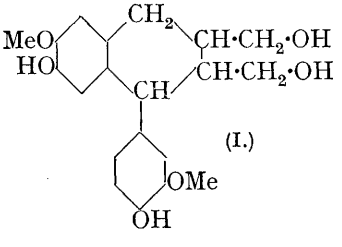
346. *The Constitution of Natural Phenolic Resins. Part IX. The Structure of Lariciresinol and Preliminary Experiments on the Synthesis of Lignandiols.**

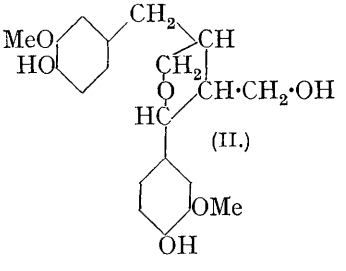
By Robert D. Haworth and William Kelly.

The structures suggested in Part VIII (this vol., p. 384) for lariciresinol and *iso*lariciresinol have been confirmed by new observations. Experiments aiming at the synthesis of lignandiols have, so far, been unsuccessful, but a number of the preliminary experiments, including a new method for the preparation of aryltetronic acids, are now described.

In Part VIII (this vol., p. 384), structure (I) was advanced for *iso*lariciresinol and of the two alternative formulæ for lariciresinol, (II) was preferred to (III). The *iso*lariciresinol formula (I) has now been confirmed by dehydrogenation of the dimethyl ether with lead tetra-acetate, which yielded the optically inactive *dehydro*-derivative (IV). The structure (II) for lariciresinol was favoured, first because it rendered the lariciresinol–*iso*lariciresinol change analogous to the olivil–*iso*olivil conversion, and secondly because lariciresinol dimethyl ether behaved as a primary alcohol in reacting with phthalic anhydride in boiling benzene solution. The product was an acidic oil and renewed efforts to obtain this in a crystalline state or to prepare crystalline *p*-nitrobenzoyl or *p*-phenylphenacyl derivatives have been unsuccessful.



(I.)



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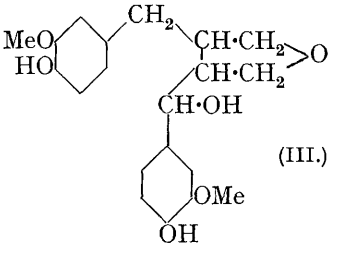


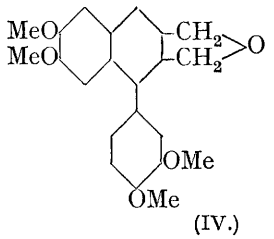
(III.)

A crystalline *triphenylmethyl ether* of lariciresinol dimethyl ether has been prepared by treatment with triphenylmethyl chloride in pyridine solution. Although there are indications that triphenylmethyl chloride may attack the secondary alcoholic group of small molecules such as *iso*propyl alcohol (Helferich, Spiedel, and Toldte, *Ber.*, 1923, **56**, 766), there is evidence (Josephson, *Annalen*, 1929, **472**, 230) suggesting that this reagent combines with the primary alcoholic group only in more complex molecules. When the triphenylmethyl ether of lariciresinol dimethyl ether is boiled with 80% formic acid, the triphenylmethyl group is eliminated, cyclisation occurs, and the *diformyl* derivative of *iso*lariciresinol dimethyl ether is produced. The lariciresinol–*iso*lariciresinol change is difficult to explain on the basis of formula (III) for lariciresinol; the formation of anhydro-*iso*lariciresinol derivatives would be anticipated and subsequent hydration to the diol is improbable because it has been shown that anhydro*iso*lariciresinol dimethyl ether is not attacked under the conditions of the isomeric change.

* The generic term lignan has been introduced (*Ann. Reports*, 1936, **33**, 267) to include all members of the bis-coniferyl family.

Methods are now available for the preparation of lactones of the lignan series, but no attempts to synthesise other types have been recorded. Some experiments in this direction have been initiated and the results of the preliminaries are now reported. From a stereochemical point of view, the most attractive route to the lignandiols of types (I) and (V) involves the reduction of lactones of the conidendrin or matairesinol types, but efforts to reduce the ethers of these lactones by means of sodium in ethyl or amyl alcohol, or by the use of aluminium amalgam, have so far been unsuccessful.

Attempts have been made to employ αβ-dibenzoylethane or its derivatives such as ethyl αβ-dibenzoylpropionate (VI) (Kapf and Paal, *Ber.*, 1888, **21**, 1487) and ethyl αβ-dibenzoylsuccinate (VII) (Knorr, *Annalen*, 1896, **293**, 74; 1899, **306**, 389). The methylene



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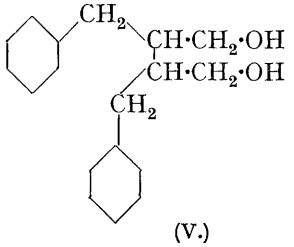

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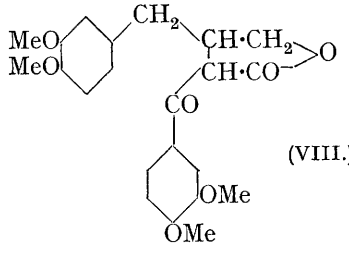
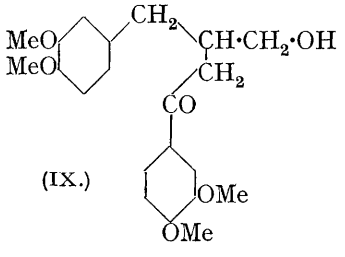


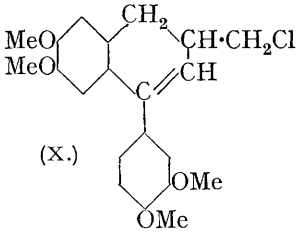
(VIII.)

groups of αβ-dibenzoylethane proved surprisingly unreactive and no condensation occurred with formalin, ethyl formate, or ethyl oxalate. The esters (VI) and (VII) were similarly unreactive, although in the presence of alkaline condensing agents the ester (VI) yielded the lactone of γ-hydroxy-α-benzoyl-γ-phenyl-Δ^{β}-butenoic acid (Kapf and Paal, *loc. cit.*; Borsche and Fels, *Ber.*, 1906, **39**, 1813), whilst in the presence of formalin and a slight excess of alkali, ester (VII) was converted into benzoic acid. The ester (VII) is readily converted by concentrated sulphuric acid into ethyl 2 : 5-diphenylfuran-3 : 4-dicarboxylate (Perkin, J., 1885, **47**, 271), but reduction of either the furan nucleus or the ester groups could not be effected. Similar behaviour has been observed with *αβ-diveratroylethane* and *ethyl αβ-diveratroylpropionate*.

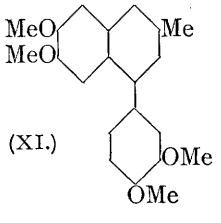
Reaction between *O*-methyleugenol oxide and reactive methylene groups has previously been observed with malonic, acetoacetic, and cyanoacetic esters, but no reaction has been detected with acetoveratrone, veratroylacetonitrile, ethyl acetylpyruvate, or ethyl veratroylpyruvate. The possibility of utilising α-veratroyl-β-(3′ : 4′-dimethoxybenzyl)butyrolactone (VIII) (J., 1936, 725) has been explored. In cold alkaline solution this lactone (VIII) and formalin yielded veratric acid and a water-soluble product which has not been identified. On the other hand, warm dilute alkali converts (VIII) into *δ-keto-β-hydroxymethyl-αδ-diveratrylbutane* (IX), and a similar ketone has been prepared from the



(IX.)



(X.)

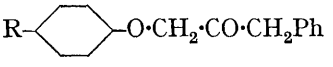


(XI.)

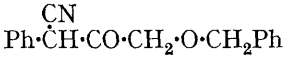
methylenedioxy-analogue of (VIII) (J., 1936, 747). It has also been observed that benzoylacetone and benzoylacetaldehyde are readily converted into benzoic acid in the presence of cold alkali and formalin, but in the absence of the formalin, acetophenone is the main product of the hydrolysis. It is probable that in all these cases the formalin condenses with the methylene group and facilitates acid hydrolysis in the product (Dieckmann, *Ber.*, 1900, **33**, 2670).

The action of a mixture of acetic and hydrochloric acids on (IX) resulted in cyclisation to 6 : 7-*dimethoxy*-1-*veratryl*-3-*chloromethyl*-3 : 4-*dihydronaphthalene* (X), which, when warmed

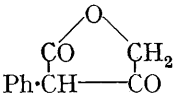
with methyl-alcoholic potassium hydroxide, was converted into a compound, probably 6 : 7-*dimethoxy*-1-*veratryl*-3-*methylnaphthalene* (XI) : a confirmatory synthesis is in progress. The conversion of (X) into (XI) involves elimination of hydrogen chloride and an isomeric change of the eugenol–*iso*eugenol type, which is doubtless facilitated by the aromatic condition of (XI). Attempts to obtain crystalline products by the action of formalin and alkalis on (IX) have been unsuccessful; reaction occurs, but treatment of the amorphous product with acetic and hydrochloric acids has not yielded recognisable products.



(XII.)



(XIII.)



(XIV.)

A method for the synthesis of aryltetronic acids has been found during experiments aiming at the preparation of derivatives of γ-hydroxy-β-keto-α-phenylpropane, by using reactions analogous to those employed by Pfeiffer and Willems (*Ber.*, 1929, **62**, 1242) in the preparation of β-keto-γ-phenoxy-α-phenylpropane (XII; R = H). The conditions necessary for the removal of the phenoxy-group rendered this compound unsuitable for our purpose, and attempts to utilise the *p*-nitrophenoxy-derivative (XII; R = NO_2) were abandoned because the yield of the condensation product of phenylacetonitrile and methyl *p*-nitrophenoxyacetate was small. Protection with the benzyloxy-group was therefore examined. Good yields of β-*keto*-α-*cyano*-γ-*benzyloxy*-α-*phenylpropane* (XIII) were obtained from phenylacetonitrile and methyl benzyloxyacetate, but attempts to hydrolyse the nitrile resulted in elimination of the benzyl group with the formation of phenyltetronic acid (XIV). The reaction appears to be of wide application and *veratryl-* and *piperonyl-tetronic acids* have been prepared. Phenyltetronic acid (XIV) may be converted into phenylacetylcarbinol, or a tautomer (see Danilow and Danilowa, *Ber.*, 1930, **63**, 2765), by heating with water at 200°, but the yield is poor and so far similar conversions have not been realised with the veratryl and piperonyl analogues.

Experimental.

Dehydroanhydroisolariciresinol Dimethyl Ether (IV).—Anhydro*iso*lariciresinol dimethyl ether (0·2 g.) and lead tetra-acetate (0·5 g.) were heated at 70—80° for 45 minutes. After dilution with water, the product was extracted with chloroform and washed successively with water and sodium hydroxide solution, and the solvent removed. The residue was refluxed with 5% alcoholic potassium hydroxide (5 c.c.) for 1 hour, the alcohol removed, and water added. The *product*, isolated with chloroform, crystallised from chloroform–methyl alcohol in stout rhombic prisms (0·07 g.), m. p. 201—202° (Found : C, 71·9; H, 6·4. $C_{22}H_{22}O_5$ requires C, 72·1; H, 6·1%). The alcoholic potassium hydroxide treatment was necessary to remove traces of lactonic or acidic products, which were recovered by acidification of the alkaline liquors but have not been investigated.

Triphenylmethyl Ether of Lariciresinol Dimethyl Ether.—Lariciresinol dimethyl ether (2 g.) and triphenylmethyl chloride (1·6 g.) were heated in pyridine (5 c.c.) at 70° for 4 hours. After addition of water, the product was isolated with ether; it crystallised from methyl alcohol in colourless rectangular prisms (2·5 g.), m. p. 134—135° (Found : C, 77·9; H, 6·6. $C_{41}H_{42}O_6$ requires C, 78·1; H, 6·7%). Under similar conditions *iso*lariciresinol dimethyl ether gave a semi-solid unrecognisable product. The *triphenylmethyl ether*, m. p. 134° (0·5 g.), was boiled for 15 minutes with 80% formic acid and cooled, and triphenylcarbinol, m. p. 162°, collected. The filtrate was diluted with water and extracted with ether, and the extract washed with sodium bicarbonate solution, dried, and concentrated; the *diformyl* derivative of *iso*lariciresinol dimethyl ether separated in slender needles, m. p. 102—103° (Found : C, 64·5; H, 6·3; CHO, by hydrolysis and back titration, 13·1. $C_{24}H_{28}O_8$ requires C, 64·8; H, 6·3; 2CHO, 13·0%). Hydrolysis of this diformyl derivative with sodium hydroxide gave *iso*lariciresinol dimethyl ether, m. p. 168°, which could be reconverted into the diformyl derivative by heating with formic acid as described above.

Ethyl αβ-*Diveratroylpropionate.*—ω-Bromoacetoveratrone (5·3 g.) was added to ethyl sodioveratroylacetate [prepared from the ester (5 g.), m. p. 37—38° (compare Appel, Baker, Hagenbach, and Robinson, this vol., p. 742), and sodium ethoxide (0·45 g.)] in dry ether (50

c.c.). After 24 hours, water was added, the ethereal layer separated, and the solvent removed. The residue crystallised from methyl alcohol in small rectangular prisms (5·7 g.), m. p. 110—111° (Found: C, 64·3; H, 6·0. $C_{23}H_{26}O_8$ requires C, 64·2; H, 6·1%).

Lactone of γ-Hydroxy-α-veratroyl-γ-veratryl-Δ$^{\beta}$-butenoic Acid.—Ethyl αβ-diveratroylpropionate (0·2 g.) and 10% methyl-alcoholic potassium hydroxide (10 c.c.) were boiled for ½ hour. The yellow *potassium* salt was collected, washed with methyl alcohol, dissolved in boiling water, and acidified. The precipitate crystallised from alcohol–chloroform in yellow prisms, m. p. 155—156° (Found: C, 65·4; H, 5·3. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2%).

αβ-Diveratroylethane.—Ethyl αβ-diveratroylpropionate (0·2 g.) was dissolved in methyl alcohol (0·2 c.c.) and water (0·5 c.c.); N/10-sodium hydroxide (1 c.c.) was added drop by drop to the boiling solution, which turned yellow and deposited colourless needles. After 5 minutes, the crystals were collected and recrystallised from chloroform–alcohol, forming needles (0·15 g.), m. p. 180—181° (Found: C, 67·0; H, 6·2. $C_{21}H_{22}O_6$ requires C, 67·0; H, 6·2%).

2 : 5-*Diveratrylfuran.*—This was prepared in 90% yield by boiling αβ-diveratroylethane with methyl-alcoholic hydrogen chloride (10 parts) for ½ hour; it separated from chloroform–methyl alcohol in slender prisms, m. p. 154—155° (Found: C, 70·8; H, 6·0. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%). The insolubility of this *compound* in sodium hydroxide and the negative ferric test exclude the isomeric 6 : 7-dimethoxy-4-veratryl-1-naphthol structure.

Ethyl Veratroylpyruvate.—Ethyl oxalate (1·6 g.) was added with ice cooling to a mixture of acetoveratrone (2 g.) and potassium ethoxide (from 0·45 g. of potassium) in ether (25 c.c.). After 24 hours, water was added, the aqueous layer acidified, and the precipitate crystallised from methyl alcohol; yellow prisms (1·8 g.), m. p. 104—105° (Found: C, 59·9; H, 5·8. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%), were obtained which gave a violet ferric test. Hydrolysis with the calculated quantity of warm 5% potassium hydroxide solution yielded the *acid*, which separated from methyl alcohol in slender prisms, m. p. 192—193° (decomp.) (Found: C, 57·0; H, 4·6. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%).

Action of Formaldehyde on α-Veratroyl-β-(3′ : 4′-dimethoxybenzyl)butyrolactone (VIII).—The lactone (VIII) (2·0 g.) was dissolved in 2% sodium hydroxide solution (40 c.c.), and 20% formalin (0·8 g.) added. After 3 days, the solution was acidified and extracted with chloroform; the extract yielded veratric acid (0·75 g.), m. p. 180°. The aqueous liquors gave only an oil.

δ-Keto-β-hydroxymethyl-αδ-diveratroylpropane (IX).—The lactone (VIII) (0·5 g.) was boiled with 2% sodium hydroxide solution (20 c.c.) for 2 hours. The oil which gradually separated, and solidified on cooling, was collected; it crystallised from methyl alcohol–ether in slender needles, m. p. 98—99° (Found: C, 67·5; H, 6·8. $C_{21}H_{26}O_6$ requires C, 67·3; H, 6·9%). The *bismethylenedioxy*-analogue of (IX), prepared similarly, crystallised from methyl alcohol in noodles, m. p. 103 104° (Found: C, 66·6; H, 5·3. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%), and gave an *oxime*, which separated from methyl alcohol in colourless needles, m. p. 139—140° (Found: C, 64·1; H, 5·5. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·4%). These compounds were first prepared in collaboration with Dr. T. Richardson.

6 : 7-*Dimethoxy*-1-*veratryl*-3-*chloromethyl*-3 : 4-*dihydronaphthalene* (X).—Attempts to cyclise the ketone (IX) with methyl-alcoholic hydrogen chloride gave unrecognisable products. The ketone (IX) (1 g.) was dissolved in acetic acid (3 c.c.), and concentrated hydrochloric acid (6 c.c.) added. After 24 hours, the crimson solution was diluted with water and extracted with chloroform. The extract was washed successively with water and sodium bicarbonate solution, the solvent removed, and the residue crystallised from methyl alcohol; colourless rectangular prisms, m. p. 108—109° (Found: C, 67·5; H, 6·1. $C_{21}H_{23}O_4Cl$ requires C, 67·3; H, 6·3%), were obtained.

6 : 7-*Dimethoxy*-1-*veratryl*-3-*methylnaphthalene* (XI).—The chloro-compound (X) (0·1 g.) was refluxed with 5% methyl-alcoholic potassium hydroxide (10 c.c.) for 1 hour. The alcohol was removed, and water added; the product, isolated with ether, crystallised from methyl alcohol in well-formed prisms, m. p. 140° (Found: C, 74·4; H, 6·5. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·6%). The *compound* (XI) can also be purified by sublimation at 0·1 mm. (bath 200—220°) or by crystallisation from light petroleum (b. p. 60—80°).

β-*Keto-α-cyano-γ-p-nitrophenoxy-α-phenylpropane* (XII; R = NO_2).—A solution of ethyl *p*-nitrophenoxyacetate (2 g.) (Minton and Stephen, J., 1922, **121**, 1591) and phenylacetonitrile (1·2 g.) in benzene (5 c.c.) was added to a suspension of potassium ethoxide (from potassium, 0·36 g.) in benzene (20 c.c.). After boiling for 3 hours, the mixture was diluted with water, the alkaline layer acidified, and the product extracted with ether. Removal of the solvent and crystallisation of the residue from methyl alcohol gave cream-coloured needles (0·2 g.), m. p. 156—157° (Found: N, 9·7. $C_{15}H_{12}O_4N_2$ requires N, 9·5%).

β-*Keto*-α-*cyano*-γ-*benzyloxy*-α-*phenylpropane* (XIII).—Benzyloxyacetic acid (Fischer and Gohlke, *Helv. Chim. Acta*, 1933, **16**, 1130) was esterified with 10% methyl-alcoholic sulphuric acid (Rothstein, *Bull. Soc. chim.*, 1932, **51**, 691). The methyl ester (3 g.), b. p. 160—162°/2 mm., and phenylacetonitrile (1·6 g.) were heated for 2 hours on the water-bath with a solution of sodium ethoxide (from sodium, 0·36 g.) in absolute alcohol (10 c.c.). Most of the alcohol was evaporated, water added, and neutral substances removed in ether. The alkaline liquors were acidified; the *product*, isolated with ether, crystallised from ether–light petroleum (b. p. 60—80°) in colourless plates (3 g.), m. p. 72—73° (Found: C, 77·2; H, 5·4. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·3%), which gave a deep blue ferric test.

β-*Keto*-α-*cyano*-γ-*benzyloxy*-α-*veratrylpropane*, prepared similarly from veratrylacetonitrile (2 g.), separated from ether–light petroleum (b. p. 60—80°) in colourless prisms (2·5 g.), m. p. 78—79° (Found: C, 70·2; H, 6·1. $C_{19}H_{19}O_4N$ requires C, 70·2; H, 5·9%), which gave with ferric chloride a blue colour which gradually became green.

β-*Keto*-α-*cyano*-γ-*benzyloxy*-α-*piperonylpropane*, prepared from piperonylacetonitrile (2 g.), separated from ether–light petroleum (b. p. 60—80°) in colourless felted needles (2·3 g.), m. p. 72—73° (Found: C, 70·1; H, 5·0. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·8%), which gave with ferric chloride a blue colour, which rapidly became green and finally colourless.

Phenyltetronic Acid (XIV).—The cyano-ketone (XIII) (5 g.) was dissolved in methyl alcohol (20 c.c.), and dry hydrogen chloride passed through the boiling solution for 4 hours. The alcohol and benzyl chloride were removed under diminished pressure; the residue was taken up in sodium bicarbonate solution, filtered, and recovered. The product crystallised from methyl alcohol in colourless stout prisms (1·6 g.), m. p. 252—253° (Dimroth and Elble, *Ber.*, 1906, **39**, 3929, give m. p. 254°) (Found: C, 68·1; H, 4·7. Calc. for $C_{10}H_8O_3$: C, 68·2; H, 4·6%), which gave a dark green ferric test. This tetronic acid (0·5 g.) was heated with water (5 c.c.) in a sealed tube at 200° for 8 hours. The product was extracted with ether, the extract washed with dilute sodium hydroxide solution, and the solvent removed; the residue crystallised from light petroleum (b. p. 40—60°) in colourless plates (0·05 g.), m. p. 51—52° (Danilow and Danilowa, *loc. cit.*) (Found: C, 72·3; H, 7·0. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%), which reduced Fehling's solution and ammoniacal silver nitrate solution.

Veratryltetronic acid, prepared similarly, crystallised from methyl alcohol in cream-coloured cubes, m. p. 211—213° (Found: C, 61·4; H, 5·3. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%), which gave a green ferric test.

Piperonyltetronic acid crystallised from glacial acetic acid in colourless prisms, m. p. 268° (decomp.) (Found: C, 59·7; H, 3·9. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%), which gave a green ferric test.

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