

Anal. Calcd. for $C_{24}H_{20}O_{10}$: C, 61.54; H, 4.30. Found: C, 61.61; H, 4.25.

The infrared spectrum (chloroform) had peaks at 5.39 and 5.62 μ (anhydride) and at 6.10 μ (conjugated double bond); a shoulder was present at 5.70 μ (enol ester). The infrared spectrum of 3,4-dimethoxyphenylitaconic anhydride⁷ was

obtained for comparison; it had peaks at 5.42, 5.64 and 6.06 μ (chloroform).

The compound was slowly soluble in 5% sodium hydroxide solution and insoluble in sodium bicarbonate solution.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE LABORATORY ON CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE; NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

Podophyllotoxin Studies. Reductive Methods in the Synthesis of Tetralin Lactones from α -Tetralone Derivatives

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2-Hydroxymethylene-3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (V) was prepared. Catalytic hydrogenolysis of this compound and the corresponding acid (VII) led, respectively, to 1-(3',4'-dimethoxyphenyl)-2-carbethoxy-3-methyl-6,7-dimethoxytetralin (VIII) and the corresponding acid (IX) while sodium borohydride reduction of V gave 2-hydroxymethyl-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralol (XIII), a tetramethoxy analog of podophyllinic acid. From XIII, three lactones, XIV, XV and XVI, were prepared by dehydration under various conditions. A fourth lactone, IV, in the 3',4'-dimethoxyphenyltetralin series was prepared both *via* sodium borohydride reduction of I and by catalytic hydrogenation of II. The ethylene acetal (X) of V was transformed by sodium borohydride reduction and hydrolysis into a dihydrocarbethoxynaphthaldehyde (XII).

A preceding paper¹ described the preparation of the ketoester, I, together with proof of the tetralone structure for this compound and evidence that the 3-carbethoxy group and the 4-(3',4'-dimethoxyphenyl) group were disposed in a *trans* configuration in the B-ring. The present report deals with catalytic hydrogenolysis and sodium borohydride reduction of this ketoester and of a hydroxymethylene derivative, V, prepared from it. Certain products of these reactions are close analogs of compounds in the podophyllotoxin series.

Compound V, a crystalline enol, was obtained in high yield when I was treated with ethyl formate in the presence of sodium methoxide. In view of its chemical properties there is no question that V has a keto-enol formula as shown, rather than a naphthalenic structure. It is enolic, as indicated by a ferric chloride test, and it reacts with 2,4-dinitrophenylhydrazine in two stages. Hydrolysis under alkaline conditions is extremely easy and leads to an enolic acid, VII. Chemical and catalytic reductions of V and VII gave products (VI, VIII, IX and XIII) which could be explained best by assuming that V and VII are carbonyl, rather than naphtholic, compounds. These reactions are discussed in detail below. The infrared spectrum² of V is unusual inasmuch as no band is present which can be assigned to an enolic hydroxyl group, although a peak at 6.08 μ , representing either a conjugated double bond or a conjugated carbonyl group, is observed, as well as another peak (5.76 μ) representing the carbonyl moiety of an unconjugated ester. The latter is common to the spectra of all 3-carbethoxy tetralins and tetralones which were studied. The spectrum indicates that chelation between the groups at positions 1 and 2 in V is present, resulting in damping of their

individual vibrations. An infrared spectrum of hydroxymethylenecyclohexanone indicates that the same phenomenon takes place to a lesser degree in that compound. The infrared spectrum of the enolacid, VII, is similar to that of V except that a very weak band at 6.00 μ , probably due to the conjugated carbonyl group, is also present.

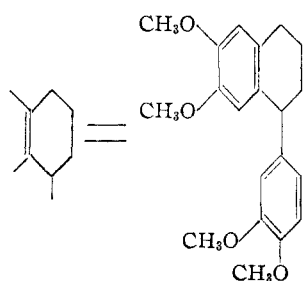
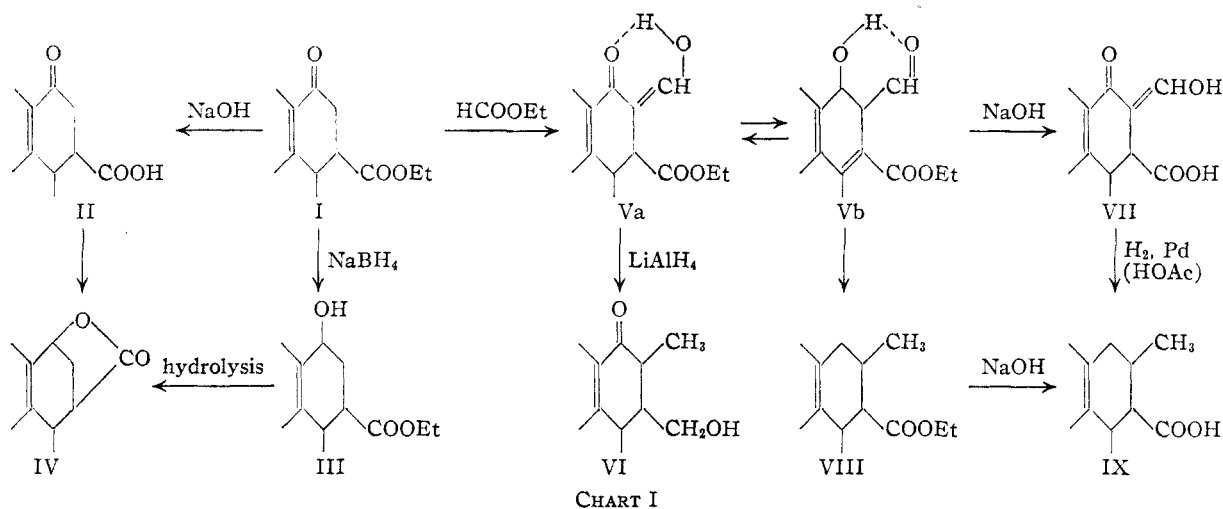
Because of the behaviors of V and VII in catalytic reduction, it is possible that a structure such as V(b) represents these compounds more accurately than does V(a) from the point of view of chemical reactivity. Hydrogenolysis of V in acetic acid at 80° in the presence of a palladium-carbon catalyst involves both oxygen atoms of the keto-enol system and leads to the ester, VIII. This reaction may be explained by assuming that there occurs a stepwise transformation of V(b) in which the aldehyde group, now in a conjugate relationship to the aromatic ring, is affected first. The hydrogenolysis of V could not be carried out stepwise by operating at a lower temperature.

Hydrolysis of VIII in aqueous ethanol leads to the acid, IX, in solvated form. The same acid is obtained in a non-solvated form but in lower yield by hydrogenolysis of the enolacid, VII. Attempts to prepare a lactone directly from VII by partial hydrogenation were not successful.

With ethylene glycol, the hydroxymethylene ketoester, V, forms a mono ethylene acetal, X. Structure X was assigned to the material on the basis of its infrared spectrum, which indicates that a conjugated ketone is present. That the carbonyl group of X is highly hindered is indicated by the extreme slowness with which X reacts with 2,4-dinitrophenylhydrazine. In spite of this fact, reduction with sodium borohydride converts X readily to the corresponding alcohol, XI. The presence in XI of a hydroxyl group is shown clearly through its infrared spectrum. Hydrolysis of the ethylene acetal function in XI under mild acid conditions is accompanied seemingly by elimination of the hydroxyl group. The product, which could

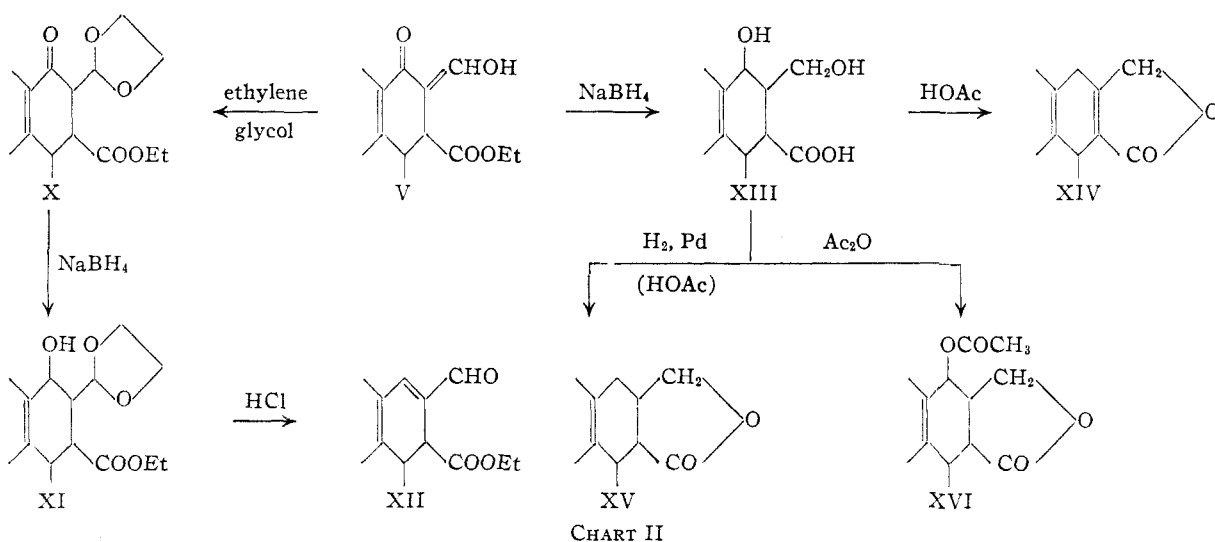
(1) G. N. Walker, *THIS JOURNAL*, **75**, 3387 (1953).

(2) Copies of the full infrared spectra discussed in this paper can be obtained as Document 3858 from the American Documentation Institute, c/o Library of Congress, Washington 25, D. C., remitting \$1.25 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or \$1.25 for photostats readable without optical aid.



jugated carbonyl group (5.98μ) and a hydroxyl group (2.9μ) and indicates that a conjugated double bond is no longer present. The results here are in accord with those obtained in lithium aluminum hydride reduction of several enol ethers. The low yield experienced may be due to sparing solubility of the starting material or its salts in the solvent employed (ether-benzene).

None of the foregoing methods was suitable for preparation of lactones, or precursors thereof, in which an oxygen function was preserved at position



not be purified successfully, appears to be XII, rather than a hydroxyaldehyde, since its infrared spectrum lacks the peak characteristic of a hydroxy group and incorporates bands at 5.96 and 6.11μ , indicative of a conjugated carbonyl group and a conjugated double bond, respectively. The unsaturated aldehyde, XII, was identified when the 2,4-dinitrophenylhydrazone was prepared from this crude product.

Lithium aluminum hydride reduction of V gives VI in low yield. No other pure compounds were isolated from the crude product of this reaction. Structure VI was assigned to the crystalline product on the basis of analysis and the infrared spectrum. The latter discloses the presence of both a con-

1. In order to accomplish this end, sodium borohydride was employed directly as an agent capable of effecting partial reduction of carbonyl functions in preference to ester groups. With this reagent, I is converted to the hydroxy-ester, III. The product appeared to be a mixture of isomers; the presence of a hydroxyl group was confirmed by the infrared spectrum. Hydrolysis of III and acidification of the resulting solution led directly to the lactone, IV. A peak is present in the infrared spectrum of this compound at 5.65μ , characteristic of the carbonyl function of a five-membered lactone.

The single instance in this study in which catalytic hydrogenation in an acidic medium led directly to a lactone consisted of the preparation of IV in

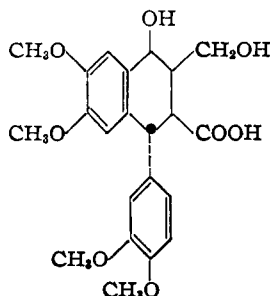
this way. Hydrogenation of ketoacid II in acetic acid in the presence of a palladium-carbon catalyst gave IV in very low yield. The unfavorable yield may have been due in part to the fact that there are two isomers of the intermediate hydroxyacid, only one of which may lactonize.

A procedure was developed wherein V was reduced and hydrolyzed in one step by the action of aqueous sodium borohydride and the dihydroxyacid, XIII, was obtained. Although the over-all reaction obviously consists of a number of steps, no attempt was made to determine the order in which these occurred. The infrared spectrum of XIII is in agreement with the structure shown and indicates that hydrogen bonding is present between the acid carbonyl group and one hydroxy group, presumably the neighboring one; the carbonyl band here is located at 5.91μ .

Compound XIII lactonizes at a relatively low temperature (150°). The product was not isolated, but was acetylated, and the acetoxy lactone, XVI, was identified. Structure XVI was assigned in view of absorption bands in the infrared region at 5.58 and 5.74μ which this compound displays. In hot acetic acid, XIII underwent dehydration in two ways. The product was shown to be XIV, rather than any of several alternatively possible products, by the infrared spectrum, which points to conjugation of the double bond with the carbonyl group (5.68μ) and by the ultraviolet spectrum, in which no absorption at long wave lengths caused by conjugation of the double bond with either aromatic nucleus is found.

Catalytic hydrogenation of XIII in hot acetic acid over a palladium-carbon catalyst leads to the saturated lactone, XV, the infrared spectrum of which is characterized by a band at 5.60μ . This reaction may have proceeded *via* XIV or another unsaturated lactone. No change in structure occurred when XV was cleaved in alkaline medium and converted again to the lactone, and thus it was assumed that XV is a *cis*, rather than a *trans*, lactone.

It may be assumed that a mechanism involving 1,4-attack on the keto-enol system is involved in the reaction $V \rightarrow XIII$. With this assumption and the fact that protonic elimination occurs readily in XIII in an acid environment, it may be assumed tentatively that the groups at positions 1 and 2 in XIII are disposed in a *cis* manner. The fact that XIII lactonizes on heating points to a *cis* arrangement of groups 2 and 3. In the light of these conclusions and of the preferred *trans* configuration of groups 3 and 4¹ one may conclude tentatively that XIII obtained in the manner described has the stereochemical structure



This structure corresponds to the structure currently accepted for podophyllinic acid³ in regard to the disposition of groups in the B-ring.

Acknowledgment.—The author is indebted to Dr. William C. Alford and his staff for the analyses reported herein, to Mrs. Iris Siewers and Miss Alice Bernardi of this Laboratory for spectral measurements, and to Mr. Clifford E. Sisler for assistance in carrying out several preparations.

Experimental⁴

1-Hydroxy-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxytetralin Lactone (IV), (A) Sodium Borohydride Reduction.—To a suspension of 1.4 g. (0.0034 mole) of 3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone in 50 ml. of methanol was added 0.45 g. (0.012 mole) of sodium borohydride. When effervescence subsided, the solution was refluxed for one-half hour. Most of the methanol was removed by evaporation, and the residue was treated with water. The product (hydroxy ester) was extracted with ethyl acetate. The ethyl acetate solution was washed with water and the solvent was evaporated. The residue, an infrared spectrum of which showed a band at 2.85 – 3.0μ , was boiled for 2.5 hours with a solution of 10 g. of sodium hydroxide in 50 ml. of water. The resulting solution was cooled, diluted to 125 ml., filtered and acidified strongly with hydrochloric acid. After chilling the mixture for several days, the crystals were extracted with ethyl acetate. The organic solution was washed with several portions each of sodium bicarbonate solution and water, and was dried over magnesium sulfate. Evaporation of the ethyl acetate gave 0.25 g. (20%) of discolored material which crystallized readily in methanol. Further recrystallization from the same solvent led to colorless crystals, m.p. 180.5 – 181.5° .

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.10; H, 6.15.

The infrared spectrum of this lactone (chloroform) was characterized by an intense peak at 5.65μ . The ultraviolet spectrum measured in ethanol, had λ_{max} $283 m\mu$.

(B) Catalytic Reduction.—A suspension of 0.9 g. (0.0023 mole) of 3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone¹ and 0.8 g. of 5% palladium-carbon catalyst in 100 ml. of glacial acetic acid was shaken under hydrogen (40 lb.) at 80° for two hours. The solution was filtered to remove the catalyst, and the acetic acid was evaporated. The residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with sodium bicarbonate solution and with water, and was dried over magnesium sulfate. Removal of the solvent by evaporation afforded 0.05 g. (6%) of material. Recrystallization from methanol gave colorless crystals, m.p. 179 – 181° . The mixed m.p. with the product of (A) was 179 – 181° (undepressed). The infrared spectrum of this product was identical with that of product (A).

Acidification of the sodium bicarbonate solution gave 0.5 g. of crystals. After several recrystallizations from ethyl acetate this material had m.p. 180 – 190° . Further attempts to purify it were not made.

2-Hydroxymethylene-3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (V).—Sodium methoxide was prepared from 12.0 g. (0.52 atom) of sodium and was dried *in vacuo* at 100° for 15 minutes. A suspension of 54.5 g. (0.132 mole) of 3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone in 170 g. (2.30 mole) of ethyl formate and 800 ml. of dry ether was added. The mixture was swirled for several hours and allowed to stand overnight. An equal volume of cold water was added, and the mixture was shaken thoroughly. The organic layer was washed with 5% sodium hydroxide solution. The combined alkaline solutions were acidified with hydrochloric acid and chilled. The product was collected, washed with several portions of water, and pressed dry. Trituration with a small quantity of methanol afforded 54.9 g. (94%) of nearly colorless crystals, m.p. 166 – 170° ; this material was suitable for further reactions. Extensive recrystallization

(3) J. L. Hartwell and A. W. Schrecker, *THIS JOURNAL*, **73**, 2909 (1951).

(4) All melting points are corrected.

from methanol, benzene or ethyl acetate gave crystals, m.p. 174–177.5°, which retained a yellow cast.

Anal. Calcd. for $C_{24}H_{28}O_8$: C, 65.15; H, 5.92. Found: C, 64.61; H, 5.91.

The infrared spectrum of this hydroxymethylene derivative (chloroform) included peaks at 5.76 and 6.08 μ ; no bands representing either the hydroxyl group or the conjugated carbonyl group were present. The compound was soluble in 5% sodium hydroxide solution and insoluble in sodium bicarbonate solution. With ferric chloride a deep red color was produced. A dark red, gummy precipitate was obtained with 2,4-dinitrophenylhydrazine; on standing in alcohol in the presence of sulfuric acid, this material slowly became crystalline. Recrystallization from ethanol-ethyl acetate gave a derivative, red-orange crystals, m.p. 236–237.5°. Analysis of this material gave results which did not agree with any of several possible formulas.

Hydrolysis to the corresponding acid, 2-hydroxymethylene-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (VII) was achieved as follows: A solution of 3.4 g. of the hydroxymethylene ketoester in 100 ml. of 5% sodium hydroxide solution was warmed on the steam-bath for 15 minutes and acidified with hydrochloric acid. The gum initially formed crystallized as the solution was allowed to cool to room temperature. The crystals were collected, washed with several portions of cold water, and air-dried. The yield of crude material was 3.1 g. Oily material was obtained when this acid was brought into contact with methanol, ether or benzene. The compound was soluble in sodium bicarbonate solution and gave a deep greenish-brown color with ferric chloride. The infrared spectrum showed broad absorption in the neighborhood of 3.0 μ , peaks at 5.85 and 6.09 μ , and a very weak absorption band at 6.00 μ .

2-Methyl-3-hydroxymethyl-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (VI).—A suspension of 1.5 g. (0.0034 mole) of 2-hydroxymethylene-3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone and 2.1 g. (0.055 mole) of lithium aluminum hydride in 500 ml. of dry ether and 100 ml. of dry benzene was stirred for three weeks at room temperature. Water (40 ml.) and 50% sulfuric acid (30 ml.) were added, and the mixture was stirred for a half hour. The ether solution was washed with two small portions of 5% sodium hydroxide solution and with successive small portions of dilute acetic acid, sodium bicarbonate solution and water. Drying (magnesium sulfate) and evaporation of the solvents gave 0.6 g. of a gum. A solution of this material in acetone was allowed to evaporate slowly, whereupon partial crystallization took place. The crystals, after washing with methanol, weighed 0.3 g. (23%). Recrystallization from methanol gave colorless crystals, m.p. 168.5–170°.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.37; H, 6.87. Found: C, 68.45; H, 7.06.

The infrared spectrum (chloroform) of this hydroxy ketone showed peaks at 2.90 and 5.98 μ , representative of alcoholic hydroxyl and conjugated carbonyl groups, respectively. A red precipitate was formed with 2,4-dinitrophenylhydrazine.

1-(3',4'-Dimethoxyphenyl)-2-carbethoxy-3-methyl-6,7-dimethoxytetralin (VIII).—A solution of 1.1 g. (0.0025 mole) of 2-hydroxymethylene-3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone in 100 ml. of glacial acetic acid, containing 1.0 g. of 5% palladium-carbon catalyst, was shaken under hydrogen (40 lb.) at 80° for two hours. The solution was filtered, and the acetic acid was evaporated. An oil (1.1 g.) was obtained; this material crystallized slowly in methanol-ethyl acetate. Recrystallization from methanol afforded colorless crystals, m.p. 141–143°.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.23; H, 7.38.

The infrared spectrum (chloroform) was characterized by a peak at 5.80 μ . The compound was insoluble in alkali and did not give a test with ferric chloride.

When the reaction was carried out at room temperature, a product m.p. 134–136.5° (from ethanol) was obtained. *Anal.* Found: C, 68.25; H, 7.33. The infrared spectrum (chloroform) was nearly identical with that of the above compound.

1-(3',4'-Dimethoxyphenyl)-2-carboxy-3-methyl-6,7-dimethoxytetralin (IX). (A) **Hydrolysis of Ester.**—The

ester described in the preceding experiment (1.0 g.) was refluxed for two hours in a solution of 5 g. of sodium hydroxide in 15 ml. of water and 5 ml. of ethanol. The solution was diluted with 150 ml. of water, was filtered, and was acidified with hydrochloric acid. After the suspension had been chilled overnight, the crystals were collected, washed with one portion of water, and pressed dry. The yield of crude acid was 0.8 g. Recrystallization from methanol afforded the hemiethanolate; colorless crystals, m.p. 224.5–227° (shrinking).

Anal. Calcd. for $C_{26}H_{30}O_7$: C, 67.46; H, 7.14. Found: C, 67.45; H, 6.93.

The infrared spectrum was characterized by a peak at 5.84 μ . The compound was soluble in sodium bicarbonate solution.

(B) **Reduction of Hydroxymethylene Ketoacid.**—A mixture of 3.1 g. of crude 2-hydroxymethylene-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone, 3 g. of 5% palladium-carbon catalyst and 100 ml. of glacial acetic acid was shaken under hydrogen (40 lb.) at 80° for three hours. After filtration of the hot solution to remove the catalyst, there was added 3 g. of fresh catalyst, and the mixture was again hydrogenated under the same conditions for an additional hour. The solution was filtered, and the acetic acid was evaporated. The residue was partitioned between ethyl acetate and water. The ethyl acetate solution was washed with water and extracted with two portions of sodium hydroxide solution. The aqueous extract was acidified with hydrochloric acid and chilled. The crystals which separated were collected, washed with water, and air-dried. The yield of crude acid was 0.7 g. (24%). Recrystallization from methanol gave colorless crystals, m.p. 233–236° (shrinking and browning), soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. Found: C, 68.20; H, 6.88.

The infrared spectrum of this sample, like that of the hemiethanolate, included a peak at 5.84 μ .

The yield of acid from this reduction was variable, and in some cases there was formed an extremely insoluble colorless solid. The latter was soluble in water and did not melt below 350°; its composition was not ascertained.

Ethylene Acetal of 2-Hydroxymethylene-3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (X).—A solution of 1.25 g. (0.0028 mole) of the hydroxymethylene ketoester (V), 1.1 g. (0.017 mole) of ethylene glycol, and 0.22 g. of *p*-toluenesulfonic acid in 25 ml. of dry toluene was refluxed under a constant water separator for three hours. Additional ethylene glycol (2.0 g.) was added after one hour. The solution was cooled and diluted with ten volumes of ethyl acetate. It was washed with 5% sodium hydroxide solution, dilute acetic acid, sodium bicarbonate solution and water. Drying (magnesium sulfate) and evaporation of the solvents afforded a viscous oil which crystallized slowly in methanol. After trituration with methanol there remained 0.7 g. (51%) of colorless crystals, m.p. 165–167.5°. Recrystallization from the same solvent afforded colorless crystals, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{26}H_{30}O_7$: C, 64.18; H, 6.22. Found: C, 64.21; H, 6.43.

The infrared spectrum (chloroform) consisted in part of bands at 5.76 and 5.98 μ . The compound reacted very slowly with 2,4-dinitrophenylhydrazine with the formation of a red precipitate.

3-Carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde (XII). (A) **Reduction of Ethylene Acetal.**—A solution of 0.7 g. (0.0014 mole) of the ethylene acetal in 50 ml. of methanol was treated with 0.20 g. (0.0053 mole) of sodium borohydride. The solution was refluxed for a half hour and was evaporated to dryness. The residue was shaken with water and ethyl acetate. The ethyl acetate solution was washed with several portions of water, and was dried over magnesium sulfate. Evaporation of the solvent afforded 0.7 g. of crude 1-hydroxy-2-ethylenedioxymethyl-3-carbethoxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxytetralin (XI), in the form of a glass. The infrared spectrum (chloroform) incorporated peaks at 2.86 and 5.77 μ ; the peak at 5.99 μ , present in the spectrum of the starting material, was absent.

(B) **Hydrolysis and Dehydration.**—The crude material obtained in (A) (0.7 g.) was dissolved in 75 ml. of water and

25 ml. of methanol. Concentrated hydrochloric acid (5 ml.) was added. The solution was warmed on a steam-cone for one hour. The methanol was evaporated, and the material which separated was extracted with ethyl acetate. The ethyl acetate solution was washed with several portions of sodium bicarbonate solution and water, and was dried (magnesium sulfate) and evaporated. The infrared spectrum of the residual oil included bands at 5.77, 5.96 and 6.11 μ , and lacked the peak characteristic of a hydroxyl group. The material darkened slowly in air.

The red 2,4-dinitrophenylhydrazone formed rapidly and was recrystallized from dry benzene, after trituration with ethanol; m.p. 234–237°.

Anal. Calcd. for $C_{30}H_{30}O_{10}N_4$: C, 59.40; H, 4.99. Found: C, 59.40; H, 5.07.

2-Hydroxymethyl-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralol (XIII).—A suspension of 4.0 g. (0.0091 mole) of 2-hydroxymethylene-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone in 80 ml. of water and 40 ml. of methanol was treated with 8.0 g. (0.21 mole) of sodium borohydride in several portions. When the initial vigorous reaction was complete and solution was attained, the mixture was refluxed for three hours. After two hours, frothing was no longer observed, and the solution, after acidification, did not give a color test with ferric chloride. Most of the methanol was removed by evaporation or distillation, and the solution was diluted with 150 ml. of water and filtered. The clarified solution was chilled in ice and acidified gradually with a cold solution of 20 ml. of concentrated hydrochloric acid in 40 ml. of water. The voluminous precipitate was collected, washed with two 25-ml. portions of cold water, and pressed dry. The solid was dissolved immediately in 50 ml. of methanol. This solution was diluted with 300 ml. of ether and stirred until crystallization was complete. The crystals were collected and air-dried. The yield of crude dihydroxy acid, m.p. 178–188°, was 1.0 g. (26%). Recrystallization from methanol led to colorless, fluffy crystals, m.p. 217–217.5° (shrinking and dec.).

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.23; H, 6.23.

The infrared spectrum (Nujol mull) showed peaks at 2.80 and 5.91 μ . This compound was soluble in sodium bicarbonate solution. All modifications of the procedure which were attempted led to lower yields of the product. These included the use of various proportions of water to methanol and smaller amounts of sodium borohydride.

1-(3',4'-Dimethoxyphenyl)-2-carboxy-3-hydroxymethyl-6,7-dimethoxy-1,4-dihydronaphthalene Lactone (XIV).—A suspension of 0.7 g. of 2-hydroxymethyl-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralol in 90 ml. of glacial acetic acid was refluxed for 2.5 hours. The material dissolved within 15 minutes. The solution was distilled to remove most of the acetic acid, and the residue was dissolved in a small amount of methanol. Crystallization occurred

when this solution was refrigerated overnight. The crystals were collected; the yield of crude material was 0.4 g. Recrystallization from methanol led to colorless, dense crystals, m.p. 213–215°.

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.09; H, 5.80. Found: C, 68.91; H, 5.83.

The infrared spectrum (chloroform) had a peak at 5.68 μ ; no band was observed in the vicinity of 6.1 μ . The ultraviolet absorption spectrum (ethanol) had λ_{max} 284 m μ .

1-(3',4'-Dimethoxyphenyl)-2-carboxy-3-hydroxymethyl-6,7-dimethoxytetralin Lactone (XV).—A mixture of 0.5 g. of 2-hydroxymethyl-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxy-1-tetralol, 1.0 g. of 5% palladium-carbon catalyst and 100 ml. of glacial acetic acid was shaken under hydrogen (40 lb.) at 80° for two hours. The mixture was filtered, and the solution was evaporated to dryness. The residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with successive portions of 5% sodium hydroxide solution (two portions), dilute acetic acid, sodium bicarbonate solution and water, and was dried over magnesium sulfate. Evaporation of the ethyl acetate afforded 0.4 g. of material which crystallized in methanol. Recrystallization from the same solvent gave colorless crystals, m.p. 189–190.5° (softening).

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.84; H, 6.26.

The infrared spectrum (chloroform) was characterized by a peak at 5.60 μ . The ultraviolet spectrum (ethanol) had λ_{max} 283 m μ .

Alkaline hydrolysis of this lactone required two hours at 100° in 30% sodium hydroxide for complete solution of the material and the formation of a sparingly soluble salt. The latter dissolved upon dilution with water. The solution, after clarification, was acidified strongly with hydrochloric acid and allowed to stand at ice temperature overnight. The crystals, after collecting, washing with water, and recrystallizing from methanol, had m.p. 187–191°; the mixed m.p. with the starting material was 188.5–190.5° (undepressed).

1-Acetoxy-2-hydroxymethyl-3-carboxy-4-(3',4'-dimethoxyphenyl)-6,7-dimethoxytetralin Lactone (XVI).—The dihydroxyacid, XIII (0.7 g.) was heated at 150° for a half hour. The solid obtained was insoluble in sodium bicarbonate solution. It was taken up in 50 ml. of acetic anhydride and the mixture was refluxed for three hours. The resulting solution was evaporated to dryness on a steam-cone. The remaining crystals were recrystallized several times from methanol; colorless needles, m.p. 211–213°.

Anal. Calcd. for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.07; H, 6.18.

The infrared spectrum (chloroform) had bands at 5.58 and 5.74 μ . The ultraviolet spectrum, measured in ethanol, had λ_{max} at 282 m μ .

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