[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MARYLAND]

Podophyllotoxin and Picropodophyllin. II.[1] The Synthesis of an Open-Chain Analog[2]

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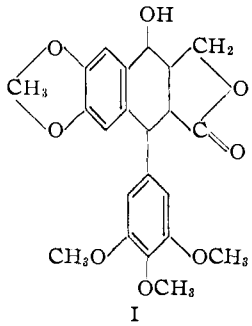
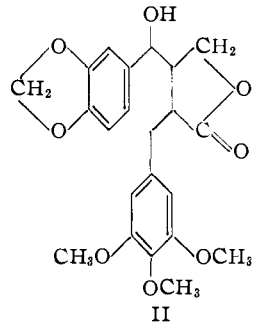
The synthesis of α-(3,4,5-trimethoxybenzyl)-β-(α'-hydroxy-3,4-methylenedioxybenzyl)-butyrolactone (II), an open-chain analog of podophyllotoxin, is described. In addition, the stripped, open-chain analog, α-benzyl-β-(α'-hydroxybenzyl)-butyrolactone (XVII) is reported.

Despite the damaging effect of podophyllotoxin (I)[4] on malignant tumors,[5] its use in cancer therapy has been prevented by its toxicity. This fact has prompted a search for analogs retaining the desirable properties of podophyllotoxin but having lower toxicities.[6] The sequel reports the synthesis of an open-chain analog II of podophyllotoxin. The analog II bears the same relationship to podophyllotoxin as does matairesinol to conidendrin.



I

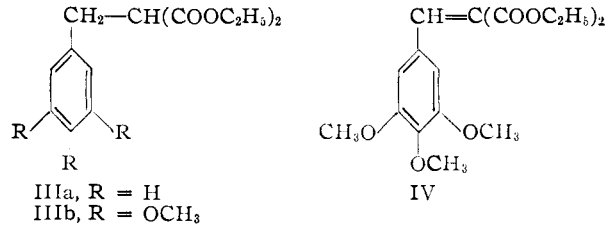


II

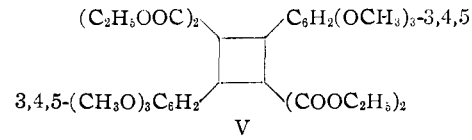
The synthetic route to II was explored using the more accessible unsubstituted series, a, and the procedures developed were applied with minor modifications to the substituted series, b.

The synthesis of ethyl 3,4,5-trimethoxybenzylmalonate (IIIb) was accomplished by a variation of the procedure described by Cook and co-workers.[7] 3,4,5-Trimethoxybenzyl alcohol was prepared by reduction of ethyl 3,4,5-trimethoxybenzoate with lithium aluminum hydride, or, in lower yield, by a similar reduction of 3,4,5-trimethoxybenzoic acid. Conversion of the alcohol to 3,4,5-trimethoxybenzyl chloride by thionyl chloride, followed by reaction of the chloride with ethyl sodiomalonate in excess ethyl malonate afforded IIIb in 61% yield based on 3,4,5-trimethoxybenzoic acid.

As an alternative route to IIIb, the Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde with ethyl malonate and subsequent hydrogenation of the benzylidenemalonate IV led to IIIb in 64% yield based on the aldehyde. On prolonged standing, IV was partially converted to a product believed to be the dimer V.[8]

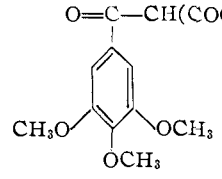


R IV



V

An attempted synthesis of IIIb by the catalytic hydrogenation of ethyl 3,4,5-trimethoxybenzoylmalonate (VI) was unsuccessful. Although ethyl benzoylmalonate can be reduced catalytically to ethyl benzylmalonate in the presence of strong acids,[9] VI underwent cleavage to 3,4,5-trimethoxybenzaldehyde and ethyl malonate under a variety of conditions. Further reduction of the aldehyde to the alcohol took place in the presence of platinum and hydrogen. Tarbell and co-workers[10] reported an attempt to prepare β-(3,4,5-trimethoxyphenyl)-propionic acid by the hydrogenation of VI followed by acid hydrolysis and decarboxylation of the presumed intermediate IIIb. We have shown that their unidentified product, m.p. 201–202°. is undoubtedly 1,2.3,5,6,7-hexamethoxy-9,10-dihydroanthracene (VII) which was first obtained by Cook and co-workers[7] from the reaction of syringyl alcohol with methyl *p*-toluenesulfonate. Under the hydrolytic conditions employed by Tarbell 3,4,5-trimethoxybenzyl alcohol, the secondary product of reductive cleavage of VI, affords a low yield of VII.



VI

(1) Previous paper, N. L. Drake and E. H. Price, THIS JOURNAL, **73**, 201 (1951).

(2) From a thesis submitted to the Graduate School of the University of Maryland by William B. Tuemmler in partial fulfillment of the requirements for the Ph.D. degree, July, 1953.

(3) University of Maryland Research Fellow, 1951–1952, supported by a grant-in-aid from the National Cancer Institute, National Institutes of Health. Du Pont Fellow, 1952–1953.

(4) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **73**, 2909 (1951), have assigned structure I to podophyllotoxin. These authors, *ibid.*, **75**, 5916 (1953), have also investigated the stereochemistry of podophyllotoxin and its C-3 epimer, picropodophyllin.

(5) J. L. Hartwell and M. J. Shear, *Can. Research*, **7**, 716 (1947).

(6) (a) K. N. Campbell, J. A. Cella and B. K. Campbell, THIS JOURNAL, **75**, 4681 (1953); (b) G. N. Walker, *ibid.*, **75**, 3387, 3393 (1953).

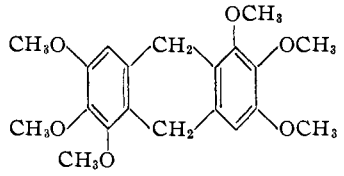
(7) J. W. Cook, W. Graham, A. Cohen, R. W. Lapsley and C. A. Lawrence, *J. Chem. Soc.*, 322 (1944).

(8) This assignment is by analogy to the well known dimerizations of cinnamic acid to α-truxillic acid and ethyl methylenemalonate to 1,1,3,3-tetracarbethoxycyclobutane (P. Karrer, "Organic Chemistry," 3rd edition, Elsevier Publishing Co., New York, N. Y., 1947, p. 636).

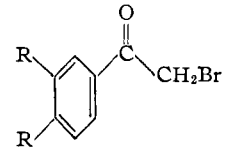
(9) K. Kindler and L. Blaas, *Ber.*, **76B**, 1211 (1943).

(10) H. T. Huang, D. S. Tarbell and H. R. V. Arnstein, THIS JOURNAL, **70**, 4181 (1948).

The method of Walker and Hauser[11] was used to prepare 3,4-methylenedioxyacetophenone, which upon bromination afforded VIIIb in 63% yield based on piperonylic acid.



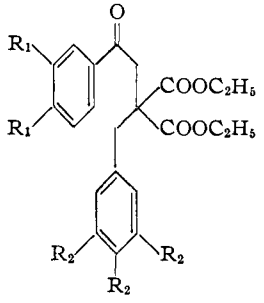
VII



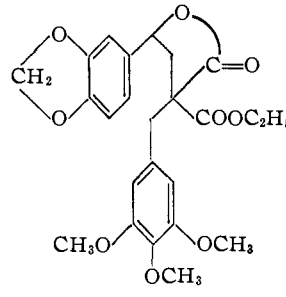
VIIIa, R = H
VIIIb, RR = OCH_2O

The phenacylation step was conducted by a modification of the procedure of Lund.[12] This method is reported applicable to halides of the type $=C(R)CH_2X$, but has not been used with phenacyl halides. In preliminary experiments, the reaction of phenacyl bromide with a small excess of ethyl ethoxymagnesiomalonate afforded a considerable proportion of ethyl diphenacylmalonate in addition to ethyl phenacylmalonate. Diphenacylation was somewhat unexpected in view of the ease of monoacylation of ethyl malonate by this procedure. Apparently the failure of the initially formed monosubstituted product to form an insoluble magnesium complex, as happens in the acylation procedure, permits exchange to occur and disubstitution results.

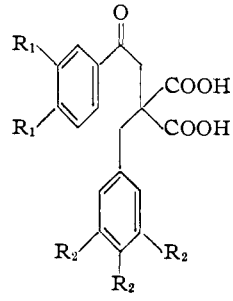
Hydrogenation of IXb proceeded slowly over palladium–charcoal to give a low yield of material believed to be the lactone ester X. By contrast, the unsubstituted keto diester IXa was invariably converted by hydrogenolysis to the methylene derivative when attempts were made to reduce its carbonyl catalytically.



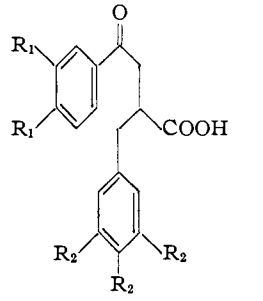
IXa, $R_1 = R_2 = H$
IXb, $R_1R_1 = O—CH_2—O$
$R_2 = OCH_3$



X

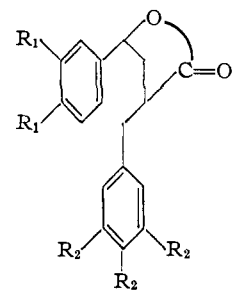


XIa, $R_1 = R_2 = H$
XIb, $R_1R_1 = O—CH_2—O$,
$R_2 = OCH_3$

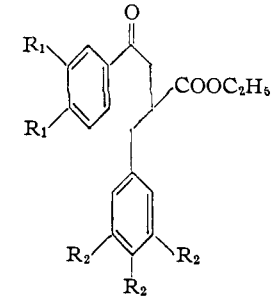


XIIa, $R_1 = R_2 = H$
XIIb, $R_1R_1 = O—CH_2—O$
$R_2 = OCH_3$

The keto diesters IXa and b were best saponified by employing a large excess of concentrated alcoholic potassium hydroxide and isolating the potassium salt which precipitated. More conventional techniques gave lower yields of less pure product. Thermal decarboxylation of the keto malonic acids XIa and b proceeded readily to give the keto acids XIIa and b. Reduction of XIIb by sodium borohydride afforded the lactone XIIIb. Repeated attempts to formylate the keto esters XIVa and b failed to afford more than traces of enolic material (see following paper).



XIIIa, $R_1 = R_2 = H$
XIIIb, $R_1R_1 = OCH_2O$,
$R_2 = OCH_3$



XIVa, $R_1 = R_2 = H$
XIVb, $R_1R_1 = —O—CH_2—O$
$R_2 = OCH_3$

The reaction of XIIa with a small excess of formaldehyde produced a mixture of isomeric keto lactones XVa from which a crystalline racemate was isolated. When a large excess of formaldehyde was employed, the keto methylol lactone (XVI) was obtained in addition to XVa.[13] While XVa readily formed a 2,4-dinitrophenylhydrazone, the keto methylol lactone failed to react. Similar feeble carbonyl activity was observed by Haworth and Sheldrick[14] in a closely related keto methylol lactone.

Hydrogenation of crystalline XVa proceeded rapidly in either ethanol or cyclohexane to afford a 40% yield of crystalline material which persisted in melting over a ten-degree range despite recrystallizations from different solvents. Analysis indicated the presence of an impurity of higher carbon content, although the data were in better agreement with the hydroxy lactone structure than any other reasonable alternative. The non-crystalline keto lactone was also easily hydrogenated over palladium–charcoal to an isomeric, sharp-melting hydroxy lactone.

The reaction of the substituted keto acid XIIb with formaldehyde in aqueous alkali afforded a mixture from which a 63% yield of the methylol acid XVIII was isolated. The failure of XVIII to lactonize spontaneously was apparently due to its intermediate precipitation from the aqueous mixture; upon melting, the substance underwent lactonization. The lactone XVb was also obtained when an aqueous alcoholic solution of the sodium salt of XVIII was acidified and precipitation took place slowly.

When the keto lactone XVb was boiled with excess dilute alkali, the original formaldehyde conden-

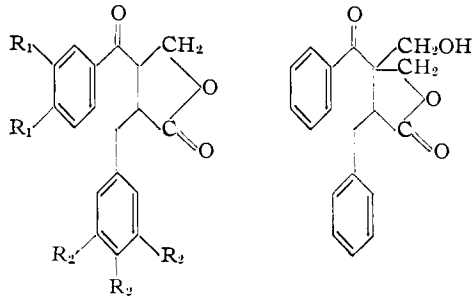
(11) H. G. Walker, Jr., and C. R. Hauser, THIS JOURNAL, **68**, 1386 (1946).

(12) H. Lund, *Ber.*, **67B**, 935 (1934).

(13) Compare with the results obtained by Campbell and coworkers, ref. 6a.

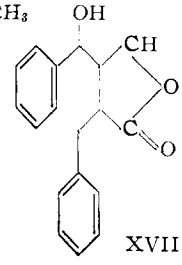
(14) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 289 (1941).

sation was reversed, and the keto acid XIIb was isolated.



XVa, $R_1 = R_2 = H$
XVb, $R_1R_1 = OCH_2O$,
$R_2 = OCH_3$

XVI



XVII

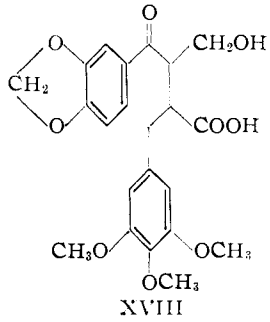
Hydrogenation of the keto lactone XVb proceeded with the absorption of one molar equivalent of hydrogen. The product II, which crystallized with difficulty, absorbed at 2.80 μ (hydroxyl) and 5.67 μ (γ-lactone carbonyl).[15]

The non-crystalline fraction from the formaldehyde condensation with XIIb was hydrogenated in the hope of obtaining an isomer of II. However, the only crystalline product isolated was a heat-stable acid for which structure XIX is suggested.

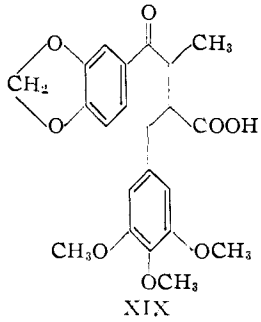
The absorption of this substance in the infrared supports the structure proposed. The compound shows weak absorption at 2.86 μ and a broad intense band with a maximum at 3.28 μ, the latter in the region of CH stretching. A sharp, intense peak at 5.86 μ undoubtedly is caused by carbonyl stretching.

Comparison of the spectrum of XIX with that of XIIb shows a striking resemblance between the two, particularly in the 5–8 μ region. In the 3.28 μ region, however, XIIb absorbs far less than XIX, a fact which is in accord with the structure proposed.

One would not expect the carbonyl of XIX to escape reduction under the conditions employed;



XVIII



XIX

(15) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949), report absorption at 5.65μ due to carbonyl stretching in γ-lactones.

however the failure of the substance to yield a 2,4-dinitrophenylhydrazone indicates feeble carbonyl activity, and is in keeping with the observed behavior of XVI and similar compounds.[14]

Experimental[16]

Ethyl 3,4,5-Trimethoxybenzoate.—This ester was conveniently prepared from 3,4,5-trimethoxybenzoic acid[17] using *p*-toluenesulfonic acid as the catalyst; water was removed from the mixture as the ternary azeotrope with benzene. On a one mole scale, a 95% yield of product, b.p. 117° (1 mm.), m.p. 52.5–54.5° (lit.[18] 53–55°), was obtained.

3,4,5-Trimethoxybenzyl Alcohol.—A solution of 24.0 g. (0.1 mole) of ethyl 3,4,5-trimethoxybenzoate in 50 ml. of tetrahydrofuran was added over a period of 20 minutes to 50 ml. of 2.1 *M* lithium aluminum hydride in tetrahydrofuran under nitrogen. Gentle refluxing was continued for 2 hours. The clear, chilled mixture was then decomposed by the cautious addition of water followed by 10% sulfuric acid. The aqueous phase was extracted thoroughly with ether, and the combined organic solutions were washed with 5% sodium bicarbonate and dried over magnesium sulfate. Distillation afforded 15.6 g. (79%) of viscous oil, b.p. 115–120° (0.03 mm.).

Incomplete reduction took place when ether was used as the solvent.[19] The use of tetrahydrofuran also permitted the reduction of 3,4,5-trimethoxybenzoic acid. A mixture of 25.2 g. (0.119 mole) of acid and 5.0 g. (0.12 mole) of lithium aluminum hydride in 185 ml. of tetrahydrofuran was heated under reflux for 21 hours. After working up the mixture as above, there was obtained 13.7 g. (58%) of alcohol, b.p. 115–120° (0.02 mm.), $n^{25}D$ 1.5431.

3,4,5-Trimethoxybenzyl Chloride.—A stirred, chilled solution of 15.6 g. (0.0785 mole) of 3,4,5-trimethoxybenzyl alcohol and 9.7 g. (0.080 mole) of dimethylaniline in 100 ml. of anhydrous benzene was slowly treated with 9.4 g. (0.079 mole) of pure thionyl chloride dissolved in 25 ml. of benzene. The mixture was warmed to room temperature, then heated under reflux for 1 hour; it was then cooled and treated with 30 ml. of 1:5 hydrochloric acid. The organic phase was freed of acid and concentrated. Distillation of the residue afforded 15.0 g. (88.5%) of 3,4,5-trimethoxybenzyl chloride, b.p. 110° (0.1 mm.), m.p. 58–61°. Recrystallization of the distillate from petroleum ether gave 12.9 g. (76%) of white crystals, m.p. 60–62° (lit.[7] m.p. 60–61°).

Better over-all yields were obtained if the crude alcohol was used directly. Thus, 56.9 g. of ethyl 3,4,5-trimethoxybenzoate was converted to 38.8 g. (76% over-all) of the chloride, m.p. 59.5–61.0°.

Ethyl 3,4,5-Trimethoxybenzylmalonate (IIIb).—A solution of 15.4 g. (0.61 mole on the basis of 95% purity) of sodium hydride in 550 ml. of ethyl malonate was treated during 1 hour with 131 g. (0.606 mole) of 3,4,5-trimethoxybenzyl chloride, m.p. 60–62°, dissolved in 350 ml. of ethyl malonate. The resulting mixture was heated at 105–110° for 20 hours. The cooled mixture was then treated with a few drops of acetic acid and 50 ml. of water, and the amber solution was decanted from the coagulated salt. Removal of excess ethyl malonate left a residue which was recrystallized from 2.5 l. of petroleum ether to afford 172.5 g. (84%) of white needles, m.p. 77.0–79.0° (lit.[20] m.p. 67–71°). Further recrystallization from petroleum ether afforded material, m.p. 78.0–79.0°. *Anal.* Calcd. for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.75, 59.84; H, 7.15, 7.10.

(16) Melting points are corrected; boiling points are uncorrected. The petroleum ether employed was the 60–80° fraction (Skelly B) supplied by the Skelly Oil Co.

(17) M. T. Bogert and B. B. Coyne, THIS JOURNAL, **51**, 571 (1929).

(18) J. Herzig, *Monatsh.*, **33**, 846 (1912).

(19) While this work was in progress, a report appeared (M. U. Tsao, THIS JOURNAL, **73**, 5495 (1951)) describing the lithium aluminum hydride reduction of methyl 3,4,5-trimethoxybenzoate in ethereal solution (yield 73%). Our experience with the ethyl ester indicated that reduction was incomplete even with excess reducing agent and prolonged reaction time. This may have been due to mechanical difficulties caused by the separation of a gummy complex from the ether solution.

(20) Material prepared in low yield by treating an ethanolic solution of ethyl sodiomalonate with 3,4,5-trimethoxybenzyl chloride (ref. 7) had a lower, broad melting range

Ethyl 3,4,5-Trimethoxybenzylidenemalonate (IV).—A solution of 0.75 g. (0.0038 mole) of 3,4,5-trimethoxybenzaldehyde, m.p. 73.8–75.0°, 0.63 g. (0.0039 mole) of ethyl malonate, 0.45 g. (0.0039 mole) of caproic acid and 0.15 g. (0.0018 mole) of piperidine in 35 ml. of benzene was heated under reflux until no more water was collected in a Dean–Stark trap.[21] The solution was washed with water and 5% sodium bicarbonate and concentrated. Recrystallization of the residue from 25 ml. of petroleum ether afforded 0.95 g. (74%) of product, m.p. 68–70°. An analytical sample, m.p. 69.2–70.4°, was prepared by recrystallization from petroleum ether. *Anal.* Calcd. for $C_{17}H_{22}O_7$: C, 60.34; H, 6.56. Found: C, 60.45; H, 6.67.

Approximately one-half of a sample of IV which had stood at room temperature for 20 months no longer dissolved in boiling petroleum ether. Recrystallization from benzene–petroleum ether afforded material, m.p. 212–213°. *Anal.* Found: C, 60.49; H, 6.70. The essential identity of this analysis with that reported above, as well as the mode of formation of the high melting substance, makes it seem likely that the product, m.p. 212–213°, is a dimer, probably 1,3-bis-(3,4,5-trimethoxyphenyl)-2,2,4,4-tetracarbethoxycyclobutane (V).[8]

The catalytic hydrogenation of IV over Adams catalyst proceeded readily to give ethyl 3,4,5-trimethoxybenzylmalonate (IIIb), identical with material prepared in the alternative fashion.

Ethyl 3,4,5-Trimethoxybenzoylmalonate (VI).—Although this material could be prepared as described[10] from 3,4,5-trimethoxybenzoyl chloride and a suspension of ethyl sodiomalonate in benzene, some improvement in yield and convenience resulted from the use of Lund's procedure[12] as modified by Walker and Hauser.[11] From 155 g. (0.674 mole) of 3,4,5-trimethoxybenzoyl chloride[22] there was obtained 217 g. (91%) of white solid, m.p. 90.5–91.5°, which crystallized from 1.2 l. of 50% aqueous ethanol. It was important to conduct the recrystallization as quickly and at as low a temperature (50–60°) as possible to obtain good recovery.

Hydrogenation of VI.—A mixture of 4.5 g. (0.013 mole) of VI and 2.0 g. of 10% palladium–charcoal in 100 ml. of absolute ethanol was shaken at room temperature with hydrogen under pressure of 2.5 atmospheres. After the rapid absorption of 1 molar equivalent of hydrogen, absorption ceased. The crystalline residue obtained after removal of the catalyst and solvent was recrystallized from 50 ml. of petroleum ether to afford 2.4 g. (94%) of crude 3,4,5-trimethoxybenzaldehyde, m.p. 60–67°. An analytical sample melted at 73.4–74.0° (lit.[10] m.p. 74–75°). *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.42, 61.36; H, 6.40, 6.20.

When the hydrogenation of VI was conducted using Adams catalyst, a rapid absorption of two molar equivalents of hydrogen took place. Distillation of the resulting oil afforded a 59% yield of ethyl malonate and a 68% yield of 3,4,5-trimethoxybenzyl alcohol, identified by conversion to the chloride in good yield.

1,2,3,5,6,7-Hexamethoxy-9,10-dihydroanthracene (VII).—A solution of 1.0 g. of 3,4,5-trimethoxybenzyl alcohol in 20 ml. of 10% sulfuric acid was boiled for 3 hours. The insoluble material which separated was taken up in ether, and the solution was filtered to remove carbonaceous material. Upon slow evaporation, the ethereal solution deposited a small quantity of crystalline solid. After two recrystallizations from ethanol, there was obtained 20 mg. of product, m.p. 201.5–203° (lit. m.p.[7] 201–202°). *Anal.* Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; OCH_3, 51.67. Found: C, 66.57, 66.82; H, 6.58, 6.75; OCH_3, 51.66.

3,4-Methylenedioxybenzoyl Chloride.—A mixture of 113.5 g. (0.684 mole) of piperonylic acid,[23] m.p. 230–232°, and 123 ml. (1.71 moles) of pure thionyl chloride was heated under reflux for 5 hours. After removal of excess thionyl chloride, distillation of the residue afforded 124 g. (98.5%) of colorless product, b.p. 92° (0.02 mm.), m.p. 78–83°, which was pure enough to use directly.

When the acid chloride was prepared according to published directions[24] calling for the use of benzene as a diluent, there was obtained a considerable amount of piperonylic anhydride, m.p. 152.6–154.2°, which could be recrystallized from ethanol. *Anal.* Calcd. for $C_{16}H_{10}O_7$: C, 61.15; H, 3.21. Found: C, 61.43; H, 3.43. Hydrolysis to piperonylic acid, m.p. 231–233°, was accomplished using boiling 107% sodium hydroxide.

Ethyl 3,4-Methylenedioxybenzoylmalonate.—An ethereal solution of 0.85 mole of ethyl ethoxymagnesiomalonate was treated with a solution of 139 g. (0.755 mole) of 3,4-methylenedioxybenzoyl chloride in 1 l. of ether. The mixture was heated under reflux for 0.5 hour, then cooled and acidified with 10% sulfuric acid. Upon standing overnight, the ethereal solution deposited large, white crystals, a few of which were withdrawn and recrystallized from a mixture of ethyl acetate and petroleum ether to afford a product, m.p. 69.5–71.0°. *Anal.* Calcd. for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.47, 58.45; H, 5.39, 5.28. The crude material obtained by evaporation of the ether was used directly in the next step.

3,4-Methylenedioxyacetophenone.—The crude residue from the above experiment was boiled for 5 hours with a mixture of 210 ml. of acetic acid, 140 ml. of water and 27 ml. of sulfuric acid. The orange-red solution was made alkaline with 40% hydroxide, and the mixture was thoroughly extracted with ether. The ethereal solution was washed with water, dried and concentrated, and the residue was recrystallized from 3 l. of petroleum ether to give 97 g. (78%) of pale yellow solid, m.p. 84–87° (lit.[25] m.p. 87–88°). Acidification of the aqueous solution afforded 6.4 g. of piperonylic acid, m.p. 230°.

α-Bromo-3,4-methylenedioxyacetophenone (VIIIb).—A suspension of 49.2 g. (0.30 mole) of 3,4-methylenedioxyacetophenone in 1.5 l. of ice-cold, anhydrous ether was treated with 48 g. (0.30 mole) of bromine during 40 minutes. The ether was immediately removed at the aspirator, and the brick-red residue was treated with 500 ml. of water. The solid was washed with more water and recrystallized from 4 l. of petroleum ether (carbon). There was obtained 56 g. (77%) of white plates, m.p. 90–92.5° (lit.[26] m.p. 86–87°). Omission of the carbon treatment afforded a product which soon became pink.

Phenacylation of Ethyl Malonate.—An ethereal solution of 0.11 mole of ethyl ethoxymagnesiomalonate was treated with 19.9 g. (0.10 mole) of phenacyl bromide dissolved in dry ether. The resulting solution was heated under reflux for 1.5 hours, cooled and acidified with 75 ml. of 10% sulfuric acid. The oil obtained by concentrating the ether solution deposited 3 g. of solid, m.p. 117–120°. A purified sample, m.p. 120.0–121.2°, gave analytical data in agreement with ethyl diphenacylmalonate. *Anal.* Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.82; H, 6.04; (lit.[27] m.p. 118–119°).

Distillation of the remaining oil afforded 8.2 g. of ethyl malonate, 3.1 g. of phenacyl bromide and 9.1 g. of ethyl phenacylmalonate.

Ethyl Benzylphenacylmalonate (IXa).—A mixture of 2.43 g. (0.10 mole) of magnesium, 2.5 ml. of absolute ethanol and 0.25 ml. of carbon tetrachloride was treated with a solution of 25.0 g. (0.10 mole) of ethyl benzylmalonate (b.p. 100° (0.03 mm.), $n^{22}D$ 1.4862) in 10 ml. of absolute ethanol. After heating under reflux for 1.5 hours, the evolution of hydrogen ceased. The clear solution was treated with 150 ml. of dry benzene, and the excess ethanol was removed as the benzene azeotrope. A solution of 19.9 g. (0.10 mole) of phenacyl bromide in 125 ml. of benzene was added all at once, and the amber solution allowed to stand at room temperature for 7 days. It was then acidified with 75 ml. of 10% sulfuric acid. The residue obtained upon concentration of the benzene solution was recrystallized from 400 ml. of petroleum ether to give 29.8 g. (81%) of white crystals, m.p. 75–77°.

Ethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (IXb).—An alcohol-free benzene solution of 0.23 mole of ethyl 3,4,5-trimethoxybenzylethoxymagnesiomalonate was prepared as described above except that

(21) The procedure employed is that of E. F. Pratt and E. Werble, THIS JOURNAL, **72**, 4638 (1950). The use of piperidine benzoate in ethanol at room temperature afforded only a 35% yield.

(22) W. Reeve and J. D. Sterling, Jr., *ibid.*, **71**, 3657 (1949).

(23) R. L. Shriner and E. C. Kleiderer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 538.

(24) F. N. Bruchhausen and H. Gerhard, *Ber.*, **72B**, 830 (1939).

(25) F. Mautner, *J. prakt. Chem.*, **116**, 321 (1927).

(26) E. Späth and E. Lederer, *Ber.*, **63B**, 743 (1930). The photochemical bromination described by these authors afforded only a 40% yield upon repetition.

(27) W. Kues and C. Paal, *Ber.*, **19**, 3144 (1886).

a benzene solution of IIIb was added initially. The clear solution was treated with 56 g. (0.23 mole) of VIIIb dissolved in 1 l. of benzene. After 7 days at room temperature, the yellow-green solution was acidified with 100 ml. of 10% sulfuric acid. The benzene solution was freed of acid and concentrated, and the residue was recrystallized from 2 l. of 50% aqueous alcohol. There was obtained 95 g. (82%) of the keto diester, m.p. 101–104°; a further recrystallization yielded 88 g. (76%) of white product, m.p. 104–105°. *Anal.* Calcd. for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.32, 62.33; H, 6.17, 6.07.

2,4-Dinitrophenylhydrazone of IXb.—A 2,4-dinitrophenylhydrazone, m.p. 172.5–174.0°, was obtained on prolonged standing of the usual reagents. *Anal.* Calcd. for $C_{32}H_{34}O_{13}N_4$: C, 56.30; H, 5.02; N, 8.21. Found: C, 56.39, 56.21; H, 5.04, 5.14; N, 8.49, 8.37.

α-(3,4,5-Trimethoxybenzyl)-α-carbethoxy-γ-(3,4-methylenedioxyphenyl) butyrolactone (X).—A mixture of 1.0 g. (0.002 mole) of the keto diester IXb, 1.0 g. of 10% palladium–charcoal and 50 ml. of ethanol was shaken with hydrogen at room temperature and atmospheric pressure, until the slow absorption of one-mole equivalent of hydrogen was complete. The crude product was recrystallized twice from ethanol to give 0.3 g. of product, m.p. 146–147.5°. An analytical sample melted at 149.5–151.0°. *Anal.* Calcd. for $C_{24}H_{26}O_9$: C, 62.87; H, 5.72. Found: C, 63.07, 63.29; H, 5.78, 5.82.

Benzylphenacylmalonic Acid (XIa).[28]—To a solution of 200 g. of potassium hydroxide in 600 ml. of absolute ethanol was added a warm solution of 56.8 g. (0.158 mole) of ethyl benzylphenacylmalonate in 150 ml. of absolute ethanol. Within a few minutes, a precipitate separated from the deep red solution. After chilling, the salt was collected and washed with small portions of cold, absolute ethanol followed by dry ether. The white salt was dissolved in 400 ml. of water, and the acid was precipitated by hydrochloric acid. Material prepared in this way melted at 168–170° with decomposition.

3,4,5-Trimethoxybenzyl-3′,4′-methylenedioxyphenacylmalonic Acid Dihydrate (XIb).—A solution of 33.8 g. (0.0673 mole) of the keto diester IXb in 200 ml. of warm, absolute ethanol was added all at once to a solution of 175 g. of potassium hydroxide in 600 ml. of absolute ethanol. A precipitate formed within a few minutes. After 30 minutes at room temperature, the mixture was chilled and the precipitate was collected and washed with small portions of cold, absolute ethanol and then with dry ether. Acidification of an aqueous solution of the salt precipitated the acid, m.p. 130–133° dec. Recrystallization was accomplished from ethyl acetate–petroleum ether to afford material melting at 132–133° dec. Satisfactory analyses were not obtained. However, the neutralization equivalent was in good agreement with theory for the dihydrate (calcd., 241.2; found, 240.6, 240.4), as was the weight loss on thermal decarboxylation.

Benzylphenacylacetic Acid (XIIa).[28]—Thermal decarboxylation of the crude, moist acid XIa (obtained from 56.8 g. of ethyl benzylphenacylmalonate) followed by recrystallization from a mixture of 400 ml. of acetic acid and 250 ml. of water, yielded 35 g. (82.5% over-all) of benzylphenacylacetic acid, m.p. 173–174.5°.

The **methyl ester**, m.p. 68.2–69.0°, was prepared in 82% yield. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.59, 76.72; H, 6.52, 6.52.

3,4,5-Trimethoxybenzyl-3′,4′-methylenedioxyphenacylacetic Acid (XIIb).—Thermal decarboxylation of the crude, still moist acid XIb (from the experiment described above) was conducted at 150°. The resulting yellow glass crystallized from ethyl acetate–petroleum ether (carbon) to afford 22.8 g. (84.5% over-all) of the keto acid, m.p. 133.8–135.4°. *Anal.* Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; OCH_3, 23.14; neut. equiv., 402.4. Found: C, 62.71, 62.91; H, 5.77, 5.81; OCH_3, 23.05, 23.12; neut. equiv., 402.1, 403.9, 404.6.

The **methyl ester** was prepared in 68% yield by dissolving the acid in methanolic hydrogen chloride. After recrystallization from ethyl acetate–petroleum ether, the ester melted at 91.0–92.5°. *Anal.* Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.43, 63.55; H, 5.97, 5.79.

The **ethyl ester** was prepared in 94% yield by allowing a solution of the acid in ethanolic hydrogen chloride to stand at room temperature for 18 hours. The ester melted at 117–118° after recrystallization from ethanol. *Anal.* Calcd. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.04, 64.26; H, 6.14, 5.94.

The **2,4-dinitrophenylhydrazone** was prepared; it melted at 144–145° after recrystallization from ethanol. *Anal.* Calcd. for $C_{29}H_{30}O_{11}N_4$: C, 57.04; H, 4.95; N, 9.18. Found: C, 57.19, 57.00; H, 4.92, 4.92; N, 9.39, 9.26.

α-(3,4,5-Trimethoxybenzyl)-γ-(3′,4′-methylenedioxyphenyl)-butyrolactone (XIIb).—A solution, prepared by titrating 3.1 g. of the keto acid XIIb with 0.1 *N* sodium hydroxide, was treated with 1.0 g. of sodium borohydride and allowed to stand at room temperature for 24 hours. Acidification precipitated an oil which was taken up in ether and separated into two fractions by washing with sodium bicarbonate. The bicarbonate-insoluble fraction was not obtained crystalline. The bicarbonate-soluble fraction crystallized from ethanol on prolonged standing to give a product which was no longer soluble in bicarbonate, indicating that lactonization had occurred. The solid was recrystallized twice from aqueous ethanol to afford 0.9 g. (30%) of lactone, m.p. 95.5–97.5°. *Anal.* Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.04, 64.93; H, 6.03, 5.92.

α-Benzyl-β-benzoylbutyrolactone (XVa).—A solution prepared by dissolving 7.12 g. (0.0265 mole) of benzylphenacylacetic acid in 31.7 ml. (0.0294 mole) of 0.926 *N* sodium hydroxide was treated with 2.40 ml. (0.032 mole) of 37% formalin. After 48 hours at room temperature, the mixture was acidified with dilute hydrochloric acid. The gum which precipitated was dissolved in benzene and chromatographed on silicic acid. Elution with benzene afforded 6.4 g. (86.5%) of non-crystalline keto lactone XVa. The material was seeded with some previously obtained crystalline material and triturated with a benzene–petroleum ether mixture (35:50). The granular residue was recrystallized from benzene–petroleum ether (20:80) to give 2.40 g. (32.5%) of white solid, m.p. 108.0–110.0°. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; sapon. equiv., 280. Found: C, 77.40; H, 5.85; sapon. equiv., 279.

A yellow **2,4-dinitrophenylhydrazone**, m.p. 197–199°, was obtained. *Anal.* Calcd. for $C_{24}H_{20}O_5N_4$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.75; H, 4.39; N, 11.90, 12.11.

When the reaction was conducted using 12 equivalents of formaldehyde, chromatography on silicic acid afforded approximately equal amounts of the keto lactone XVa and the keto methylol lactone XVI. The latter was not crystalline, nor did it form a 2,4-dinitrophenylhydrazone. *Anal.* Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85; sapon. equiv., 310. Found: C, 73.97; H, 6.03; sapon. equiv., 293.

α-(3,4,5-Trimethoxybenzyl)-β-(3′,4′-methylenedioxybenzoyl)-γ-hydroxybutyric Acid (XVIII).—A solution prepared by dissolving 16.1 g. (0.040 mole) of XIIb in 48 ml. of 0.926 *N* sodium hydroxide was treated with 4.5 ml. (0.060 mole) of 37% formalin. Upon standing at room temperature for 44 hours, the originally yellow solution was nearly colorless. The chilled mixture was acidified, and the gummy precipitate which formed was collected and washed with water. After several triturations with ether, 10.9 g. (63%) of the methylol acid XVIII, m.p. 131–134° dec., was obtained. When the melting point was taken slowly, the material melted from 131–140°, apparently because of gradual conversion to the lactone. A sample purified for analysis by recrystallization from ethyl acetate–petroleum ether melted at 135–137° dec. *Anal.* Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59; OCH_3, 21.53; neut. equiv., 432. Found: C, 61.10, 61.29; H, 5.73, 5.76; OCH_3, 21.53, 21.33; neut. equiv., 435, 442.

α-(3,4,5-Trimethoxybenzyl)-β-(3′,4′-methylenedioxybenzyl)-butyrolactone (XVb).—Lactonization of the methylol acid was accomplished in 90% yield by heating at 150° until the sample was completely melted. The glassy product crystallized from ethanol to give material which melted at 140.4–143.0°. A sample purified for analysis melted at

(28) Compounds IXa, XIa and XIIa were originally described by A. E. Brown, Ph.D. Thesis, University of Maryland, 1950. The following melting points and analysis were reported by Brown: for IXa, m.p. 74.6–76.4°. *Anal.* Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.85, 71.67; H, 6.62, 6.59. For XIa, m.p. 161°d. *Anal.* Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16; neut. equiv., 156. Found: C, 68.45, 68.86; H, 5.36, 5.69; neut. equiv., 157. For XIIa, m.p. 174.0–174.7°. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 76.10; H, 6.01; neut. equiv., 268. Found: C, 76.20, 76.02; H, 6.24, 6.17; neut. equiv., 268.

141.0–143.0°. *Anal.* Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; OCH_3, 22.47; sapon. equiv., 414. Found: C, 63.72, 63.75; H, 5.44, 5.43; OCH_3, 22.64, 22.45; sapon. equiv., 416.

The saponification equivalent was determined by treating a warm, ethanolic solution of the lactone with excess 0.1 *N* sodium hydroxide, allowing the mixture to stand 0.5 hour at room temperature and back-titrating. If the mixture was boiled, variable, low values were obtained depending on the duration of the boiling. From this treatment a keto acid XIIb was recovered whose mixed melting point with an authentic sample was undepressed.

The keto lactone formed a yellow precipitate with 2,4-dinitrophenylhydrazine, but the product did not exhibit a sharp melting point despite repeated recrystallizations.

α-Benzyl-β-(α'-hydroxybenzyl)-butyrolactone (XVII).—A mixture of 2.38 g. (0.0085 mole) of the crystalline keto lactone XVa, 50 ml. of ethanol and 0.5 g. of 10% palladium–charcoal was shaken with hydrogen at room temperature and atmospheric pressure. The absorption of one molar equivalent of hydrogen was complete within 20 minutes. After removal of the catalyst and concentration of the solution, there was obtained 1.18 g. (49%) of white solid, m.p. 150–160°. Recrystallization of this substance from 5 ml. of ethanol gave 1.01 g. (42%) of product, m.p. 149–160°. A sample which was recrystallized from benzene–petroleum ether melted at 149–160°. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 77.4, 77.41; H, 6.50, 6.48. This material was also prepared by the palladium-catalyzed hydrogenation of the keto lactone in cyclohexane. The same wide melting range was observed.

An isomeric hydroxy lactone XVII was obtained by the palladium-catalyzed hydrogenation of 3.9 g. (0.014 mole) of the non-crystalline keto lactone XVa in ethanol. The absorption of 0.92 molar equivalent of hydrogen was complete in 6 hours. The hydroxy lactone crystallized on concentration of the solution and was recrystallized from benzene–petroleum ether to give 1.11 g. (28%) of product, m.p. 102–104°. An analytical sample melted at 103.0–103.6°. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.61, 76.77; H, 6.62, 6.49.

α-(3,4,5-Trimethoxybenzyl)-β-(α'-hydroxy-3',4'-methylenedioxybenzyl)-butyrolactone (II).—A mixture of 4.14 g. of the keto lactone XVb, 1.3 g. of 10% palladium–charcoal and 50 ml. of ethanol was shaken with hydrogen at room temperature and atmospheric pressure. The absorption of one molar equivalent of hydrogen took place in 3.5 hours, after which the rate slowed markedly. The glassy product was very resistant to crystallization but a sample eventually crystallized from ethyl acetate–petroleum ether, m.p. 100–105°. A solution of 3.5 g. of the crude glassy product in a mixture of ethyl acetate (45 ml.) and petroleum ether (60 ml.) was seeded and kept at −20° for several days. There was obtained 2.53 g. (72%) of white powder, m.p. 102–108°. Two more recrystallizations gave 1.87 g. (53%) of product, m.p. 104–108°. *Anal.* Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; OCH_3, 22.36. Found: C, 63.61, 63.35; H, 6.13, 5.81; OCH_3, 22.36, 22.42. The infrared spectrum showed absorptions at 2.80 and 5.67 μ, consistent with the presence of hydroxyl and γ-lactone functions.

α-(3,4,5-Trimethoxybenzyl)-β-(3',4'-methylenedioxybenzoyl)-butyric Acid (XIX).—Hydrogenation of the non-crystalline fraction obtained from the reaction of the keto acid XVIII with formaldehyde took place with a very rapid initial uptake of hydrogen. Approximately 13% of an acid melting at 166–167° without decomposition was isolated. Analysis indicated that it was the keto acid XIX which could arise from hydrogenation of the corresponding methylene keto acid. The similarity between the infrared spectra of the product and the keto acid XIIb supports this structure. *Anal.* Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; OCH_3, 22.36; neut. equiv., 414. Found: C, 63.84, 63.90, 63.85; H, 5.99, 5.85, 5.89; OCH_3, 22.53, 22.65; neut. equiv., 415.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MARYLAND]

Podophyllotoxin and Picropodophyllin. III.[1] The Synthesis of a Stripped Analog[2]

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The synthesis of a lactone derived from 1-hydroxy-2-hydroxymethyl-4-phenyltetralin-3-carboxylic acid (Xa or b) is described. This represents a stripped analog of podophyllotoxin. The condensation of ethyl formate with acylic γ-keto esters appears to be prevented or greatly inhibited by the steric effect of an α-substituent. The cyclic γ-keto ester, 4-phenyl-3-carbethoxytetralone-1, condenses readily with ethyl formate.

In the course of a synthesis of an open-chain analog of podophyllotoxin,[1] the problem arose of converting the γ-keto acid I to the hydroxy lactone III. Two approaches were considered: (1) the condensation of I with formaldehyde followed by lactonization and reduction of the keto group, and (2) the condensation of the ethyl ester II with ethyl formate followed by reduction of the hydroxymethylene ketone system to the diol and lactonization. Because of the difficulties often encountered in formaldehyde condensations, the latter approach was investigated first.

Repeated attempts to formylate the keto ester II using sodium methoxide as described by Johnson and co-workers[4] as well as sodium hydride and potassium *t*-butoxide afforded at best only traces of enolic material. The only crystalline product isolated proved to be the enol lactone IV which evidently arose from an intramolecular attack of the enolate oxygen on the ester carbonyl. Attempted formylation of the ring-substituted keto ester (preceding paper) was likewise unsuccessful.

Since the formylation of cyclic ketones has been a widely used reaction, comparison of the reaction with the cyclic analog VII was made. This substance was prepared essentially according to Hewitt.[5] It was found advantageous to reduce the

(1) Previous paper, N. L. Drake and W. B. Tuemmler, THIS JOURNAL, **77**, 1204 (1955).

(2) From a thesis submitted to the Graduate School of the University of Maryland by William B. Tuemmler in partial fulfillment of the requirements for the Ph.D. degree, July, 1953.

(3) Du Pont Fellow, 1952–1953.

(4) W. S. Johnson, J. M. Anderson and W. E. Shelberg, THIS JOURNAL, **66**, 218 (1944).

(5) C. L. Hewitt, *J. Chem. Soc.*, 596 (1936).