316. *The Constituents of Natural Phenolic Resins. Part XII. The Action of Selenium on Lignans.*

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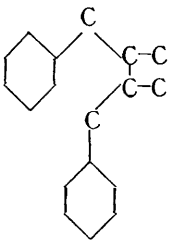
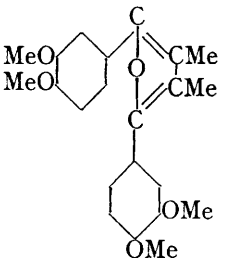
The action of selenium on a number of lignans has been examined. The dimethyl ethers of olivil, *iso*olivil, lariciresinol, and *iso*lariciresinol give dehydroguaiaretic acid dimethyl ether, but eudesmin and the dimethyl ethers of pinoresinol and *epi*pinoresinol yield 2 : 5-*diveratryl*-3 : 4-*dimethylfuran* (II). The structure of this has been established by synthesis, and experimental support has therefore been obtained for the suggestion that pinoresinol contains the carbon framework (I).

A transformation analogous to the olivil–*iso*olivil change has been realised by the conversion of the *diol* (VI), obtained by reducing the *diketone* (III), into the *naphthalene* derivative (VII), and the constitutions of olivil and pinoresinol are discussed in view of the contrasting behaviour of these substances towards acid and selenium treatment.

THE suggestion that members of the lignan family contain the characteristic carbon skeleton (I) has received experimental confirmation in all known representatives of the class with the exception of pinoresinol and eudesmin, and the methylenedioxy-analogues sesamin and asarinin. During the course of the present research experimental evidence has been obtained that pinoresinol and eudesmin conform to the general type (I).



(I.)



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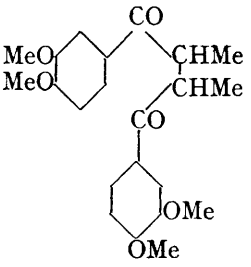


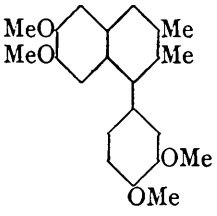
(III.)

When *d*-pinoresinol dimethyl ether (*d*-eudesmin) or *l*-eudesmin was heated with selenium at 280—300°, a 3% yield of a tetramethoxy-compound, $C_{22}H_{24}O_5$, m. p. 170°, was obtained. This compound was oxidised to veratric acid by means of chromic acid in acetic acid solution and it gave 3 : 4-dinitroveratrole in yields exceeding 50% of the theoretical on heating with concentrated nitric acid. The stability of the compound towards acids, alkalis, methylmagnesium iodide and carbonyl reagents indicated the ethereal nature of the fifth oxygen atom, and structure (II), consistent with the properties of the substance, has been confirmed by synthesis.

Preliminary attempts to prepare β*γ-diveratroylbutane* (III) by the action of αβ-dimethylsuccinyl chloride on veratrole, or by the action of iodine on the sodio-derivative of *ethyl*

α-veratroylpropionate were unsuccessful. The diketone (III) was eventually obtained by heating β-bromopropioveratrone with copper powder in boiling xylene solution and on warming with methyl-alcoholic hydrogen chloride it was smoothly converted into 2 : 5-*diveratryl*-3 : 4-*dimethylfuran* (II), identical with the compound, $C_{22}H_{24}O_5$, obtained from *d*-pinoresinol dimethyl ether or *l*-eudesmin.

In the absence of profound structural alteration during the selenium treatment, the above observation provides the first experimental evidence that the constitutions of pinoresinol and eudesmin are based on type (I), and an examination of the behaviour of other lignans towards selenium has led to interesting results. Recognisable products were not obtained from matairesinol dimethyl ether, hinokinin or cubebin, the earlier observation (Haworth and Sheldrick, J., 1935, 644) that conidendrin dimethyl ether is converted without structural alteration into the lactone of 6 : 7-dimethoxy-1-veratryl-2-hydroxymethylnaphthalene-3-carboxylic acid has been confirmed, and dehydroguaiaretic acid dimethyl ether (IV) has been isolated in 8% yields by the action of selenium on the dimethyl ethers of lariciresinol, *iso*lariciresinol, olivil, and *iso*olivil. The conversion of lariciresinol and olivil into conidendrin dimethyl ether (Haworth and Kelly, J., 1937, 384) and the lactone of 6 : 7-dimethoxy-1-veratryl-3-hydroxymethylnaphthalene-2-carboxylic acid (Dreyfuss, *Gazzetta*, 1936, **66**, 96; Haworth and Sheldrick, *loc. cit.*) respectively establishes the constitutional framework (I) for these substances and it will be observed that in all these cases the original carbon skeleton of the lignan is retained in its selenium dehydrogenation product. Consequently the isolation of the furan derivative (II) from pinoresinol and eudesmin constitutes strong evidence that these lignans conform to the general type (I), and structure (V) suggested for sesamin (Böeseken and Cohen, *Biochem. Z.*, 1928, **197**, 1; see also Cohen, *Rec. Trav. chim.*, 1938, **57**, 653) can be excluded.



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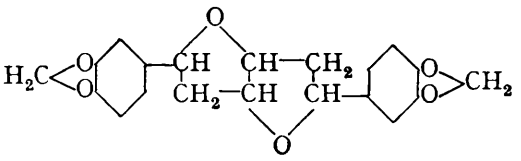

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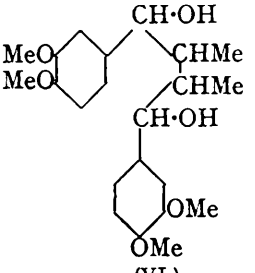
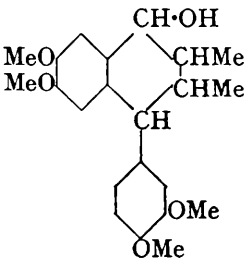


(VI.)

The methods of preparation of the furan derivative (II) show that this substance is stable towards selenium or acid treatment, but *αδ-diveratryl-βγ-dimethylbutane-αδ-diol* (VI), obtained as an oil (possibly containing a mixture of stereoisomerides) by reducing *βγ*-diveratroylbutane (III) with sodium and alcohol, was readily converted by methyl-alcoholic hydrogen chloride or 50% acetic acid into 4-*hydroxy*-1-*veratryl*-6 : 7-*dimethoxy*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII). This substance (VII) has not been



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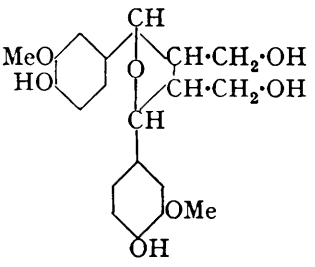
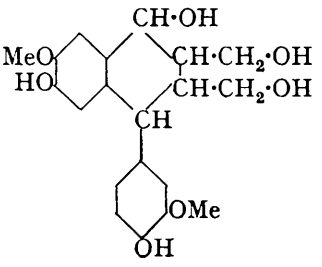


(VIII.)

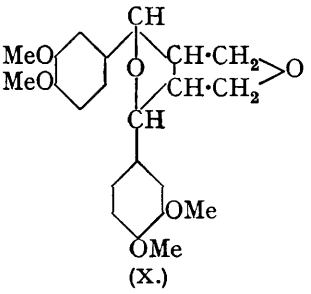


(IX.)

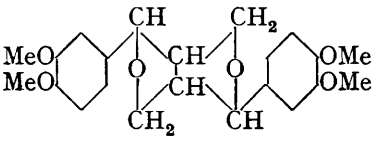
obtained crystalline, but Zerewitinoff determinations show the presence of a hydroxyl group, and it was converted into dehydroguaiaretic acid dimethyl ether (IV) on heating with selenium. The naphthalene structure (VII) is therefore preferred to the isomeric

tetrahydrofuran structure, and the facile formation of (VII) supports the Vanzetti formula (VIII) for olivil and provides the first experimental demonstration of the conversion of a 2 : 5-diveratryltetrahydrofuran (or the diol equivalent) into the isomeric tetrahydronaphthalene structure as postulated by Vanzetti and Dreyfuss (*Gazzetta*, 1934, **64**, 381) for the conversion of olivil (VIII) into *iso*olivil (IX).

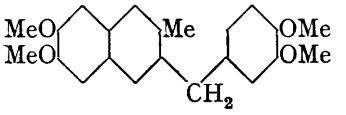
Of the two formulæ (X) and (XI) advanced by Erdtman (*Annalen*, 1935, **516**, 162; *Svensk Kem. Tids.*, 1936, **48**, 230, 236) for pinoresinol, the latter was preferred because the anhydro-olivil structure (X) did not account for the failure to convert pinoresinol into 1-phenylnaphthalene derivatives. Huang-Minlon (*Ber.*, 1937, **70**, 951) and Kaku and Ri (*J. Pharm. Soc. Japan*, 1938, **57**, 289) on the other hand favour formula (X) and suggest that certain comparatively high-melting substances, obtained in small yield by the action of acids on asarinin and eudesmin, may prove to be phenylnaphthalene derivatives. No evidence in support of the structure of these compounds has yet been advanced and, as 1-phenylnaphthalene derivatives may be accommodated on the basis of structure (XI), their isolation in small yield would not enable a decision to be made between the two structures (X) and (XI). Olivil (VIII) is resinified by the action of mineral acids, but it is converted into *iso*olivil (IX) under the influence of aqueous organic acids. Kaku and Ri (*loc. cit.*) have shown that pinoresinol dimethyl ether is partly converted into the diastereoisomeride, *epi*pinoresinol dimethyl ether, by the action of alcoholic hydrogen chloride, and it has now been shown that the same equilibration is effected by 50% acetic acid, under conditions identical with those employed by Vanzetti and Dreyfuss (*Gazzetta*, 1938, **68**, 87) for the conversion of olivil dimethyl ether into *iso*olivil dimethyl ether. The anhydro-olivil formula (X) is inconsistent with this marked contrast between the facile naphthalene formation from olivil and the resistance to cyclisation exhibited by pinoresinol dimethyl ether under similar acidic conditions or selenium treatment, and on these grounds, as well as for biogenetic and stereochemical reasons, the alternative formula (XI) for pinoresinol dimethyl ether is more acceptable.



(X.)

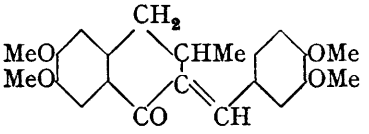


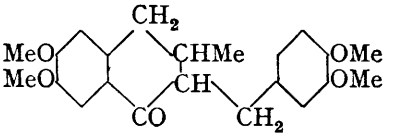
(XI.)



(XII.)

The production of 2 : 5-diveratryl-3 : 4-dimethylfuran (II) from pinoresinol dimethyl ether was accompanied by traces of impurity, which were eventually removed by the method described in the experimental section. This impurity, which was unsuspected for some time, did not influence the melting point, but it resulted in high analytical values, approximating to $C_{22}H_{24}O_4$, and the 6 : 7-*dimethoxy*-2-(3′ : 4′-*dimethoxybenzyl*)-3-*methyl naphthalene* (XII) structure, which might have arisen from (XI) by cyclisation, was excluded by an independent synthesis. 1-Keto-6 : 7-dimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Atkinson and Haworth, this vol., p. 807) reacted with veratraldehyde in

(XIII.)




(XIV.)

presence of hydrogen chloride to give 1-*keto*-6 : 7-*dimethoxy*-2-*veratrylidene*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII), which was reduced by hydrogen in the presence of an active palladium–carbon catalyst to 1-*keto*-6 : 7-*dimethoxy*-2-(3′ : 4′-*dimethoxybenzyl*)-

3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (XIV). Clemmensen reduction of (XIV) gave an oil which yielded the naphthalene derivative (XII), m. p. 115—116°, on dehydrogenation with selenium.

Experimental.

Reactions with Selenium.—The following method was adopted. The lignan (0·2 g.) and selenium (0·2 g.) were heated at 270—280° for 24 hours and the product was extracted with hot chloroform. The chloroform was removed, ether added, the filtered solution evaporated, and the residue distilled over sodium at 1 mm. The distillate solidified on trituration with methyl alcohol. The addition of *p-cyclo*hexylphenol (compare Thiele and Trautmann, *Ber.*, 1935, **68**, 2245) to the dehydrogenation mixture did not improve the yields.

Dehydroguaiaretic acid dimethyl ether (IV), obtained in 8% yield from the dimethyl ether of olivil, *iso*olivil, lariciresinol or *iso*lariciresinol, crystallised from alcohol or acetic acid in colourless plates, m. p. 178—179° (Found : C, 74·9; H, 6·9. Calc. for $C_{22}H_{24}O_4$: C, 75·0 : H, 6·8%), which gave no depression in m. p. when mixed with an authentic specimen (Haworth, Mavin, and Sheldrick, J., 1934, 1428).

2 : 5-*Diveratryl*-3 : 4-*dimethylfuran* (II) was obtained in 3% yield from *d*-pinoresinol dimethyl ether, *d-epi*pinoresinol dimethyl ether or *l*-eudesmin, and purified by crystallisation from methyl alcohol–chloroform and then from acetic acid. The colourless prisms, m. p. 169—170° [Found : C, 72·5; H, 6·9; OMe, 34·2%; *M* (Rast), 352], contained an impurity which was removed by washing with ether and filtration of a benzene solution of the residual crystals through a layer of alumina. The residue from the benzene filtrate separated from acetic acid in colourless prisms, m. p. 169—170° [Found : C, 71·7; H, 6·5; OMe, 34·1; *M* (Rast), 360. $C_{22}H_{24}O_5$ requires C, 71·7; H, 6·5; OMe, 33·7%; *M*, 368], depressed to 150° by dehydroguaiaretic acid dimethyl ether but unchanged by a synthetic specimen (see below) of the furan (II). 2 : 5-Diveratryl-3 : 4-dimethylfuran (II) was sparingly soluble in alcohol or ether, but soluble in chloroform or benzene, and the colourless solutions exhibited a marked blue fluorescence. A solution of chromic acid (0·5 g.) in acetic acid (5 c.c.) was gradually added to a solution of the furan (II) (0·5 g.) in acetic acid (10 c.c.) at 90°. After 1 hour the mixture was diluted with water; the product, isolated with ether, crystallised from hot water in colourless needles (0·1 g.), m. p. 180°, which were identified as veratric acid. The furan (II) (0·5 g.) was boiled with concentrated nitric acid (5 c.c.) for 5 minutes, and water added; the product, isolated with ether and washed with sodium bicarbonate solution, separated from a little methyl alcohol in pale yellow needles (0·3 g.), m. p. 127—129°, which were identified as 4 : 5-dinitroveratrole.

Ethyl α-Veratroylpropionate.—A solution of sodium ethoxide (from sodium, 2·3 g.) in alcohol (30 c.c.) was added to a solution of ethyl veratroylacetate (26 g.) in alcohol (50 c.c.). Methyl iodide (15 g.) was gradually introduced, and the mixture heated on the water-bath for 1·5 hours. Most of the alcohol was removed, water added, and the product isolated with ether. *Ethyl α-veratroylpropionate* (22 g.) was obtained as a colourless oil, b. p. 190—195°/1 mm., which gradually solidified and then crystallised from ether–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 52—54° (Found : C, 63·4; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%), which slowly gave a green colour in the ferric chloride test.

βγ-Diveratroylbutane (III).—β-Bromopropioveratrone (1 g.) and freshly precipitated copper powder (1·0 g.) were refluxed in xylene (10 c.c.) for 24 hours. The filtered solution was evaporated under reduced pressure; crystallisation of the residual oil from methyl alcohol yielded *βγ-diveratroylbutane* (III) in colourless rhombic prisms (0·2 g.), m. p. 189—190° (Found : C, 68·5; H, 6·7. $C_{22}H_{26}O_6$ requires C, 68·3; H, 6·8%). When this diketone (III) (0·25 g.) was boiled with methyl-alcoholic hydrogen chloride (5 c.c.), crystals of 2 : 5-diveratryl-3 : 4-dimethylfuran (II) rapidly separated. After 1 hour these were collected and recrystallised from acetic acid, forming colourless prisms (0·2 g.), m. p. 169—170° (Found : C, 71·7; H, 6·5%), which gave no depression in m. p. when mixed with a specimen obtained by the action of selenium on pinoresinol dimethyl ether.

αδ-Diveratryl-βγ-dimethylbutane-αδ-diol (VI).—A boiling solution of βγ-diveratroylbutane (III) (0·5 g.) in boiling alcohol (100 c.c.) was gradually poured upon molten sodium (4 g.), and after 2 hours' refluxing water was added, most of the alcohol removed, and the product extracted with ether. The extract yielded an oil, which was taken up in ether, filtered, and the solvent removed. The residual *diol* (VI) (0·4 g.) was an oil, b. p. 180—185°/1 mm. (Found : C, 67·5; H, 7·9. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7%).

4 - *Hydroxy* - 1 - *veratryl* - 6 : 7 - *dimethoxy* - 2 : 3 - *dimethyl* - 1 : 2 : 3 : 4 - *tetrahydronaphthalene* (VII).—The diol (VI) (0·4 g.) was (*a*) refluxed with methyl-alcoholic hydrogen chloride (15

c.c.) for ½ hour or (*b*) heated with 50% acetic acid (15 c.c.) on the water-bath for 8 hours. After dilution with water, the product, isolated with ether and washed with sodium hydroxide solution, was refluxed with 10% sodium hydroxide solution (10 c.c.) and methyl alcohol (5 c.c.) for 1 hour in order to hydrolyse chloro- or acetoxy-derivatives, and recovered with ether. The *naphthalene* derivative (VII) (0·3 g.) was obtained as an oil, b. p. 178—182°/1 mm. [Found: C, 70·7; H, 7·7; OH(Zerewitinoff), 5·1. $C_{22}H_{28}O_5$ requires C, 71·0; H, 7·6; OH, 4·6%]. This oil was dehydrogenated with selenium in the usual way; dehydroguaiaretic acid dimethyl ether (IV) was obtained in 70% yield.

1 - *Keto* - 6 : 7 - *dimethoxy* - 2 - *veratrylidene* - 3 - *methyl* - 1 : 2 : 3 : 4 - *tetrahydronaphthalene* (XIII).—An ice-cold acetic acid solution (4 c.c.) of veratraldehyde (1·5 g.) and 1-keto-6 : 7-dimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (1·6 g.) was saturated with dry hydrogen chloride. After 12 hours water was added to the crimson solution; the *product*, isolated with chloroform and washed with sodium bicarbonate solution, crystallised from methyl alcohol in colourless plates (2 g.), m. p. 146° (Found: C, 71·7; H, 6·5. $C_{22}H_{24}O_5$ requires C, 71·8; H, 6·6%), which gave a yellow solution in acetic acid.

1 - *Keto* - 6 : 7 - *dimethoxy* - 2 - (3′ : 4′ - *dimethoxybenzyl*) - 3 - *methyl* - 1 : 2 : 3 : 4 - *tetrahydronaphthalene* (XIV), obtained in 80% yield by reducing (XIII) in acetic acid (10 parts) by hydrogen in the presence of a freshly prepared palladium–charcoal catalyst, separated from methyl alcohol in stout prisms, m. p. 128—129° (Found: C, 71·3; H, 6·9. $C_{22}H_{26}O_5$ requires C, 71·3; H, 7·0%), which gave a colourless solution in acetic acid.

6 : 7-*Dimethoxy*-2-(3′ : 4′-*dimethoxybenzyl*)-3-*methylnaphthalene* (XII).—The above ketone (XIV) (2 g.) was refluxed for 12 hours with amalgamated zinc (10 g.) and concentrated hydrochloric acid (15 c.c.). The resultant oil, isolated with ether and distilled at 1 mm., was heated with selenium (2 g.) at 280° for 24 hours; the *product*, isolated in the usual manner, crystallised from ether–light petroleum (b. p. 60—80°) or methyl alcohol in colourless plates (0·9 g.), m. p. 115—116° (Found: C, 75·2; H, 6·7. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·9%).

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