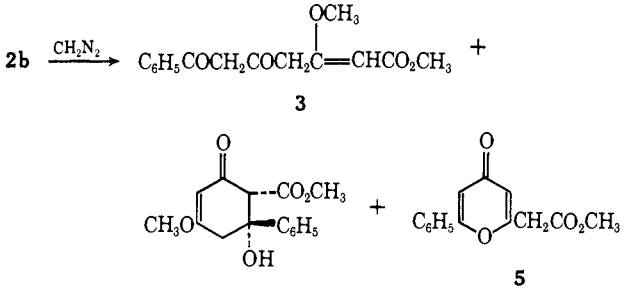
As a part of a larger study of the chemistry of polyketide compounds,[12] we have investigated the synthesis, structures, and reactions of enol ethers of methyl 3,5,7-trioxo-7-phenylheptanoate (**2a**) and of the cyclohexanedionecarboxylic ester obtained from its cyclization. Particular emphasis has been placed on aromatization reactions. We consider that these represent reasonable models of the processes by which the biosynthesis of polyketide-type phenolic ethers occurs.

$C_6H_5COCH_2COCH_2COCH_2CO_2R$

2a, R = CH_3
b, R = H

Results

Methylation of triketo acid **2b** with 2 equiv of diazomethane gave a number of products which appeared to have arisen by O-methylation of one or more of the three keto groups followed in some cases by cyclization reactions. Three of the products (**3–5**) were isolated by chromatography on silicic acid.



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

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

(4) A. J. Birch, *Proc. Chem. Soc. London*, 3 (1962).

(5) A. Rhodes, B. Boothroyd, M. P. Mcgonagle, and G. A. Somerfield, *Biochem. J.*, **81**, 28 (1961); A. Rhodes, G. A. Somerfield, and M. P. Mcgonagle, *ibid.*, **88**, 349 (1963).

(6) M. Jackson, E. L. Dulaney, I. Putter, H. M. Shafer, F. J. Wolf, and H. B. Woodruff, *Biochim. Biophys. Acta*, **62**, 616 (1962).

(7) M. W. Steward and N. M. Pachter, *Biochem. J.*, **109**, 1 (1968).

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

(9) S. Gatenbeck and U. Brunsberg, *ibid.*, 20, 2334 (1966).

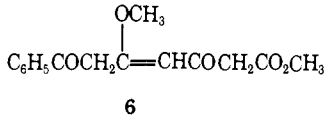
(10) H. Taguchi, U. Sankawa, and S. Shibata, *Tetrahedron Lett.*, 5211 (1966).

(11) J. R. D. McCormick, Congress on Antibiotics, Prague, 1964, Butterworths, London, 1966.

(12) See T. T. Howarth and T. M. Harris, *J. Amer. Chem. Soc.*, **93**, 2506 (1971), and references cited therein.

The mass spectrum of 3-methoxy ester **3** contained ions at *m/e* 147, $(C_6H_5COCH_2CO)^+$, and 130, $(CH_2{=}C(OCH_3)CH_2CO_2CH_3)\cdot^+$, indicating that methylation had occurred at the 3-carbonyl group. The nmr spectrum was consistent with this assignment and showed that enolization of the 5,7-diketo system was essentially complete. The double bond was assigned to the 2 position on the basis of the ir and uv spectra. The ir spectrum contained a sharp band at 1703 cm^{-1} (α,β-unsaturated ester). The uv spectrum (231 and 314 nm) compared favorably with a composite of the spectra of enolized benzoylacetone (310.5 nm)[13] and the enol ether of methyl acetoacetate (232 nm).[14]

The second compound (**4**) was shown to be a cyclization product of 5-methoxy ester **6**. The cyclic nature of the compound was suggested by the nmr spectrum. The 5-methylene protons were slightly nonequivalent and were more shielded (*ca.* δ 2.72) than can be accounted for by acyclic structures in which the methylene group would lie between two trigonal carbon atoms. Similarly the 1-proton (δ 4.13) and hydroxyl proton (δ 4.88) were at too high field to represent ethylenic or enolic protons. The β-methoxycyclohexenone structure was supported[15] by the uv spectrum (252 nm) and by the ir spectrum (1650 and 1720 cm^{-1}, α,β-unsaturated ketone and aliphatic ester, respectively). On the basis of this information, the compound could be assigned as **4**, **7**, **8**, or **9**.



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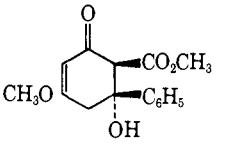

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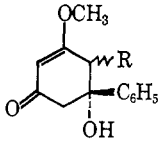
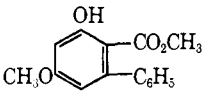


8, R = ---CO_2CH_3

9, R = ▬CO_2CH_3

Dehydration of this material by anhydrous hydrogen chloride in tetrahydrofuran gave benzoate ester **10**. The structure of **10** is supported by spectra and by independent synthesis.[16] This establishes that the cyclohexenone is either **4** or its epimer, **7**. The assignment of relative configuration as that depicted by structure **4** is made subsequently in this paper.



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The third product isolated from the methylation reaction was pyrone **5**. The structure of this compound was suggested by the uv spectrum (275 nm) which was very similar to that of 2-methyl-6-phenyl-4-pyrone.[17] Pyrone **5** has been independently synthesized by methylation of the corresponding acid with diazomethane.[18] It seems likely that **5** arose by cyclization of undetected 7-methoxy diketo ester **11** because the alternative precursors, **2a**, **2b**, and **3**, were shown to be stable to the reaction and isolation conditions.

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Cyclization reactions of **3** were investigated in the pH range 5–9.5; the results are summarized in Table I.

Table I. Cyclizations of 3-Methoxy Ester **3**

Reaction conditions	Product yields, % **9**	**5**	**12**	**13**
pH 9.5			34	12
pH 8.5	39			
Methanolic sodium acetate	72	16		7
pH 5.0	38	54		Trace

Treatment of **3** with pH 9.5 aqueous buffer gave benzoate ester **12** and benzophenone **13** as the only isolable products. The former arises by an aldol-type cyclization and the latter by a Claisen type. Ester **12** is isomeric with **10**; they can be distinguished by the absence of intramolecular hydrogen bonding in **12**. Benzophenone **13** was identical with an authentic sample obtained from a natural source.[19] These two cyclization products confirm the assignment of **3** as a 3-methoxy ester.

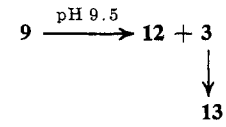
12 **13**

Cyclization of **3** at pH 8.5 gave **9** as the only isolable product (39%). The structure of **9** was assigned on the basis of the following information. The uv and mass spectra of **9** were similar to those of **4**. However, dehydration of **9** with anhydrous hydrogen chloride in tetrahydrofuran gave benzoate ester **12**. The ir spectrum (3600 cm^{-1}) showed that the hydroxyl group was not intramolecularly hydrogen bonded to the carbomethoxy group. For this condition to be met, both groups must be axial and thus located trans to each other. The axial location of the carbomethoxy group was confirmed by the absence of allylic coupling between the 1 and 3 protons. In cyclohexene derivatives allylic coupling with equatorial protons is generally not observed.[20]

(13) R. A. Morton, A. Hassan, and T. C. Calloway, *J. Chem. Soc.*, 883 (1934).
(14) P. Kurtz, H. Gold, and H. Disselnkölter, *Justus Liebigs Ann. Chem.*, 624, 1 (1959).
(15) E. E. Ayling and R. F. K. Meredith, *Chem. Ind. (London)*, 989 (1954).
(16) T. T. Howarth and T. M. Harris, *Can. J. Chem.*, 46, 3739 (1968).
(17) P. Franzosini, G. Traverso, and M. Sanesi, *Ann. Chim. (Rome)*, 45, 128 (1955).
(18) J. J. Cleary, unpublished observation.
(19) Benzophenone 13 (cotoin) is isolated from *Coto* bark; the structure has been established by independent synthesis: J. Jobst and O. Hesse, *Justus Liebigs Ann. Chem.*, 199, 17 (1879); J. Pollak, *Monatsh. Chem.*, 22, 996 (1901); E. Spath and K. Fuchs, *ibid.*, 42, 267 (1921).
(20) S. Sternhell, *Rev. Pure App. Chem.*, 14, 15 (1964); *Quart. Rev., Chem. Soc.*, 23 (1969).

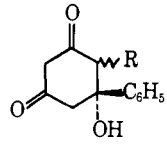
The yield of **9** was raised to 72% by the use of methanolic sodium acetate as the cyclizing agent; a small amount of pyrone **5** was formed, as well. The yield of pyrone **5** rose to 54% at the expense of **9** when a weakly acidic buffer (pH 5.0) was employed.

The overall yield of products in the pH 8.5 and 9.5 aqueous buffers was low, presumably due to hydrolytic cleavage of **3**. However, in methanolic media cleavage of **3** was unimportant and the yield of isolable products was high. It appears that formation of pyrone **5** is facilitated by acid. Conversely, base catalysis favors carbocyclic ring formation to give either aldol products **9** and **12** or the Claisen product **13**. Furthermore, at pH 8.5 the only aldol product which could be detected was cyclohexenone **9**; at pH 9.5, benzoic ester **12** was the only aldol product. This implied instability of **9** at pH 9.5 was confirmed by treating **9** with pH 9.5 buffer, whereupon the dehydration product **12** was obtained. An additional product from this treatment was benzophenone **13** which was formed in low yield by retroaldol cleavage of **9** and subsequent Claisen condensation of the intermediate ester **3**.



In view of this result, cyclohexenone **4** was treated with a variety of basic reagents in a search for retroaldol cleavage and Claisen-type recyclization. However, only benzoic ester **10**, the direct aromatization product, was obtained. The reagents that were employed included pH 7.0 aqueous buffer, methanolic sodium acetate, and aqueous potassium hydroxide.

Next, the methylation of cyclohexanedione **14** was investigated to see whether this would provide another route to cyclohexenone derivatives **4**, **9**, and/or their epimers. The accompanying paper describes the preparation of **14** by cyclization of **2a** in aqueous sodium bicarbonate. The reaction gives both epimers of **14** but only one has been isolated.[12]



14a, R = - - - CO_2CH_3

b, R = ◀ CO_2CH_3

Methylation of the isolable epimer with diazomethane gave two products which were separated by chromatography. Uv spectra indicated that both were cyclohexenones resulting from methylation of enolic hydroxyl groups. Dehydration of one of the products with anhydrous hydrogen chloride in tetrahydrofuran gave benzoate ester **12**. However, the compound was not cyclohexenone **9**, which had been prepared by cyclization of **3**. Therefore, it was the epimer of **9**, *i.e.*, cyclohexenone **8**.

This assignment was confirmed by nmr and ir spectra. Whereas the allylic, equatorial 1 proton of **9** was not coupled with the 3 proton, the 1 proton of **8** was axial, and a coupling constant of 2 Hz was observed.[20] Intramolecular hydrogen bonding between the axial hydroxyl and equatorial carbomethoxy groups was observed in the ir spectrum of **8** (3490 cm^{-1}), but the hydroxyl group of **9** was free. This comparison further substantiates the original assignment of the relative configuration of **9**.[21]

The second product of the methylation reaction was **4**, which had also been obtained from methylation of **2b**. The relative configuration of **4** was not revealed by its spectra for, although the ir spectrum indicated hydrogen bonding between the hydroxyl and carbomethoxy groups, there was no assurance that the phenyl group had remained equatorial in this compound.[21] In spite of this, structure **4** can be assigned to the compound with reasonable confidence because the methylation of **14** had been carried out with a single epimer of **14** under conditions which were unlikely to cause epimerization of the starting material or the products. Thus it can be concluded that the two products of the methylation reaction, cyclohexenones **4** and **8**, have the same relative configuration.[22] By the same argument the isolable epimer of **14** is **14a** and the anion of **14a** was the kinetically and thermodynamically preferred product of cyclization of **2a**.

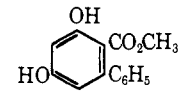
An attempt was made to isolate cyclohexenone **7**, the remaining enol ether of **14**. Triketo ester **2a** was cyclized in sodium bicarbonate solution, as reported previously,[12] to give a mixture of the epimeric anions of **14**. The solution was acidified and rapidly extracted with ether. The ethereal solution was immediately treated with diazomethane in the hope that all of the cyclohexenone derivatives (**4**, **7**, **8**, and **9**) would be formed.[23] Nmr assay of the crude reaction mixture indicated the presence of cyclohexenones **4**, **8**, and **9** and benzoate **10** in the ratio of *ca.* 2.3:2:1:3.1. No evidence was obtained to suggest that **7** was present. Whether **7** was not formed or underwent rapid epimerization or dehydration is not known.

In summary, O-methyl derivatives of a resorcylic ester have been prepared by methylation of a triketo ester followed by cyclization to cyclohexenone derivatives and dehydration. They were also prepared by methylation of a cyclohexanedionecarboxylic ester followed by dehydration. An O-methylated acylphloroglucinol has been prepared from a methylated precursor of the aromatic system. The reactions were studied with the intention of modelling biosynthetic pathways for the formation of phenolic ethers. In addition, the results suggest the feasibility of employing 3,5,7-triketo acids and their aldol cyclization products in studies of enzymic synthesis of phenolic ethers.

(21) In view of the paucity of information concerning steric preferences in cyclohexane rings containing multiple trigonal carbon atoms, it is noteworthy that the bulky phenyl group resides in an equatorial position in both **8** and **9** (see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, Chapter 2; and G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heydon and Son, Ltd., London, 1967, Chapter 13.

(22) It also follows that the phenyl group of **4** is equatorial.[21]

(23) In the previous study[12] acidification of a solution of anions of **14** gave, after extraction into ether, cyclohexanedione **14a** and benzoate i. Cyclohexanedione **14b** was not detected; it is not known whether the compound underwent rapid epimerization to **14a** or dehydration to i.



i

Experimental Section[24]

Dimethylation of 3,5,7-Trioxo-7-phenylheptanoic Acid (2b). To triketo acid **2b**[2] (6 g) in ether (100 ml) was added diazomethane (2 equiv) in ether (150 ml) and the solution was left at 5° for 12 hr. The solvent was removed *in vacuo* and the residual oil was fractionated on silicic acid, eluting with benzene–ether mixtures. Evaporation of the first fraction gave 1.15 g (17%) of methyl 3-methoxy-5,7-dioxo-7-phenylhept-2-enoate (**3**) as minute needles, mp 65–68°. Recrystallization from ether–hexane raised the melting point to 70–71°: uv (95% ethanol) 314 (log ε 4.23) and 231 nm (4.25); ir[25] (KBr) 1705, 1520–1640 cm^{-1}; ir[25] ($CHCl_3$) 1703, 1603 (broad), 1568 cm^{-1}; nmr δ 3.66 (s, 6, 1- and 3-OC*H*$_3$), 3.98 (s, 2, 4-C*H*$_2$), 5.27 (s, 1, 2- or 6-C*H*), 6.20 (s, 1, 6- or 2-C*H*), 7.3–7.9 (m, 5, C_6H_5), 15.6 ppm (s, 1, O*H*); mass spectrum[26] (direct insertion) *m/e* 276 (44%, p$^+$), 245 (48), 203 (51), 157 (31), 147 (90), 130 (20), 105 (100), 77 (49), 69 (60).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.28; H, 5.87.

Further elution gave 1.01 g (15%) of methyl 6-hydroxyl-4-methoxy-6-phenylcyclohex-3-en-2-onecarboxylate (**4**), mp 127–129°. Recrystallization from chloroform–hexane gave prisms: mp 130–132°; uv (95% ethanol) 252 nm (log ε 4.19); ir[25] (KBr) 3500, 1720, 1650, 1620 cm^{-1}; ir[27] (CCl_4) 1730, 1621 cm^{-1}; ir[28] (CCl_4) 3480 cm^{-1}; nmr δ 2.72 (broad s, 2, 5-C*H*$_2$), 3.62 (s, 3, OC*H*$_3$), 3.72 (s, 3, OC*H*$_3$), 4.13 (s, 1, 1-*H*), 4.88 (broad s, 1, exchangeable with D_2O, 6-O*H*), 5.54 (s, 1, 3-C*H*), 7.6–7.2 ppm (m, 5, C_6H_5); mass spectrum[26] (direct insertion) *m/e* 276 (2%, p$^+$), 258 (43), 77 (98), 69 (100), 68 (72), 59 (26) 51 (47).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.35; H, 5.79.

Elution with ether–methanol (9:1) gave 134 mg (2.3%) of methyl 6-phenyl-4-pyrone-2-acetate (**5**): mp 92–94°, which was unchanged after recrystallization from cyclohexane; uv (95% ethanol) 286 nm (log ε 4.32); ir[25] (KBr) 1730, 1660, 1610 cm^{-1}; nmr δ 3.66 (s, 2, 2-C*H*$_2$), 3.77 (s, 3, OC*H*$_3$), 6.28 (d, 1, *J* = 2 Hz, 3- or 5-C*H*), 6.68 (d, 1, *J* = 2 Hz, 5- or 3-C*H*), 7.9–7.2 ppm (m, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.83; H, 5.01.

Cyclization of Methyl 3-Methoxy-5,7-dioxo-7-phenylhept-2-enoate (3). a. At pH 9.5. A solution of 3-methoxy diketo ester **3** (200 mg) in tetrahydrofuran (2 ml) was combined with 20 ml of aqueous, 1 *M* tris(hydroxymethyl)aminomethane (Tris) buffer (pH 9.5). The mixture was stirred under nitrogen at room temperature for 21 hr, during which the initially formed precipitate slowly dissolved. The solution was cooled (ice bath), acidified with dilute hydrochloric acid, and extracted with three 50-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was fractionated on silicic acid, eluting with ether–hexane mixtures. Evaporation of the first fraction gave 22 mg (12%) of **13**, mp 116–117 and 128–130° after recrystallization from hot water. The product was identical (tlc, nmr, ir) with an authentic sample.[19]

Further elution gave 60 mg (34%) of benzoate ester **12** as plates, mp 137–139°. Recrystallization from chloroform–hexane and sublimation at 120° (0.01 mm) raised the melting point to 143–144°: uv (95% ethanol) 228 (log ε 3.50) and 224 nm (3.92); ir[25] (KBr) 3400, 1688, 1600 cm^{-1}; nmr δ 3.54 (s, 3, OC*H*$_3$), 3.68 (s, 3, OC*H*$_3$), 6.38 (s, 2, aromatic C*H*) 7.27 ppm (s 5, C_6H_5); mass spectrum[26] (direct insertion) *m/e* 258 (39%, p$^+$), 227 (100).

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.90; H, 5.68.

b. In Methanolic Sodium Acetate. 3-Methoxy diketo ester **3** (100 mg) was dissolved in methanol containing anhydrous sodium acetate (1.0 g) and the solution was stirred at room temperature for 28 hr under nitrogen. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The ether extracts were dried ($MgSO_4$), evaporated, and fractionated on silicic acid to give three products. Elution with ether–hexane (1:4) gave cotoin (**13**) (6 mg, 7%), mp 129–130°. Elution with ether–methanol (99:1) gave 72 mg (72%) of cyclohexenone **9**, mp 168–170°. Recrystallization from chloroform–hexane gave minute prisms: mp 174–175°; uv (95% ethanol) 248 nm (log ε 4.16); ir[25] ($CHCl_3$) 3590, 1732, 1651, 1521 cm^{-1}; ir[25] (KBr) 3300, 1743, 1640, 1621 cm^{-1}; ir[28] (CCl_4) 3600 cm^{-1}; nmr δ 2.62 (d, 1, *J* = 17 Hz, 5-C*H*$_2$), 3.27 (s, 1, exchangeable with D_2O, O*H*), 3.30 (s, 3, OC*H*$_3$), 3.70 (d, 1, *J* = 17 Hz, 5-C*H*$_2$), 3.70 (s, 1, 1-C*H*), 3.73 (s, 3, OC*H*$_3$), 5.56 (s, 1, 3-C*H*), 7.42 ppm (m, 5, C_6H_5); mass spectrum;[26] (direct insertion) *m/e* 276 (61%, p$^+$), 258 (26), 245 (24), 227 (56), 203 (24), 157 (68), 129 (20), 128 (100), 125 (29), 113 (21), 105 (98), 77 (35).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 65.21; H, 5.84. Found: C, 65.33; H, 5.59.

Elution with ether–methanol (9:1) gave 15 mg (16%) of pyrone **5**, mp 90–92°.

c. At pH 5.0. To a solution of anhydrous sodium acetate (4.1 g) in methanol (50 ml) was added glacial acetic acid so that the pH of aliquots, after addition of an equal volume of water, was 5.0. 3-Methoxy diketo ester **3** (100 mg) in methanol (15 ml) was combined with the above anhydrous buffer (10 ml) and the solution was left at room temperature for 80 hr. The solvent was removed *in vacuo* and the residue was partitioned between chloroform and water. The chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give an oil which was shown (tlc) to comprise two major components and a trace of cotoin. Chromatography on silicic acid gave 37.8 mg (38%) of **9**, mp 171–173° after recrystallization from chloroform–hexane. Further elution gave 47.6 mg (54%) of pyrone **5**, mp 91–93°.

d. At pH 8.5. 1 *M* Tris buffer (20 ml, pH 8.5) was added to **3** (200 mg) in tetrahydrofuran (2 ml) and the suspension was stirred at room temperature for 25 hr under nitrogen. An oil was initially deposited which crystallized during the reaction. The suspension was extracted with three 50-ml portions of chloroform and the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The semisolid residue was triturated with ether–hexane to give 78.5 mg (39%) of **9**, mp 165–169°. Recrystallization from chloroform–hexane gave prisms, mp 172–175°.

Dehydration of 9. a. In Anhydrous Tetrahydrofuran–Hydrogen Chloride. Cyclohexenonecarboxylic ester **9** (40 mg) was dissolved in tetrahydrofuran and dry hydrogen chloride was passed through the solution for 1 min. The solution was set aside under anhydrous conditions at room temperature for 30 min. The solution was neutralized with aqueous sodium bicarbonate solution and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a colorless oil. Trituration with hexane gave 33 mg (88%) of methyl 4-hydroxy-2-methoxy-6-phenylbenzoate (**12**), mp 137–140°. Recrystallization from chloroform–hexane gave plates, mp 141–142°.

b. Tris Buffer (pH 9.5). To 100 mg of **9** in tetrahydrofuran (1 ml) was added 10 ml of 1 *M* Tris buffer (pH 9.5) and the turbid solution was stirred at room temperature for 40 hr under nitrogen. The solution was acidified to pH 3 with dilute hydrochloric acid and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a colorless oil (87 mg) which was shown (tlc) to contain three major components. Fractionation on silicic acid gave cotoin (**13**, 9 mg, 10%), mp 127–130°, benzoate ester **12** (52 mg, 56%), mp 140–142°, and starting cyclohexenone **9** (21 mg, 21%).

Dehydration of 4. a. Potassium Phosphate Buffer (pH 7.0). To 30 mg of cyclohexenone **4** in tetrahydrofuran (1 ml) was added 1 *M* potassium phosphate buffer (pH 7.0, 10 ml) and the solution was stirred at room temperature for 36 hr. The mixture was acidified with cold hydrochloric acid and extracted with three 50-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Crystallization from ether–hexane gave a nearly quantitative yield of benzoate ester **10** as minute prisms, mp 110–111°. Recrystallization from hexane raised the melting point to 110.5–111.5° (lit.[16] mp 110–111°): uv (95% ethanol) 302 (log ε 3.75), 261 (4.04), and 224 nm (4.45); ir[21] (KBr) 2940, 1560–1650 cm^{-1}; nmr δ 3.44 (s, 3, OC*H*$_3$), 3.80 (s, 3 OC*H*$_3$), 6.35 (d, 1 *J* = 2.5 Hz, aromatic C*H*), 6.50 (d, 1, *J* = 2.5 Hz, aromatic C*H*) 7.3 (m, 5, C_6H_5), 11.3 ppm (broad s, 1, O*H*).

b. 2 *M* Potassium Hydroxide. Cyclohexenone **4** (56 mg) in 2 *M* potassium hydroxide (10 ml) was left at 0° for 20 hr. The solution was acidified with dilute hydrochloric acid to pH 3 and extracted with ether. The ether extracts were dried ($MgSO_4$)

(24) Melting points were determined with a 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 in deuteriochloroform at ambient temperature using TMS as internal standard. Uv spectra were recorded with Beckman DB and Cary spectrophotometers. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

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

(26) We wish to thank Mr. A. H. Struck and Mrs. D. Franks, Perkin-Elmer Co., Norwalk, Conn., for recording the spectrum on a Hitachi RMU-6 mass spectrometer.

(27) Obtained with a Perkin-Elmer 621 spectrophotometer.

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

and evaporated *in vacuo* to give 43.5 mg (84%) of **10**, mp 109–111°.

c. Tetrahydrofuran–Hydrogen Chloride. A solution of **4** (30 mg) in dry tetrahydrofuran (5 ml) was saturated with dry hydrogen chloride for 1 min and the solution was set aside for 1 hr at room temperature under anhydrous conditions. The solvent was removed *in vacuo* and the residual oil crystallized from hexane to give 22 mg (79%) of **10**, mp 108–110°.

d. Sodium Acetate–Methanol. Cyclohexenone **4** (100 mg) was dissolved in methanol (25 ml) containing anhydrous sodium acetate (1 g) and the solution was left at room temperature for 22 hr under nitrogen. The solvent was removed *in vacuo* and the residue was partitioned between ether (100 ml) and water (100 ml). The ether extract was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Fractionation on silicic acid (preparative tlc), eluting with ether–hexane (3:1), gave 49 mg (52%) of **10**, mp 109–110°, and recovered **4** (17 mg, 17%).

Methylation of 14a. To cyclohexanedione **14a** (170 mg) in ethanol (5 ml) was added a solution of diazomethane (10 equiv) in ether (40 ml) and the solution was set aside at room temperature for 15 min. The solvent was removed *in vacuo* and the residual oil was fractionated on silicic acid. Elution with ether–hexane (4:1) gave 87 mg (43%) of cyclohexenone **4**, mp 126–128°. Recrystallization from chloroform–hexane raised the melting point to 131–132°. Admixture with an authentic sample gave no depression.

Further elution gave 69 mg (38%) of cyclohexenone **8** as minute crystals, mp 124–126°. Recrystallization from chloroform–hexane raised the melting point to 125.5–126.5: uv (95% ethanol) 250 nm (log ϵ 4.14); ir[25] (KBr) 1726, 1652, and 1610 cm^{-1}; ir[25] ($CHCl_3$) 1720, 1656, and 1615 cm^{-1}; ir[28] (CCl_4) 3490 cm^{-1}; nmr δ 2.80 (broad s, 2, 5-CH_2), 3.63 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 4.22 (d, 1, J = 1.5 Hz, 1-CH), 4.27 (broad s, exchangeable with D_2O, 6-OH), 5.57 (d, 1, J = 1.5 Hz, 3-CH), 7.4 ppm (m, 5, C_6H_5); mass spectrum[29] (direct insertion) *m/e* 276 (25%, p^+), 157 (38), 128 (51), 125 (24), 105 (100), 77 (35), 69 (21).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.49; H, 5.93.

Methylation of 14a and b. Triketo ester **2a** (262 mg) in methanol (15 ml) was diluted with 0.2 *M* aqueous sodium bicarbonate solution (15 ml) and the solution was set aside at room temperature for 30 min. The solution was diluted with water (100 ml) and extracted several times with ether to remove most of the methanol. The aqueous layer was acidified with dilute hydrochloric acid to pH 3 and ether extracted, and the ether extracts were immediately treated with diazomethane (10 equiv) in ether (50 ml). The solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give a pale yellow oil. A portion of the oil was fractionated (preparative tlc) to give **4**, **8**, **9**, and **10** in a molar ratio of *ca.* 2.3:2:1:3.1 (**4** and **10** were isolated as discrete compounds, but **8** and **9** had identical R_f values and were inseparable; the ratio of these was obtained by nmr).

Dehydration of 8. Cyclohexenone **8** (23 mg) was dissolved in dry tetrahydrofuran (5 ml) and hydrogen chloride was passed through the solution for 1 min. After 1 hr at room temperature the solvent was removed *in vacuo*. The residual oil was dissolved in ether, washed with water, dried ($MgSO_4$), and the ether was removed *in vacuo*. The oil crystallized from ether–hexane to give 13 mg (60%) of benzoate ester **12**, mp 140–142°.

(29) Recorded by Mr. C. T. Wetter on an LKB 9000 mass spectrometer.

Ultraviolet Irradiation of α-Apopicropodophyllin

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Abstract: Ultraviolet irradiation isomerizes α-apopicropodophyllin, a 1-phenyltetralin lignan, to a dihydroanthracene derivative. The dihydroanthracene can be dehydrogenated with triphenylmethyl perchlorate to the corresponding anthracene. When tetracyanoethylene is present during irradiation, a diene adduct is formed. The behavior of the ultraviolet absorption spectra during and after irradiation as well as the loss of optical activity is rationalized by postulating an initial photochemical cleavage of α-apopicropodophyllin to a short-lived *o*-quinodimethane intermediate, which can react in several ways.

The final stage in a published synthesis of picropodophyllin (**2**) calls for adding the elements of water to the double bond of α-apopicropodophyllin (**1**).[1] The prospect of improving the yields in this conversion[2] led us to try a photochemical process by which ROH is induced to add as RO– and H– to carbon–carbon unsaturation.[3] However, instead of the anticipated reaction giving **3**, an unwelcome ring cleavage intervened. The present report describes our work.

Ultraviolet irradiation of α-apopicropodophyllin (**1**) in slightly acidified aqueous acetic acid transformed the compound to an isomer whose properties are in accord with structure **5**. Thus, disappearance of the characteristic α-apopicropodophyllin absorption maximum at 311 nm in favor of a new 292-nm maximum is consistent

(1) W. J. Gensler, C. M. Samour, Shih Yi Wang, and F. Johnson, *J. Amer. Chem. Soc.*, **82**, 1714 (1960).

(2) A closely related hydration gave product in yield no higher than 50%; *cf.* E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963).

(3) Several reports appearing before 1960 first attracted our attention and led to the present work [*cf.* R. Stoermer, *Ber.*, **44**, 627 (1911); R. Stoermer and H. Stockmann, *ibid.*, **47**, 1786 (1914); but in this connection see P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967); A. Stoll and W. Schlientz, *Helv. Chim. Acta*, **38**, 585 (1955); H. Hellberg, *Acta Chem. Scand.*, **11**, 219 (1957); Shih Yi Wang, M. Apicella, and B. R. Stone, *J. Amer. Chem. Soc.*, **78**, 4180 (1956)]. More recently many new examples of this kind of photochemically induced addition have been described. In addition to the references included in a survey by J. A. Marshall [*Accounts Chem. Res.*, **2**, 33 (1969)] note P. J. Kropp, *J. Amer. Chem. Soc.*, **91**, 5783 (1969); P. J. Kropp and H. J. Krauss, *ibid.*, **91**, 7466 (1969); T. D. Roberts, L. Ardemagni, and H. Shechter, *ibid.*, **91**, 6185 (1969); J. C. Sircar and G. S. Fisher, *J. Org. Chem.*, **34**, 404 (1969); J. A. Waters and B. Witkop, *ibid.*, 34, 3774 (1969); A. C. Waiss, Jr., and M. Wiley, *Chem. Commun.*, 512 (1969); W. M. Horspool and P. L. Pauson, *ibid.*, 195 (1967); J. A. Marshall and R. D. Carroll, *J. Amer. Chem. Soc.*, **88**, 4092 (1966); C. D. Gutsche and B. A. M. Oude-Alink, *ibid.*, **90**, 5855 (1968); P. de Mayo and J. S. Wasson, *Chem. Commun.*, 970 (1967); M. T. McCall and D. G. Whitten, *J. Amer. Chem. Soc.*, **91**, 5681 (1969); S. Fujita, T. Nômi, and H. Nozaki, *Tetrahedron Lett.*, 3557 (1969); H. Kato and M. Kawanisi, *ibid.*, 865 (1970).