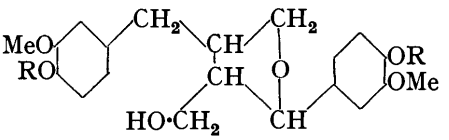
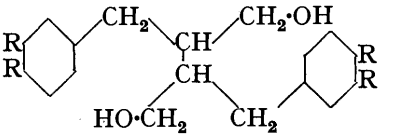
227. *The Constituents of Natural Phenolic Resins. Part XV. The Stereochemical Relationship of Lariciresinol and Pinoresinol.*

By Robert D. Haworth and David Woodcock.

Reduction of *d*-lariciresinol dimethyl ether (I; R = Me) in presence of a palladised charcoal catalyst yields a lævorotatory *diol* (II; R = OMe), the structure of which is established by oxidation with sodium hypobromite to *l*-matairesinol dimethyl ether. Similarly *d*-pinoresinol dimethyl ether (IV; R = OMe) may be reduced either partially to *d*-lariciresinol dimethyl ether or completely to the lævorotatory diol (II; R = OMe). The reduction of *l*-olivil dimethyl ether (VII)to the *triol* (VIII) supports the suggestion of Bruchhausen and Gerhard (*Ber.*, **1939**, **72**, 830) that reduction is limited to the benzyl ether linkages. The results establish the structural formulæ previously suggested for lariciresinol and pinoresinol and indicate a common stereochemical configuration.

In previous experiments (Haworth and Kelly, J., 1937, 384) attempts to reduce *d*-lariciresinol (I; R = H) and its derivatives by catalytic methods were unsuccessful, but reduction of *d*-lariciresinol dimethyl ether (I; R = Me) has now been effected in glacial

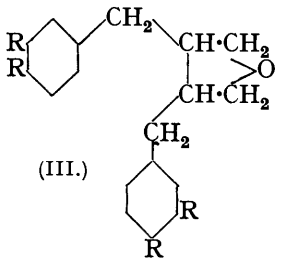
(I.) 

 (II.)

acetic acid solution in presence of a palladised charcoal catalyst, prepared in an all-glass apparatus. The reduction product is a lævorotatory *diol*, $C_{22}H_{30}O_6$, m. p. 122°, which gave an *anhydro*-derivative on treatment with potassium hydrogen sulphate, and veratric acid on oxidation with potassium permanganate. Zerewitinoff determinations showed the presence of two active hydrogen atoms, no acetic acid was detected by the Kuhn–Roth method, and structures (II; R = OMe) and (III; R = OMe) were established for the diol and its anhydro-derivative respectively by oxidising the diol with sodium hypobromite in aqueous dioxan to *l*-matairesinol dimethyl ether. The yield of 30% was most satisfactory in

view of the proved instability of *l*-matairesinol dimethyl ether towards hypobromite (J., 1938, 797), and the conversion provides conclusive proof of the diol structure.

Erdtmann (*Annalen*, 1935, **516**, 612) was unable to reduce *d*-pinoresinol dimethyl ether (IV; R = OMe) with hydrogen in presence of platinic oxide and Robinson and Smith (*J. Proc. Roy. Soc. N.S.W.*, 1915, **48**, 458) failed to reduce *l*-eudesmin (the optical antipode



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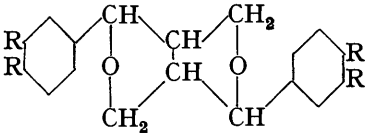

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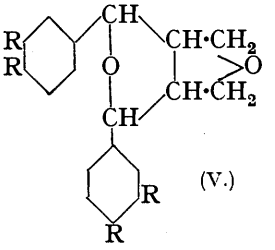
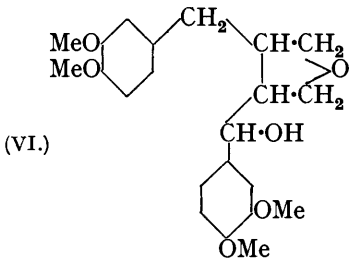


(V.)

of *d*-pinoresinol dimethyl ether) in presence of colloidal palladium. It has now been discovered that *d*-pinoresinol dimethyl ether may be reduced in acetic acid solution in presence of the active palladised charcoal, either partially to *d*-lariciresinol dimethyl ether (I; R = Me) or completely to the lævorotatory diol (II; R = OMe).

The observations of Bruchhausen and Gerhard (*Ber.*, 1939, **72**, 830), published during



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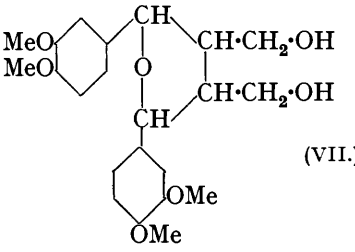
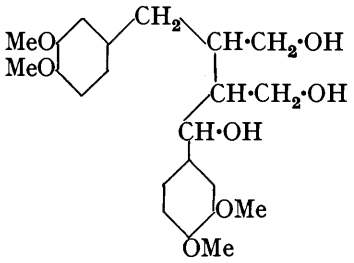
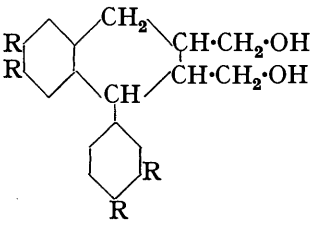


(VII.)

the course of our experiments, strongly support the structure (II; R = OMe) assigned to the diol. These investigators reduced *d*-sesamin (IV; RR = CH_2O_2) to an optically active diol identical with *l*-dihydrocubebin (II; RR = CH_2O_2), the structure of which is established (Ishiguro, *J. Pharm. Soc. Japan*, 1936, **56**, 68; Haworth and Kelly, *loc. cit.*). Bruchhausen and Gerhard advance the interesting and reasonable suggestion that the reduction of *d*-sesamin is confined to the piperonyl ether linkages and consider their results support



(VIII.)

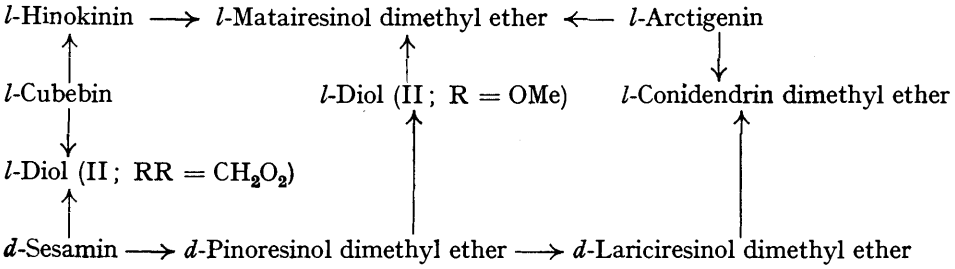


(IX.)

structure (IV; RR = CH_2O_2) for *d*-sesamin and exclude the alternative (V; RR = CH_2O_2). In a similar way we believe that the results now reported support (IV; R = OMe) and (I; R = Me) and exclude the alternatives (V; R = OMe) and (VI) for *d*-pinoresinol and *d*-lariciresinol dimethyl ethers respectively. In the presence of the active catalyst *l*-olivil dimethyl ether (VII) has been reduced to a lævorotatory *triol*, for which structure (VIII) is advanced. Attempts to reduce this triol by catalytic methods were unsuccessful in accordance with the suggestion that reduction is limited to the benzyl ether linkages.

The reduction of *d*-pinoresinol dimethyl ether (IV; R = OMe) to *d*-lariciresinol dimethyl ether (I; R = Me) establishes the configurational relationship of the two lignans and further-

more the observed optical activity of the diol (II; R = OMe) indicates that the two hydrogen atoms attached to the di-propylbenzene junction are "*cis*" in both lariciresinol and pinoresinol. This arrangement has been suggested previously for pinoresinol (Erdtmann, *Svensk Kem. Tids.*, 1936, **48**, 236) and a "*trans*" arrangement is probable for *l*-olivil dimethyl ether (Vanzetti and Dreyfuss, *Rend. R. Accad. Lincei*, 1937, **25**, 133) and the lactonic lignans (J., 1938, 1985; this vol., p. 154, and earlier communications). The numerous interconversions realised in the lignan group, the more important types of which are summarised in the table, find a simple explanation on the basis of a common stereochemical configuration, and the experimental work is at present entirely consistent with the suggestion advanced in 1937 (*Ann. Reports*, 1936, **33**, 277; J., 1937, 1645; Vanzetti and Dreyfuss, *loc. cit.*) that the configurations of members of the lignan group may be derived from an optically active form of a compound of type (II):



The synthesis of optically inactive forms of diols of types (II) and (IX) has already been effected, and the results of these and other synthetical experiments will be reported in a later communication.

Experimental.

αδ-Di-(3 : 4-dimethoxyphenyl)-βγ-di(hydroxymethyl)butane (II; R = OMe).—The absence of rubber connections is essential in the preparation of the 15% palladised charcoal catalyst and also in the reduction experiments described below.

d-Lariciresinol dimethyl ether (I; R = Me) or *d*-pinoresinol dimethyl ether (IV; R = OMe) (0·2 g.) was dissolved in glacial acetic acid (10 c.c.) and shaken in a hydrogen atmosphere in the presence of the catalyst (0·2 g.). After 5 hours a further quantity (0·1 g.) of catalyst was introduced, and the agitation continued for another 7 hours; 12 and 25 c.c. respectively of hydrogen were absorbed. After filtering from the catalyst, the acetic acid was removed under diminished pressure, the residual gum taken up in ether, washed with dilute sodium hydroxide solution, and dried, and the solvent removed. The crystalline residue separated from ether containing a little methyl alcohol in stout prisms (0·14 g.), m. p. 121—122° (Found: C, 67·5; H, 7·9; OH, 9·1. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7; 2OH, 8·7%); in chloroform * (*c*, 1·142), $[\alpha]_D^{17°}$ − 26·2°. This *diol* (II; R = OMe) (0·1 g.) was heated with potassium hydrogen sulphate (0·2 g.) at 180° for ½ hour; the product, isolated with chloroform and washed with dilute sodium hydroxide solution, yielded 3 : 4-*di*-(3′ : 4′-*dimethoxybenzyl*)*tetrahydrofuran* (III; R = OMe), which crystallised from methyl alcohol in large prisms (0·08 g.), m.p. 118—119° (Found: C, 70·7; H, 7·6. $C_{22}H_{28}O_5$ requires C, 71·0; H, 7·5%); in chloroform (*c*, 0·7776), $[\alpha]_D^{17°}$ − 58·9°. A solution of the diol (II; R = OMe) (0·2 g.) in acetone (20 c.c.) was treated with finely powdered potassium permanganate (1·0 g.) and, after remaining in the cold for 12 hours, the mixture was refluxed for 2 hours. A hot dilute sodium hydroxide extract of the manganese dioxide residue was acidified, and the product, isolated with ether, crystallised from hot water; veratric acid (0·08 g.), m. p. 180°, was obtained.

A solution of bromine (0·6 c.c.) in 10% sodium hydroxide solution (15 c.c.) was gradually added to a solution of the diol (II; R = OMe) (0·5 g.) in freshly distilled dioxan (10 c.c.). The solution was refluxed for 3 hours, most of the dioxan was removed, and, after saturation with sulphur dioxide, the solution was acidified with dilute sulphuric acid and extracted with chloroform. The solvent was removed, the residual gum boiled for 10 minutes with 5% methyl-alcoholic potassium hydroxide (5 c.c.) and diluted, and the methyl alcohol removed. Neutral matter was extracted with ether and, after the alkaline layer had been boiled for 15 minutes with

* All α_D values were determined in a micro-polarimeter tube.

excess of dilute hydrochloric acid, sodium bicarbonate was added, and the lactonic material isolated with chloroform. Removal of the solvent gave an oil, which after two crystallisations from methyl alcohol yielded *l*-matairesinol dimethyl ether (0·15 g.), m. p. 125°, undepressed by admixture with an authentic specimen. Acidification of the bicarbonate solution yielded veratric acid (0·1 g.), m. p. 180° after crystallisation from hot water (carbon).

Reduction of d-*Pinoresinol Dimethyl Ether* (IV; R = OMe) *to* d-*Lariciresinol Dimethyl Ether* (I; R = Me).—The reduction, carried out as described above, was interrupted after 4 hours; 14 c.c. of hydrogen were absorbed. The product, recovered from the acetic acid, was dissolved in a little ether and inoculated with *d*-lariciresinol dimethyl ether; the colourless prisms (0·08 g.), m. p. 79° (Found: C, 67·8; H, 7·4. Calc. for $C_{22}H_{28}O_6$: C, 68·0; H, 7·3%), which gradually separated were identified by direct comparison with an authentic specimen. In chloroform (*c*, 1·252), $[\alpha]_D^{18°}$ 21·5°. This experiment was repeated on three occasions, but the product from a fifth experiment did not crystallise. The presence of *d*-lariciresinol dimethyl ether (I; R = Me) was, however, readily demonstrated by refluxing for ¼ hour with acetyl chloride (2 c.c.); conversion into the oily diacetate of *d-iso*lariciresinol dimethyl ether (IX; R = OMe) then occurred. Hydrolysis with 5% methyl-alcoholic potassium hydroxide yielded *d-iso*lariciresinol dimethyl ether, which separated from ether–methyl alcohol in slender needles, m. p. 167—168° (Found: C, 67·7; H, 7·6%); in chloroform (*c*, 1·978), $[\alpha]_D^{17°} = 16·4°$. Identity was established by direct comparison and by conversion into anhydro*iso*lariciresinol dimethyl ether, which was obtained in prisms, m. p. 146—147°, from methyl alcohol (Found: C, 71·3; H, 7·2. Calc. for $C_{22}H_{26}O_5$: C, 71·4; H, 7·1%).

α-Hydroxy-αδ-di-(3 : 4-*dimethoxyphenyl*)-*βγ-di*(*hydroxymethyl*)*butane* (VIII).—*l*-Olivil dimethyl ether (VII) (0·2 g.) was reduced for 12 hours as described above in the preparation of the diol (II; R = OMe); 14 c.c. of hydrogen were absorbed. The product, isolated in the usual manner, crystallised from ether or methyl alcohol in stout prisms, m. p. 137—138° (Found: C, 64·9; H, 7·5; OH, 13·2. $C_{22}H_{30}O_7$ requires C, 65·0; H, 7·4; 3OH, 12·6%); in chloroform (*c*, 0·646), $[\alpha]_D^{17°} = -14·7°$. Attempts to dehydrate this *triol* (VIII) with potassium hydrogen sulphate, 80% formic acid, or acetyl chloride yielded intractable products.

UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-UPON-TYNE.

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