at controlled temperatures, *viz.*, 5, 15 and 25°, produced poorer and variable yields of chloroamine). The clear, colorless solution was allowed to cool gradually to room temperature.

Cyclization.—The reaction mixture from the reduction was added dropwise to a rapidly stirred, ice-cooled solution of 2 moles of sodium hyroxide in a liter of water. The alkaline mixture was distilled into an ice-cooled receiver until a freshly collected portion of the distillate was found to be neutral. The distillate was made strongly basic with potassium hydroxide and extracted twice with ether. Fractionation (over sodium metal) afforded a 79% yield of 2,2,3,3-tetramethylaziridine (I, R = Me), b.p. 104–104.5° (744 mm.), n^{20}D 1.4220. Gas chromatography through a 6' column containing 30% triethylene glycol on acid-washed firebrick (50–60 mesh) at 100° and a helium flow rate of 100 ml./min. revealed a peak corresponding to >98% tetramethylaziridine with a retention time of 23.0 minutes. The infrared spectrum of the neat liquid in a 25 μ cell was characterized by several prominent absorptions at 3200, 2910, 1465, 1380, 1175, 1065 and 830 cm.$^{-1}$. The n.m.r. spectrum showed a single, sharp peak at 217 c.p.s. (relative to external benzene at 40 megacycles).

Anal. Calcd. for $C_6H_{13}N$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.96; H, 13.47; N, 13.75.

2,2,3-Trimethyl-3-ethylaziridine.—In precisely the same manner, 0.1 mole of 2,3-dimethyl-2-pentene was quantitatively converted to the nitroso chloride. The blue product was not characterized but directly reduced with stannous chloride. Ring closure of the resulting chloroamine was accomplished with 4 equivalents of aqueous sodium hydroxide. Fractional distillation over sodium metal gave a 71% yield of the desired aziridine analog, b.p. 129–129.5° (751 mm.), n^{20}D 1.4312. Vapor phase chromatographic analysis (triethylene glycol column 102°) disclosed a peak corresponding to >98% imine with a retention time of 26.6 minutes. The infrared spectrum disclosed prominent absorption bands at 3200, 2920, 1465, 1385, 1165 and 830 cm.$^{-1}$. The infrared and n.m.r. spectra were in accord with the assigned structure.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.35; N, 12.37. Found: C, 74.47; H, 13.34; N, 12.00.

2,2,3-Trimethyl-3-propylaziridine.—The conversion of 0.1 mole of 2,3-dimethyl-2-hexene to the nitroso chloride proceeded smoothly at −70° in quantitative yield. The nitroso compound (probably a mixture of isomers) was processed successively with stannous chloride–HCl and then an excess of aqueous alkali. Careful distillation of the basic product afforded an 84% yield of the desired ethylenimine derivative, b.p. 150–150.5° (747 mm.), n^{20}D 1.4339. Gas chromatography at 102.5° indicated the imine was >98% pure and possessed a retention time of 44.0 minutes. The infrared spectrum was characterized by several prominent absorption frequencies at 3200, 2920, 1465, 1380, 1260, 1165, 1080, 1050 and 835 cm.$^{-1}$. The n.m.r. spectrum appeared to be consistent with expectations.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.64; H, 13.67; N, 10.62.

1,2,-Dimethylcyclopentenimine.—Treatment of 0.1 mole of 1,2-dimethylcyclopentene with gaseous nitrosyl chloride in a Dry Ice–acetone-bath afforded the desired 1,2-dimethyl-1-chloro-2-nitroso cyclopentane in excellent yield. After careful reduction with $SnCl_2$–concd. HCl, the resulting chloroamine was basified with an excess of sodium hydroxide solution to induce cyclization to the bicyclic imine. Fractional distillation of the basic material through a 24" tantalum spiral column produced a 73% yield of the ethylenimine analog, b.p. 134–135°, n^{20}D 1.4550. Gas chromatographic analysis revealed that the imine was 93% pure and had a retention time of 30.5 minutes at 108°. The n.m.r. spectrum of this compound revealed resonance lines at 214 c.p.s. (methyl protons) and 198 c.p.s. (ring hydrogens). The infrared spectrum showed prominent absorptions at 3225, 2920, 1445, 1410, 1385, 1292, 1262, 1220, 1050, 990, 865, 780 and 685 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}N$: C, 75.61; H, 11.78; N, 12.60. Found: C, 75.31; H, 11.76; N, 12.68.

1,2-Dimethylcyclohexenimine.—The chloronitrosation of 0.1 mole of 1,2-dimethylcyclohexene at −70° produced in excellent yield the desired 1,2-dimethyl-1-chloro-2-nitrosocyclohexane which on crystallization from absolute ethanol gave a melting point of 78–79°.

Anal. Calcd. for $C_8H_{14}NOCl$: Cl, 20.19. Found: Cl, 20.29.

The bicyclic imine was obtained by successive treatment of the nitroso chloride with stannous chloride–concd. HCl reagent and four equivalents of aqueous sodium hydroxide solution. Purification afforded a 76% yield of the fully substituted imine, b.p. 165–165.5° (750 mm.), n^{20}D 1.4665. Vapor phase chromatographic analysis at 105° disclosed that the imine was homogenous (>98% pure) and had a retention time of 62.0 minutes. The n.m.r. spectrum disclosed resonance lines at 217 (methyl protons), 210 and 201 c.p.s. (ring hydrogens). The infrared spectrum showed prominent absorption bands at 3225, 1445, 1385, 1360, 1292, 1250, 1190, 1145, 1087, 1035, 1015, 985, 970, 905, 865, 825 and 805 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{15}N$: C, 76.73; H, 12.07; N, 11.18. Found: C, 76.52; H, 11.87; N, 10.95.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY, BOSTON 15, MASS.]

Compounds Related to Podophyllotoxin. XI. An Unusual Stobbe Condensation[1]

BY WALTER J. GENSLER, FRANCIS JOHNSON AND WILLIAM F. SULLIVAN

RECEIVED JUNE 2, 1960

Stobbe condensation of methyl 2-(3',4',5'-trimethoxybenzoyl)-4,5-methylenedioxybenzoate with dimethyl succinate gives a product which was previously regarded as methyl 1-(3',4',5'-trimethoxyphenyl)-4-hydroxy-6,7-methylenedioxy-2-naphthoate but which is now shown to be methyl 1-hydroxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-2-naphthoate. The revision of structure follows from the infrared absorption of the condensation product, its reluctance to methylate with diazomethane, its mode of synthesis, and its non-identity with the authentic 4-hydroxy-2-naphthoate isomer. The tetralone, methyl 1-(3',4',5'-trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate, on dehydrogenation with sulfur gives the authentic 4-hydroxy-2-naphthoate isomer. Acetylation yields the corresponding 4-acetoxy-2-naphthoate. The tetralone starting material with isopropenyl acetate plus a trace of acid forms the enol acetate, which with sulfur aromatizes to the same 4-acetoxy-2-naphthoate. A reaction path by which the Stobbe condensation can give rise to the 1-hydroxy-2-naphthoate isomer is suggested.

Cyclization of benzhydrylsuccinic acid I gave a keto acid, for which several structures could be written.[2] To show that structure II for the cyclized keto acid was correct, its methyl ester III was aromatized to the corresponding 4-hydroxy-2-naphthoic methyl ester V. This hydroxy ester V was expected to be identical with the same compound reported before as the product from a Stobbe condensation.[3] However, the two ma-

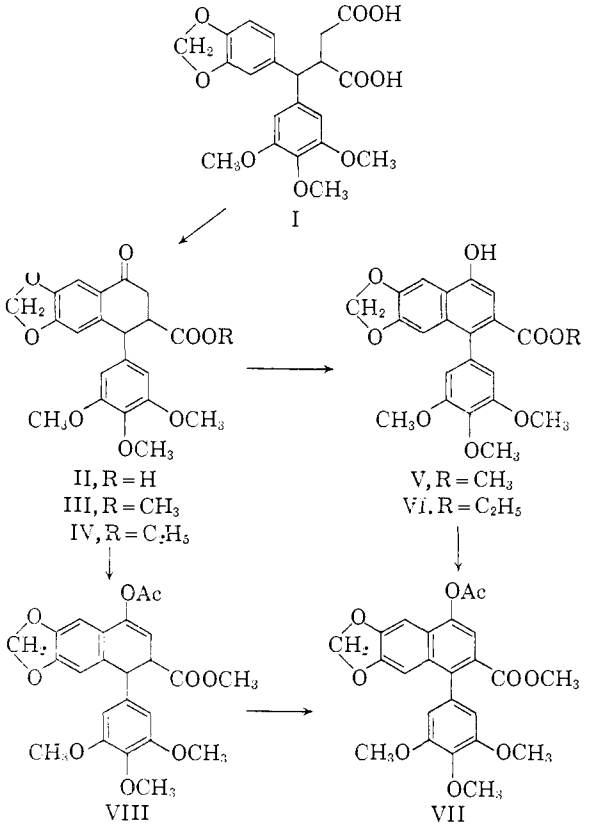
(1) This investigation was supported by Research Grant CY-2891 from the National Cancer Institute, Public Health Service.

(2) W. J. Gensler, C. M. Samour, Shih Yi Wang and F. Johnson, THIS JOURNAL, **82**, 1714 (1960).

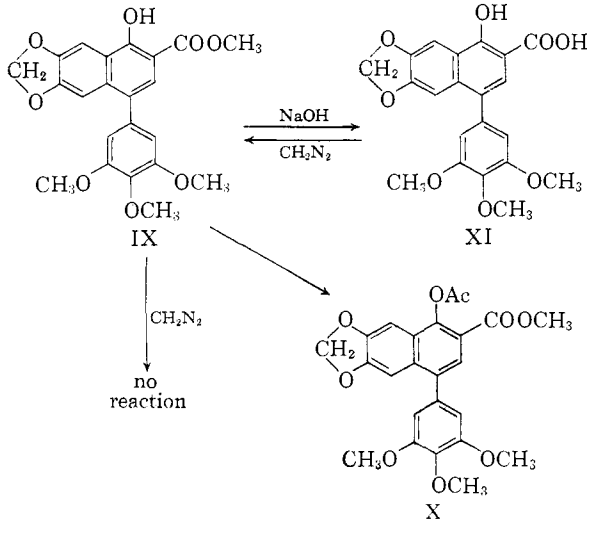
(3) W. Reeve and H. Myers, *ibid.*, **75**, 4957 (1953).

terials were found *not* to be the same. This paper describes and interprets our observations.

Dehydrogenation of tetralone III to naphthol V (as well as of ethyl ester IV to naphthol ethyl ester VI) was effected with sulfur. Acetylation converted naphthol methyl ester V to its acetate VII. The same acetate could be obtained by treating tetralone III with isopropenyl acetate in the presence of *p*-toluenesulfonic acid, and dehydrogenating the resulting enol acetate VIII with sulfur.



A sample of the earlier hydroxy naphthoic methyl ester, which we now consider to be IX, could be acetylated to the acetate methyl ester



X, and also could be saponified to the naphthol acid XI. The properties of the two hydroxy methyl esters V and IX, as well as of the two acetate methyl esters VII and X, showed that the materials were not identical, but instead were isomeric. Meanwhile, work along other lines with keto acid II had made its assigned structure secure.[2] Since this result also established the structure of derived compound V, the compound reported before must have a structure different from V.

Several observations make formulation IX, that of an *o*-hydroxy ester, highly probable. Infrared absorption peaks at 5.68 and 5.8μ for both the *meta* (VII) and the *ortho* (X) acetate esters correspond to acetate and naphthoate carbonyl, respectively. However, while *m*-hydroxy ester V shows absorption as expected at 3.0μ (hydroxy) and at 5.8μ (naphthoate carbonyl), the *o*-hydroxy ester IX shows no absorption in the 3μ region, and shows carbonyl absorption not at 5.8μ but instead at 6.0μ. Hydrogen bonding between hydroxy and carbomethoxy groups in the *o*-isomer IX accounts satisfactorily both for the absence of 3.0μ absorption, and for the shift of naphthoate carbonyl absorption from 5.8 to 6.0μ.[4]

Another property consistent with a hydrogen bonded hydroxyl group in compound IX is its failure to react with diazomethane. The corresponding *o*-hydroxycarboxylic acid XI, even with excess diazomethane, gives only the monomethylated ester IX. The same behavior has been observed with salicylic acid,[5] and even more apropos, with 1-hydroxy-2-naphthoic acid.[6] A further indication of strong hydrogen bonding in the *o*-hydroxy ester IX is its insolubility in 10% aqueous sodium hydroxide[3]; the *m*- isomer V is soluble even in 1% aqueous sodium hydroxide.

Why hydroxy ester IX gives a positive azo coupling test[3] is not clear. Possibly the diazonium grouping takes the place of the carbomethoxy group by an electrophilic *displacement* process, or possibly the open position *meta* to the hydroxyl group is the site of coupling.

Compound IX was formed as the minor product (16%) by condensation of benzophenone XII with dimethyl succinate in the presence of sodium hydride.[3] The major product was a mixture of itaconic acids XVI, the result of ester hydrolysis during or after the condensation. According to the generally accepted course of the Stobbe process,[7] lactone XIII should be formed first. Itaconic acids XVI would be derived from this lactone XIII by way of the usual β-elimination.[7] In addition, an intermediate naphthol acid, formulated as XV, could be traced through as the result

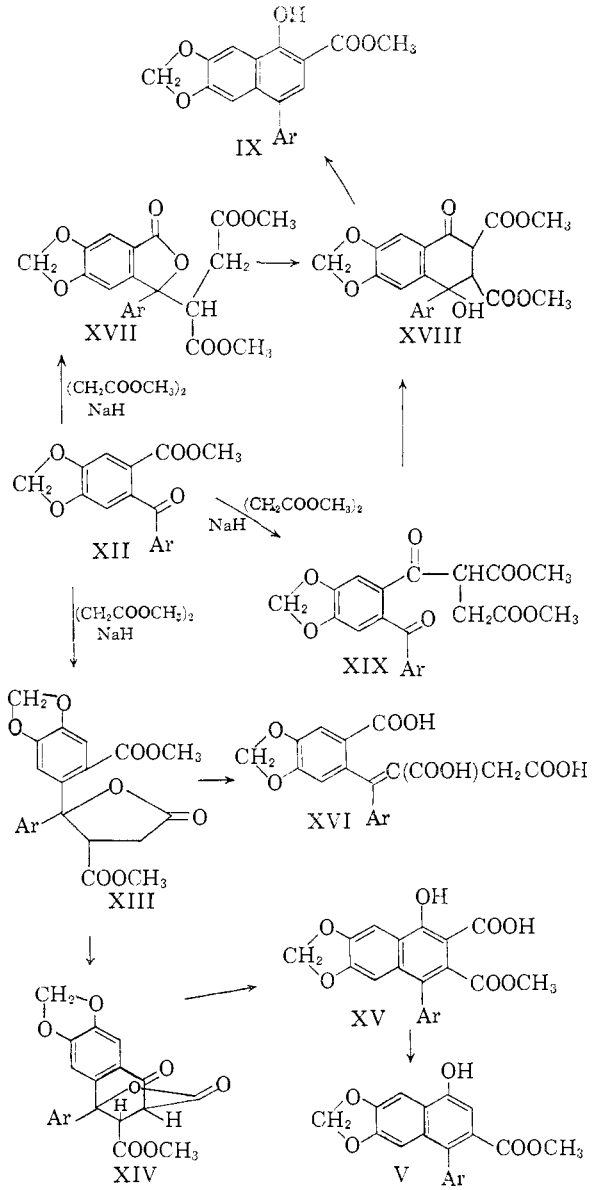
(4) The infrared results are consistent with the report that butyl salicylate absorbs at 5.97 μ, while butyl acetylsalicylate absorbs at 5.65 (acetate carbonyl) and at 5.805 μ (aromatic ester carbonyl) [R. S. Rasmussen and R. B. Brattain, THIS JOURNAL, **71**, 1073 (1949)].

(5) J. Herzig and T. Tichatschek, *Ber.*, **39**, 1557 (1906).

(6) W. Hückel and E. Goth, *ibid.*, **57**, 1285 (1924). Also pertinent are the smooth conversions, wth excess diazomethane in ether–methanol, of 4-hydroxy-1-methoxy-2-naphthoic acid to 1,4-dimethoxy-2-naphthoic methyl ester, and of 1-hydroxy-4-methoxy-2-naphthoic acid to 1-hydroxy-4-methoxy-2-naphthoic methyl ester [A. H. Homeyer and V. H. Wallingford, THIS JOURNAL, **64**, 798 (1942)].

(7) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

of a Dieckmann cyclization (XIII to XIV[8]) followed by β-elimination and enolization. Decarboxylation would then convert naphthol acid XV to the final product, formulated as V. However, alternate reaction pathways that do not necessarily predict structure V are possible. There is no compelling reason to favor lactone XIII to the exclusion of isomeric lactone XVII.[9] If XVII is admitted, it could give diester XVIII by intramolecular cyclization. The same diester XVIII could also arise by a *Claisen* process (XII to XIX) followed by cyclization.[8] Contrary to the earlier assumption, it does not follow that XVIII, the product of an *intramolecular* cyclization, would be too unstable to form and exist without γ-lactonization. Which of the two carbomethoxy groups would be expected to cleave when diester XVIII goes on to give a hydroxy naphthoic methyl ester is problematical. However, *a posteriori*, the ester group farther from the ketone is lost, so that the final product is the *o*-hydroxy ester IX and not the *m*-hydroxy isomer V.



Acknowledgment.—We wish to acknowledge with thanks the help of Professor Wilkins Reeve, who very kindly supplied a sample of the Stobbe condensation product.

Experimental[10]

Methyl 1-(3′,4′,5′-Trimethoxyphenyl)-4-hydroxy-6,7-methylenedioxy-2-naphthoate (V) from Methyl 1-(3′,4′,5′-Trimethoxyphenyl-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate (III).—Biphenyl (5.0 g.) containing 0.5 g. (0.0012 mole) of tetralone methyl ester III[2] and 0.115 g. of sulfur (0.0036 mole) was boiled for 1.5 hours. The cooled dark-brown reaction mixture was dissolved in 15 ml. of benzene and placed on a 12 × 1 cm. column containing 15 g. of Merck acid-washed alumina. The following solvents were then passed through the column: 260 ml. of benzene, 180 ml. of benzene–ether (95:5), and 240 ml. of benzene–ether (90:10). The material in each 20-ml. portion of eluate was examined separately. Biphenyl appeared in eluate fractions 1–4; starting material (37 mg.) was noted in fractions 6–11. The crystalline solids in fractions 17–34, after combination and crystallization from chloroform–methanol, furnished 0.16 g. of light-brown crystalline dehydrogenation product V, m.p. 233–235°. Further purification was effected by sublimation at 215–245° (2 × 10^{-4} mm.) followed by several crystallizations, or more simply by crystallization (including a treatment with decolorizing carbon) from chloroform–methanol followed by three recrystallizations from methanol. Analytically pure, very faintly yellow naphthol methyl ester V showed m.p. 239–239.5°. This product fluoresced under ultraviolet light, and showed absorption maxima at 263 mμ (log ε 4.62), 308 mμ (log ε 3.97) and 348 mμ (log ε 3.385) in absolute alcohol. The compound in a mull with mineral oil showed absorption peaks at 3.0μ (hydroxyl group) and 5.80μ (ester carbonyl).

Anal. Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 64.1; H, 4.9.

Other methods tried for converting the tetralone III to the α-naphthol system—for example, selenium dioxide with the keto acid, selenium dioxide with the keto methyl ester, N-bromosuccinimide with the keto methyl ester, or palladium-on-carbon dehydrogenation with either keto acid or keto methyl ester—were uniformly unsatisfactory.

Ethyl 1-(3′,4′,5′-Trimethoxyphenyl)-4-hydroxy-6,7-methylenedioxy-2-naphthoate (VI) from Ethyl 1-(3′,4′,5′-Trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate (IV).—The dehydrogenation was performed by heating a mixture of 0.64 g. (0.0015 mole) of tetralone ester IV[2] and 0.148 g. of sulfur (0.0046 g. atom) for 2 hours at 250°. The reaction mixture was processed in a manner similar to that described for the preparation of the corresponding naphthol methyl ester V. Some starting material (100 mg. after crystallization) was obtained. The yellow crystalline product after one crystallization from methanol weighed 0.12 mg. and melted at 203°; recrystallization from the same solvent brought the melting point to 202.5–203°.

Anal. Calcd. for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.6; H, 5.2.

The naphthol ethyl ester VI, which as a mull with mineral oil showed infrared absorption peaks at 2.95 (hydroxyl) and 5.87μ (α, β-unsaturated ester carbonyl), was soluble in 1% sodium hydroxide solution but not in saturated bicarbonate solution. A 1.92 × 10^{-5} *M* alcohol solution showed maxima at 206 mμ (log ε 4.66), 226 mμ (shoulder, log ε 4.49), 262 mμ (log ε 4.62), 306 mμ (log ε 3.93) and 348 mμ (log ε 3.04).

(8) Structures somewhat analogous to XIV and XV have been encountered in the Stobbe condensation of a β-keto nitrile [W. S. Johnson, J. W. Petersen, and C. D. Gutsche, THIS JOURNAL, **69**, 2942 (1947)].

(9) Involvement of the ester group of *o*-carbethoxybenzophenone in a condensation related to the Stobbe process is made highly probable by the work of W. S. Johnson, A. L. McCloskey and D. A. Dunnigan, [*ibid.*, **72**, 514 (1950)].

(10) Elementary analyses were performed by Carol K. Fitz, 115 Lexington Ave., Needham Heights, Mass., and by S. M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass.

Methyl 1-(3',4',5'-Trimethoxyphenyl)-4-acetoxy-6,7-methylenedioxy-2-naphthoate (VII) by Acetylation of the Corresponding Hydroxy Compound V.—A mixture of 2 ml. of pure pyridine, 1 ml. of freshly distilled acetic anhydride and 70 mg. of naphthol methyl ester V was heated on the steam-bath for 1 hour, and then set aside for 2 days at room temperature. The reaction mixture, after hydrolysis with 10 ml. of water and 15 g. of ice, was extracted with three portions of ether, and the combined extracts were washed twice with 10% hydrochloric acid, once with water, once with saturated sodium bicarbonate solution, and finally with water. The ether solution was dried with sodium sulfate, and was evaporated on the steam-bath. The pale yellow crystalline residue (70 mg.) was recrystallized once from methanol containing a trace of methylene chloride, and twice from methanol to give the pure acetoxy methyl ester VII, m.p. 197.5–198°. The ultraviolet absorption curve, determined in 3.42×10^{-5} *M* alcoholic solution, showed maxima at 255 mμ (log ε 4.73), 297 mμ (log ε 4.03) and 342 mμ (shoulder log ε 3.47). Absorption peaks at 5.68 and 5.78 μ corresponded to acetate and carbomethoxy carbonyls, respectively.

Anal. Calcd. for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88. Found: C, 63.2; H, 4.8.

Methyl 1-(3',4',5'-Trimethoxyphenyl)-4-acetoxy-6,7-methylenedioxy-1,2-dihydro-2-naphthoate (VIII).—Redistilled isopropenyl acetate (12 ml.) containing 0.30 g. of tetralone methyl ester III, m.p. 176°, and 0.15 g. of *p*-toluenesulfonic acid was boiled for 6 hours. The mixture was concentrated by slow distillation over a period of 2 hours, and then exposed at 100° to the vacuum of an oil-pump. An ether solution of the residual brown gum was washed twice with water, twice with 2% sodium bicarbonate solution, and finally with water. The dried (calcium chloride) ether solution was distilled on the steam-bath. The solvent-free residual gum, on crystallization from a small volume of methanol, was transformed into a mat of faintly yellow, fine, needle-like crystals (0.27 g.), m.p. 149–152°, with preliminary softening at 145°. Further purification of this enol acetate methyl ester VIII by recrystallizations from methanol gave fluffy needles, m.p. 151–152°.

Anal. Calcd. for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Found: C, 63.1; H, 5.5.

The enol acetate methyl ester VIII in 95% alcohol solution (3.5×10^{-5} *M*) showed absorption maxima at 280 mμ (log ε 3.76) and 314 mμ (log ε 3.83), and shoulders at 322 mμ (log ε 3.81) and 225 mμ (log ε 4.52). A mull with mineral oil showed infrared absorption bands at 5.76 (ester carbonyl) and 5.68μ (enol acetate carbonyl).

Methyl 1-(3',4',5'-Trimethoxyphenyl)-4-acetoxy-6,7-methylenedioxy-2-naphthoate (VII) by Dehydrogenation of Enol Acetate VIII.—A mixture of 110 mg. of enol acetate VIII, 2 g. of biphenyl and 50 mg. of sulfur after boiling for 1 hour was digested with 40 ml. of petroleum ether (b.p. 30–60°), and filtered. The insoluble material was dissolved in 20 ml. of benzene. The petroleum ether filtrate, followed by 100 ml. of fresh petroleum ether and then by the benzene solution, was allowed to percolate through a column (¾ × 3 cm.) of Merck acid-washed alumina (4 g.). The column was developed with 20 ml. of fresh benzene followed by 50 ml. of benzene–ether (9:1). The brown solid obtained on evaporation of the benzene–ether eluates was dissolved in methanol, and was treated with decolorizing carbon at the boiling point. The clear, almost colorless filtrate was concentrated and cooled to give 18 mg. of crystalline product, m.p. 194–196°. An additional crystallization from methanol gave the acetoxy methyl ester VII melting alone or admixed with the material described above at 195–196°. The infrared absorption spectra of the two samples of acetoxy methyl ester VII were identical.

The results of attempted dehydrogenation of enol acetate VIII with selenium dioxide, or with lead tetraacetate, or catalytically over a palladium-on-charcoal catalyst were not promising, and these experiments were not pursued.

Methyl 1-Hydroxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-2-naphthoate (IX).—A sample of this compound,[3] after extraction with 10 ml. of boiling petroleum ether (b.p. 30–60°), was dissolved in methylene chloride. The filtered solution was diluted with 10 ml. of methanol and then concentrated. The fine needle-like crystals deposited (0.2 g.) showed m.p. 202–203°. Further purification was effected by allowing a solution of 40 mg. of the compound in 10 ml. of benzene to flow through a 1 × 2 cm. column of Merck acid-washed alumina (2 g.). When the column was almost empty an additional 50 ml. of benzene was passed through. The emergent benzene solution was evaporated to dryness; the residue, after three recrystallizations from methanol–methylene chloride, showed m.p. 204°. The melting point reported[3] for IX is 204–205°.

Anal. Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89; CH_3O, 30.1; active H, 0.243. Found: C, 63.9; H, 5.0; CH_3O, 31.3; active H, 0.199.

A 3.8×10^{-5} *M* alcohol solution showed absorption maxima at 268 mμ (log ε 4.65), 274 mμ (a shoulder, log ε 4.64), 304 mμ (log ε 4.04) and 314 mμ (log ε 4.01). Compound IX as a mull with mineral oil gave infrared absorption peaks at 6.00, 6.18 and 6.32μ, but none at the hydroxyl region. A chloroform solution of the compound also showed no sign of hydroxyl absorption at 2.5–3.5μ; the 6.00μ band persisted.

Methyl 1-Acetoxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-2-naphthoate (X).—The corresponding hydroxy compound IX was acetylated by boiling a solution of the material (100.7 mg.) in 4 ml. of acetic anhydride containing approximately 10 mg. of *p*-toluene sulfonic acid for 2 hours. Volatile material was removed by distillation on the steam-bath under reduced pressures. A solution of the light-brown crystalline residue in 20 ml. of benzene containing 40 ml. of petroleum ether (b.p. 30–60°) was percolated through a column of 3 g. of Merck acid-washed alumina. The solution was followed with fresh solvents (total volume, 325 ml.), 25-ml. fractions of eluate being taken and processed individually. The solvents consisted of benzene–petroleum ether (b.p. 30–60°) mixtures in which the proportion of benzene was increased in several steps from 33 to 80%, and then to 100%. Fractions 6–13 furnished 54 mg. of colorless crystals (m.p. 170–176°), which after crystallization from methanol gave 43 mg. of product (m.p. 176.5–177.3°). A sample of the acetylated ester X after two further crystallizations showed m.p. 176.5–177.5°.

Anal. Calcd. for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88. Found: C, 63.2; H, 4.8.

The acetyl derivative X in 3.1×10^{-5} *M* alcohol solution showed λ_{max} 261 mμ (log ε 4.70), 310 mμ (log ε 4.10), and an inflection at 348 mμ (log ε 3.53). A mull of the compound with mineral oil showed infrared absorption peaks at 5.68 μ (phenolic acetate carbonyl), 5.81 μ (α, β-unsaturated ester carbonyl) and 6.34 μ. No hydroxylic absorption was evident.

1-Hydroxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic Acid XI by Saponification of Its Methyl Ester IX.—A mixture of 10 ml. of methanol, 2 g. of potassium hydroxide, 5 ml. of water and 150 mg. of naphthol methyl ester IX was boiled under reflux for 3 hours, after which period most of the methanol was removed by distillation. The alkaline concentrate, after dilution with water to a volume of 50 ml., was treated with 3 ml. of concentrated hydrochloric acid in 10 ml. of water. The organic solids were taken up in methylene chloride, and the methylene chloride solution was washed twice with water, was dried with magnesium sulfate, and was evaporated *in vacuo*. The residual powder (119 mg.) was redissolved in methylene chloride containing a small amount of methanol, ether was added to the warm solution, and the solution was then concentrated to 3 ml. and cooled. The heavy precipitate (75 mg., m.p. 224–225° dec.) was recrystallized four times from methanol–methylene chloride to yield 36 mg. of the hydroxynaphthoic acid XI, m.p. 251–252° with preliminary softening at 248°.

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.5; H, 4.5.

The compound showed λ_{max} 269 mμ (log ε 4.626), 272 mμ (shoulder log ε 4.62), 304 mμ (log ε 3.97), 314 mμ (shoulder log ε 3.91) and 352 mμ (log ε 3.52) in 2.2×10^{-5} *M* alcoholic (95%) solution. Hydroxyl group absorption was evident at 2.90μ. Other peaks appeared at 6.33, 6.18 and 6.04μ, the last absorption being attributed to the hydrogen-bonded carbonyl group.

Treatment of 1-Hydroxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic Acid (XI) and the Corresponding Methyl Ester IX with Diazomethane.—Naphthol acid XI (3 mg.) was treated with 2 ml. of ethereal diazomethane (excess). After 5 minutes, one drop of glacial acetic acid was added, and solvent was removed by

evaporation on the steam-bath. Crystallization of the residue from methanol afforded long needles of the hydroxy methyl ester IX, m.p. 198–200°. The mixture melting point with the original purified hydroxy methyl ester IX was 199–200°.

Further methylation was attempted by adding 7 ml. of ethereal diazomethane (excess) to a solution of 40 mg. of hydroxy methyl ester IX in 8 ml. of methylene chloride. The reaction mixture was allowed to stand at 5° for 18 hours. Removal of volatile material left 40 mg. of unchanged starting material melting at 200–203° and, after admixture with starting material, at 201–203°.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY, BOSTON 15, MASS.]

Compounds Related to Podophyllotoxin. XII. Podophyllotoxone, Picropodophyllone and Dehydropodophyllotoxin[1]

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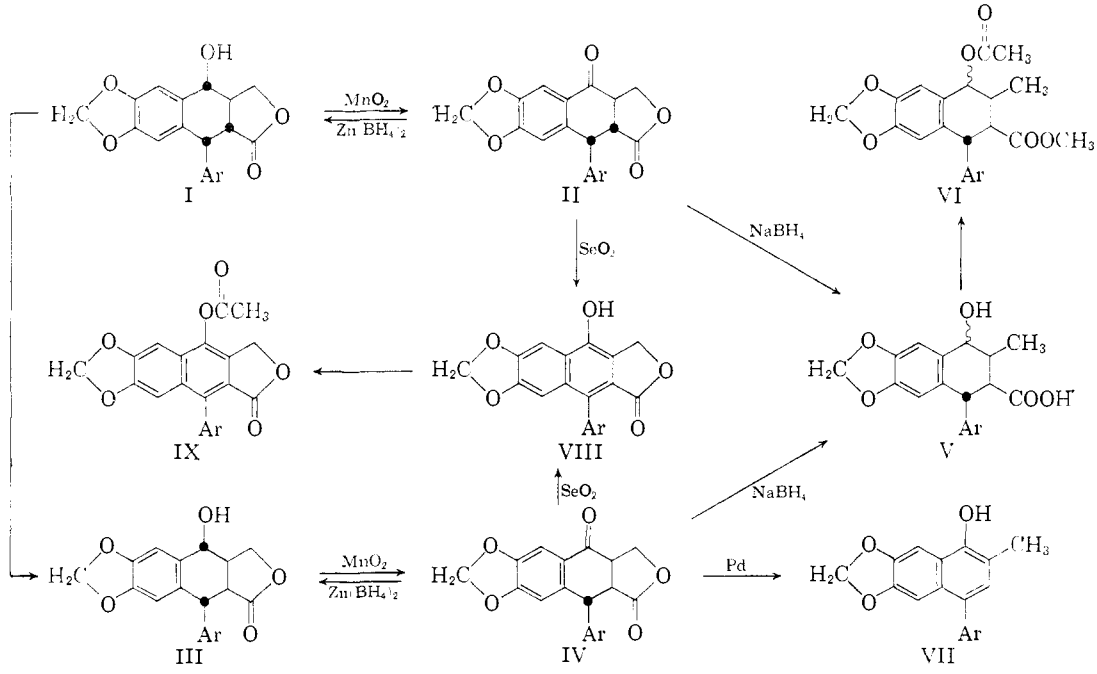
Manganese dioxide converts podophyllotoxin and picropodophyllin to the corresponding ketones, podophyllotoxone and picropodophyllone. The ketones with sodium borohydride give the same product, a hydroxy acid. In contrast, zinc borohydride regenerates podophyllotoxin from podophyllotoxone, and regenerates picropodophyllin from picropodophyllone. Both podophyllotoxone and picropodophyllone on treatment with selenium dioxide give the naphthol, dehydropodophyllotoxin, identical with the material isolated by Kofod and Jørgensen from podophyllin resin. The ultraviolet and infrared absorption data, the fact that manganese dioxide readily oxidizes podophyllotoxin and picropodophyllin to the ketones, and the fact that an oxidative process converts the ketones to a naphthol all point to the α-tetralol structures of podophyllotoxin and picropodophyllin. Accordingly, the present work provides independent evidence for the presence of a secondary hydroxyl group, and, when the known carbon skeleton is taken into account, provides independent evidence for the position of the hydroxyl group. Methylmagnesium bromide adds to podophyllotoxone to give two stereoisomeric methylpodophyllotoxins. Phenylhydrazine reacts with podophyllotoxone to give a pyrazoline acid instead of the phenylhydrazone.

Continued work on podophyllotoxin compounds has developed a method of converting podophyllotoxin (I)[2] to the corresponding ketone, podophyllotoxone (II). This report describes the preparation and reactions of podophyllotoxone (II), as well as of its stereoisomer, picropodophyllone (IV), and its dehydrogenation product, dehydropodophyllotoxin (VIII).[3]



Podophyllotoxone (II) and Picropodophyllone (IV).—Finely divided manganese dioxide in an inert solvent[4] converted podophyllotoxin (I) to podophyllotoxone (II), and similarly converted picropodophyllin (III) to picropodophyllone (IV). Thus manganese dioxide proved effective where other reagents–*e.g.*, potassium dichromate,[5] chromic anhydride,[5] ethylene with copper chromite catalyst at 280°,[6] acetone with aluminum isopropoxide,[7]

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(2) In all the structural formulas, Ar stands for 3,4,5-trimethoxyphenyl.

(3) A short description of some of this work has already appeared; *cf.* W. J. Gensler and F. Johnson, THIS JOURNAL, **77**, 3674 (1955).

(4) Compare J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(5) E. H. Price, Doctoral Thesis, University of Maryland, College Park, Md., 1949.

(6) H. Myers, Doctoral Thesis, University of Maryland, College Park, Md., 1951.