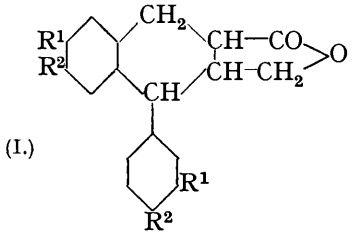
154. *The Constituents of Natural Phenolic Resins. Part XI. Synthesis of 2- and 3-Methyl-6 : 7-dimethoxy-1-veratrylnaphthalenes.*

By Robert D. Haworth and David Woodcock.

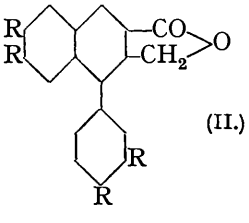
A further example of the irregular behaviour observed with lead tetra-acetate and members of the lignan group is reported. *l*-Conidendrin dimethyl ether (I; $R^1 = R^2 =$ OMe) is dehydrogenated by means of the tetra-acetate to (II; R = OMe) (J., 1935, 636), which is reduced by sodium amalgam to a racemic form of (I; $R^1 = R^2 =$ OMe). On treatment with lead tetra-acetate, this racemate loses hydrogen and carbon dioxide and is converted into 6 : 7-*dimethoxy*-1-*veratryl*-2-*methylnaphthalene* (V), the structure of which has been established by an independent synthesis.

6 : 7-Dimethoxy-1-veratryl-3-methylnaphthalene (X; R = Me) has been prepared by an unambiguous method, and its identity with a substance in Part IX (J., 1937, 1647, 1648) confirms the structural suggestions advanced in the previous communication.

The action of lead tetra-acetate on lignan derivatives has been studied in several previous papers of this series. Usually dehydrogenation occurs and compounds of type (I) are converted into the corresponding naphthalene derivatives (II). The conversion of diarylbutanes of type (IV) into mixtures of naphthalene derivatives (II) and (III) has been observed with matairesinol dimethyl ether (IV; $R^1 = R^2 =$ OMe) and arctigenin ethyl ether (IV; $R^1 =$ OMe, $R^2 =$ OEt), and in the conversion of *O*-acetylarctigenin (IV; $R^1 =$ OMe, $R^2 = O{\cdot}CO{\cdot}CH_3$) into a monomethyl ether of conidendrin (I; $R^1 =$ OMe, $R^2 =$ OH) (Omaki, *J. Pharm. Soc. Japan*, 1937, **57**, 22) the dehydrogenation is arrested at the tetrahydronaphthalene stage. Abnormal results have, however, been reported; the methylenedioxy-groups of hinokinin (IV; $R^1R^1 = R^1R^2 = CH_2O_2$) are attacked by the tetra-acetate and indefinite phenolic compounds are obtained, although in the case of anhydropicropodophyllin (J., 1936, 352) the methylenedioxy-groups do not interfere appreciably with the normal dehydrogenation reaction. The present work discloses a further abnormality observed with lead tetra-acetate.



(I.)



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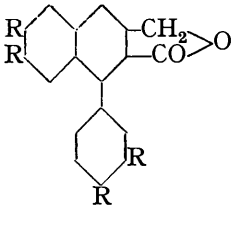

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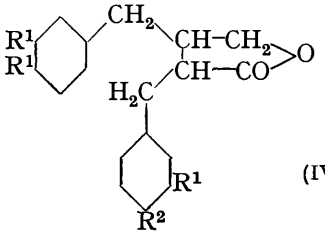
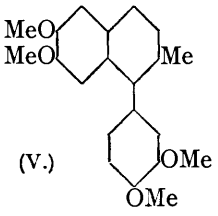


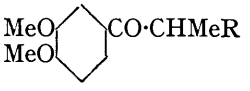
(IV.)

In the course of other experiments the lactone (II; R = OMe) of 6 : 7-dimethoxy-1-veratryl-2-hydroxymethylnaphthalene-3-carboxylic acid was reduced with sodium amalgam in boiling alkaline solution to a crystalline *lactone*, $C_{22}H_{24}O_6$, and, as this lactone was oxidised by sodium hypobromite to a mixture of 2-veratroylveratric acid and an acid whose methyl ester gave analytical figures in agreement with a racemic form of methyl 6 : 7-dimethoxy-1-veratryl-1 : 2 : 3 : 4-tetrahydronaphthalene-2 : 3-dicarboxylate, there can be little doubt that it represents one of the four theoretically possible racemates of conidendrin dimethyl ether (I; $R^1 = R^2 =$ OMe). Unlike the latter, which is

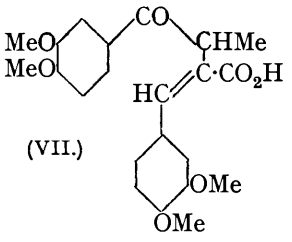
converted into (II; R = OMe) by the action of lead tetra-acetate, the racemate was dehydrogenated and decarboxylated to 6 : 7-*dimethoxy*-1-*veratryl*-2-*methylnaphthalene* (V). The structure of (V) was established by an independent synthesis from propioveratrone (VI; R = H), obtained by the action of propionyl chloride on veratrole.



(V.)

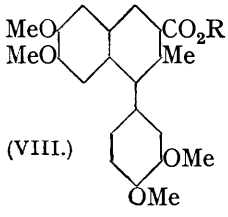


(VI.)

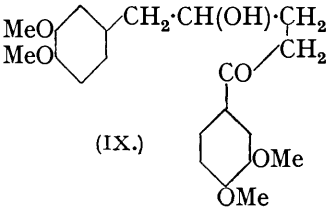


(VII.)

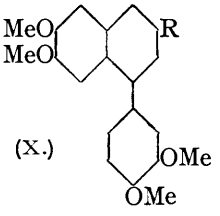
Bromination yielded α-*bromopropioveratrone* (VI; R = Br), which was converted into β-*veratroyl*-n-*butyric acid* (VI; R = $CH_2 \cdot CO_2H$) by condensation with ethyl sodiomalonate in the usual way. The sodium salt of (VI; R = $CH_2 \cdot CO_2H$) reacted with veratraldehyde to give the orange-coloured *lactone* of β-*veratroyl*-α-*veratrylidene*-n-*butyric acid* (VII). The acid (VII) has not been isolated in a pure condition, largely on account of the ease with which it undergoes lactonisation, but the methyl ester, prepared by the action of diazomethane on the crude acid, was converted into *methyl* 6 : 7-*dimethoxy*-1-*veratryl*-2-*methylnaphthalene*-3-*carboxylate* (VIII; R = Me) by the action of methyl-alcoholic hydrogen chloride. Decarboxylation of the corresponding *acid* (VIII; R = H) with quinoline and copper-bronze gave 6 : 7-dimethoxy-1-veratryl-2-methylnaphthalene (V), identical with the lead tetra-acetate dehydrogenation product of the racemate of conidendrin dimethyl ether.



(VIII.)



(IX.)



(X.)

In Part IX (J., 1937, 1646) veratryl γ-hydroxy-δ-veratrylbutyl ketone (IX; see this vol., p. 802) was converted into a compound for which structure (X; R = Me) was tentatively advanced : this suggestion has now been confirmed by an unambiguous synthesis. 6 : 7-Dimethoxy-1-veratrylnaphthalene-3-carboxylic acid (X; R = CO_2H) (J., 1935, 636) was converted into the *acid chloride* (X; R = COCl), which was reduced by Rosenmund's method to the *aldehyde* (X; R = CHO). The aldehyde gave amorphous products on attempted reduction by Clemmensen's method, but reduction to (X; R = Me) was effected by subjecting the *hydrazone* or *semicarbazone* to the Wolff–Kishner process. Demethylation occurred during the reaction, but subsequent methylation of the phenolic fraction with diazomethane gave small yields of 6 : 7-dimethoxy-1-veratryl-3-methylnaphthalene (X; R = Me), which was identical with the substance obtained as described in Part IX (*loc. cit.*). It is noteworthy that the conversion of (IX) into the naphthalene derivative (X; R = Me) is effected by the use of acidic cyclising agents and subsequent treatment with alkali, and dehydrogenating agents such as selenium, lead tetra-acetate, and palladium-black are not involved in the reaction.

Experimental.

Lactone of 6 : 7-*Dimethoxy*-1-*veratryl*-2-*hydroxymethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-3-*carboxylic Acid* (I; $R^1 = R^2$ = OMe).—The lactone of 6 : 7-dimethoxy-1-veratryl-2-hydroxymethylnaphthalene-3-carboxylic acid (II; R = OMe) (1 g.) (J., 1935, 1580) was refluxed with methyl alcohol (15 c.c.) and 10% potassium hydroxide solution (20 c.c.) until solution was complete. The alcohol was removed, water (30 c.c.) added, and the solution boiled for 6—7 hours during the gradual addition of 4% sodium amalgam (130 g.). The filtered solution was

acidified with dilute sulphuric acid, boiled for 1 hour, cooled, and extracted with chloroform. The extract, after being washed with sodium bicarbonate solution, was dried, and the solvent removed; the light brown residue (0·7 g.) crystallised from methyl alcohol (carbon) in colourless slender prisms (0·3 g.), m. p. 180° (Found: C, 69·1, 69·2; H, 6·3, 6·5. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·3%). A solution of bromine (0·8 c.c.) in 10% sodium hydroxide solution (20 c.c.) was added to a boiling solution of the lactone (I; $R^1 = R^2 = OMe$) (1 g.) in N/2-sodium hydroxide (20 c.c.) and dioxan (10 c.c.). After boiling for 3 hours, the dioxan was removed and the products were separated as described in a similar case (J., 1937, 391). The lactonic fraction crystallised from methyl alcohol (carbon) in stout rhombic prisms, m. p. 205—206° (Found: C, 65·8; H, 6·1. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%); the figures correspond to a hydroxy-substitution product of the lactone (I; $R^1 = R^2 = OMe$), but the product has not been fully examined. The acidic fraction on esterification yielded methyl 2-veratroylveratrate, m. p. 154—155°, which was identified by comparison with an authentic specimen, and a small amount of a *dimethyl* ester, which separated from a little methyl alcohol in colourless nodules, m. p. 148—149° (Found: C, 64·5; H, 6·6. $C_{24}H_{28}O_8$ requires C, 64·9; H, 6·4%).

6 : 7-*Dimethoxy*-1-*veratryl*-2-*methylnaphthalene* (V).—The above lactone (0·2 g.) and lead tetra-acetate (0·4 g.) were heated for ½ hour at 70—80° in glacial acetic acid (10 c.c.). Water was added; the product, isolated with chloroform and washed with sodium bicarbonate solution, was crystallised from methyl alcohol (carbon), and traces of lactonic matter were removed by boiling for 1 hour with 10% methyl-alcoholic potassium hydroxide and pouring into water. The *compound* (V), isolated with chloroform, separated from methyl alcohol–chloroform in stout prisms (0·09 g.), m. p. 141° (Found: C, 74·6; H, 6·8. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%).

Propioveratrone (VI; R = H).—The yields recorded by previous workers (Martegiani, *Gazzetta*, 1912, **42**, ii, 347; Johnson and Hodge, *J. Amer. Chem. Soc.*, 1913, **35**, 1022) were considerably improved by using nitrobenzene as solvent in the Friedel–Crafts reaction. Propionyl chloride (7 g.) was gradually added with cooling to a mixture of veratrole (12 g.) and aluminium chloride (16 g.) in nitrobenzene (40 c.c.). After 24 hours, dilute sulphuric acid was added, the nitrobenzene removed in steam, and the product isolated with ether and distilled. Propioveratrone, b. p. 137°/0·2 mm., crystallised from ether–light petroleum (1 : 5) in colourless cubes (12·5 g.), m. p. 59—60°. The semicarbazone separated from methyl alcohol in colourless prisms, m. p. 192—193° (Martegiani, *loc. cit.*, gives 190—192°).

α-Bromopropioveratrone (VI; R = Br).—Bromine (3·0 c.c.) in chloroform (9 c.c.) was gradually added to a solution of propioveratrone (11·6 g.) in chloroform (50 c.c.). After 4 hours, hydrogen bromide was removed in a stream of dry air, the chloroform was washed with sodium bicarbonate solution and dried, and the solvent removed. The residue, which solidified on trituration with ether, crystallised from ether–light petroleum (1 : 10) in long rectangular prisms (12 g.), m. p. 83—84° (Found: Br, 28·9. $C_{11}H_{13}O_3Br$ requires Br, 29·3%).

β-Veratroyl-n-*butyric acid* (VI; R = $CH_2 \cdot CO_2H$).—A solution of β-bromopropioveratrone (8·5 g.) in benzene (30 c.c.) was added to ethyl sodiomalonate (from 0·96 g. of sodium and 6·6 g. of ethyl malonate) in benzene (30 c.c.). After 3 hours' boiling, water was added, the benzene layer separated, and the solvent removed. The residual brown oil was boiled for 1 hour with 10% methyl-alcoholic potassium hydroxide (80 c.c.), the alcohol removed, a slight excess of dilute sulphuric acid added, and the product isolated with chloroform and heated at 180° for ½ hour. The crude *acid* (VI; R = $CH_2 \cdot CO_2H$) was taken up in sodium bicarbonate solution, recovered (6·0 g.), and crystallised from hot water (carbon), giving colourless prismatic plates, m. p. 129° (Found: C, 61·5, 61·6; H, 6·4, 6·5; equiv., 254. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%; equiv., 252).

Lactone of β-Veratroyl-α-veratrylidene-n-*butyric Acid* (VII).—A methyl-alcoholic solution of the above acid (VI; R = $CH_2 \cdot CO_2H$) (1·2 g.) was neutralised with sodium hydroxide and evaporated to dryness. The dry sodium salt, veratraldehyde (0·8 g.), and acetic anhydride (2 c.c.) were heated at 100° for 12 hours. After cooling, methyl alcohol was added and the product was collected, washed successively with water and a little methyl alcohol, and crystallised from methyl alcohol–chloroform; orange yellow prisms (1·0 g.), m. p. 183°, were obtained (Found: C, 69·4; H, 5·8. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%). This *lactone* was refluxed for ½ hour with a slight excess of sodium methoxide in methyl alcohol; water was added, and the alcohol removed. Acidification of the filtered solution yielded the crude acid (VII) as a white precipitate, m. p. 70—73°, which has not been crystallised. Attempts to cyclise this crude acid with methyl-alcoholic hydrogen chloride gave the yellow lactone, m. p. 183°.

6 : 7-*Dimethoxy*-1-*veratryl*-2-*methylnaphthalene*-3-*carboxylic Acid* (VIII; R = H).—This was

obtained in small yield by the action of cold acetic–hydrochloric acid on the crude acid described above, but better results were obtained by the following method. The crude acid (VII) (0·5 g.) was dissolved in ether (20 c.c.), dried with sodium sulphate, and treated with a solution of diazomethane (from 2 c.c. of nitrosomethylurethane) in ether (10 c.c.). After 4 hours, the solution was washed first with dilute hydrochloric acid and then with dilute sodium hydroxide solution, and dried, and the solvent removed. The residual oily methyl ester was refluxed for ½ hour with methyl-alcoholic hydrogen chloride (10 c.c.); *methyl* 6 : 7-*dimethoxy*-1-*veratryl*-2-*methylnaphthalene*-3-*carboxylate* (VIII; R = Me) separated on cooling and crystallised from methyl alcohol, containing a little chloroform, in cream-coloured needles (0·3 g.), m. p. 178° (Found : C, 69·7; H, 6·4. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·6%). Hydrolysis of this methyl ester with the calculated amount of methyl-alcoholic potassium hydroxide gave the *acid* (VIII; R = H), which separated from methyl alcohol–chloroform in colourless prisms, m. p. 252° (Found : C, 68·7; H, 6·0. $C_{22}H_{22}O_6$ requires C, 68·8; H, 5·8%). The acid (0·25 g.) was boiled for 2 hours with pure quinoline (2 c.c.) in the presence of a trace of copper powder. Ether was added, the copper removed by filtration, the filtrate washed several times with dilute hydrochloric acid and then with dilute sodium hydroxide solution, and the ether removed. The residue crystallised from methyl alcohol in stout prisms (0·19 g.), m. p. 140—141° (Found : C, 74·6; H, 6·7%), not depressed by 6 : 7-dimethoxy-1-veratryl-2-methylnaphthalene (V) obtained as described on p. 811.

6 : 7-*Dimethoxy*-1-*veratrylnaphthalene*-3-*carboxylic Acid Chloride* (X; R = COCl).—The acid (X; R = CO_2H) (1 g.) and thionyl chloride (2 c.c.) were refluxed for 1 hour. The excess of thionyl chloride was removed, the residue dissolved in benzene (10 c.c.) and filtered through a 3 cm. column of alumina, and the benzene evaporated. The *acid chloride* (X; R = COCl) (0·85 g.))separated from benzene in colourless needles, m. p. 183—184° (Found : C, 65·4; H, 5·1; Cl, 9·5. $C_{21}H_{19}O_5Cl$ requires C, 65·2; H, 4·9; Cl, 9·1%). The purification with alumina removes traces of sulphur compounds which otherwise inhibit the catalytic reduction described below.

6 : 7-*Dimethoxy*-1-*veratrylnaphthalene*-3-*aldehyde* (X; R = CHO).—A rapid stream of hydrogen was passed through a solution of the acid chloride (X; R = COCl) (0·85 g.) in boiling xylene (10 c.c.) containing 5% palladium–barium sulphate (0·5 g.). Estimation of the hydrogen chloride eliminated proved the reduction to be complete after 1 hour. The filtered solution was evaporated in a vacuum; the *aldehyde* crystallised from benzene in clumps of needles (0·65 g.), m. p. 163—164° (Found : C, 71·9; H, 5·5. $C_{21}H_{20}O_5$ requires C, 71·6; H, 5·7%). The *oxime*, prepared in alcoholic solution, crystallised from methyl alcohol in colourless rectangular prisms, m. p. 185° (Found : C, 68·7; H, 5·8. $C_{21}H_{21}O_5N$ requires C, 68·7; H, 5·7%). The *hydrazone*, obtained by refluxing for 12 hours an alcoholic solution of the aldehyde with excess of hydrazine hydrate, separated on cooling in rectangular prisms, which melted at 175—176°, resolidified, and melted again at 305—306° (Found : C, 68·8; H, 6·0. $C_{21}H_{22}O_4N_2$ requires C, 68·8; H, 6·0%). The *semicarbazone*, prepared in hot alcoholic solution, crystallised from alcohol in rosettes of colourless rectangular prisms, which melted at 223—224°, resolidified, and melted again at 308—309° (Found : C, 64·3; H, 5·4. $C_{22}H_{23}O_5N_3$ requires C, 64·5; H, 5·6%).

6 : 7-*Dimethoxy*-1-*veratryl*-3-*methylnaphthalene* (X; R = Me).—The hydrazone (0·4 g.) or semicarbazone (0·5 g.) described above was heated at 180° for 18 hours with a solution of sodium ethoxide (from 0·4 g. of sodium) in alcohol (18 c.c.). Water was added, neutral matter removed with chloroform, the alkaline solution acidified, and the crude phenol isolated with ether, dried and added to an ethereal solution of diazomethane (from 2·5 c.c. of nitrosomethylurethane). After 12 hours, the solution was washed successively with dilute hydrochloric acid and dilute sodium hydroxide solution, and the solvent removed. The residue was dissolved in a little alcohol and converted into the red picrate, which was collected and decomposed by shaking with dilute aqueous ammonia. The hydrocarbon, isolated with ether, was purified first by sublimation at 0·1 mm. and finally by crystallisation from light petroleum. 6 : 7-Dimethoxy-1-veratryl-3-methylnaphthalene (X; R = Me) was obtained in stout prisms (0·07 g.), m. p. 141° (Found : C, 74·6; H, 6·6%), not depressed by the specimen obtained previously (J., 1937, 1646). The *picrate*, prepared in alcoholic solution from (X; R = Me) obtained by either method, separated from alcohol in slender red needles, m. p. 133° (Found : C, 56·9; H, 4·1. $C_{21}H_{22}O_4,C_6H_3O_7N_3$ requires C, 57·1; H, 4·4%).

The following compounds were obtained during some preliminary experiments.

6 : 7-*Dimethoxy*-1-*veratryl*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid*.—Ethyl hydroxymethylenemethylsuccinate (Fichter and Rudin, *Ber.*, 1904, **37**, 1611) (5 g.) and veratrole (6 g.) in acetic acid (20 c.c.) were gradually added with shaking to an ice-cold mixture

of concentrated sulphuric acid (30 c.c.) and acetic acid (30 c.c.). After 12 hours, water was added and the product, isolated with chloroform, was hydrolysed by boiling with 10% methyl-alcoholic potassium hydroxide (50 c.c.) for 2 hours. The alcohol was removed, water (25 c.c.) added, and hydrolysis completed by boiling for a further 2 hours. After acidification, the product, isolated with chloroform, was refluxed with acetyl chloride (10 c.c.) for 1 hour, and the excess of the latter removed. The oily residue (4 g.), dissolved in nitrobenzene (10 c.c.), was added with shaking to an ice-cold solution of aluminium chloride (6 g.) in nitrobenzene (30 c.c.); after 12 hours, dilute hydrochloric acid was added, and the nitrobenzene removed in steam. Without purification the crude keto-acid (3·5 g.), isolated with chloroform, was reduced by boiling with amalgamated zinc (15 g.) and concentrated hydrochloric acid (20 c.c.) for 12 hours; 6 : 7-*dimethoxy*-1-*veratryl*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic acid*, isolated with chloroform, separated from benzene in colourless nodules (0·5 g.), m. p. 220—222° (Found: C, 68·3; H, 7·0. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7%). Attempts to decarboxylate this acid were unsuccessful.

6 : 7-*Dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-3-*carboxylic Acid*.—4% Sodium amalgam (120 g.) was gradually added to a boiling solution of 6 : 7-dimethoxy-1-veratryl-naphthalene-3-carboxylic acid (1 g.) (J., 1935, 640) in 10% potassium hydroxide solution (30 c.c.). After 6 hours, the filtered solution was acidified, and the product collected. The *acid* crystallised from methyl alcohol in colourless needles (0·65 g.), m. p. 133°, containing one molecule of water of crystallisation (Found: C, 64·7; H, 6·5. $C_{21}H_{24}O_6,H_2O$ requires C, 64·6; H, 6·7%). The anhydrous acid crystallised from benzene in small needles, m. p. 170° (Found: C, 67·7; H, 6·5. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%). The *methyl* ester, prepared by the action of methyl-alcoholic hydrogen chloride, separated from methyl alcohol in rosettes of slender needles, m. p. 143—144° (Found: C, 68·1; H, 6·5. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7%).

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