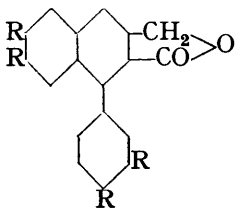
162. *The Constituents of Natural Phenolic Resins. Part V. Synthesis of* dl-*Matairesinol Dimethyl Ether and* dl-*Cubebinolide.*

By ROBERT D. HAWORTH, WILLIAM KELLY, and THOMAS RICHARDSON.

THE synthetical work communicated in earlier parts of this series aimed at the preparation of lactones of types (I) and (II), but hitherto no method for the synthesis of lactones of type (III) has been recorded. The combination of reactive methylene groups with safrole oxide (this vol., p. 348) suggested a method for the preparation of lactones of this class, and the synthesis of *dl*-matairesinol dimethyl ether (III; R = OMe) and *dl*-cubebinolide (RR = CH_2O_2) is now described.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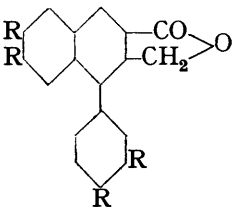
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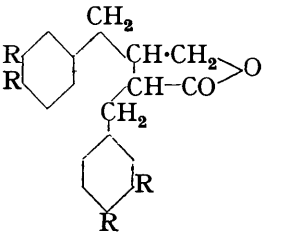
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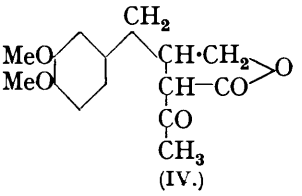
O-Methyleugenol oxide and ethyl sodioacetoacetate reacted in cold alcoholic solution to give *α-acetyl-β-(3 : 4-dimethoxybenzyl)butyrolactone* (IV). The constitution of this lactone was established by condensing the sodio-derivative with 3 : 4-dimethoxybenzoyl chloride, and converting the alkali-insoluble product into *α-(3 : 4-dimethoxybenzoyl)-β-(3′ : 4′-dimethoxybenzyl)butyrolactone* (V) by hydrolysis with cold dilute sodium hydroxide solution. Following the methods described in Part IV (*loc. cit.*), this lactone (V) was cyclised with methyl-alcoholic hydrogen chloride, and the *lactone* of *1-hydroxy-6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid* (VI) thus obtained was converted by dehydration into the *lactone* of *6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethyl-3 : 4-dihydronaphthalene-2-carboxylic acid* (VII). Dehydrogenation of this dihydro-compound (VII) with lead tetra-acetate yielded the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid (I; R = OMe), m. p. 254°, identical with the compound synthesised in Part II (J., 1935, 636) and the preparation of (I; R = OMe) by this new method establishes the structure of (IV).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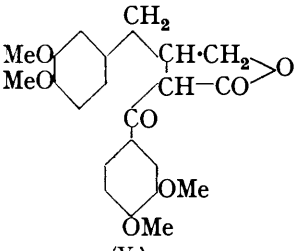
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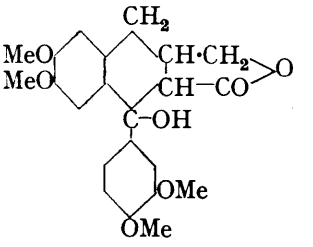
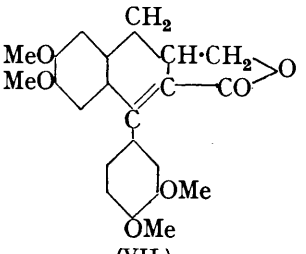

(VI.)

After unsuccessful attempts had been made to convert (V) into (III; R = OMe) by applying the Clemmensen and the Wolff–Kishner process, the condensation of the sodio-derivative of (IV) and 3 : 4-dimethoxybenzyl chloride was investigated. *α-Acetyl-αβ-bis-(3 : 4-dimethoxybenzyl)butyrolactone* (VIII) was obtained as an alkali-insoluble oil, which on hydrolysis with methyl-alcoholic barium hydroxide yielded an acidic fraction from which *αβ-bis-(3 : 4-dimethoxybenzyl)butyrolactone* (dl-*matairesinol dimethyl ether*) (III; R = OMe), m. p. 106—107°, was obtained. The yield was extremely small, but the method, though of little preparative value, is of importance from the constitutional standpoint. An excellent method for the preparation of *dl*-matairesinol dimethyl ether has, however, been developed.

O-Methyleugenol oxide and methyl sodio-3 : 4-dimethoxybenzyl-α-cyanoacetate reacted in alcoholic solution, giving an acidic product which yielded a lactonic oil when warmed with dilute hydrochloric acid. This lactonic oil was converted into *dl*-matairesinol dimethyl



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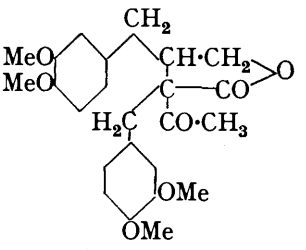
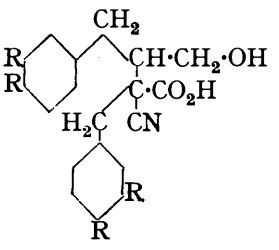
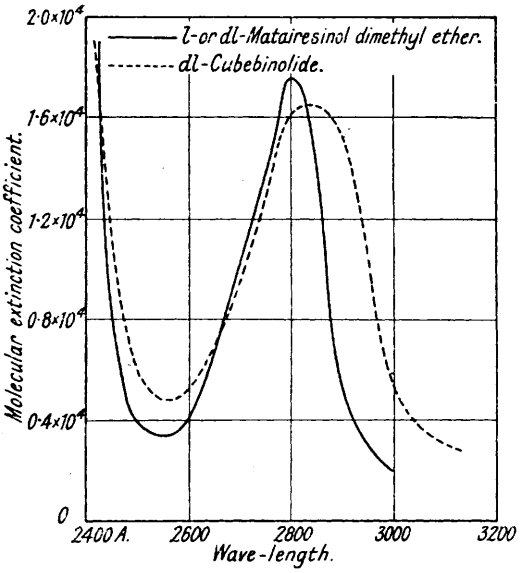


(VIII.)



(IX.)

ether, m. p. 106—107°, by boiling with concentrated hydrochloric acid, the overall yield being 36% of the theoretical. The nature of the acidic product mentioned above has not been investigated and such products have not been observed in similar reactions between



ethylene oxides and derivatives of ethyl acetoacetate or ethyl malonate. In view of the work of Thorpe (J., 1900, **79**, 923) on ethyl sodiocyanoacetate, the acidic product is probably (IX; R = OMe) and the lactonic oil may be the corresponding α-cyano-lactone. A further examination of these intermediate products is contemplated.

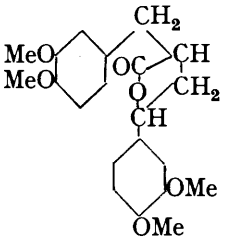
dl-Matairesinol dimethyl ether has been converted into *dibromo-*, *dinitro-*, and *tetranitro*-derivatives and the synthetic lactone and its derivatives closely resemble those of *l*-matairesinol dimethyl ether both in solubility in organic solvents and in colour reactions. The ultra-violet absorption spectra of *l*- and *dl*-matairesinol dimethyl ether are identical (fig.) and there can be little doubt that the natural and the synthetic product differ only in stereochemical configuration, but a rigid comparison must await a solution of the stereochemical problem. In Part I (J., 1935, 633) it was shown that lead tetra-acetate converted *l*-matairesinol dimethyl ether into a mixture of the dehydro-lactones (I; R = OMe) and (II; R = OMe), but this reaction does not occur with the *dl*-dimethyl ether. It is unlikely that this difference in behaviour is due to impurity in the natural matairesinol dimethyl ether, because repeated crystallisation does not affect the yield* of mixed

* The yield of mixed dehydro-lactones is approximately 10% as stated in Part I, p. 634; the amount recorded on p. 635 should be 0·05—0·08 g. instead of 0·5—0·8 g.

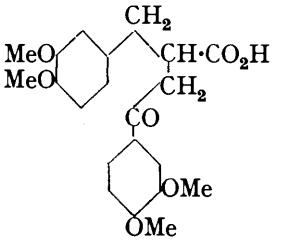
dehydro-lactones, and stereochemical factors are probably responsible for the discrepancy. In support of this opinion it may be recalled that stereoisomerides show marked differences in reactivity towards lead tetra-acetate. Criegee (*Ber.*, 1931, **64**, 360) showed that *cis*-glycols were attacked much more rapidly than the *trans*-isomerides, and in Part II (*loc. cit.*, p. 603) a similar difference was observed in the ease of dehydrogenation of the α- and the β-form of the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid.

The dextrorotatory lactone, cubebinolide, was obtained by Mameli (see Part I for references) during his researches on cubebin, a constituent of the unripe fruit of *Piper cubeba*, and in 1922 the structure (III; RR = CH_2O_2) was advanced for the lactone. Later, Yoshiki and Ishiguro (*J. Pharm. Soc. Japan*, 1933, **53**, 11) examined Japanese hinokiresin and isolated a lævorotatory lactone, hinokinin, which they regarded as the enantiomorph of cubebinolide. This suggestion was supported by Keimatsu and Ishiguro (*ibid.*, 1935, **55**, 45), Briggs (*J. Amer. Chem. Soc.*, 1935, **57**, 1383), and Mameli (*Gazzetta*, 1935, **65**, 877, 886) and the formulation of cubebinolide as the methylenedioxy-analogue of matairesinol dimethyl ether led us to extend the scope of our experiments.

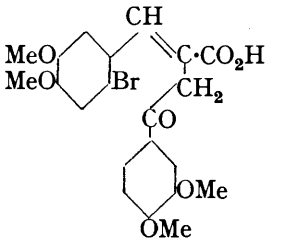
Safrole oxide and methyl sodio-3 : 4-methylenedioxybenzyl-α-cyanoacetate reacted in cold alcoholic solution, giving an alkali-soluble product, probably (IX; RR = CH_2O_2), which yielded an oily lactone when warmed with dilute hydrochloric acid. This lactonic oil was hydrolysed with concentrated hydrochloric acid and converted into αβ-*bis*-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (dl-*cubebinolide*) (III; RR = CH_2O_2), m. p. 106—107°, from which *dibromo*- and *dinitro*-derivatives have been prepared. The ultra-violet absorption of *dl*-cubebinolide (fig.) resembles that of *dl*-matairesinol dimethyl ether, but the absorption band is displaced in the direction of longer wave-length. While these experiments were in progress, Keimatsu, Ishiguro, and Nakamura (*J. Pharm. Soc. Japan*, 1935, **55**, 185) reduced αβ-bis-(3 : 4-methylenedioxybenzyl)succinic anhydride with amalgamated aluminium and obtained *dl*-hinokinin, m. p. 106—107°, probably identical with *dl*-cubebinolide described above. The absorption spectra of *dl*- and *l*-hinokinin are indistinguishable and are in harmony with our results for *dl*-cubebinolide. With the object of providing other methods of comparison, the dehydro-lactones (I; RR = CH_2O_2) and (II; RR = CH_2O_2) have been synthesised, but a description of this work is deferred until the completion of experiments, at present in progress, on the dehydrogenation of synthetic and natural cubebinolide.



(X.)



(XI.)



(XII.)

The compounds (X), (XI), and (XII) were prepared during unsuccessful preliminary experiments.

Experimental.

α-*Acetyl*-β-(3 : 4-*dimethoxybenzyl*)*butyrolactone* (IV).—*O*-Methyleugenol oxide (4·5 g.) (Fourneau and Tiffeneau, *Compt. rend.*, 1905, **140**, 1595; **141**, 662) was added to a solution of ethyl sodioacetoacetate (prepared from sodium, 0·5 g., and ethyl acetoacetate, 3·3 g.) in ethyl alcohol (20 c.c.). After 7 days water was added and neutral impurities were removed with ether. The alkaline liquor was acidified and extracted with benzene, and the solvent removed. Distillation of the residue gave an oil (4·5 g.), b. p. 218—220°/0·5 mm., which slowly solidified; it crystallised from benzene–light petroleum in colourless prisms (4 g.), m. p. 69—70°, which gave a purple ferric test (Found : C, 64·6; H, 6·6. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

α-(3 : 4-*Dimethoxybenzoyl*)-β-(3′ : 4′-*dimethoxybenzyl*)*butyrolactone* (V).—The lactone (IV)

(5·5 g.) was allowed to react with " molecular " sodium (0·5 g.) in benzene (20 c.c.) for 12 hours. 3 : 4-Dimethoxybenzoyl chloride (4·2 g.) was added and after 12 hours the mixture was refluxed for ½ hour. After addition of water, the separated benzene layer was washed with dilute sodium hydroxide solution and dried, and about half of the solvent removed. The residual benzene solution was diluted with ether (50 c.c.) and shaken with 5% sodium hydroxide solution (40 c.c.) for 7 hours. The *product*, liberated by acidification and isolated with chloroform, crystallised from methyl alcohol in colourless needles (2 g.), m. p. 125—126°, which slowly gave a green and later a purple colour with ferric chloride (Found : C, 66·3; H, 6·2. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%).

Lactone of 1-*Hydroxy*-6 : 7-*dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-3-*hydroxymethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid* (VI).—The lactone (V) (0·5 g.) was heated with methyl-alcoholic hydrogen chloride (15 c.c.) for 20 minutes, the mixture poured into water, the product extracted with chloroform, and the solvent removed. The residue crystallised from ether–light petroleum (b. p. 40—60°) in slender needles (0·3 g.), m. p. 124—126° (Found : C, 65·7; H, 6·1. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%), which gave no coloration with ferric chloride.

Lactone of 6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-3-*hydroxymethyl*-3 : 4-*dihydronaphthalene*-2-*carboxylic Acid* (VII).—The lactone (VI) (0·5 g.) was heated with potassium hydrogen sulphate (1·0 g.) at 180° for ½ hour. The *product*, isolated with chloroform, crystallised from methyl alcohol–chloroform in prisms (0·4 g.), m. p. 216—217° (Found : C, 68·8; H, 6·1. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·9%). This lactone (VII) (0·1 g.), lead tetra-acetate (0·2 g.), and glacial acetic acid (2 c.c.) were heated at 80° for 10 minutes. After dilution with water, the product, isolated with chloroform, crystallised from methyl alcohol–chloroform in colourless prisms (0·05 g.), which gave no depression in m. p. with a specimen of the lactone of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid, m. p. 254°, prepared as described in Part II (*loc. cit.*).

α-*Acetyl*-αβ-*bis*-(3 : 4-*dimethoxybenzyl*)*butyrolactone* (VIII).—The sodio-derivative, prepared from (IV) (3·5 g.) as described above, 3 : 4-dimethoxybenzyl chloride (2 g.) (Tiffeneau, *Bull. Soc. chim.*, 1911, **9**, 928), and benzene (30 c.c.) were heated in a sealed tube at 100° for 18 hours. After washing, first with water and then with dilute sodium hydroxide solution, the benzene was removed, the residue distilled in a vacuum, and the fraction (1·5 g.), b. p. 270—280°/0·5 mm., collected (Found : C, 67·8; H, 7·0. $C_{24}H_{28}O_7$ requires C, 67·3; H, 6·6%). This viscous oil was insoluble in cold alkali and gave no colour with ferric chloride.

αβ-*Bis*-(3 : 4-*dimethoxybenzyl*)*butyrolactone* (dl-*Matairesinol Dimethyl Ether*) (III; R = OMe).—(a) The lactone (VIII) (1 g.) was boiled with 10% methyl-alcoholic barium hydroxide (10 c.c.) for 1 hour. Water was added, the methyl alcohol removed, the liquid filtered, and neutral impurities removed from the filtrate by extraction with chloroform. Excess of hydrochloric acid was added to the alkaline liquor and after boiling for 1·5 hours the product was extracted with chloroform and the extracts were washed thoroughly with sodium bicarbonate solution. Removal of the chloroform gave an oil, which slowly crystallised from aqueous methyl alcohol; the crystals were twice recrystallised from methyl alcohol (yield, 0·01 g.).

(b) *Methyl* 3 : 4-*dimethoxybenzyl*-α-*cyanoacetate*, prepared by heating the corresponding acid (Baker and Robinson, J., 1925, **127**, 1432) with 4% methyl-alcoholic hydrogen chloride (4 parts) for 4 hours, crystallised from methyl alcohol in colourless prisms, m. p. 75—76° (Found : C, 62·7; H, 6·0. $C_{13}H_{15}O_4N$ requires C, 62·65; H, 6·0%). *O*-Methyleugenol oxide (2·5 g.) was added to a cold solution of the above ester (3 g.) and sodium ethoxide (prepared from 0·3 g. of sodium) in absolute alcohol (30 c.c.), and the mixture kept for 3 days at room temperature. Water was then added, neutral impurities were removed in ether, the aqueous liquor was acidified and heated at 100° for 1 hour, and the oil which separated was isolated with ether. This nitrogenous oil, which was insoluble in aqueous sodium bicarbonate but slowly soluble in warm sodium hydroxide solution, was refluxed with concentrated hydrochloric acid (15 c.c.) for 4 hours. Water was added, the mixture extracted with chloroform, the extract washed with sodium hydroxide solution and dried, and the solvent removed; the residual oil was purified by a crystallisation from methyl alcohol (yield, 1·8 g.).

dl-*Matairesinol dimethyl ether*, prepared by method (a) or (b), separated from methyl alcohol in colourless slender prisms, m. p. 106—107° (Found : C, 68·2, 68·3; H, 6·6, 6·8. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7%). It dissolved in concentrated sulphuric acid, giving an orange solution which became brown on addition of a drop of concentrated nitric acid. The statement made in Part I, p. 635, that *l*-matairesinol dimethyl ether gives a blue-green colour with concentrated sulphuric acid is incorrect; the reaction is identical with that described above for the *dl*-dimethyl ether.

dl-*Dibromomatairesinol dimethyl ether*, prepared by the addition of bromine (2 mols.) to *dl*-matairesinol dimethyl ether in glacial acetic acid, crystallised from methyl alcohol in colourless slender needles, m. p. 109—110° (Found: C, 48·5; H, 4·3. $C_{22}H_{24}O_6Br_2$ requires C, 48·5; H, 4·4%). It dissolved in concentrated sulphuric acid to a light brown solution, which became bright red on addition of a drop of concentrated nitric acid.

dl-*Dinitromatairesinol dimethyl ether*, prepared by the action of concentrated nitric acid (2 mols.) on the ether in glacial acetic acid, crystallised from methyl alcohol–chloroform in pale yellow needles, m. p. 179—180° (Found: C, 55·5; H, 5·2. $C_{22}H_{24}O_{10}N_2$ requires C, 55·4; H, 5·0%). With concentrated sulphuric acid it gave a bright red solution, which became orange on addition of a drop of concentrated nitric acid.

dl-*Tetranitromatairesinol dimethyl ether*, prepared by boiling *dl*-matairesinol dimethyl ether with concentrated nitric acid (15 parts) for 5 minutes, crystallised from methyl alcohol–chloroform in almost colourless plates, m. p. 185—186° (Found: C, 47·0; H, 4·0. $C_{22}H_{22}O_{14}N_4$ requires C, 46·6; H, 3·9%).

αβ-*Bis*-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (dl-*Cubebinolide*) (III; RR = CH_2O_2).—*Methyl* 3 : 4-*methylenedioxybenzyl*-α-*cyanoacetate*, prepared by heating the corresponding acid (Baker and Lapworth, J., 1924, 2336) with 4% methyl-alcoholic hydrogen chloride for 4 hours, crystallised from methyl alcohol in colourless prisms, m. p. 79—80° (Found: C, 62·0; H, 4·6. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·8%). Safrole oxide (4 g.) was added to a solution of the above ester (4 g.) and sodium ethoxide (from sodium, 0·4 g.) in absolute alcohol (50 c.c.), and the mixture kept for 3 days at room temperature. Water was then added, and the mixture was extracted with ether; the aqueous layer was acidified and heated at 100° for 1 hour and the nitrogenous lactone was isolated with ether and boiled with concentrated hydrochloric acid (20 c.c.) for 4 hours. After addition of water the mixture was extracted with chloroform, the extract washed several times with sodium hydroxide solution and dried, and the solvent removed; the residual oil crystallised from methyl alcohol in colourless prisms (1·0 g.), m. p. 106—107° (Found: C, 67·6; H, 5·1. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%). dl-*Cubebinolide* dissolved in concentrated sulphuric acid to a purple solution, which became red on addition of a drop of concentrated nitric acid.

dl-*Dibromocubebinolide*, prepared in glacial acetic acid solution, crystallised from alcohol in rhombic plates, m. p. 119—120° (Found: C, 46·8; H, 3·3. $C_{20}H_{16}O_6Br_2$ requires C, 46·9; H, 3·15%). It dissolved in concentrated sulphuric acid to a red-purple solution, which became brown on addition of a drop of concentrated nitric acid.

dl-*Dinitrocubebinolide*, prepared in acetic acid solution, crystallised from much alcohol or from ethyl acetate in stout, pale yellow prisms, m. p. 160—161° (Found: C, 54·0; H, 3·8. $C_{20}H_{16}O_{10}N_2$ requires C, 54·0; H, 3·6%). It gave with concentrated sulphuric acid a bright red solution, which became slightly paler on addition of concentrated nitric acid.

α-(3 : 4-*Dimethoxybenzyl*)-γ-(3′ : 4′-*dimethoxyphenyl*)*butyrolactone* (X).—The γ-lactone of β-(3 : 4-dimethoxybenzoyl)-α-(3′ : 4′-dimethoxybenzylidene)propionic acid (2 g.) (J., 1935, 636) in glacial acetic acid (150 c.c.) was shaken with hydrogen under a pressure of 95 pounds per square inch for 14 hours in presence of platinic oxide (0·05 g.). The *product* crystallised from methyl alcohol in colourless needles (1·5 g.), m. p. 126—127° (Found: C, 67·6; H, 6·4. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·4%). It is remarkable in view of the work of Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601) that the lactone ring does not undergo reductive fission.

β-(3 : 4-*Dimethoxybenzoyl*)-α-(3′ : 4′-*dimethoxybenzyl*)*propionic Acid* (XI).—The above lactone (0·4 g.) was dissolved in hot 5% methyl-alcoholic potassium hydroxide (10 c.c.), the methyl alcohol was removed, water was added, and potassium permanganate (0·1 g.) in water (25 c.c.) was gradually added. The manganese dioxide was removed, and the filtrate acidified; the *acid*, isolated with ether, crystallised from methyl alcohol in colourless needles, m. p. 107—108° (Found: C, 65·2; H, 6·3. $C_{21}H_{24}O_7$ requires C, 65·0; H, 6·2%).

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2′-*bromo*-4′ : 5′-*dimethoxybenzylidene*)*propionic Acid* (XII).—The sodium salt of β-(3 : 4-dimethoxybenzoyl)propionic acid (2·6 g.), 2-bromo-4 : 5-dimethoxybenzaldehyde (3·6 g.), and acetic anhydride (12 c.c.) were heated at 100° for 2 hours; water was then added. The yellow *γ-lactone* crystallised from methyl alcohol–chloroform in orange needles, m. p. 202° (Found: C, 56·4; H, 4·3. $C_{21}H_{19}O_6Br$ requires C, 56·4; H, 4·3%). The lactone (3·2 g.) and sodium methoxide (from sodium, 0·16 g.) in methyl alcohol (25 c.c.) were refluxed for 1 hour. Water was added, the methyl alcohol removed, the filtered solution acidified, and the *acid* collected and crystallised from methyl alcohol–chloroform; colourless needles (2·8 g.), m. p. 225°, were obtained (Found: C, 54·3; H, 4·7. $C_{21}H_{21}O_7Br$ requires C, 54·2; H, 4·5%). The *methyl* ester, prepared by the action of methyl-alcoholic hydrogen

chloride, crystallised from methyl alcohol in felted needles, m. p. 140—141° (Found : C, 55·0; H, 4·9. $C_{22}H_{23}O_7Br$ requires C, 55·1; H, 4·8%).

Spectrographic Data.—Measurements were made with a Hilger medium quartz spectrograph. The light source was a condensed spark between tungsten-steel electrodes. The values are expressed as molecular extinction coefficients (ε). Approx. $M/10{,}000$ alcoholic solutions were used.

	$\lambda_{max.}$ A.	$\epsilon \times 10^{-4}$.
l-Matairesinol dimethyl ether	2,800	1·76
dl-Matairesinol dimethyl ether	2,800	1·76
dl-Cubebinolide	2,840	1·65

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