

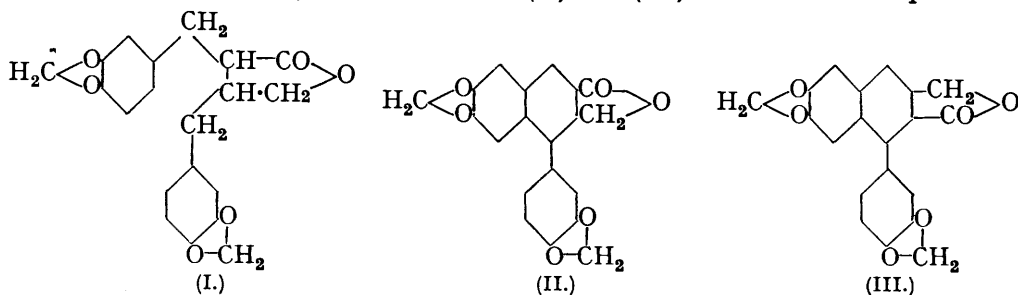
170. *The Constituents of Natural Phenolic Resins. Part VI.*
Synthesis of Compounds Related to Cubebinolide (Hinokinin).

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ANALOGY with the experiments described in Part I (J., 1935, 633) suggested that cubebinolide (hinokinin) (I) (see Part I, *loc. cit.*, and Part V, this vol., p. 725, for references) would yield the lactones (II) and (III) when treated with lead tetra-acetate. The present communication describes the synthesis of (II) and (III), which were prepared for comparison purposes. The lactone (II) was obtained by applying the method described in Part III (J., 1935, 1576). Owing to the instability of the methylenedioxy-group in the presence of acidic condensing agents, the method described in Part II (J., 1935, 636) does not provide a satisfactory route to the lactone (III); this, however, has been synthesised by employing reactions similar to those described in Part IV (this vol., p. 348).

Recently Dr. T. Ishiguro kindly sent us a generous specimen of *l*-hinokinin, but we have

been unable to discover appropriate conditions for the conversion of either *l*- or *dl*-hinokinin (compare Part V, *loc. cit.*) into the lactones (II) and (III). In numerous experiments,



either unchanged hinokinin or amorphous substances, probably catechol derivatives, which dissolved and rapidly darkened in warm dilute aqueous alkalis, were obtained. This attack of the methylenedioxy-group by lead tetra-acetate is not consistent with the stability of the group during the synthesis of dehydroanhydripropodophyllin (Part IV, *loc. cit.*).

EXPERIMENTAL.

6 : 7-Methylenedioxy-1-(3' : 4'-methylenedioxyphenyl)naphthalene-2 : 3-dicarboxylic Acid.—3 : 4-Methylenedioxyphenylpropionic acid (2.8 g.), m. p. 165° (Baude and Reychler, *Bull. Soc. chim.*, 1897, 17, 617) and acetic anhydride (18 c.c.) were heated at 100° for 4 hours. The *anhydride*, which separated on cooling, crystallised from glacial acetic acid in yellow prisms (2 g.), m. p. 244—246° (Found : C, 66.1; H, 2.9. C₂₀H₁₀O₇ requires C, 66.3; H, 2.8%). The *methyl ester*, prepared by heating the anhydride with methyl-alcoholic hydrogen chloride for 12 hours, crystallised from methyl alcohol-chloroform in colourless prisms, m. p. 214—215° (Found : C, 64.8; H, 4.2. C₂₂H₁₆O₈ requires C, 64.7; H, 3.9%).

Methylenedioxybenzene.—The following method, suggested by the work of Stevens (J., 1935, 725), proved most convenient. 4 : 5-Dibromo-1 : 2-methylenedioxybenzene (10 g.) (prepared from piperonylic acid by the method of Jones and Robinson, J., 1917, 913) was dissolved in 70% methyl alcohol (120 c.c.), and 4% sodium amalgam added. After boiling for 24 hours, most of the alcohol was removed through a good column, and the residue extracted with light petroleum (b. p. 40—60°). Yield, 3.5 g.; b. p. 172°.

β-(3 : 4-Methylenedioxybenzoyl)propionic Acid.—In spite of considerable demethylenation the following method is more convenient than Bougault's (*Ann. Chim.*, 1908, 15, 515). Aluminium chloride (5.5 g.) in nitrobenzene (30 c.c.) was gradually added to an ice-cold mixture of methylenedioxybenzene (2 g.) and succinic anhydride (2 g.) in nitrobenzene (10 c.c.). After standing for 6 hours at room temperature, the mixture was cautiously acidified, the nitrobenzene removed in steam, and the hot residue filtered; on cooling, the filtrate deposited the crude acid (1 g.), which was obtained in colourless prisms (0.5 g.), m. p. 136° after three crystallisations from hot water (Bougault, *loc. cit.*, gives m. p. 136°).

β-(3 : 4-Methylenedioxybenzoyl)-α-(3' : 4'-methylenedioxybenzylidene)propionic Acid.—The dry powdered sodium salt of the above acid (1.2 g.), piperonal (1.2 g.), and acetic anhydride (2 c.c.) were heated at 100° for 2 hours. Water was added, and the *γ-lactone* collected, washed successively with water, methyl alcohol and ether, and crystallised from acetic acid (carbon); small greenish-yellow needles (1.2 g.), m. p. 236—237°, were obtained (Found : C, 67.6; H, 3.8. C₁₉H₁₂O₆ requires C, 67.7; H, 3.6%). The *γ-lactone* (1.2 g.) was boiled for 1 hour with sodium ethoxide solution prepared from sodium (0.9 g.) and alcohol (7 c.c.). Water was added and the alcohol removed; the *acid*, precipitated by hydrochloric acid, crystallised from methyl alcohol in small colourless needles (0.7 g.), m. p. 193° (Found : C, 64.8; H, 4.1. C₁₉H₁₄O₇ requires C, 64.4; H, 4.0%).

β-(3 : 4-Methylenedioxybenzoyl)-α-(3' : 4'-methylenedioxybenzylidene)-β-methylenepropionic Acid.—A mixture of the above acid (0.4 g.), 10% sodium hydroxide solution (2 c.c.), and 20% formalin (1 c.c.) was allowed to react for 12 hours. After addition of dilute sulphuric acid the *product* was isolated with chloroform; it crystallised from benzene in small colourless nodules (0.3 g.), m. p. 184—185° (Found : C, 65.4; H, 3.7. C₂₀H₁₄O₇ requires C, 65.6; H, 3.9%).

Lactone of 6 : 7-Methylenedioxy-1-(3' : 4'-methylenedioxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic Acid (II).—A mixture of the above methylene acid (0.5 g.), glacial acetic acid (9 c.c.),

and concentrated hydrochloric acid (10 c.c.) was kept for 12 hours. After addition of water, the product was collected, heated at 100° with 5% sodium hydroxide solution (5 c.c.) for 15 minutes, and filtered off. The filtrate was acidified and heated at 100° for 1 hour and the product, after digestion with sodium bicarbonate solution for $\frac{1}{2}$ hour, was collected and crystallised from methyl alcohol-chloroform (carbon); colourless prisms (0.3 g.), m. p. 264°, were obtained (Found: C, 68.8; H, 3.5. $C_{20}H_{12}O_6$ requires C, 69.0; H, 3.5%). This lactone can also be purified by sublimation at 0.5 mm. The lactone (II) was converted into 6 : 7-methylenedioxy-1-(3' : 4'-methylenedioxyphenyl)naphthalene-2 : 3-dicarboxylic acid by oxidation with potassium permanganate under conditions similar to those employed for the corresponding tetramethoxy-lactone (Part II, *loc. cit.*, p. 643).

Bis-(3 : 4-methylenedioxyphenyl)methylsuccinic Acid.—A mixture of glacial acetic acid (8 c.c.) and concentrated sulphuric acid (8 c.c.) was gradually added to an ice-cold solution of methylenedioxybenzene (2.4 g.) and ethyl hydroxymethylenesuccinate (2 g.) in acetic acid (8 c.c.). After 12 hours, ice was added and the product, isolated with chloroform, was hydrolysed by warming with 10% methyl-alcoholic potassium hydroxide (10 c.c.) for 2 hours. Unchanged methylenedioxybenzene was removed in steam and acidification of the residue yielded the acid, which crystallised from 20% acetic acid (carbon) in colourless prisms (0.6 g.), m. p. 140° with previous shrinking from 130° (Found: C, 58.6; H, 4.6; equiv., 183. $C_{19}H_{16}O_8 \cdot H_2O$ requires C, 58.5; H, 4.6; equiv., 186). Attempts to convert this acid into the corresponding 4-ketotetrahydronaphthalene derivative were unsuccessful.

α -(3 : 4-Methylenedioxybenzoyl)- β -(3 : 4-methylenedioxybenzyl)butyrolactone.—The sodio-derivative prepared from α -acetyl- β -(3 : 4-methylenedioxybenzyl)butyrolactone (5 g.) (Part IV, *loc. cit.*, p. 357) and sodium (0.45 g.) in benzene (10 c.c.), and 3 : 4-methylenedioxybenzoyl chloride (5.2 g.) in benzene (10 c.c.) were kept for 12 hours and then heated at 100° for 1 hour. The mixture was decomposed with water and washed with 2% sodium hydroxide solution, the benzene layer dried, and most of the solvent removed. The residue was dissolved in ether and shaken for 7 hours with 5% sodium hydroxide solution (120 c.c.). Water was added to dissolve the sodium salt which had separated and the alkaline liquor was separated, acidified, and extracted with chloroform. The extract was washed with sodium bicarbonate solution, the solvent removed, and the residue triturated with alcohol. The lactone crystallised from benzene in colourless prisms (2 g.), m. p. 136—137° (Found: C, 65.4; H, 4.4. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%). A violet colour gradually developed when ferric chloride was added to an alcoholic solution of the lactone.

Lactone of 6 : 7-Methylenedioxy-1-(3' : 4'-methylenedioxyphenyl)-3-hydroxymethyl-3 : 4-dihydronaphthalene-2-carboxylic Acid.—The above butyrolactone (1 g.) was warmed with methyl-alcoholic hydrogen chloride (15 c.c.) for 15 minutes; the product isolated with ether was an oil (0.9 g.), which was heated in a carbon dioxide stream in an oil-bath with potassium hydrogen sulphate (1.8 g.) at 155° for 6 hours. The dihydro-lactone, isolated with chloroform, was purified by repeated crystallisation from alcohol-chloroform; colourless prisms (0.1 g.), m. p. 228—229°, were obtained (Found: C, 68.3; H, 4.3. $C_{20}H_{14}O_6$ requires C, 68.6; H, 4.0%).

Lactone of 6 : 7-Methylenedioxy-1-(3' : 4'-methylenedioxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic Acid (III).—The above dihydro-lactone (0.1 g.) and palladium-black (0.01 g.) were heated for $\frac{1}{2}$ hour at 220°, and the mixture sublimed at 220°/0.2 mm. The sublimate, twice crystallised from alcohol-chloroform and finally from glacial acetic acid, was obtained in small slender prisms, m. p. 273—275° (Found: C, 69.0; H, 3.8. $C_{20}H_{12}O_6$ requires C, 69.0; H, 3.5%).

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