Synthesis of 3,5,7-Triketo Acids and Esters and Their Cyclizations to Resorcinol and Phloroglucinol Derivatives. Models of Biosynthesis of Phenolic Compounds[1]

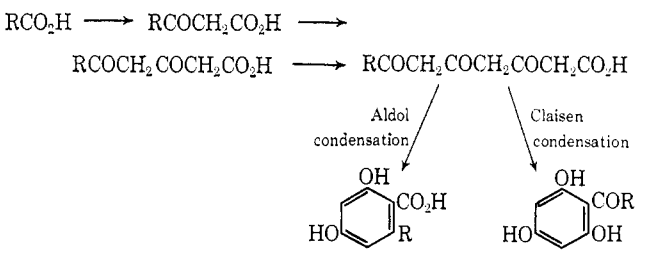
Thomas M. Harris and Robert L. Carney

Contribution from the Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203. *Received June 14, 1967*

Abstract: Seven 3,5,7-triketo acids were prepared by carboxylation of the trianions of the corresponding triketones. Four of the acids were obtained as crystalline solids; the remaining three were oils which were not fully characterized. Cyclization of the triketo acids in aqueous buffer, pH 5.0, afforded high yields of the corresponding β-resorcylic acids. The methyl esters of 7-phenyl-3,5,7-trioxoheptanoic acid and 9-phenyl-3,5,7-trioxo-8-nonenoic acid were prepared by treatment of the acids with diazomethane. The esters were converted efficiently into the corresponding β-resorcylate esters by treatment with aqueous buffer, pH 8.5, or with methanolic potassium hydroxide. However, treatment with cold, aqueous potassium hydroxide gave mainly acylphloroglucinols. Cinnamoylphloroglucinol cyclized on heating to the flavanone, pinocembrin. The relationship of these results to the biogenesis of phenolic compounds is discussed.

In recent years there has been considerable interest in the synthesis and reactions of poly-β-carbonyl compounds. This interest has stemmed from the postulate by Birch and Donovan in 1953 that naturally occurring, acetate-derived phenols are formed by way of 3-keto acids, 3,5-diketo acids, 3,5,7-triketo acids, etc. (Scheme A).[2] They suggested that cyclization of 3,5,7-triketo acids to give aromatic compounds occurs in two fashions, the first route involving aldol condensation to form β-resorcylic acids and the second an internal Claisen condensation to form acylphloroglucinols.

Scheme A

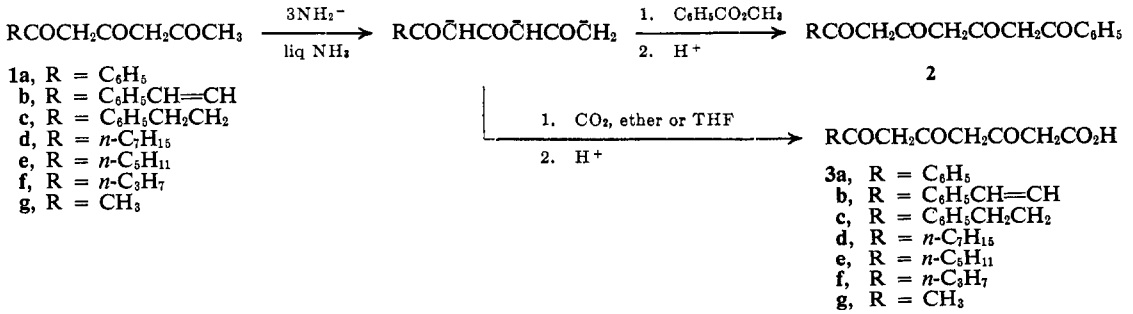


accumulated.[3] Progress in the study of these pathways has been retarded by the synthetic inaccessibility of triketo acids and their derivatives.

In this paper is described a method by which many 3,5,7-triketo acids can be synthesized. The specific examples that were chosen for study are structurally related to known phenolic natural products. A second aspect of this paper is to describe biogenetically modeled syntheses of certain of these natural products employing the triketo acids or the corresponding methyl esters. By the appropriate choice of conditions, either aldol or Claisen condensations can be effected selectively.

Recently we showed that 1-phenyl-1,3,5-hexanetrione (**1a**) can be converted at least partially into the trianion by means of 3 or more equiv of sodium amide in liquid ammonia.[4] The trianion undergoes condensations with electrophilic reagents at the terminal position. The reactions reported include acylation with methyl benzoate to give tetraketone **2** (R = C_6H_5) and carboxylation (in ether) to give 7-phenyl-3,5,7-trioxoheptanoic acid (**3a**) (Scheme B).[4]

Scheme B



No direct proof has yet been obtained for the existence of triketo acids and higher polyketo acids in biological systems, although much inferential evidence has

The trianion of 1-(*p*-methoxyphenyl)-1,3,5-hexanetrione (**1**, R = *p*-$CH_3OC_6H_4$) was prepared similarly, although neither acylation nor carboxylation was attempted.[4] However, no evidence could be obtained for trianion formation with the aliphatic triketone,

(1) This investigation was supported by the General Medical Sciences Institute of the National Institutes of Health, Grant No. GM-12848. Preliminary accounts of portions of this work have appeared: (a) T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.*, **88**, 2053 (1966); (b) *ibid.*, **88**, 5686 (1966).

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

(3) See 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).

2,4,6-heptanetrione (**1g**).[4] This raised the question of whether trianion formation was a general reaction of triketones. The method has now been extended to the preparation of a number of aromatic and aliphatic triketo acids.

Results

Preparation of Triketo Acids and Esters. Seven triketones, including the previously studied **1a** and **1g**,[4] were employed in the present investigation. Triketones **1a**, **1b**, and **1g** were prepared by published procedures (see Experimental Section). Triketone **1c** was prepared by acetylation (19%) of the dilithium salt of 6-phenyl-2,4-hexanedione (Scheme C, R = $C_6H_5CH_2CH_2$). The triketone had previously been prepared by Birch, *et al.*, by a multistep route from dehydroacetic acid.[5] Triketones **1d–f** were prepared by octanoylation (41%), hexanoylation (38%), and butyrylation (42%) of dilithioacetylacetone (Scheme D, R = *n*-C_7H_{15}, *n*-C_5H_{11}, and *n*-C_3H_7, respectively). Alternate preparations of **1c** and **1d** were investigated but were less satisfactory. Triketones **1d–f** were new compounds; their structures were confirmed by elemental analyses and spectral data.

Scheme C

$$RCOCH_2COCH_3 \xrightarrow[\text{liq } NH_3]{2LiNH_2} RCOCHCOCH_2Li \xrightarrow[2.\ H^+]{1.\ CH_3CO_2C_2H_5} RCOCH_2COCH_2COCH_3$$

Scheme D

$$CH_3COCH_2COCH_3 \xrightarrow[\text{liq } NH_3]{2LiNH_2} CH_3COCHCOCH_2Li \xrightarrow[2.\ H^+]{1.\ RCO_2CH_3} RCOCH_2COCH_2COCH_3$$

The advantageous use of lithium salts in the acylation of diketones with aliphatic esters to form triketones **1** has been demonstrated previously.[6] When dipotassio diketones are employed, aliphatic esters having α-hydrogens undergo ionization at the α position rather than condensation. With dilithium salts proton transfer no longer competes appreciably with acylation.

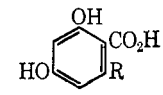
Triketo acids **3a** and **3b** were prepared in the following manner. The corresponding triketone was added to a solution of more than 3 equiv of sodium amide in anhydrous, liquid ammonia. Replacement of the ammonia by ether gave a suspension of the trisodium salt which was carboxylated by treatment with solid carbon dioxide. The product was separated from unaltered triketone by extraction into aqueous sodium bicarbonate followed by acidification. It was necessary to conduct this step expeditiously to avoid cyclization and decarboxylation of the triketo acids. Triketo acids **3a** (46%) and **3b** (52%) are solids at room temperature and were purified readily by recrystallization. In the present study the yield of **3a** was improved slightly over the previously reported values.[1a,4] The procedure afforded only 16% of the triketo acid **3c**. A modification of the procedure involving carboxylation of the tripotassium salt of the triketone in tetrahydrofuran gave 57%. Similarly for the preparation of **3d** a yield of <2% was obtained with the trisodium salt of **1d**, whereas the tripotassium salt gave 30%. Triketo acid **3e** was prepared in 16% yield by the potassium procedure. A smaller amount of **3f** and only a trace of **3g** were obtained. In both of these cases the amount was too small to warrant isolation. However, the crude products were subsequently employed in cyclization reactions.

Triketo acids **3a** and **3b** were converted into the corresponding methyl esters **4a** and **4b** by treatment with diazomethane. The diazomethane was added to the triketo acids and care was taken to avoid excess of the reagent since preliminary experiments had shown that the enolic carbonyl groups react fairly rapidly to give enol ethers. Difficulty was experienced in the complete removal of the ethers from the triketo esters. On the other hand, unreacted triketo acid was readily removed by extraction with cold, aqueous sodium bicarbonate. Both triketo esters were solids at room temperature. Their structures were confirmed by spectral and elemental analysis.

$$RCOCH_2COCH_2COCH_2CO_2CH_3$$

4a, R = C_6H_5
b, R = $C_6H_5CH{=}CH$

Aromatic Cyclization Reactions. In preliminary experiments with **3a** designed to find conditions under which cyclization of the triketo acids would occur, it was found that the compound is quite stable in the range of pH 3–4. However, at higher pH cyclization to β-resorcylic acid **5a** was observed. The rate of cyclization increased with pH, but a concomitant decarboxylation of **3a** to give triketone **1a** was observed in solutions near pH 7. Optimization of reaction rate without loss of yield occurred at pH 5.0; the β-resorcylic acid was isolated in 86% yield. The other three crystalline triketo acids, **3b**, **3d**, and **3e**, were treated similarly to give the corresponding β-resorcylic acids in excellent yields. Cyclization of **3c** gave only 19% of resorcylic acid **5c**. Decarboxylation of the triketo acid and of the resorcylic acid appeared to be major side reactions. The remaining acids, **3f** and **3g**, which had been obtained as oils and had been only partially purified, were also cyclized. Yields were not determined because of uncertainties concerning the purity of the triketo acids. However, on the basis of thin layer chromatograms of starting materials and of crude products, the yields appeared to have been good.

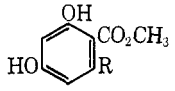


5a, R = C_6H_5
b, R = $C_6H_5CH{=}CH$
c, R = $C_6H_5CH_2CH_2$
d, R = *n*-C_7H_{15}
e, R = *n*-C_5H_{11}
f, R = *n*-C_3H_7
g, R = CH_3

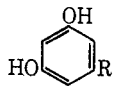
Three of the β-resorcylic acids (**5a–c**) are new compounds. The acids **5a** and **5c** analyzed satisfactorily, but **5b** only poorly. Elemental analyses of **5b** varied with recrystallization and drying conditions and it is suspected that solvents were occluded. In accordance with this is the fact that determination of neutralization equivalents gave consistently high but varying values. The structure of **5b** was confirmed by treatment of the compound with diazomethane to give ester **6b**, which

(5) A. J. Birch, D. W. Cameron, and R. W. Richards, *J. Chem. Soc.*, 4395 (1960).
(6) S. D. Work and C. R. Hauser, *J. Org. Chem.*, **28**, 725 (1963).

gave satisfactory analytical results. In addition thermal decarboxylation of **5b** gave the known resorcinol (**7b**). Decarboxylations of **5a** and **5c** also gave the corresponding resorcinols **7a** and **7c**.



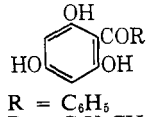
6a, R = C_6H_5
b, R = $C_6H_5CH{=}CH$



7a, R = C_6H_5
b, R = $C_6H_5CH{=}CH$
c, R = $C_6H_5CH_2CH_2$
d, R = n-C_7H_{15}

The β-resorcylic acids **5d–g** are known compounds and the melting points and other physical properties of these products corresponded satisfactorily to literature values. The structure of **5d** was further confirmed by decarboxylation of the compound to give the known resorcinol **7d**.

Triketo ester **4a** underwent cyclization in alkaline solution to give β-resorcylic ester **6a** and/or acylphloroglucinol **8a**. The product mixture was highly dependent on the conditions chosen for the reaction. The use of potassium phosphate buffer, pH 8.5, gave a 92% yield of resorcylic ester **6a** with no apparent formation of acylphloroglucinol **8a**. Similarly with 10% methanolic potassium hydroxide solution, the resorcylic ester was the only cyclization product that could be detected. On the other hand, when the triketo ester was treated with aqueous 2 *M* potassium hydroxide at −5° for 19 hr, a mixture of acylphloroglucinol **8a** with lesser amounts of resorcylic ester **6a**, resorcylic acid **5a**, and resorcinol **7a** was obtained. Nmr analysis of the product mixture indicated that it contained 66 mole % of the acylphloroglucinol and 34 mole % of the resorcinol derivatives **5a**, **6a**, and **7a**. Of the latter **7a** was present in only trace quantities. The acylphloroglucinol was separated from the mixture chromatographically in 47% yield.



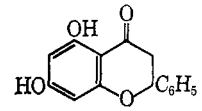
8a, R = C_6H_5
b, R = $C_6H_5CH{=}CH$

The structure of resorcylic ester **6a** was established by elemental analysis and by comparison with material prepared by treatment of acid **5a** with diazomethane. The identification of benzoylphloroglucinol (**8a**) was made by comparison with authentic material prepared by benzoylation of phloroglucinol by the method of Rosenmund and Rosenmund.[7]

Triketo ester **4b** showed similar behavior. With tris(hydroxymethyl)aminomethane hydrochloride buffer, pH 8.5, resorcylic ester **6b** was formed in 69% yield. The ester was identical with the methyl ester formed previously by treatment of acid **5b** with diazomethane. This provides further support for the structure of **5b** for which poor analytical results were obtained.

Treatment of triketo ester **4b** with aqueous potassium hydroxide at −5° for 40 min gave a mixture, tlc of which indicated the presence of cinnamoylphloroglucinol (**8b**), resorcylic ester **6b**, flavanone **9**, unreacted starting ester **4b**, and two unidentified compounds. Cinnamoylphloroglucinol (**8b**) was separated from the other components by column chromatography on silicic acid. When 24 hr was allowed for the cyclization a more complex mixture of products was obtained and the yield of **8b** was diminished.

Cinnamoylphloroglucinol (**8b**) was cyclized to flavanone **9** by heating at 190°.[8] The flavanone was isolated by sublimation in 63% yield based on the original triketo ester **4b**. Flavanone **9** is the racemic form of naturally occurring pinocembrin. The physical properties of **9** were consistent with previous reports.



9

Recent interest by others in the effect of magnesium ion on the course of cleavage–recyclization reactions of pyranopyrones[9,10] led us to investigate the effect of magnesium ion in the present system. No gross effect of the ion was detected. An aqueous mixture of magnesium and potassium hydroxides gave a mixture of benzoylphloroglucinol (**8a**) and resorcinol derivatives similar to that obtained with potassium hydroxide alone. Aqueous magnesium hydroxide, pH 9.7, methanolic magnesium methoxide, and aqueous magnesium tris(hydroxymethyl)aminomethane hydrochloride buffer, pH 8.5, all gave resorcylic ester **6a** but none of acylphloroglucinol **8a**. The reaction mixtures were heavily precipitated and the reactions in some cases were significantly slower than those effected by potassium salts.

Discussion

Although 1,3-dicarbonyl[11] and 1,3,5-tricarbonyl[5,6,12] compounds can be prepared by many methods, 1,3,5,7-tetracarbonyl compounds have not been readily available. One acyclic tetraketone (**2**, R = C_6H_5) has been synthesized by several procedures. The first preparation involved condensations of acetylacetone with 2 equiv of methyl benzoate and 1-phenyl-1,3,5-hexanetrione (**1a**) with 1 equiv of methyl benzoate (Scheme E).[13] The condensations were effected by means of sodium hydride in ethereal solvents. The mechanism of these condensations remains uncertain because treatment of a diketone with sodium hydride under the reaction conditions has failed to produce the dianion.[12b] The reactions have not been extended to the preparation of diketo acids and triketo acids.[14]

(7) K. W. Rosenmund and M. Rosenmund, *Ber.*, **61**, 2608 (1928).

(8) Cinnamoylphloroglucinol (**8b**) was not fully characterized because it is thermally unstable. Shinoda and Sato observed cyclization to flavanone **9** at the melting point and in refluxing acetic acid. They reported **8b** melted at 189–190°: J. Shinoda and S. Sato, *J. Pharm. Soc. Japan*, **48**, 791 (1928); *Chem. Abstr.*, **23**, 836 (1929).

(9) T. Money, J. L. Douglas, and A. I. Scott, *J. Am. Chem. Soc.*, **88**, 624 (1966).

(10) L. Crombie and A. W. G. James, *Chem. Commun.*, 357 (1966).

(11) See (a) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 59 (1954); (b) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 61 (1965), and related papers; (c) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(12) See (a) F. B. Kirby, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 2266 (1963); (b) M. L. Miles, T. M. Harris, and C. R. Hauser, *ibid.*, **30**, 1007 (1965); (c) S. Ruhemann, *J. Chem. Soc.*, **93**, 1281 (1908).

(13) M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3884 (1963).

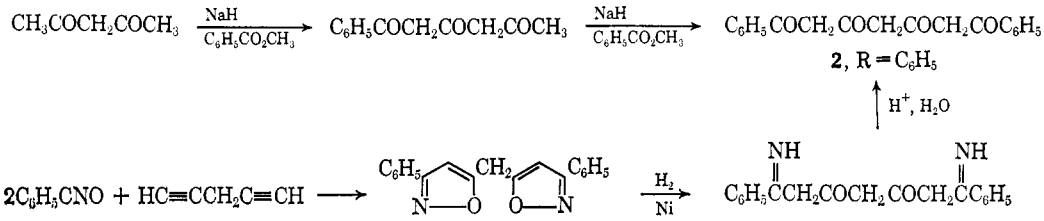
(14) A related (and earlier) example of the formation of a tetraketo compound in a cyclic system was reported. The synthesis of tetracycline precursor i was accomplished by a Dieckmann-type ring closure at the indicated point. The reaction was achieved by means of excess sodium hydride in dimethylformamide. Compound i differs from acyclic tetracarbonyl compounds in that it is not susceptible to intra-

The tetraketone has also been prepared by the condensation of a nitrile oxide with a bisacetylene to give a bisisoxazole, followed by reduction and hydrolysis (Scheme E).[15] The generality of this reaction has not been established. Most recently, the tetraketone was prepared by benzoylation of the trianion of **1a** (Scheme B).[4]

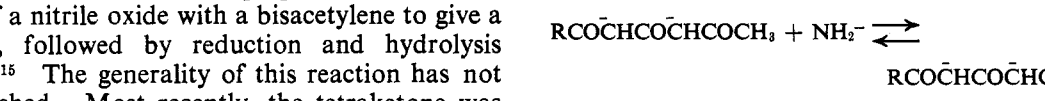
A number of reactions have been reported that probably involve tetra- (and higher) carbonyl compounds as intermediates.[9,10,16] In general the reaction conditions have been such that subsequent intra- and intermolecular condensations have occurred. Certain of these are discussed below.

The present study shows that carboxylation of the trianion of a triketone is a general method for the synthesis of both aromatic and higher aliphatic 3,5,7-triketo acids. It can be concluded from a study of the yields obtained in the carboxylation of aliphatic triketones that significantly better results are obtained with the longer chain compounds than with the shorter. It is unlikely that electronic factors play a major role in the differences among the aliphatic triketones. It is more probable that the differences lie in the relative solubilities of the dianion and trianion salts of the triketones. Under conditions where the dianion is less soluble than the trianion, the equilibrium point will be shifted toward the dianion if the dianion and the trianion are in a mobile equilibrium. This situation can exist only in the presence of protonic solvents, such as ammonia (Scheme F). After the anion mixture has been transferred into ether or tetrahydrofuran, interconversion can no longer occur. A possible solution to the problem that exists with **1f**, **1g**, and related compounds would be to use a solvent in which the dianions have satisfactory solubility. This is currently being investigated.

Scheme E



Scheme F



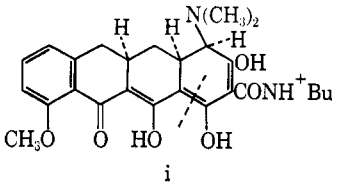
The traces of resorcinols **8a** and **8b** observed in the cyclizations of the corresponding triketo acids probably arose by decarboxylation of the β-resorcylic acids rather than by decarboxylation of the triketo acids to the triketones followed by cyclization. Triketone **1a** when treated under comparable conditions underwent little or no cyclization. On the other hand, extensive decarboxylation of β-resorcylic acid **5a** occurred. Cyclization of triketones to resorcinols has been observed previously only at high temperatures and in poor yields.[5,9,17] However, the facile decarboxylation of β-resorcylic acids in base has been noted.[16f,18]

The triketo acids and cyclization products synthesized in the present study were chosen because of their relationship to known natural products. The β-resorcylic acids **5d–g** are constituents of depsides produced by lichens.[19] In addition, orsellinic acid (**5g**) is elaborated by fungi.[20] The resorcylic acids **5a–c** have not been detected. However, the resorcinols, pinosylvin (**7b**) and dihydropinosylvin (**7c**) have been found and are presumably the decarboxylation products of the corresponding resorcylic acids.[21] Phloroglucinol derivatives found in nature include cotoin which is a methyl ether of benzoylphloroglucinol (**8a**),[22] and flavanone **9**, pinocembrin.[21]

In the present study triketo acids and/or esters have been cyclized by both paths suggested by Birch and Donovan and these "chemical" cyclizations would appear to be reasonable models of the biological processes. One difference between the "chemical" and biological processes is that in the latter triketo acids are likely to exist as thiol esters rather than as free acids or methyl esters. A second is that biological processes are usually enzyme catalyzed. Nevertheless, the ease with which β-resorcylic acid formation can be effected chemically suggests that the corresponding biological process may not be enzymatically catalyzed in some cases.

Some support for this proposal comes from the work of Bentley and Zwitkowits with ethionine-inhibited cultures of *Penicillium stipitatum*.[16f] These cultures produced orsellinic acid (**5g**) and 6-acetonyl-4-hydroxy-

molecular condensations: L. H. Conover, K. Butler, J. D. Johnston, J. J. Korst, and R. B. Woodward, *J. Am. Chem. Soc.*, **84**, 3222 (1962); and R. B. Woodward, *J. Pure Appl. Chem.*, **6**, 561 (1963).



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(15) G. Casnati, A. Quilico, A. Ricca, and P. Vita Finzi, *Tetrahedron Letters*, 233 (1966).

(16) (a) A. J. Birch, P. Fitton, D. C. C. Smith, D. E. Steere, and A. R. Stelfox, *J. Chem. Soc.*, 2209 (1963); (b) H. Stetter and S. Vestner, *Chem. Ber.*, **97**, 169 (1964); (c) T. Money, I. H. Qureshi, G. B. Webster, and A. I. Scott, *J. Am. Chem. Soc.*, **87**, 3004 (1965); (d) F. W. Comer, T. Money, and A. I. Scott, *Chem. Commun.*, 231 (1967); (e) P. F. Hedgecock, P. F. G. Praill, and A. L. Whitear, *Chem. Ind.* (London), 1268 (1966); (f) R. Bentley and P. M. Zwitkowits, *J. Am. Chem. Soc.*, **89**, 676 (1967); (g) T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, **23**, 3435 (1967).

(17) N. Collie and W. S. Myers, *J. Chem. Soc.*, **63**, 122 (1893).

(18) Y. Asahina and H. Akagi, *Ber.*, **68**, 1130 (1935).

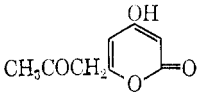
(19) See Y. Asahina and S. Shibata, "Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Tokyo, 1954.

(20) R. Bentley, J. A. Ghaphery, and J. G. Keil, *Arch. Biochem. Biophys.*, **3**, 80 (1965).

(21) (a) H. Erdtman, *Ann.*, **539**, 116 (1939); (b) G. Lindstedt, *Acta Chem. Scand.*, **4**, 448 (1950).

(22) J. Jobst and O. Hesse, *Ann.*, **199**, 17 (1879); J. Pollak, *Monatsh.*, **22**, 996 (1901).

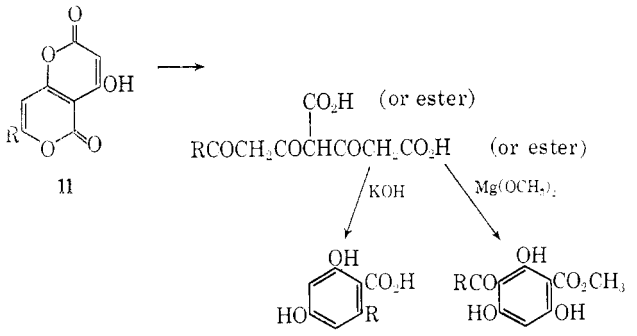
2-pyrone (**10**) in addition to other metabolites. Pyrone **10** was found to be unstable under culture conditions and gradually underwent conversion nonenzymatically to orsellinic acid. Triketo acid **3g** is presumably an intermediate in this process. However, the rate of the reaction did not appear to be sufficient to account for all the orsellinic acid formation.



10

Money and co-workers[9,16c,g] and also Crombie and James[10] have studied the conversion of pyranopyrones **11** to aromatic compounds under basic conditions. Resorcylic acids were formed when potassium hydroxide was used as the base, whereas phloroglucinol derivatives were produced when magnesium methoxide was employed. These reactions are considered to involve ring opening to the triketo dicarboxylic acids (or esters) followed by cyclization. At some point during β-resorcylic acid formation the γ-carboxy group is lost, but the γ-carbomethoxy group is retained during phloroglucinol formation (see Scheme G). In neither process has the presence of polyketo compounds been detected.

Scheme G



11

The reaction of pyranopyrones to produce phloroglucinol derivatives requires magnesium ion catalysis, whereas with triketo esters **4** no substantial effect of magnesium ion could be detected. Crombie and James postulated a mechanism for phloroglucinol formation that accounted for the magnesium ion catalysis as involving coordination of the γ-carbomethoxy group during aromatic cylization.[10] The lack of magnesium ion effect in our study is in accord with their mechanism since triketo esters **4** differ from their intermediates in that esters **4** do not contain the γ-carbomethoxy group.

Experimental Section[23]

Preparation of Triketones 1. Triketone **1a** was prepared from methyl benzoate and acetylacetone by the method of Miles, *et al.*[7] Triketone **1b** was prepared from 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrone by the method of Birch, *et al.*[5] 2,4,6-Heptanetrione (**1g**) was prepared from dehydroacetic acid by the procedure of Collie and Reilly.[24]

8-Phenyl-2,4,6-octanetrione (1c). To a suspension of 0.48 mole of lithium amide (prepared from 3.4 g of lithium metal) in 900 ml of liquid ammonia was added 30.5 g (0.16 mole) of 6-phenyl-2,4-hexanedione[11b] in ether solution. After 1 hr, 24.3 g (0.32 mole) of ethyl acetate was added rapidly. A vigorous reaction was accompanied by a color change from olive green to dark gray. After 5 min, the ammonia was evaporated on a steam bath with simultaneous addition of 500 ml of ether. The resulting suspension was poured into a solution of 35 ml of acetic acid in 200 ml of water. The ethereal layer was separated, washed with 5% aqueous sodium bicarbonate, with 2% aqueous potassium dihydrogen phosphate, and with water, dried over magnesium sulfate, and evaporated. Ethyl acetoacetate and unaltered diketone were removed by distillation at reduced pressure to leave a residue of 21.9 g. An 8.0-g aliquot was chromatographed on a column of 62 g of 100-mesh silicic acid by eluting with mixtures of hexane and chloroform. Collection of the appropriate fractions afforded 2.6 g (19% yield) of triketone **1c** as an amber oil which crystallized on cooling and melted at 23°: ν_{max}^{neat} 1600 and 1725 cm^{-1} (lit. $\nu_{max}^{CS_2}$ 1674 and 1727 cm^{-1}); λ_{max} 273 mμ (log ϵ 3.87) and 319 (3.59) (lit.[5] λ_{max} 276 mμ (log ϵ 3.76) and 317 (3.73)). The nmr spectrum indicated that the compound existed as a mixture of mono- and dienol tautomers. The spectrum was consistent with the assigned structure.

Treatment of the triketone with pyrrolidine by the procedure of Birch, *et al.*,[5] gave the bis(enamine) as slightly yellow needles: mp 139.5–141.5° (lit.[5] mp 142–144°); ν_{max}^{KBr} 1530 and 1420 cm^{-1} (lit.[5] ν_{max}^{Nujol} 1533 cm^{-1}).

The preparation of **1c** was also attempted by the acylation of dilithioacetylacetone with methyl hydrocinnamate. The product was contaminated with hydrocinnamamide and complete purification was not achieved.

2,4,6-Tridecanetrione (1d). 2,4-Undecanedione was prepared by treatment of 0.20 mole of disodioacetylacetone with 35.8 g (0.22 mole) of *n*-hexyl bromide in liquid ammonia by the general method of Hampton, *et al.*[11b] Distillation of the reaction product gave 25.2 g (69% yield) of the diketone, bp 79° (0.15 mm) (lit.[25] bp 93–95° (2.3 mm)).

The diketone was converted into the dilithium salt and acylated with ethyl acetate by the procedure employed above for the preparation of **1c** to give after distillation 17% of 2,4,6-tridecanetrione (**1d**), bp 114° (0.25 mm). Decomposition of the triketone during distillation was at least partially responsible for the poor yield obtained. On cooling the product gave large, waxy crystals: mp 27°; ν_{max}^{neat} 2940, 2870, 1730, 1600, and 900 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.82; H, 9.87.

A better yield was obtained when triketone **1d** was prepared by the method of Scheme D. To a suspension of 0.30 mole of lithium amide (prepared from 2.1 g of lithium) in 800 ml of liquid ammonia was added an ethereal solution of 10 g (0.10 mole) of acetylacetone by means of a syringe. After 1 hr, 31.6 g (0.20 mole) of methyl octanoate was added rapidly from an addition funnel. The gray reaction mixture immediately turned black and a black precipitate formed. After 10 min, the ammonia was evaporated with simultaneous addition of ether. The dark red ethereal solution was washed with a solution of 25 ml of acetic acid in 125 ml of water, with aqueous sodium bicarbonate, and finally with water. The solution was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. Pentane was added to the partially crystalline residue and the mixture was filtered to remove crystalline octanamide. The solvent was evaporated at reduced pressure and residual methyl octanoate was removed by distillation. The distillation residue was diluted with ethanol and chilled to −20° to give crystals (9.3 g, 41% yield) of 2,4,6-tridecanetrione (**1d**), mp 27°. The crystals were washed with cold, absolute ethanol and dried under reduced pressure.

2,4,6-Undecanetrione (1e). Similarly, 30 g (0.30 mole) of acetylacetone was added to 0.90 mole of lithium amide in 900 ml of liquid ammonia. After 1 hr, 78 g (0.60 mole) of methyl hexanoate was added rapidly and after 5 min the ammonia was removed. The iso-

(23) All melting points unless otherwise noted were taken with a Thomas-Hoover apparatus in unsealed capillaries and are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared and ultraviolet spectra were obtained with Beckman IR-10 and DB spectrophotometers, respectively. Ultraviolet spectra were determined of solutions in 95% ethanol. Nmr spectra of approximately 10% solutions in deuteriochloroform were determined with a Varian A-60 spectrometer. Tetramethylsilane was employed as an internal standard. The nmr spectrometer was purchased with funds obtained from the National Science Foundation (GP-1683). Fluorescent silica gel G with binder was used for tlc. Visualization of spots was accomplished with ultraviolet light, ferric chloride, or tetrazotized benzidine.

(24) J. N. Collie and A. A. B. Reilly, *J. Chem. Soc.*, **121**, 1984 (1922).

(25) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **62**, 2184 (1940).

lation procedure involved removal of hexanamide by crystallization from cold pentane. The pentane solution was evaporated to give 22.6 g (38% yield) of a thick oil, which crystallized on chilling at −20°. The material was washed with cold ethanol to give large, almost colorless plates of **1e** melting at 0° to give an oil which was freed of residual solvent by evaporation at room temperature and 0.2 mm.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 67.01; H, 9.20.

2,4,6-Nonanetrione (1f). Similarly, 20 g (0.20 mole) of acetylacetone was added to 0.60 mole of lithium amide in 800 ml of liquid ammonia. After 1 hr, 46.4 g (0.40 mole) of ethyl butyrate in 50 ml of ether was added and after an additional 5 min the ammonia was removed. The isolation procedure involved distillation of a fraction, bp 59–81° (0.15 mm), which was diluted with pentane and filtered to remove butyramide. The solution was washed three times with water, dried, and evaporated under reduced pressure. Redistillation gave two fractions: bp 59–67° (0.15 mm) (5.6 g) and 67–81° (0.15 mm) (8.5 g). The two fractions of **1f** gave identical infrared spectra; the combined yield was 42%.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.70; H, 8.36.

Preparation of Triketo Acids 3. 7-Phenyl-3,5,7-trioxoheptanoic Acid (3a). The procedure of Hampton, *et al.*, was modified as follows.[4] Triketone **1a** (10.0 g, 0.049 mole) was added to 0.20 mole of sodium amide (prepared from 4.6 g of sodium) in 800 ml of liquid ammonia. Anhydrous ether was added to maintain a constant volume over 3 hr. The remaining ammonia was evaporated rapidly with simultaneous replacement by ether. The ethereal suspension was refluxed to remove dissolved ammonia. The previously described carboxylation and isolation technique[4] was employed, except crystallization was effected in cold pentane rather than ether–hexane, to give 5.6 g (46% yield) of triketo acid **3a**, mp 99–100°. Recrystallization from chloroform–hexane gave sparkling, yellow plates, mp 101–102° dec (lit.[4] mp 98–99°).

9-Phenyl-3,5,7-trioxo-8-nonenoic Acid (3b). By the above procedure 5.2 g (0.023 mole) of triketone **1b** dissolved in a minimum amount of anhydrous ether was added to 0.24 mole of sodium amide in 800 ml of liquid ammonia. Carboxylation and isolation as above gave, after evaporation of the ethereal solution, 3.2 g (52% yield) of triketo acid **3b**, mp 123°. Recrystallization from chloroform gave glistening, yellow plates: mp 125–126° dec; ν_{max}^{KBr} 3000, 1700, 1620, and 1570 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.31; H, 5.23.

9-Phenyl-3,5,7-trioxononanoic Acid (3c). By the above procedure triketone **1c** was carboxylated in 16% yield. Improved results were obtained as follows. To a solution of 0.030 mole of potassium amide (from 1.2 g of potassium metal) in 400 ml of liquid ammonia was added 2.01 g (0.0087 mole) of chromatographically purified triketone **1c**. Over a period of 2 hr, 170 ml of tetrahydrofuran was gradually introduced into the reaction mixture. At the end of this time the remaining ammonia was removed by warming the solution to reflux on a steam bath. Carboxylation was effected by addition of lumps of solid carbon dioxide to the reaction mixture. The color changed immediately from red-black to pale green. The mixture was poured into excess, cold, dilute hydrochloric acid. A portion of the tetrahydrofuran was removed with a rotary film evaporator at room temperature. The aqueous suspension was extracted with ether and the resulting ethereal solution was extracted three times with 5% aqueous sodium bicarbonate. The aqueous extracts were acidified immediately with cold, dilute hydrochloric acid and extracted with ether. The ethereal solution was dried over magnesium sulfate and evaporated at reduced pressure to give 1.36 g (57% yield) of triketo acid **3c** as a red oil. Tlc with chloroform showed that the triketo acid was contaminated by the cyclization products, resorcylic acid **5c** and resorcinol **7c**. The triketo acid failed to crystallize and no further purification was attempted.

3,5,7-Trioxotetradecanoic Acid (3d). Treatment of triketone **1d** by the sodium amide procedure gave less than 2% of the desired product. However, by the potassium amide procedure employed with **3c**, 5.65 g (0.025 mole) of triketone **1d** was added to 0.077 mole of potassium amide in 800 ml of liquid ammonia. Treatment with carbon dioxide gave after crystallization from hexane 2.0 g (30% yield) of triketo acid **3d**, mp 76–79°, as waxy, white plates. Recrystallization from hexane and then from benzene–hexane gave mp 83–84°; ν_{max}^{KBr} 2930, 2870, 1720, 1640, 1400, and 1290 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.25; H, 8.17.

3,5,7-Trioxododecanoic Acid (3e). By the procedure used for preparation of **3c**, 3.0 g (0.015 mole) of triketone **1e** was combined with 0.15 mole of potassium amide in 900 ml of liquid ammonia and then carboxylated in tetrahydrofuran. Isolation afforded 0.58 g (16%) of triketo acid **3e**, mp 74–78°. Five recrystallizations from chloroform–hexane gave mp 80–81°; ν_{max}^{KBr} 2930, 2870, 1715, 1620, 1400, and 1280 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.22; H, 7.39.

3,5,7-Trioxodecanoic Acid (3f) and 3,5,7-Trioxooctanoic Acid (3g). Similar treatment of mixtures of 3.4 g (0.020 mole) of triketone **1f** and 0.060 mole of potassium amide and of 2.8 g (0.020 mole) of triketone **1g** and 0.060 mole of potassium amide with carbon dioxide led to small amounts of liquids which contained the triketo acids **3f** and **3g**, respectively. The yield of **3f** appeared to be higher than that of **3g** although both were less than 5%. Tlc of the first of these with water-saturated 2-butanone indicated that the material was primarily the triketo acid **3f**. Tlc of the other product in the same solvent indicated the presence of triketone **1g** and another component, which was presumably **5g**, in addition to a low R_f material believed to be **3g**.

The use of sodium amide and of lithium amide in the preparation of **3f** was investigated without success.

Preparation of Triketo Esters 4. Methyl 7-Phenyl-3,5,7-trioxoheptanoate (4a). Approximately 1 equiv of diazomethane in ether was added dropwise to a slurry of 10.0 g (0.040 mole) of triketo acid **3a** in ether at 0°. After the addition was complete, approximately 1 ml of acetic acid was added. The solution was extracted with cold sodium bicarbonate solution to remove acetic acid and unreacted triketo acid. The ethereal solution was dried over magnesium sulfate and evaporated under reduced pressure. The residue was crystallized from cyclohexane to give 8.8 g (83% yield) of triketo ester **4a**, mp 67–74°. Recrystallization from ether–hexane and from hexane gave pale yellow needles: mp 73–76°; ν_{max}^{KBr} 1750, 1605, and 1580 cm^{-1}; λ_{max} 346 mμ (log ε 4.14), 280 sh (4.07), 250 (3.83), and 220 sh (3.83). The nmr spectrum was similar to that of triketo acid **3a** and indicated that the ester was a mixture of at least two enol forms.

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.36; H, 5.62.

Methyl 9-Phenyl-3,5,7-trioxo-8-nonenoate (4b). A solution of 1.00 g (0.0036 mole) of triketo acid **3b** in 100 ml of ether and 15 ml of ethanol was treated similarly with diazomethane to give 0.66 g (63%) of methyl ester **4b** as yellow-brown crystals, mp 84–87°. Recrystallization from ether–hexane gave flat, yellow needles: mp 88–90°; ν_{max}^{KBr} 1642, 1620, and 1582 cm^{-1}. Slightly higher melting points were observed when the material was heated rapidly.

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.56; H, 5.59.

Cyclization of Triketo Acids 3 to β-Resorcylic Acids 5. The general procedure involved addition of 0.1–0.7 g of triketo acid **3** in a minimum volume of ethanol to 10–50 ml of 0.5 *M* sodium acetate buffer, pH 5.0. The mixture was allowed to stand at ice or room temperature for 1–2 days. Samples were removed for tlc assay to assure that triketo acid utilization was essentially complete. The solutions were acidified with hydrochloric acid to pH 3. The less soluble resorcylic acids crystallized after the solutions were cooled and were separated by filtration. The more soluble ones were isolated by ether extraction. In cases where triketone and/or resorcinol appeared (tlc) to contaminate the product, purification was effected by dissolving in bicarbonate solution and reprecipitating with hydrochloric acid.

6-Phenyl-β-resorcylic Acid (5a). Triketo acid **3a** (0.100 g, 0.00040 mole) afforded 0.086 g (86% yield, assuming monohydration) of resorcylic acid **5a**, mp 118–123°, with dehydration. After dehydration at 58° and 0.1 mm for several hours, the melting point was 156–157° dec. Recrystallization from wet ether–hexane and drying gave white microcrystalline material: mp 157–158° dec; ν_{max}^{KBr} 3300, 3000, 1630, and 1450 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.51; H, 4.36.

Resorcylic acid **5a** was decarboxylated by heating at 130° for 1 hr to give 5-phenylresorcinol (**6a**): mp 156–157° (lit.[26] mp 157–158°); ν_{max}^{KBr} 3380, 1620, 1490, and 1360 cm^{-1}.

6-Styryl-β-resorcylic Acid (5b). Triketo acid **3b** (0.747 g, 0.00273 mole) afforded 0.611 g (88% yield) of crude resorcylic acid **5b**, mp 149–152°. Two recrystallizations from wet ether and four from

(26) C. M. Suter and P. G. Smith, *J. Am. Chem. Soc.*, **61**, 166 (1939).

ethanol–water gave white plates, mp 164–165°, with decarboxylation. Tlc indicated the material was homogeneous. However, it analyzed poorly as **5b**. Deviations in carbon–hydrogen were as great as 1% and varied with recrystallization and drying conditions. Neutralization equivalent determinations gave values ranging 7–17% high. The infrared spectrum (KBr) showed absorption at 3300, 3000, 1720, 1600, and 1460 cm^{-1}.

Decarboxylation of **5b** occurred quantitatively at 180° to give the corresponding resorcinol, pinosylvin (**7b**): mp 152–155° after sublimation (lit.[18a] mp 155.5–156°); ν_{max}^{KBr} 3300, 1600, and 1140 cm^{-1}.

Treatment of **7b** with acetic anhydride gave pinosylvin diacetate, mp 98–99°, after recrystallization from ethanol (lit.[18a] mp 100–101°).

Treatment of **5b** with diazomethane gave the corresponding methyl ester **6b**, mp 160–161°, after chromatography on silicic acid and recrystallization from chloroform. The infrared spectrum (KBr pellet) showed absorption at 3350, 1650, 1575, 1430, 1325, and 1260 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.98; H, 5.40.

6-Phenethyl-β-resorcylic Acid (5c). Crude triketo acid **3c** (0.150 g, 0.000543 mole) gave upon treatment by the general procedure a bicarbonate-soluble fraction, 0.086 g, and a bicarbonate-insoluble fraction, 0.061 g. Tlc showed that the bicarbonate-soluble fraction contained resorcylic acid **5c**, unaltered triketo acid **3c**, triketone **1c**, and resorcinol **7c**. Chromatography of the mixture on 10 g of 100-mesh silicic acid, eluting with mixtures of hexane and ether, gave 0.026 g (19% yield) of resorcylic acid **5c**. Recrystallization from benzene–hexane gave white plates: mp 154–156° dec; ν_{max}^{KBr} 3400, 3000, 1650, and 1260 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.95; H, 5.59.

Tlc indicated that the bicarbonate-insoluble fraction contained triketone **1c** and resorcinol **7c**.

Decarboxylation of **5c** (0.012 g, 0.000047 mole) at 160–190° and 0.5 mm gave dihydropinosylvin (**7c**, 0.0089 g, 89% yield) as a colorless oil. Bromination following the procedure of Birch, *et al.*,[5] gave 2,4-dibromo-5-phenethylresorcinol as long, white needles, mp 144–146° (lit.[5] mp 146.5–148°).

6-*n*-Heptyl-β-resorcylic Acid (Spheropherolcarboxylic Acid) (5d). Treatment of 0.239 g (0.00089 mole) of triketo acid **3d** by the general procedure gave 0.211 g (95% yield) of resorcylic acid **5d**: mp 130–135 and 142–144° (needles) after recrystallization from benzene (lit.[27] mp 140°); ν_{max}^{KBr} 3350, 2940, 2870, 1630, 1480–1450, and 1260 cm^{-1}.

Decarboxylation of **5d** at 170° gave after molecular distillation (130° at 0.3 mm) a viscous liquid which crystallized under pentane at −20° to afford a good yield of spheropherol (**7d**), mp 53–55°. The material was dissolved in dilute, aqueous base and reprecipitated with acetic acid to give hydrated crystals: mp 55–57° (lit.[28] mp 57° for the monohydrate); ν_{max}^{KBr} 3350, 2940, 2870, 1610, and 1150 cm^{-1}.

6-Amyl-β-resorcylic Acid (Olivetolcarboxylic Acid) (5e). Cyclization of 0.200 g (0.0083 mole) of triketo acid **3e** gave 0.180 g (97% yield) of resorcylic acid **5e**: mp 142.5–143° (lit.[29] mp 142°); ν_{max}^{KBr} 3390, 2940, 2870, 1630, and 1250 cm^{-1}.

6-Propyl-β-resorcylic Acid (Divaric Acid) (5f). The total sample of crude triketo acid **3f** was cyclized to give after recrystallization from benzene–hexane 0.070 g (1.6% yield based on triketone) of resorcylic acid **5f** as white leaflets: mp 180–181° dec (lit.[30] mp 179°); ν_{max}^{KBr} 3400, 2970, 2890, 1630, 1470–1450, and 1250 cm^{-1}.

6-Methyl-β-resorcylic Acid (Orsellinic Acid) (5g). The crude triketo acid **3g** was cyclized to give, after sublimation of residual triketone **1g** and column chromatography on silicic acid, 0.006 g (<0.2% yield based on triketone) of resorcylic acid **5g**: mp 173.5–175° (lit.[30] mp 176°); ν_{max}^{KBr} 1630, 1460, 1360, and 1270 cm^{-1}.[31]

Cyclizations of Triketo Esters 4. Aldol Cyclization of Ester 4a. A solution of 0.197 g (0.00075 mole) of ester **4a** in 2 ml of tetrahydrofuran was added to 20 ml of 1 *M* potassium phosphate buffer, pH 8.5, at room temperature. An oil separated that crystallized and gradually redissolved. After 72 hr, the solution was acidified with concentrated hydrochloric acid and was partially evaporated under reduced pressure to remove tetrahydrofuran. Extraction with ether gave after evaporation 0.169 g (92% yield) of methyl 6-phenyl-β-resorcylate (**6a**), mp 119–121°. Chromatography on silicic acid and recrystallization from chloroform–hexane gave mp 120–121°: ν_{max}^{KBr} 3340, 1655, 1435, 1320, and 1170 cm^{-1}; λ_{max} 303 mμ (log ε 3.77), 264 (4.03), and 226 (4.40); δ 3.42 (singlet, 3 H, methyl), 6.30 (doublet, J = 2.5 cps, 1 H, ring H), 6.48 (doublet, J = 2.5 cps, 1 H, ring H), 7.0–7.5 (multiplet, 5 H, phenyl), and 11.3 ppm (broad singlet, 2 H, hydroxyls).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.75; H, 4.99.

The product was identical in all respects with the methyl ester prepared by treatment of 6-phenyl-β-resorcylic acid with diazomethane in ethereal solution.

Aldol cyclization was also observed when **4a** was treated with 10% methanolic potassium hydroxide for 17 hr at room temperature. No trace of benzoylphloroglucinol could be detected by tlc. A similar result was obtained with magnesium methoxide in methanol, with 1 *M* tris(hydroxymethyl)aminomethane hydrochloride buffer, pH 8.5, containing 1 *M* magnesium chloride, and with saturated aqueous magnesium hydroxide.

Claisen Cyclization of Ester 4a. Treatment of 0.500 g (0.0019 mole) of ester **4a** with 10 ml of aqueous 2 *M* potassium hydroxide at −5° for 19 hr gave, after acidification with hydrochloric acid, extraction with ether, drying, and evaporation of the solvent, an oily residue which tlc indicated contained two major components: methyl 6-phenyl-β-resorcylate (**6a**) and benzoylphloroglucinol (**8a**). Traces of resorcylic acid **5a** and resorcinol **7a** were present also. Nmr assay of the mixture indicated that it contained on a molar basis 66% of **8a** and 34% of **5a** and **6a**. Resorcinol **7a** was not detected by this method. Chromatography of the oil on silicic acid with hexane–ether mixtures gave after dehydration at 100° *in vacuo* 0.207 g (47% yield) of benzoylphloroglucinol (**8a**), mp 157–162 and 165–166° after recrystallization from chloroform (lit.[7] mp 165°). A mixture melting point with authentic material was undepressed. When the cyclization was carried out at 25°, the yield of **8a** decreased significantly.

Cyclization of **4a** in the presence of a mixture of magnesium hydroxide and potassium hydroxide gave a similar mixture of phloroglucinol **8a** and resorcinol derivatives.

Aldol Cyclization of Ester 4b. A solution of 0.0579 g (0.00020 mole) of ester **4b** in 2 ml of tetrahydrofuran was added to 15 ml of 1 *M* tris(hydroxymethyl)aminomethane hydrochloride buffer, pH 8.5, and the mixture was stored under nitrogen for 8 hr at room temperature. The solution was partially evaporated under reduced pressure, acidified with hydrochloric acid, and extracted with ether. Tlc of the extract indicated the presence of resorcylic ester **6b** and some unreacted starting material. Chromatography of the material on silicic acid in ether–hexane gave 0.0372 g (69% yield) of methyl 6-styryl-β-resorcylate (**6b**), mp 155–157 and 160–161°, after recrystallization from chloroform. Admixture with ester prepared above by methylation of **5b** gave an undepressed melting point.

Claisen Cyclization of Ester 4b. Ester **4b** (0.100 g, 0.000347 mole) in 20 ml of methanol was added with vigorous stirring to 330 ml of aqueous 2 *M* potassium hydroxide at −5°. After 40 min, the solution was poured into excess 5 *M* hydrochloric acid at 0° and the mixture was extracted with ether. The ethereal extract was dried over magnesium sulfate and evaporated. Tlc indicated that the residue contained cinnamoylphloroglucinol (**8b**), methyl resorcylate **6b**, flavanone **9**, triketo ester **4b**, and two unidentified components. Chromatography on silicic acid with ether–pentane gave as the final component 0.076 g (82% yield) of yellow solid, which was crude cinnamoylphloroglucinol (**8b**), mp 169–171°. The molten material in the melting point capillary underwent immediate conversion into flavanone **9**, mp 197–199°. The crude cinnamoylphloroglucinol was heated at 190° at atmospheric pressure for 1 min and then sublimed at 150–210° and 0.3 mm to give 0.056 g (63% yield based on **4b**) of 5,7-dihydroxyflavanone (pinocembrin) (**9**): mp 192–197 and 201–202° (Kofler) after recrystallization from methanol–water (lit.[8] mp 203–204°); λ_{max} 291 mμ (log ε 4.27) (lit.[32] λ_{max}^{EtOH} 290 mμ (log ε 4.22)). The infrared spectrum was essentially identical with a reported spectrum.[33]

(27) A. Hasimoto, *J. Pharm. Soc. Japan*, **58**, 776 (1938); *Chem. Abstr.*, **33**, 2504 (1939).
(28) Y. Asahina, *Ber.*, **69B**, 1643 (1936).
(29) Y. Asahina and M. Yasue, *ibid.*, **70B**, 206 (1937).
(30) O. Hesse, *Ann.*, **139**, 35 (1866).
(31) The isolation of this compound was carried out by Dr. C. M. Harris.
(32) M. Suzuki, *Nippon Kagaku Zasshi*, **76**, 1389 (1955); "Organic Electronic Spectral Data," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p 439.
(33) L. H. Briggs and L. D. Colebrook, *Spectrochim. Acta*, **18**, 939 (1962).

Comparable treatment of **4b** with 2 *M* methanolic potassium hydroxide at −5° for 40 min gave mainly aldol cyclization. Resorcylic ester **6b** was isolated in 49% yield by crystallization from chloroform. The nmr spectrum of the supernatant solution indicated that it contained principally resorcylic ester **6b** and unaltered triketo ester **4b** in approximately equal quantities.

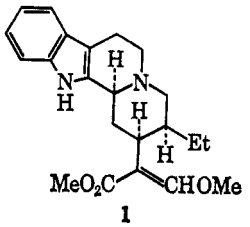
General Methods of Synthesis of Indole Alkaloids. VI. Syntheses of *dl*-Corynantheidine and a Camptothecin Model[1,2]

Ernest Wenkert, K. G. Dave, R. G. Lewis, and Peter W. Sprague

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401. *Received July 26, 1967*

Abstract: The alkaloid corynantheidine has been synthesized by a reaction scheme involving most importantly hydrogenation of an N-alkylnicotinic ester salt and acid-induced, hydrolytic, and decarboxylative cyclization of the resultant tetrahydropyridine derivative. An early synthetic intermediate, 4-methyl-5-ethylnicotinonitrile, has been employed in a four-step conversion into a heteropentacyclic compound structurally closely related to the alkaloid camptothecin. A possible biosynthetic relationship of the latter with indole alkaloids is portrayed.

The recent synthesis of eburnamonine[3] introduced a new procedure for the construction of the indoloquinolizidine skeleton common to a large group of indole alkaloids. It is based on the palladium-catalyzed, partial hydrogenation of 1-[β-(3-indolyl)ethyl]-3-acylpyridinium salts and the acid-induced cyclization of the resultant 2-piperideines. Since the first utilization of this reaction scheme it has been shown to be most successful in cases of employment of N-alkylnicotinic ester salts.[2] Furthermore its first step, the unusual hydrogenation, has been shown to be a general process.[4] Thus the time appeared ripe for the application of the two-step reaction scheme to the synthesis of further indole alkaloids. The present communication describes the synthesis of *dl*-corynantheidine (**1**)[5] and the utilization of an early intermediate in the synthesis of a heteropentacyclic substance structurally closely related to camptothecin (**2**).[6]



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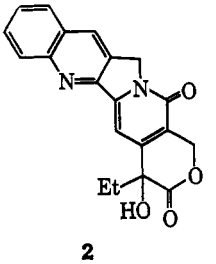
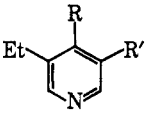
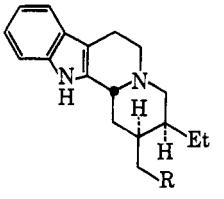


2

Corynantheidine (1). Methyl 4-carbomethoxymethyl-5-ethylnicotinate (**3a**), a vital intermediate in the syntheses of 3-isocorynantheidol (**4a**) and corynantheidol (**5a**),[2] served as starting material for the synthesis of the indole alkaloid. Alkylation of **3a** with tryptophyl bromide yielded a salt which was characterized as the perchlorate **6**. Palladium-induced hydrogenation of the latter produced the tetrahydropyridine **7**.



3a, R = CH_2CO_2Me; R′ = CO_2Me
b, R = Me; R′ = CN



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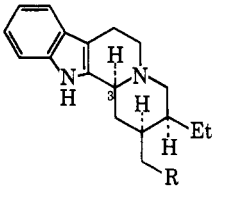
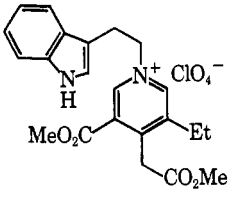
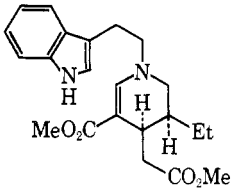


5

a, R = CH_2OH
b, R = CO_2Me



6



7

Two methods for the cyclization and decarboalkoxylation of tetrahydronicotinates of structure type **7** had been developed[2] and both were applied in the present investigation. Alkaline hydrolysis of the vinylogous urethan **7** followed by reesterification with methanolic acid led to the tetracyclic ester **4b**, isolated as its hydrochloride. Dehydrogenation of the product with palladium black in aqueous maleic acid solution yielded a tetradehydro substance which could be characterized as the perchlorate **8b**. Reduction of the latter with sodium borohydride afforded the ester **5b**, isolated as its hydrochloride. The ester conversion, **4b** into **5b**,

(1) This work was supported by the U.S. Department of Health, Education and Welfare (Grant GM-11571).
(2) Part V: E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, **87**, 5461 (1965).
(3) E. Wenkert and B. Wickberg, *ibid.*, **87**, 1580 (1965).
(4) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, in press.
(5) (a) M.-M. Janot, R. Goutarel, and J. Chabasse-Massoneau, *Bull. Soc. Chim. France*, 1033 (1953); (b) M.-M. Janot, R. Goutarel, A. LeHir, G. Tsatsas, and V. Prelog, *Helv. Chim. Acta*, **38**, 1073 (1955); (c) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).
(6) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *ibid.*, **88**, 3888 (1966).