[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

Components of Podophyllin. VIII. Study of Intermediates in the Synthesis of Dehydroanhydropicropodophyllin[1]

BY ANTHONY W. SCHRECKER AND JONATHAN L. HARTWELL

RECEIVED MARCH 27, 1952

A revised structure is proposed for one of the intermediates in Haworth and Richardson's[2] synthesis of dehydroanhydropicropodophyllin, and several new compounds are reported in this connection.

In 1936, Haworth and Richardson[2] synthesized a compound, m.p. 267–268°, which proved to be identical with dehydroanhydropicropodophyllin (V).[3] They prepared it by dehydrogenation of the 6,7 - methylenedioxy - 1 - (3,4,5 - trimethoxyphenyl)-3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone (IV), with m.p. 248–249°, which is an isomer of α- and β-apopicropodophyllin, formed[4] in the dehydration of picropodophyllin. Another isomer of these two compounds, named "γ-apopicropodophyllin," has been obtained[5] by boiling α-apopicropodophyllin with 20% potassium hydroxide for 24 hours and lactonizing the product. Subsequently, it was demonstrated[5] that γ-apopicropodophyllin is structurally identical with Haworth and Richardson's lactone IV. Their synthesis was repeated to establish this identity. However, in the course of that work, certain differences from the results published by Haworth and Richardson were found. These differences form the subject of the present communication.

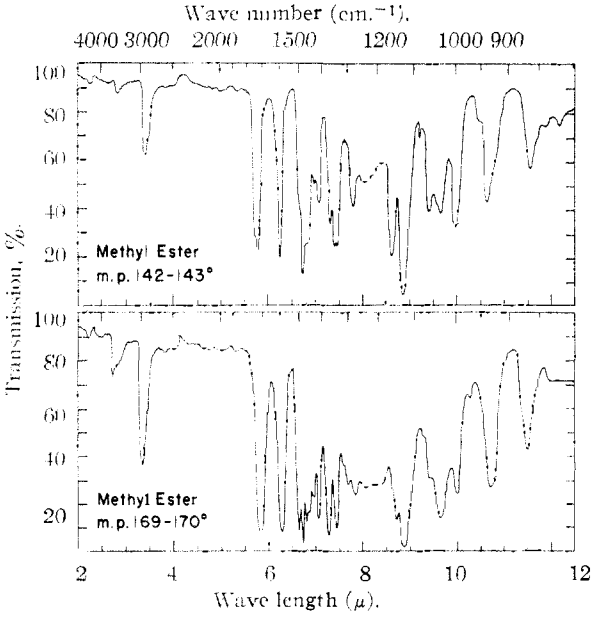


Fig. 1.—Infrared absorption spectra in chloroform.

Haworth and Richardson prepared the lactone IV by the following series of reactions: Safrole oxide was condensed with ethyl acetoacetate to yield a compound, m.p. 91–92°, which was later[5] shown to be α-acetyl-γ-(3,4-methylenedioxybenzyl)-γ-butyrolactone (I). When the sodium enolate of this compound was condensed with trimethylgalloyl chloride, and the acetyl group removed with dilute sodium hydroxide, α-(3,4,5-trimethoxybenzoyl)-γ-(3,4-methylenedioxybenzyl)-γ-butyrolactone (II), m.p. 110–111°, was obtained. This compound underwent ring closure when treated with methyl alcoholic hydrogen chloride to give a 70% yield of material, m.p. 138–139°, to which they assigned[2,6] the structure of 1-hydroxy - 6,7 - methylenedioxy - 1 - (3,4,5 - trimethoxyphenyl) - 3 - hydroxymethyl - 1,2,3,4 - tetrahydro-2-naphthoic acid lactone (III). When this compound was heated with potassium hydrogen sulfate at 180°, it was converted to lactone IV, m.p. 248–249°. In order to account for the formation of the 1-hydroxy lactone III, Haworth and Atkinson[6] postulated that a "pinacolinic transformation" took place during the ring closure with methyl alcoholic hydrogen chloride. The various steps, as formulated by Haworth and Atkinson, are summarized in Chart I.

When Haworth and Atkinson, however, treated the α-acetyl butyrolactone I with methyl alcoholic hydrogen chloride, they did not obtain a hydroxy lactone corresponding to III, but rather a methyl ester, for which they proposed the structure of methyl 6,7-methylenedioxy-3,1-endomethyleneoxyl-1-methyl-1,2,3,4-tetrahydronaphthalene-2-carboxyate (VI, R = R′ = CH_3), without excluding the alternative 7-membered-ring oxide structure (VII, R = R′ = CH_3). The corresponding acid (R′ = H) was obtained by treatment of I with a mixture of acetic and hydrochloric acids.

Our experiments showed that the compound, m.p. 138–139°, does not actually possess the hydroxy lactone constitution III, postulated by Haworth, but that its structure corresponds to VI or possibly VII (R = 3,4,5-trimethoxyphenyl, R′ = CH_3). When the α-trimethoxybenzoyl butyrolactone II was refluxed with methyl alcoholic hydrogen chloride,[2] there was isolated, in yields ranging from 26 to 50%, a colorless solid, m.p. 140°. This product, after recrystallization from ethanol or methanol, formed colorless needles, m.p. 142–143°, apparently identical with Haworth's compound, m.p. 138–139°. Analysis indicated the presence of four methoxyl groups. No free hydroxyl group could be detected by treatment with acetic anhydride or phosphorus trichloride.

(1) Paper VII: A. W. Schrecker, G. Y. Greenberg and J. L. Hartwell, THIS JOURNAL, **74**, 5069 (1952).

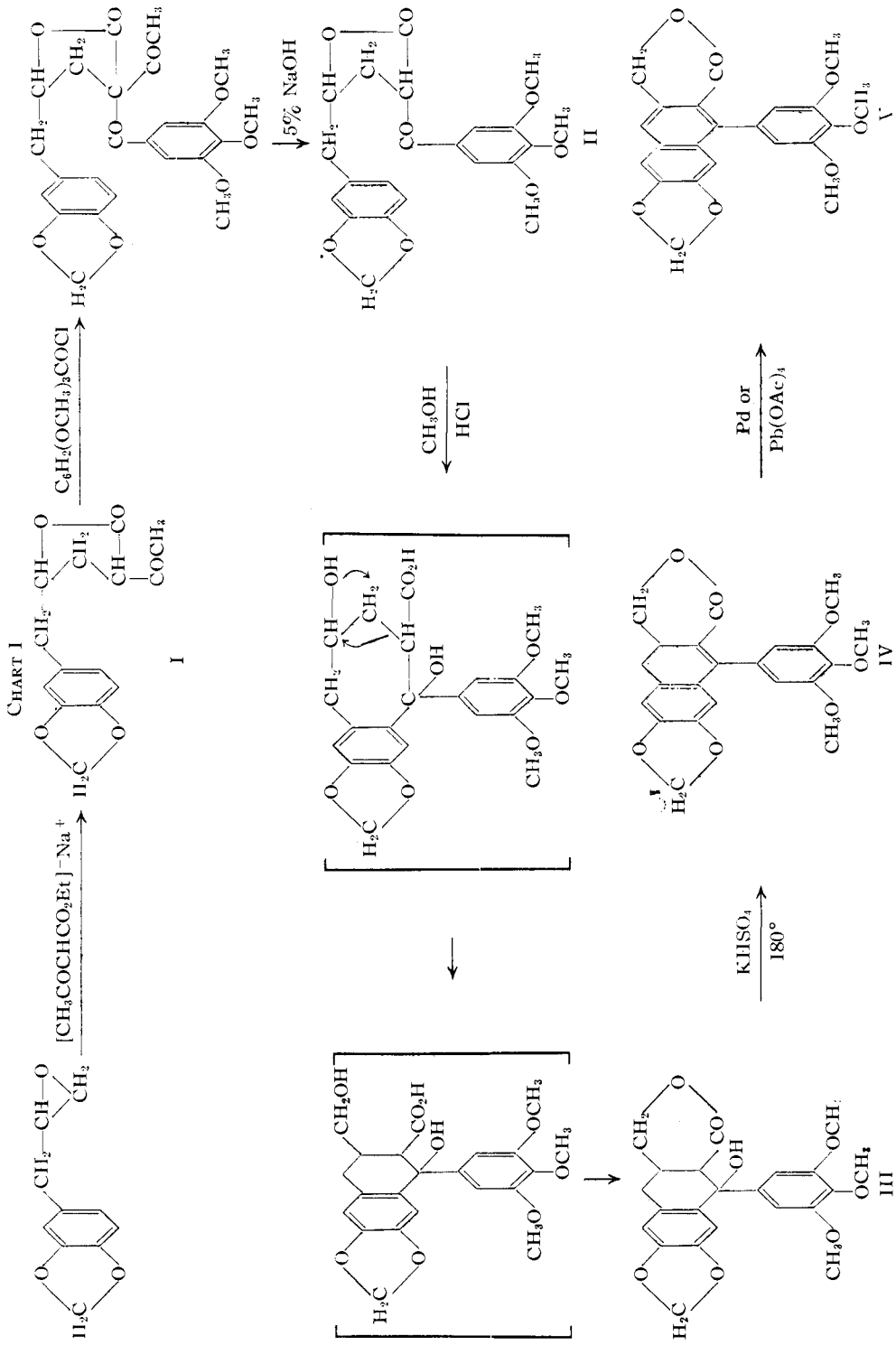
(2) R. D. Haworth and T. Richardson, *J. Chem. Soc.*, 348 (1936).

(3) E. Späth, F. Wessely and L. Kornfeld, *Ber.*, **65**, 1536 (1932).

(4) A. Robertson and R. B. Waters, *J. Chem. Soc.*, 83 (1933).

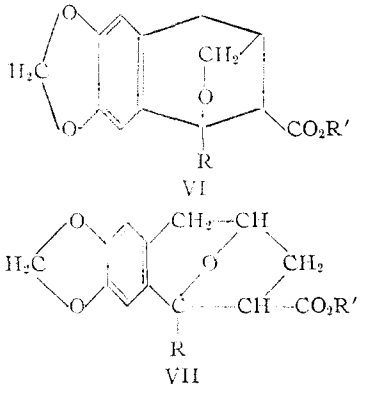
(5) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **74**, 5676 (1952).

(6) R. D. Haworth and J. R. Atkinson, *J. Chem. Soc.*, 797 (1938).



Saponification yielded an acid, m.p. 205–208°, which did not lactonize when heated with mineral acid. In addition to the compound, m.p. 142–143°, there was obtained in several experiments, in yields ranging from 7 to 17%, an isomer crystallizing from dilute ethanol as tiny colorless needles, m.p. 169–170°, which also gave an analysis indicating four methoxyl groups and which also could be saponified to an acid, m.p. 243–244° (foaming). The infrared spectra (Fig. 1) of the compounds, m.p. 142–143° and 169–170°, showed peaks at 1725 and 1710 cm.$^{-1}$, respectively, certainly corresponding to ester groups. The lactone ring present in podophyllotoxin derivatives[5,7] on the other hand, gives a maximum located in the range of 1745 to 1790 cm.$^{-1}$ All this evidence indicates that both the compounds, m.p. 142–143° and 169–170°, respectively, are methyl esters. They may be

(7) Paper XII, A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, to be published.

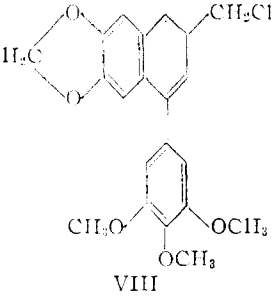


VI

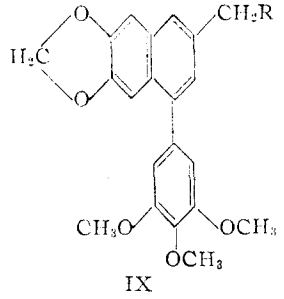
VII

stereoisomers of structure VI (R = 3,4,5-trimethoxyphenyl, R′ = CH_3) or, less probably, one or both might have the corresponding structure VII. The same applies to the acids obtained on saponification (R′ = H). It may be pointed out that while the ester, m.p. 169–170°, was readily hydrolyzed with 5% methyl alcoholic potassium hydroxide, the compound, m.p. 142–143°, was saponified only in the presence of water. Formation of the lactone IV by treatment of the ester, m.p. 142–143°, with potassium hydrogen sulfate does not involve simple dehydration, as postulated previously,[2] but rather the removal of the elements of methanol, requiring cleavage of both the ester and the tetrahydrofuran linkages. A compound of structure III might be expected to be dehydrated readily under mild conditions, such as heating with iodine in benzene; this was found not to be the case.

In addition to the esters, m.p. 142–143° and 169–170°, a third compound was obtained in the reaction of II with methyl alcoholic hydrogen chloride. It was isolated in one experiment as colorless needles, m.p. 125–127° (yield 7%). The same material, melting at 127–128°, was formed in high yield when the lactone II was treated with a mixture of acetic and hydrochloric acids; it was found to be identical with 6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl) - 3 - chloromethyl - 3,4 - dihydronaphthalene (VIII). When this compound was refluxed with 10% methyl alcoholic potassium hydroxide, it was converted to 6,7-methylenedioxy-1-(3,4,5 - trimethoxyphenyl) - 3 - methylnaphthalene (IX, R = H), m.p. 146–147°. The ultraviolet absorption spectrum of IX (R = H) (Fig. 2) greatly resembled that of the derivative in which the 3-methyl group is replaced by a 3-hydroxymethyl group (IX, R = OH)[5]; that of dehydroanhydropicropodophyllin (V), in which the chromophoric system is conjugated with the lactone carbonyl group, shows the expected shift toward longer wave lengths and increased absorption.



VIII



IX

A similar reaction has been described by Haworth and Kelly,[8] in which the action of a mixture of acetic and hydrochloric acids on veratryl γ-hydroxy-δ-veratrylbutyl ketone[9] gave 6,7-dimethoxy-1 - veratryl - 3 - chloromethyl - 3,4 - dihydronaphthalene, which in turn was converted to 6,7-dimethoxy-1-veratryl-3-methylnaphthalene[8,10] with methyl alcoholic potassium hydroxide.

It may be pointed out that when the α-acetyl lactone I was treated similarly with a mixture of acetic and hydrochloric acids, Haworth and Atkinson[6] obtained, not a chloromethyldihydronaphthalene, but rather the acid VI (R = CH_3, R′ = H). Similarly, they isolated 6,7-methylenedioxy-3,1-endomethyleneoxy-1-methyl-1,2,3,4-tetrahydronaphthalene in an analogous reaction done with methyl γ-hydroxy-δ-piperonylbutyl ketone, and the product did not react with potassium hydrogen sulfate at 180°. This indicates that formation of the 3,4-dihydronaphthalene derivatives seems to require activation of the 1-position by an aromatic substituent.

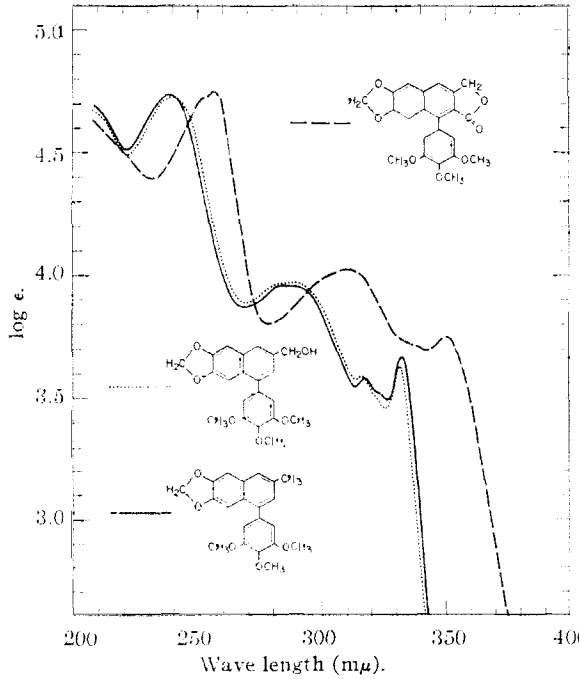


Fig. 2.—Ultraviolet absorption spectra in 95% ethanol of: ———, 6,7-methylenedioxy-(3,4,5-trimethoxyphenyl)-3-methylnaphthalene (IX, R = H); . . . . . , 6,7-methylenedioxy - 1 - (3,4,5 - trimethoxyphenyl) - 3 - hydroxymethylnaphthalene (IX, R = OH); — — —, dehydroanhydropicropodophyllin (V).

Experimental[11,12]

α-Acetyl-γ-(3,4-methylenedioxybenzyl)-γ-butyrolactone (I) and α-(3,4,5-trimethoxybenzoyl)-γ-(3,4-methylenedi-

(8) R. D. Haworth and W. Kelly, *J. Chem. Soc.*, 1645 (1937).

(9) Revised structure, *cf.* ref. 6.

(10) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 809 (1938).

(11) All our melting points are corrected and were determined with the Hershberg apparatus. Ultraviolet spectra were measured in 95% ethanol on a Beckman Model DU spectrophotometer and infrared spectra with a Perkin–Elmer model 21 spectrometer.

(12) Microanalyses were carried out by the Microanalytical Laboratory, NIAMD, National Institutes of Health, under the direction of Dr. W. C. Alford.

oxybenzyl)-γ-butyrolactone (II) were prepared according to Haworth and Richardson's procedure.[2]

Two Isomers of Methyl 6,7-Methylenedioxy-3,1-endomethyleneoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (VI, R = 3,4,5-Trimethoxyphenyl, R′ = CH_3) (or Equivalent Structure VII).—When II was refluxed with 10 volumes of cold saturated methyl alcoholic hydrogen chloride for one-half hour,[2] there was obtained, in yields ranging from 26 to 50% (generally around 40%), a colorless solid, melting at about 140°, which after recrystallization from ethanol or methanol formed colorless needles, m.p. 142–143°, apparently identical with the material, m.p. 138–139°, to which Haworth and Richardson[2] had assigned structure III. The compound appeared to retain tenaciously traces of solvent of crystallization; it could, however, be obtained analytically pure by drying in a high vacuum for two days at 110°.

Anal. Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; 4 OCH_3, 28.98. Found: C, 64.66; H, 5.85; OCH_3, 28.67.

The substance was recovered unchanged when refluxed with acetic anhydride and sodium acetate, with phosphorus trichloride in benzene, or with iodine in benzene, and also when an attempt was made to saponify it by refluxing 0.5 g. for one hour with 12.5 cc. of 5% methyl alcoholic potassium hydroxide, followed by cooling and diluting with water. Saponification to the corresponding acid (R′ = H) was accomplished by the following procedure: 1.44 g. of the compound was refluxed with 40 cc. of 10% methyl alcoholic potassium hydroxide for 2 hours, 40 cc. of water was added and refluxing continued for 16 hours. When the clear, colorless solution was acidified with 40 cc. of 2 *N* hydrochloric acid, an oil separated which crystallized on heating. The yield of colorless solid, m.p. 204–211°, was 1.35 g. (97%). Recrystallization from dilute ethanol gave felt-like needles, m.p. 205–208°. The product was soluble in aqueous sodium bicarbonate.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; 3 OCH_3, 22.47. Found: C, 63.55; H, 5.28; OCH_3, 22.59.

Fractional crystallization of the reaction product obtained with methyl alcoholic hydrogen chloride gave in three experiments, in addition to the compound, m.p. 142–143°, the isomeric methyl ester in yields ranging from 7 to 17%. This substance crystallized from 50% ethanol as tiny colorless needles, m.p. 169.4–170.0°.

Anal. Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; 4 OCH_3, 28.98. Found: C, 64.51; H, 5.56; OCH_3, 28.84.

While the compound, m.p. 142–143°, was not saponified by methyl alcoholic potassium hydroxide in the absence of water, this method of hydrolysis was successful in the case of the isomer, m.p. 169.4–170.0°. The yellow solution, obtained by refluxing 0.90 g. of the ester with 15 cc. of 10% methyl alcoholic potassium hydroxide for 3 hours, was diluted with 90 cc. of water and acidified with 15 cc. of 2 *N* hydrochloric acid. The colorless gelatinous solid became crystalline after short boiling; yield 0.82 g. (94%), m.p. 239–240° (effervescence). In a similar experiment, in which 0.32 g. of the ester was saponified with 8 cc. of 5% methyl alcoholic potassium hydroxide for 1 hour, the yield was 0.23 g. (74%), in addition to 17% of recovered starting material. Recrystallization from chloroform–ethanol, then from ethanol, gave long thin needles, m.p. 243–244° (foaming). The material was soluble in aqueous sodium bicarbonate.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; 3 OCH_3, 22.47; neut. equiv., 414.4. Found: C, 63.91; H, 5.36; OCH_3, 22.31; neut. equiv., 416.

6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-chloromethyl-3,4-dihydronaphthalene (VIII).—A solution of 5.0 g. of II in 75 cc. of glacial acetic acid, to which 50 cc. of concd. hydrochloric acid had been added, was kept at room temperature for 18 hours, then, after addition of another 25 cc. of concd. hydrochloric acid, for 5 more hours. The colorless needles which had separated from the red solution were collected and washed with 30% acetic acid, then with water. The yield was 4.26 g. (91%), m.p. 124–127° Recrystallization from absolute ethanol gave material melting at 127–128°.

Anal. Calcd. for $C_{21}H_{21}O_5Cl$: C, 64.86; H, 5.44; Cl, 9.12; OCH_3, 23.94. Found: C, 65.31, 65.35; H, 5.42, 5.74; Cl, 9.48; OCH_3, 24.20.

The same compound was isolated in 7% yield as colorless needles, m.p. 125–127° (from ethanol), in addition to a 26% yield of the ester, m.p. 142–143°, when II was refluxed for 1 hr. with 10 volumes of half-saturated methyl alcoholic hydrogen chloride.

6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-methylnaphthalene (IX, R = H).—A solution of 0.50 g. of VIII in 20 cc. of 10% methyl alcoholic potassium hydroxide was refluxed for 19 hours, then diluted gradually with 20 cc. of hot water. Colorless crystals separated; they were collected after chilling, and washed with ice-cold 50% methanol, yield 0.43 g. (95%), m.p. 143–145°. Recrystallization from 50% methanol gave colorless glistening needles, m.p. 144.5–146.0°.

Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72; OCH_3, 26.42. Found: C, 72.34, 72.25; H, 5.87, 5.85; OCH_3, 26.81.

Because of the appreciable difference between the calcd. and found values for carbon, the material was dissolved in benzene and chromatographed on alumina.[13] The apparently homogeneous adsorbate (purplish-blue fluorescence under ultraviolet light) was eluted with benzene in three fractions, each of which was evaporated and recrystallized from methanol to give material melting at 145.2–146.5°, 145.8–147.0° and 145.4–147.0°, respectively, with the following analyses: (a) C, 72.08; H, 6.27; (b) C, 72.17; H, 5.86; OCH_3, 26.56; (c) C, 72.01; H, 5.85.

6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-3,4-dihydro-2-naphthoic Acid Lactone (IV).—An intimate mixture of 1.34 g. of the ester, m.p. 142–143°, obtained in the reaction of II with methyl alcoholic hydrogen chloride and 2.7 g. of finely-ground potassium hydrogen sulfate[14] was heated at 180° for 10 minutes, and the very dark mass extracted with chloroform. The solution was concentrated and chromatographed on alumina.[13] Eluting with chloroform and concentrating with addition of ethanol yielded 0.41 g. (33%) of orange-colored crystals, m.p. 247–249°. Similar runs gave yields ranging from 24 to 37%, while the yield dropped to 15% when the reaction mixture was heated for 45 minutes.[2] Subliming the crude material in a vacuum (bath 270°), rechromatographing from chloroform on alumina, eluting the yellow band with chloroform and crystallizing twice from chloroform–ethanol furnished analytically and spectrally pure material as apparently colorless needles, m.p. 250.1–251.0° (lit.[2] 248–249°), λ_{max}^{EtOH} 350 mμ (log ε 4.10), 245.5 mμ (log ε 4.32), λ_{min}^{EtOH} 280.5 mμ (log ε 3.52), 236.5 mμ (log ε 4.29). Chloroform solutions of the compound were pale yellow and did not absorb bromine rapidly.

Anal. Calcd. for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09; OCH_3, 23.49. Found: C, 66.78, 66.85; H, 5.19, 5.23; OCH_3, 23.71, 23.57.

6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-3,4-dihydro-2-naphthoic Acid.—The pale yellow solution, obtained by refluxing 315 mg. of IV with 325 mg. of sodium hydroxide, 1.3 cc. of water and 1.3 cc. of ethanol for 10 minutes and diluting with hot water, was cooled in ice, acidified with 2 *N* hydrochloric acid, and the flocculent solid extracted with about 100 cc. of chloroform, which then was washed with water and dried over sodium sulfate. Evaporating and triturating the solid residue with benzene yielded 0.28 g. (85%) of material melting at 251° (when heated slowly from room temperature), and which melted at 203° with foaming (when immersed at 200°), resolidified and melted again at 251°. Crystallization from ethanol–benzene, followed by two recrystallizations from 30% ethanol gave tiny felt-like colorless needles, m.p. 249–250° (immersed at room temperature); melting with foaming at 203°, resolidifying and remelting at 249–250° (immersed at 200°). The acid was quite soluble in ethanol, moderately soluble in chloroform and sparingly soluble in water and benzene.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.77; H, 5.58.

Acknowledgments.—The authors wish to thank Mrs. Gertrude Y. Greenberg for some of the preparative work and for measuring the ultra-

(13) Alcoa activated alumina, grade F-20.

(14) "Potassium bisulfate, crystal"; only starting material was recovered when "fused potassium bisulfate" was used.

violet spectra. Mrs. Iris J. Siewers and Miss Alice M. Bernardi, National Heart Institute, kindly determined the infrared spectra.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

Components of Podophyllin. IX. The Structure of the Apopicropodophyllins[1,2]

BY ANTHONY W. SCHRECKER AND JONATHAN L. HARTWELL

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The constitution of α-apopicropodophyllin has been established as in formula I. Structure IIa for β-apopicropodophyllin is favored over IIb on spectroscopic evidence. A new isomer, γ-apopicropodophyllin (III), has been obtained and proven to be structurally identical with a known synthetic compound.

The revival of interest in the chemistry of podophyllotoxin and picropodophyllin[3,4] has motivated a renewed study of some of their derivatives, and especially of the apopicropodophyllins, which had been investigated in the past, but about whose precise structure little was known. Some new evidence which has now been obtained forms the subject of the present communication.

Borsche and Niemann[5] observed that when picropodophyllin,[4] $C_{22}H_{22}O_8$, was treated with acetic anhydride containing a trace of sulfuric acid, it underwent dehydration to a compound, $C_{22}H_{20}H_7$, which they named apopicropodophyllin. They were unable to purify the crude reaction product, which melted at varying temperatures ranging up to 237°, by recrystallization from organic solvents, but obtained material melting consistently at 214–216° by boiling it with acetic anhydride containing some sodium acetate. Späth, Wessely and Kornfeld[6] prepared what appeared to be the same product, m.p. 216°, by prolonged boiling of picropodophyllin with acetic anhydride; their material, however, had $[\alpha]^{22}D$ +75.31°, while Borsche's was reported to be optically inactive. It was found subsequently by Robertson and Waters[7] that the purified substance isolated by the previous investigators was not identical with the primary dehydration product. The crude material isolated in the reaction of picropodophyllin with acetic anhydride and sulfuric acid usually afforded needles, m.p. 236–237°, when crystallized repeatedly from ethanol–acetic acid, then from ethyl acetate, but in some instances further recrystallization gave a product which melted at 244–245° and had $[\alpha]^{21}_{5461}$ −17.5°. When this compound, which Robertson and Waters named α-apopicropodophyllin, was heated in acetic anhydride with pyridine or sodium acetate, it was converted to an isomer, named β-apopicropodophyllin, m.p. 216°, $[\alpha]^{21}_{5461}$ +117.6°. Saponification of either isomer yielded the same hydroxy acid, which melted at 174° with loss of water, forming again α-apopicropodophyllin. Drake and Price[3] also prepared β-apopicropodophyllin, m.p. 214.0–215.4°, by the pyrolysis of picropodophyllin benzoate.

The difficulty of obtaining pure α-apopicropodophyllin indicates that it is rather unstable and quite easily converted to the β-isomer. This conversion has previously been accomplished by the use of weakly basic reagents, such as the ones employed by Robertson and Waters,[7] and has been carried out in this Laboratory by the use of piperidine in glacial acetic acid, thus affording a practically quantitative yield of pure β-apopicropodophyllin m.p. 219–220° (in some cases 220–221° after recrystallization); $[\alpha]^{20}D$ +102° (chloroform). It appears, however, that the presence of only traces of alkaline material also produces at least partial isomerization. Thus, when α-apopicropodophyllin was dissolved in boiling ethanol, and the ultraviolet absorption spectrum of the solution studied after cooling, it was found that partial conversion to the β-isomer had taken place. Reproducible results, indicating that the spectrum was actually that of pure α-apopicropodophyllin, could be obtained by dissolving the compound in chloroform and diluting the solution with ethanol, or, preferably, with ethanol containing a small amount of hydrochloric acid. The observation that the isomerization of the α- to the β-isomer did not occur in the presence of mineral acid permitted for the first time obtaining consistently pure α-apopicropodophyllin, m.p. 243–245°, $[\alpha]^{20}D$ −18° (chloroform), by recrystallizing the crude dehydration product from glacial acetic acid containing a trace of hydrochloric acid. The conversion of α- to β-apopicropodophyllin also took place when the former was heated for a short time above its melting point.

The hydroxy acid, m.p. 174°, which Robertson and Waters[7] had obtained from both the α- and β-apolactones, appeared to be related to the α-isomer since the latter was formed by relactonization. This was confirmed by its color reaction with sulfuric acid, which was identical with that given by α-apopicropodophyllin,[7] and also by the fact that chloroform solutions of both the acid and the α-apolactone rapidly decolorized bromine, while those of the β-apolactone did not. The relationship is substantiated by the close resemblance of the ultraviolet absorption spectrum (Fig. 1) of the acid (obtained from either α- or β-apopicro-

(1) Paper VIII: A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **74**, 5672 (1952).

(2) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Ill., September 6, 1950; Abstr. Papers Am. Chem. Soc., **118**, 18 M (1950).

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

(4) J. L. Hartwell and A. W. Schrecker, *ibid.*, **73**, 2909 (1951).

(5) W. Borsche and J. Niemann, *Ann.*, **494**, 126 (1932).

(6) E. Späth, F. Wessely and L. Kornfeld, *Ber.*, **65**, 1536 (1932).

(7) A. Robertson and R. B. Waters, *J. Chem. Soc.*, 83 (1933).