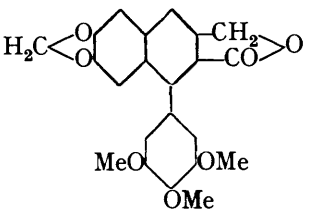
80. *The Constituents of Natural Phenolic Resins. Part IV. Synthesis of Dehydroanhydropicropodophyllin.*

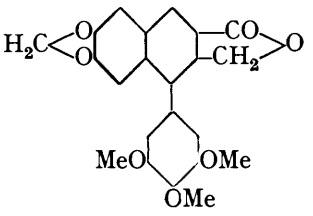
By Robert D. Haworth and Thomas Richardson.

Späth, Wesely, and Kornfeld (*Ber.*, 1932, **65**, 1536) prepared the optically inactive lactone, dehydroanhydropicropodophyllin, m. p. 266°, by converting podophyllotoxin into the isomeric picropodophyllin and dehydrogenating the latter with palladium-black, and on the basis of the Borsche–Späth formula for podophyllotoxin they represented this important degradation product as (I). The isomeric lactone (II), the synthesis of which was described in Part III of this series (J., 1935, 1576), differed from dehydroanhydropicropodophyllin, but Späth, Wesely, and Kornfeld's formula (I) was supported by the fact that the natural and the synthetic lactone were oxidised to the same dicarboxylic acid (III).

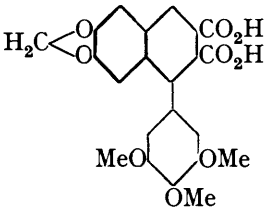
More direct proof of the accuracy of these views has now been obtained; a lactone having formula (I) has been synthesised, and its identity with dehydroanhydropicropodophyllin established.



(I.)

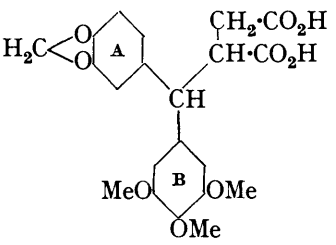


(II.)

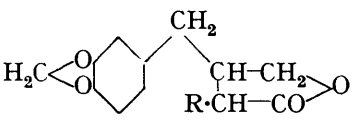


(III.)

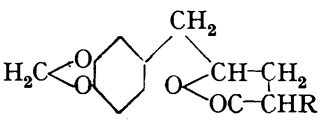
The methods employed in Part II (J., 1935, 638) for the synthesis of the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid were not applicable to the synthesis of (I). In the first place they require the preparation of (IV), and although compounds of this class are readily accessible when the rings A and B are identical, considerable difficulties are involved in the preparation of the unsymmetrical members of the class. Secondly, the subsequent conversion into the tetralonecarboxylic acid would lead to two isomeric products in a proportion determined by the relative nuclear activities of rings A and B. After several unsuccessful attempts had been made to overcome these difficulties, a new method was elaborated for the synthesis of compounds of type (I). It was found that safrole oxide and ethyl sodiomalonate reacted in alcoholic solution, yielding an oil which is considered to be *ethyl* β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone*-α-*carboxylate* (V; R = CO_2Et) and not the alternative carboxylate (VI; R = CO_2Et). The formula assigned to this lactone is, however, based entirely on analogy with the corresponding ethyl acetoacetate derivatives, which have been investigated more fully. The sodio-derivative of the lactone (V; R = CO_2Et) and 3 : 4 : 5-trimethoxybenzoyl chloride yielded *ethyl* α-(3 : 4 : 5-*trimethoxybenzoyl*)-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone*-α-*carboxylate* (VII; R = CO_2Et), but the small yield and certain difficulties encountered in the hydrolysis of this lactone led to the abandonment of this route in favour of the corresponding ethyl acetoacetate compounds.



(IV.)



(V.)

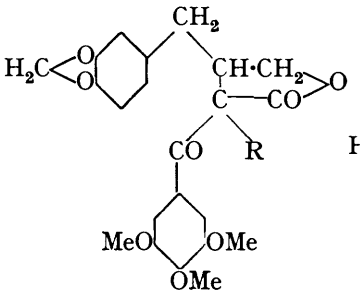


(VI.)

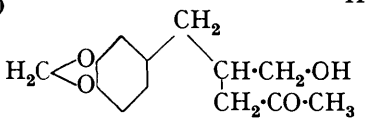
α-*Acetyl*-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (V; R = $CO{\cdot}CH_3$) was prepared from safrole oxide and ethyl sodioacetoacetate, and this crystalline lactone underwent ketonic hydrolysis with hot dilute sodium hydroxide solution, yielding *methyl* γ-*hydroxy*-β-(3 : 4-*methylenedioxybenzyl*)*propyl ketone* (VIII). When the lactone (V; R = $CO{\cdot}CH_3$) was warmed with concentrated alcoholic potassium hydroxide, an oily lactone was obtained which gave the analytical figures required for the anticipated product of acid hydrolysis (V; R = H), and a similar oil was obtained by the action of strong alkalis on the corresponding ethyl malonate derivative (V; R = CO_2Et).

α-(3 : 4 : 5-*Trimethoxybenzoyl*)-α-*acetyl*-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (VII; R = $CO{\cdot}CH_3$) was readily prepared from 3 : 4 : 5-trimethoxybenzoyl chloride and the sodio-derivative of the lactone (V; R = $CO{\cdot}CH_3$), and on hydrolysis with cold sodium hydroxide solution it yielded α-(3 : 4 : 5-*trimethoxybenzoyl*)-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (VII; R = H). This crystalline lactone (VII; R = H), which could not be prepared

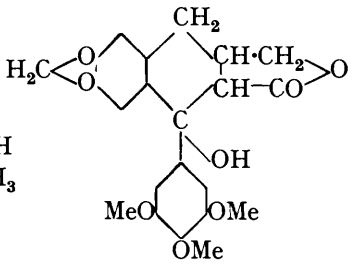
directly from safrole oxide and ethyl sodio-3 : 4 : 5-trimethoxybenzoylacetate, was isomerised by the action of methyl-alcoholic hydrogen chloride into the *lactone* of 1-*hydroxy*-



(VII.)

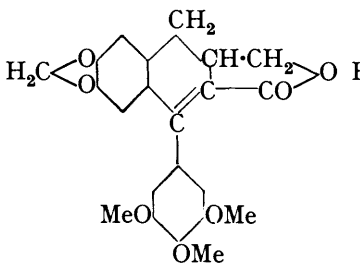


(VIII.)

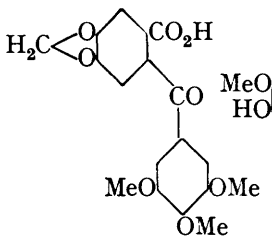


(IX.)

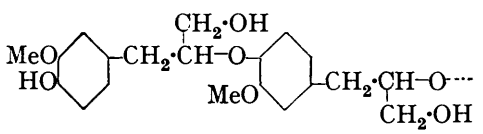
6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-3-*hydroxymethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic acid* (IX). Dehydration of (IX) with potassium hydrogen sulphate at 180° gave the *lactone* of 6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-3-*hydroxymethyl*-3 : 4-*dihydronaphthalene*-2-*carboxylic acid* (X), which was converted into 3′ : 4′ : 5′-trimethoxy-4 : 5-methylenedioxybenzophenone-2-carboxylic acid (XI). This acid was identical with the acid which Späth, Wesely, and Nadler (*Ber.*, 1933, **66**, 128) obtained by oxidation of picropodophyllin and, if the remote possibility of seven-membered ring formation is excluded, the isolation of acid (XI) provides conclusive evidence for the structures (V), (VII), (IX), and (X).



(X.)



(XI.)



(XII.)

The lactone (X) was converted into the lactone of 6 : 7-methylenedioxy-1-(3′ : 4′ : 5′-trimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid (I), m. p. 267°, either by heating with palladium-black or by the action of lead tetra-acetate in acetic acid solution. The synthetical lactone (I) was identical in all respects with dehydroanhydropicropodophyllin prepared from podophyllotoxin as described by Späth, Wesely, and Kornfeld (*loc. cit.*).

The reactions described are being exploited in other directions and the polymerisation of compounds of the safrole oxide type is also being investigated. The known reaction between ethylene oxides and phenoxides (Boyd and collaborators, J., 1908, **93**, 838; 1909, **95**, 1807; 1910, **97**, 1788; 1914, **105**, 2117) may find a particularly interesting application in the case of eugenol oxide, which under suitable conditions may polymerise to products structurally related to Freudenberg's lignin formula (XII) (*Ber.*, 1929, **62**, 1822; *Annalen*, 1935, **518**, 78).

Experimental.

Ethyl β-(3 : 4-*Methylenedioxybenzyl*)*butyrolactone*-α-*carboxylate* (V; R = CO_2Et).—Safrole oxide (4 g.) (Fourneau and Tiffeneau, *Compt. rend.*, 1905, **140**, 1595; **141**, 662) was added to ethyl sodiomalonate (prepared from sodium, 0·6 g., and ethyl malonate, 5 g.) in ethyl alcohol (30 c.c.). The sodio-derivative of (V; R = CO_2Et), which slowly separated, was collected after 48 hours and decomposed with water or dilute sulphuric acid, and the resulting oil extracted with ether and dried. The *lactone* (V; R = CO_2Et) (1·5 g.) was obtained as a colourless oil, b. p.

210—215°/0·5 mm., readily soluble in the usual organic solvents (Found: C, 61·7; H, 5·7. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%).

Ethyl α-(3 : 4 : 5-*Trimethoxybenzoyl*)-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone*-α-*carboxylate* (VII; R = CO_2Et).—The lactone (V; R = CO_2Et) (2 g.) was allowed to react with "molecular" sodium (0·15 g.) in benzene (20 c.c.) for 12 hours. 3 : 4 : 5-Trimethoxybenzoyl chloride (2 g.) was added, and the mixture heated on the water-bath for 18 hours. After the addition of water, the benzene layer was dried, the solvent removed, and the residual oil crystallised by addition of a little methyl alcohol. The *lactone* (VII; R = CO_2Et) separated from methyl alcohol, containing a small amount of chloroform, in colourless needles, m. p. 156—157° (Found: C, 59·5; H, 5·4. $C_{25}H_{26}O_{10},H_2O$ requires C, 59·5; H, 5·6%). The yield was small.

α-*Acetyl*-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (V; R = $CO{\cdot}CH_3$).—Safrole oxide (24 g.) was added to a solution of ethyl sodioacetoacetate (prepared from sodium, 3 g., and ethyl acetoacetate, 18 g.) in ethyl alcohol (100 c.c.). After 3 days, water was added, neutral impurities removed with ether, the alkaline liquors acidified and extracted with benzene, and the solvent and unchanged ethyl acetoacetate removed under reduced pressure. The residue crystallised from ether–light petroleum (b. p. 40—60°) in colourless needles (11 g.), m. p. 91—92° (Found: C, 63·7; H, 5·2. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·2%). This *lactone* (V; R = $CO{\cdot}CH_3$) is soluble in dilute sodium hydroxide solution and it gives a violet ferric test.

Methyl γ-*Hydroxy*-β-(3 : 4-*methylenedioxybenzyl*)*propyl Ketone* (VIII).—The lactone (V; R = $CO{\cdot}CH_3$) (0·6 g.) was boiled with 2% sodium hydroxide solution (20 c.c.) for 6 hours. The oil which gradually separated, and solidified on cooling, was collected; it crystallised from light petroleum (b. p. 60—80°) in slender needles, m. p. 79—80°, which gave no coloration with ferric chloride (Found: C, 65·8; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

β-(3 : 4-*Methylenedioxybenzyl*)*butyrolactone* (V; R = H) was prepared by hydrolysing the lactone (V; R = $CO{\cdot}CH_3$) with 20% methyl-alcoholic potassium hydroxide (10 parts) for 6 hours on the water-bath. After dilution with water, most of the methyl alcohol was removed by distillation and neutral impurities were removed in ether. The alkaline layer was acidified and boiled for 5 minutes, and the oil isolated with ether; it distilled at 183—186°/0·5 mm. (Found: C, 65·3; H, 5·7. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). A similar oil (Found: C, 65·2; H, 5·6%) was obtained by hydrolysing (V; R = CO_2Et) with 10% methyl-alcoholic potassium hydroxide and heating the acidic product at 180° for 1 hour.

α-(3 : 4 : 5-*Trimethoxybenzoyl*)-β-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (VII; R = H).—The lactone (V; R = $CO{\cdot}CH_3$) (11 g.) was added to "molecular" sodium (1 g.) in benzene (100 c.c.). After 12 hours, 3 : 4 : 5-trimethoxybenzoyl chloride (10 g.) was added; the mixture was kept for 12 hours at room temperature and then boiled for 1 hour. Water was added, the benzene layer washed with very dilute sodium hydroxide solution and dried, and the solvent removed. The product (VII; R = $CO{\cdot}CH_3$), which did not crystallise, was taken up in ether (100 c.c.) and shaken with 5% sodium hydroxide solution (50 c.c.) for 12 hours. The alkaline solution was acidified and extracted with chloroform, and the extract shaken with sodium bicarbonate solution in order to remove traces of 3 : 4 : 5-trimethoxybenzoic acid. The chloroform was removed, and the residue crystallised from methyl alcohol; colourless needles (7 g.), m. p. 110—111°, were obtained (Found: C, 63·8; H, 5·2. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·4%). This *lactone* (VII; R = H) gave a reddish-purple ferric test.

Lactone of 1-*Hydroxy*-6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-3-*hydroxymethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid* (IX).—The lactone (VII; R = H) (2 g.) was boiled with methyl-alcoholic hydrogen chloride (20 c.c.) for ½ hour. The product, isolated with chloroform, crystallised from methyl alcohol in slender needles (1·4 g.), m. p. 138—139° (Found: C, 63·8; H, 5·6. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·4%). This *lactone* (IX) gave no coloration with ferric chloride, but it dissolved in concentrated sulphuric acid to a green solution which became red on standing and purple on warming.

Lactone of 6 : 7-*Methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-3-*hydroxymethyl*-3 : 4-*dihydronaphthalene*-2-*carboxylic Acid* (X).—The lactone (IX) (1 g.) was heated with potassium hydrogen sulphate (2 g.) for ¾ hours at 180°. The product, isolated with chloroform, crystallised from methyl alcohol in slender needles (0·8 g.), m. p. 248—249° (Found: C, 66·7; H, 5·0. $C_{22}H_{20}O_7$ requires C, 66·6; H, 5·0%). This *lactone* (X) gave a colour reaction with concentrated sulphuric acid similar to that described above for the lactone (IX). The lactone (X) (1 g.) was boiled with 2% methyl-alcoholic potassium hydroxide (20 c.c.) for 10 minutes. Water was added, the alcohol completely removed by distillation, and 3% aqueous potassium permanganate (200 c.c.) gradually added to the cold solution. After the manganese dioxide had been removed, the filtrate was acidified and the precipitate collected. 3′ : 4′ : 5′-Trimethoxy-4 : 5-methylenedioxy-

benzophenone-2-carboxylic acid (XI) separated from dilute acetic acid in small crystals (0·2 g.), m. p. 215—216° (Found : C, 59·6; H, 4·5. Calc. for $C_{18}H_{16}O_8$: C, 60·0; H, 4·5%). The methyl ester and 3′ : 4′ : 5′-trimethoxy-3 : 4-methylenedioxybenzophenone melted at 127—128° and 126—127° respectively. Späth, Wesely, and Nadler (*loc. cit.*) give 214—216°, 128—129°, and 125—127° for the acid, the methyl ester, and the benzophenone derivative respectively.

Lactone of 6 : 7-*Methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenol*)-3-*hydroxymethylnaphthalene*-2-*carboxylic Acid* (*Dehydroanhydropicropodophyllin*) (I).—(*a*) The lactone (X) (0·6 g.) was dissolved in acetic acid (10 c.c.) at 75°, and lead tetra-acetate (1·2 g.) added; after 15 minutes, water was added, and the product isolated with chloroform. (*b*) The lactone (X) (0·1 g.) and palladium-black (0·02 g.) were heated at 240°/0·1 mm., for 6 hours, and the sublimate collected. The product from either (*a*) or (*b*) crystallised from methyl alcohol or glacial acetic acid in colourless needles, m. p. 267—268° (Found : C, 66·9; H, 4·7. Calc. for $C_{22}H_{18}O_7$: C, 67·0; H, 4·6%), and no depression in m. p. was observed when the synthetic specimen was mixed with dehydroanhydropicropodophyllin, m. p. 265—266°, prepared from podophyllotoxin. The synthetic and the natural lactone were identical in crystalline form and had similar solubilities in organic solvents. On treatment with cold concentrated sulphuric acid, both specimens dissolved to very pale yellow solutions, which became purple on warming. The addition of a crystal of sodium nitrate to the cold sulphuric acid solutions produced a blood-red colour. The synthetic lactone was converted into the dibasic acid (III) by the action of either sodium hypobromite or potassium permanganate and the oxdation product was identified by the preparation of the anhydride, m. p. 300°, and the dimethyl ester, m. p. 207° (see J., 1935, 1581).

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