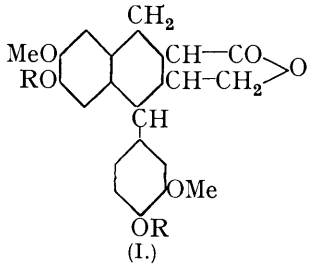
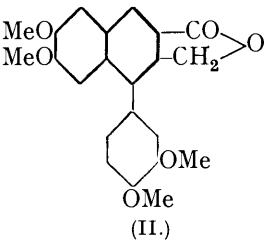
## 371. *The Constituents of Natural Phenolic Resins. Part III. Synthesis of Dehydro-"Sulphite-liquors Lactone" Dimethyl Ether and Some Observations on the Structure of Podophyllotoxin.*

By Robert D. Haworth, Thomas Richardson, and George Sheldrick.

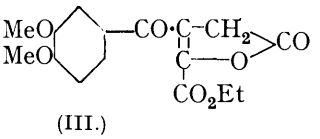
In Part II (this vol., p. 636) structure (I; R = H) was suggested for "sulphite-liquors lactone." * The positions of the hydroxyl groups were established by oxidising the diethyl ether to 5-methoxy-4-ethoxy-2-(3′-methoxy-4′-ethoxybenzoyl)benzoic acid, and the orientation of the lactonic grouping was suggested as a result of an examination of a dehydro-lactone, $C_{22}H_{20}O_6$, m. p. 215—216°, which was prepared from "sulphite-liquors lactone" dimethyl ether (I; R = Me). This dehydro-lactone was not identical with the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid, which was synthesised, and as the isomeric lactones both yielded 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboxylic acid on oxidation, they differed only in the arrangement of the lactonic groups. Consequently structure (II) was suggested for dehydro-"sulphite-liquors lactone" dimethyl ether, and these conclusions have now been confirmed by the synthesis of the lactone (II).



(I.)



(II.)



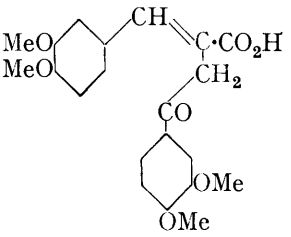
(III.)

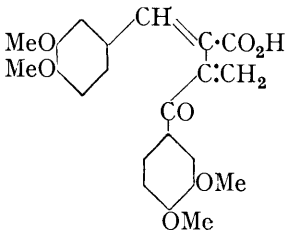
During the earlier experiments it was shown that *ethyl* β-(3 : 4-*dimethoxybenzoyl*)*propionate* underwent the Claisen condensation with ethyl formate and with ethyl oxalate, yielding *ethyl* β-*hydroxymethylene*-β-(3 : 4-*dimethoxybenzoyl*)*propionate* and a lactonic ester, probably *ethyl* β-(3 : 4-*dimethoxybenzoyl*)-$\Delta^{\beta}$-*crotonolactone*-γ-*carboxylate* (III), respectively, but these lines of approach were abandoned because recognisable reduction products of these esters could not be prepared.

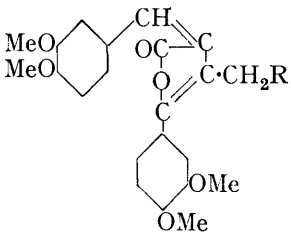
It was then discovered that β-3 : 4-dimethoxybenzoyl-α-(3′ : 4′-dimethoxybenzylidene)-propionic acid (IV) and formaldehyde reacted almost quantitatively in cold alkaline solution to yield β-3 : 4-*dimethoxybenzoyl*-α-(3′ : 4′-*dimethoxybenzylidene*)-β-*methylene-propionic acid* (V), and this acid, which is also being utilised in allied investigations, served as the starting point of the successful synthesis. It was shown in Part II (p. 640) that

* In view of the constitutional relationship between matairesinol (this vol., p. 633) and "sulphite-liquors lactone," it is of interest to record that we have isolated, in small yield, two substances, m. p. 212° and 254°, from our matairesinol mother-liquors. The compound, m. p. 254°, has been identified as "sulphite-liquors lactone" by direct comparison of the phenol, its diacetyl derivative, and its dimethyl ether with authentic specimens. Dr. L. H. Briggs (private communication) informs us that he has isolated the same substances from the resin of the matai.

the acid (IV) was converted into methyl 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-naphthalene-3-carboxylate by the action of warm methyl-alcoholic hydrogen chloride; but under similar conditions the acid (V) is only partly cyclised and two crystalline products have been isolated in approximately equal amounts. The less soluble product was the bright yellow *lactone* of β-3 : 4-*dimethoxybenzoyl*-α-(3′ : 4′-*dimethoxybenzylidene*)-β-*chloromethylpropionic acid* (VI; R = Cl); in accordance with the suggested constitution, the chlorine is labile and boiling methyl alcohol converted it into the *lactone* of β-3 : 4-*dimethoxybenzoyl*-α-(3′ : 4′-*dimethoxybenzylidene*)-β-*methoxymethylpropionic acid* (VI; R = OMe). The second product from the action of methyl-alcoholic hydrogen chloride on the acid (V)

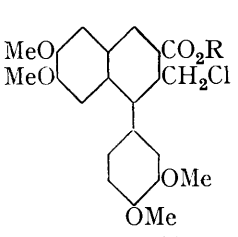

(IV.)

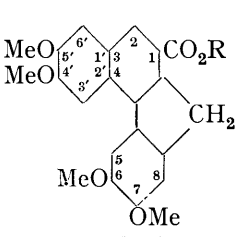

(V.)

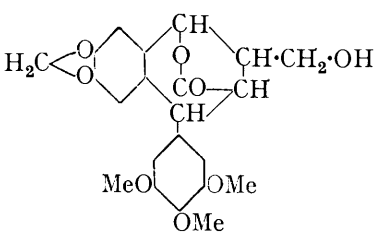

(VI.)

was *methyl* 6 : 7-*dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-2-*chloromethylnaphthalene*-3-*carboxylate* (VII; R = Me), and alkaline hydrolysis, followed by lactonisation, converted this ester almost quantitatively into the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid (II), m. p. 215—216°, which was identical with dehydro-" sulphite-liquors lactone " dimethyl ether. Attempts have been made to convert (VI; R = Cl) into (VII; R = Me) and thence into (II), but with only moderate success. By the prolonged action of hydrogen chloride the lactone (VI; R = Cl) was converted into an oil which gave a very small yield of (II) after hydrolysis and lactonisation.

The acid (V) reacted with concentrated hydrochloric acid in cold glacial acetic acid solution to give 6 : 7-*dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-2-*chloromethylnaphthalene*-3-*carboxylic acid* (VII; R = H), which was converted into the lactone (II) by alkaline hydrolysis and subsequent lactonisation, the overall yield being practically theoretical. The acid (VII; R = H), though readily soluble in cold aqueous sodium hydroxide, was insoluble in aqueous sodium bicarbonate, and this abnormality may be due to the conversion into the lactone (II), which has been observed to take place gradually in the presence of aqueous sodium bicarbonate. When the acid (VII; R = H) was heated, hydrogen chloride was eliminated and a well-defined carboxylic acid, m. p. 303—305°, probably 4′ : 5′ : 6 : 7-*tetramethoxybenzo*-3 : 4-*fluorene*-1-*carboxylic acid* (VIII; R = H), was obtained. This compound was readily soluble in aqueous sodium bicarbonate, and the structures suggested above are supported by the action of heat on the methyl ester (VII; R = Me). A similar loss of hydrogen chloride was observed and the resulting *methyl* ester (VIII; R = Me) yielded the acid (VIII; R = H), m. p. 303—305°, on hydrolysis.

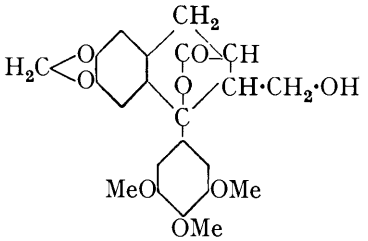

(VII.)

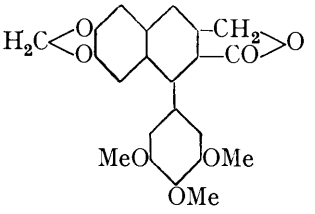

(VIII.)

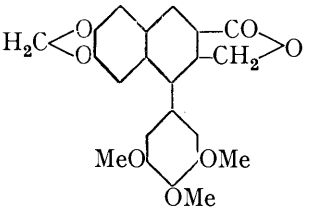

(IX.)

As the method outlined above appeared capable of wide application in the synthesis of lactones of the phenylnaphthalene series, its use in the preparation of substances related to podophyllotoxin (see this vol., p. 633 for references) has been investigated. Späth, Wesely, and Kornfeld (*Ber.*, 1932, **65**, 1536) converted picropodophyllin by dehydration and de-

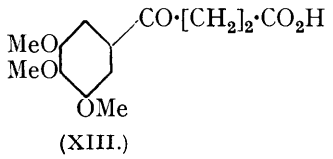
hydrogenation into a lactone, $C_{22}H_{18}O_7$, m. p. 266°, and, in accordance with the Borsche–Späth formula for podophyllotoxin (IX), the lactone $C_{22}H_{18}O_7$ was formulated as (XI), although structure (XII) is the rational representation of this lactone on the basis of the Robertson formula (J., 1933, 83) for podophyllotoxin (X). Evidence in favour of the Borsche–Späth formula (IX) has now been obtained by the synthesis of a lactone having structure (XII), which differs from the lactone $C_{22}H_{18}O_7$, m. p. 266°, prepared from picropodophyllin.

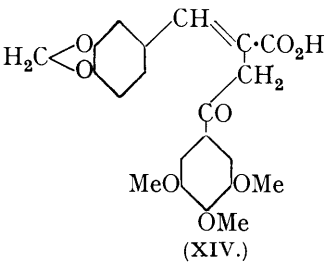

(X.)

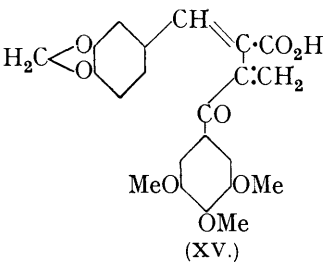

(XI.)


(XII.)

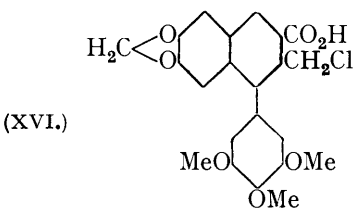
Ethyl sodio-3 : 4 : 5-trimethoxybenzoylacetate (Perkin and Weizmann, J., 1906, **89**, 1655) reacted with ethyl bromoacetate in boiling alcoholic solution and the resulting ethyl 3 : 4 : 5-trimethoxybenzoylsuccinate on hydrolysis with boiling 20% sulphuric acid was converted into β-(3 : 4 : 5-*trimethoxybenzoyl*)*propionic acid* (XIII). The sodium salt of (XIII) condensed with piperonal in acetic anhydride solution to give a yellow *γ-lactone*, yielding β-3 : 4 : 5-*trimethoxybenzoyl*-α-(3′ : 4′-*methylenedioxybenzylidene*)*propionic acid* (XIV) on treatment with sodium methoxide. The acid (XIV) reacted with formaldehyde in alkaline solution to give β-3 : 4 : 5-*trimethoxybenzoyl*-α-(3′ : 4′-*methylenedioxybenzylidene*)-β-*methylenepropionic acid* (XV), which was cyclised by a mixture of acetic and hydrochloric acids to 6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-2-*chloromethylnaphthalene*-3-*carboxylic acid* (XVI). Alkaline hydrolysis of (XVI), followed by lactonisation, gave the *lactone* of 6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-2-*hydroxymethylnaphthalene*-3-*carboxylic acid* (XII), m. p. 289°. This lactone (XII) differs from the lactone (XI), obtained from picropodophyllin, in the arrangement of the lactone group only, and on oxidation with

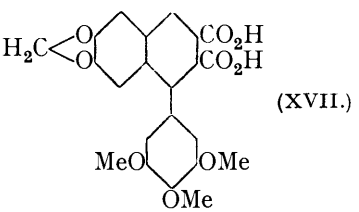

(XIII.)


(XIV.)


(XV.)

potassium permanganate both lactones yielded 6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)*naphthalene*-2 : 3-*dicarboxylic acid* (XVII), which was characterised by means of the *anhydride* and *dimethyl* ester. In Part II (p. 644) it was shown that the isomeric tetramethoxyphenylnaphthalenes differed in their behaviour towards sodium hypobromite. The lactone containing the hydroxymethyl group in position 3 was converted into the dibasic acid, but the lactone (II) containing the hydroxymethyl group in position 2 was


(XVI.)


(XVII.)

unattacked. The same difference has been observed in the methylenedioxy-trimethoxy series; the lactone (XII) was not attacked by sodium hypobromite, but the lactone (XI) obtained from picropodophyllin was converted into the dibasic acid (XVII). The steric explanation suggested in Part II applies equally well to the present case.

## Experimental.

*Ethyl* β-(3 : 4-*dimethoxybenzoyl*)*propionic acid*, obtained by the action of alcoholic hydrogen chloride on the corresponding acid, crystallised from chloroform–light petroleum in colourless needles, m. p. 57—58° (Found : C, 63·3; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%).

*Ethyl* β-(3 : 4-*Dimethoxybenzoyl*)-β-*hydroxymethylenepropionate*.—The above ester (2 g.) and ethyl formate (2 c.c.) were allowed to react in cold benzene solution (30 c.c.) in the presence of sodium wire (0·5 g.) for 12 hours. Water was added and the aqueous layer was acidified and extracted with ether. Removal of the ether left an oil; this slowly solidified and crystallised from aqueous methyl alcohol in colourless needles (1·5 g.), m. p. 114—116°, which gave a red coloration with ferric chloride (Found : C, 60·8; H, 6·2. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·2%). *Ethyl* β-(3 : 4-*dimethoxybenzoyl*)-$\Delta^{\beta}$-*crotonolactone*-γ-*carboxylate* (III), obtained similarly from ethyl β-(3 : 4-dimethoxybenzoyl)propionate (2 g.), ethyl oxalate (4 c.c.), and sodium wire (0·5 g.), crystallised from chloroform–methyl alcohol in slender yellow needles (1·7 g.), m. p. 154—156°, which gave a dark purple ferric test (Found : C, 60·2; H, 5·1. $C_{16}H_{16}O_7$ requires C, 60·0; H, 5·0%).

β-3 : 4-*Dimethoxybenzoyl*-α-(3′ : 4′-*dimethoxybenzylidene*)-β-*methylenepropionic Acid*. (V).—β-3 : 4-Dimethoxybenzoyl-α-(3′ : 4′-dimethoxybenzylidene)propionic acid (3 g.) (this vol., p. 640), 10% sodium hydroxide solution (9 c.c.), and 40% formalin (6 c.c.) were kept over-night at room temperature. The solution was acidified; the product, isolated with ether, crystallised from benzene in colourless prisms (2·7 g.), m. p. 157—158° (Found : C, 66·5; H, 5·6. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·6%).

*Lactone of* β-3 : 4-*Dimethoxybenzoyl*-α-(3′ : 4′-*dimethoxybenzylidene*)-β-*chloromethylpropionic Acid* (VI; R = Cl).—The methylene acid (V) (3 g.) was boiled with methyl alcohol (60 c.c.) saturated with hydrogen chloride. The *lactone* (VI; R = Cl) rapidly separated from the boiling solution; after ½ hour the mixture was cooled and the solid was collected (A, see below) and washed with ether; yellow needles (1·1 g.), m. p. 183—184°, were obtained (Found : C, 63·5; H, 5·2; Cl, 8·2. $C_{22}H_{21}O_6Cl$ requires C, 63·4; H, 5·1; Cl, 8·5%). This lactone (VI; R = Cl), which was also obtained by the action of cold methyl-alcoholic hydrogen chloride on the acid (V), was insoluble in sodium bicarbonate or hydroxide solution. Boiling with methyl alcohol, containing a little chloroform to assist solution, converted it into the *lactone* of β-3 : 4-*dimethoxybenzoyl*-α-(3′ : 4′-*dimethoxybenzylidene*)-β-*methoxymethylpropionic acid* (VI; R = OMe), which separated from methyl alcohol in yellow needles, m. p. 145° (Found : C, 67·0; H, 5·8; OMe, 36·9. $C_{23}H_{24}O_7$ requires C, 67·0; H, 5·8; OMe, 37·6%).

*Methyl* 6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-2-*chloromethylnaphthalene*-3-*carboxylate* (VII; R = Me).—The filtrate (A, see above) was diluted with water and extracted with ether. Removal of the ether gave an oil, which rapidly solidified and crystallised from methyl alcohol–chloroform (charcoal) in colourless needles (0·9 g.), m. p. 176—177° (Found : C, 64·1; H, 5·7. $C_{23}H_{23}O_6Cl$ requires C, 64·1; H, 5·4%).

6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-2-*chloromethylnaphthalene*-3-*carboxylic Acid* (VII; R = H).—The methylene acid (V) (3 g.) was dissolved in glacial acetic acid (20 c.c.), and concentrated hydrochloric acid (50 c.c.) gradually added with cooling. After 12 hours the pale yellow solid (3 g.) was collected; it was sparingly soluble in the usual organic solvents, but crystallised from methyl alcohol–chloroform or benzene–chloroform in colourless prisms, which melted at 244—245°, resolidified, and remelted at 294—295° (Found : C, 63·6, 63·5; H, 5·2, 5·1; OMe, 29·1; Cl, 8·2. $C_{22}H_{21}O_6Cl$ requires C, 63·4; H, 5·1; OMe, 29·7; Cl, 8·5%). An acetyl determination proved the absence of an acetyl group.

4′ : 5′ : 6 : 7-*Tetramethoxybenzo*-3 : 4-*fluorene*-1-*carboxylic Acid* (VIII; R = H).—The acid (VII; R = H) (1 g.) was mixed with camphor (10 g.) and heated with stirring at 200—210° for 10 minutes. The cold mixture was diluted with methyl alcohol and the solid was collected, washed with ether, and crystallised either from a large volume of glacial acetic acid or from nitrobenzene; cream-coloured needles (0·85 g.), m. p. 303—305°, were obtained, which were readily soluble in aqueous sodium bicarbonate (Found : C, 69·5; H, 5·5. $C_{22}H_{20}O_6$ requires C, 69·5; H, 5·3%). The *methyl* ester (VIII; R = Me), obtained similarly by the action of heat on the methyl ester (VII; R = Me), crystallised from methyl alcohol–chloroform in colourless

plates, m. p. 202—204° (Found : C, 69·7; H, 5·8. $C_{23}H_{22}O_6$ requires C, 70·0; H, 5·6%). The methyl ester was hydrolysed by boiling with 10% methyl-alcoholic potassium hydroxide for 2 hours. Addition of acid to the alkaline solution precipitated the acid (VIII; R = H), which crystallised from acetic acid in colourless needles, m. p. 303—305°.

*Lactone of* 6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-2-*hydroxymethylnaphthalene*-3-*carboxylic Acid; Dehydro-"sulphite-liquors lactone" Dimethyl Ether* (II).—(a) The acid (VII; R = H) (3 g.) was dissolved in cold 10% sodium hydroxide solution (20 c.c.) and heated at 100° for 1 hour. The solution was acidified, heated at 100° for ½ hour, and treated with sodium bicarbonate and the insoluble material was collected and crystallised from methyl alcohol containing a little chloroform; yield, 2·7 g. (b) The methyl ester (VII; R = Me) (0·5 g.) was hydrolysed by boiling with 10% methyl-alcoholic potassium hydroxide (5 c.c.) for 1 hour. The methyl alcohol was removed and the diluted solution was acidified and treated with bicarbonate as described in (a); yield, 0·38 g. (c) The lactone (VI; R = Cl) (1 g.) was boiled with methyl-alcoholic hydrogen chloride (10 c.c.) and chloroform (20 c.c.) for 6 hours. Water was added, the chloroform layer dried, and the solvent removed. The residual oil was boiled with 10% methyl-alcoholic potassium hydroxide (10 c.c.), the alcohol removed, and the residue dissolved in water and filtered. The filtrate was acidified and treated with bicarbonate as described in (a); yield, 0·01 g.

The *lactone* (II) crystallised in colourless prisms, m. p. 215—216° (Found : C, 69·5; H, 5·4. Calc. for $C_{22}H_{20}O_6$ : C, 69·5; H, 5·3%), which gave no depression in melting point when mixed with dehydro-"sulphite-liquors lactone" dimethyl ether prepared as described in Part II (p. 644). The crystalline form and colour reactions of the synthetical lactone were identical with those observed with the material prepared from natural sources.

β-(3 : 4 : 5-*Trimethoxybenzoyl*)*propionic Acid* (XIII).—Ethyl 3 : 4 : 5-trimethoxybenzoylacetate (8·3 g.), sodium ethoxide (from 0·75 g. of sodium), and ethyl bromoacetate (5·2 g.) were refluxed in alcohol (75 c.c.) for 16 hours. The cooled mixture was diluted, acidified, and extracted with ether, the solvent removed, and the residual oil boiled with 20% sulphuric acid for 48 hours. The mixture was extracted with ether, the solvent removed, and the product warmed with a mixture of methyl alcohol (25 c.c.) and 10% sodium hydroxide solution (10 c.c.) for 1 hour. After dilution and removal of the neutral impurities with ether, the alkaline solution was acidified; the *acid* (XIII), isolated with ether, crystallised from benzene in colourless needles (4·2 g.), m. p. 121—122° (Found : C, 58·3; H, 5·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

β-(3 : 4 : 5-*Trimethoxybenzoyl*)-α-(3′ : 4′-*methylenedioxybenzylidene*)*propionic Acid* (XIV).—The acid (XIII) (1 g.) was neutralised with aqueous sodium hydroxide, and the solution evaporated to dryness; the pulverised dry sodium salt was mixed with piperonal (1·2 g.) and acetic anhydride (2·5 c.c.) and heated for 2 hours on the water-bath. Water was added, and the γ-*lactone* of the acid (XIV) collected and washed with water and methyl alcohol; it crystallised from methyl alcohol–chloroform in yellow plates (1 g.), m. p. 161—162° (Found : C, 66·1; H, 4·6. $C_{21}H_{18}O_7$ requires C, 66·0; H, 4·7%). The lactone (0·7 g.) was shaken with a solution of sodium (0·1 g.) in methyl alcohol (20 c.c.); the colourless methyl ester of acid (XIV) rapidly separated. The suspension was warmed until the ester dissolved, water was added, and the methyl alcohol removed. The solution was filtered, the filtrate acidified, and the product collected and crystallised from methyl alcohol–chloroform; colourless slender needles (0·7 g.), m. p. 183—184°, were obtained (Found : C, 63·1; H, 5·0. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

β-3 : 4 : 5-*Trimethoxybenzoyl*-α-(3′ : 4′-*methylenedioxybenzylidene*)-β-*methylenepropionic acid* (XV), prepared as described in the case of (V), crystallised from benzene in colourless needles containing solvent of crystallisation. After drying at 100° in a vacuum, the crystals melted at 169—170° (Found : C, 64·2; H, 5·0. $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·8%).

6 : 7-*Methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-2-*chloromethylnaphthalene*-3-*carboxylic acid* (XVI), prepared as described in the case of (VII; R = H), crystallised from chloroform–methyl alcohol in colourless prisms, which darkened at 250° but did not melt below 300° (Found : C, 61·0; H, 4·7. $C_{22}H_{19}O_7Cl$ requires C, 61·3; H, 4·4%).

The *lactone* of 6 : 7-*methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)-2-*hydroxymethylnaphthalene*-3-*carboxylic acid* (XII), obtained as described in method (a) for the preparation of (II), crystallised from methyl alcohol–chloroform in colourless needles, m. p. 288—289° (Found : C, 66·7; H, 4·8. $C_{22}H_{18}O_7$ requires C, 67·0; H, 4·6%).

6 : 7-*Methylenedioxy*-1-(3′ : 4′ : 5′-*trimethoxyphenyl*)*naphthalene*-2 : 3-*dicarboxylic Acid* (XVII).—(a) Either dehydroanhydropicropodophyllin (XI) (0·5 g., prepared as described by Späth, Wesely, and Kornfeld, *loc. cit.*) or the synthetic lactone (XII) (0·5 g.) was dissolved in hot 1% methyl-alcoholic potassium hydroxide (25 c.c.); water was then added and the methyl

alcohol was removed. Finely powdered potassium permanganate (2 g.) was gradually added during 6 hours to the cold solution. The filtered solution was acidified, heated at 100° for ½ hour, and treated with sodium bicarbonate, and traces of unchanged lactone collected; addition of acid to the filtrate precipitated the crude acid (XVII). (b) An alkaline solution of (XI) (0·5 g.), prepared as described above, was boiled for 3 hours with a solution of sodium hypobromite obtained by the addition of bromine (0·7 c.c.) to 10% sodium hydroxide solution (15 c.c.). The cold solution was saturated with sulphur dioxide and acidified with dilute sulphuric acid, and the dibasic acid (XVII) separated from unchanged lactone as described above. The dried crude acid (XVII) was boiled with acetyl chloride (10 parts) for 2 hours. The chloride was removed, the solid residue triturated with ether, and the product crystallised from glacial acetic acid; the *anhydride* was obtained in very pale yellow plates, m. p. 299—300° (Found: C, 64·5; H, 4·2. $C_{22}H_{16}O_8$ requires C, 64·7; H, 4·0%). The anhydride prepared from either (XI) or (XII) was refluxed with methyl-alcoholic hydrogen chloride (50 parts) for 12 hours. The *dimethyl* ester, isolated with ether, crystallised from methyl alcohol in colourless prisms, m. p. 206—207° (Found: C, 63·2; H, 5·1. $C_{24}H_{22}O_9$ requires C, 63·4; H, 4·9%).

One of us (T. R.) thanks the Durham County Council Education Department for a scholarship.

UNIVERSITY OF DURHAM, ARMSTRONG COLLEGE,
NEWCASTLE-UPON-TYNE.

[*Received, October 2nd*, 1935.]